Effect of an Exercise Rehabilitation Program on Physical Function in Incident Hemodialysis Patients: A Randomized Pilot Study

by

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Abstract

This pilot study determined whether it was feasible to implement a self-managed exercise and education program (Renal Rehab) in incident hemodialysis (HD) patients. This study also determined if Renal Rehab improved the functional status of incident HD patients to a greater extent than standard care (StanC). Ten patients were randomized to either StanC (n=5) or Renal Rehab (n=5) at baseline and were followed to three-months. Physical function was assessed using the Short Physical Performance Battery test (SPPB). Baseline data was not different between groups. Many challenges were faced and addressed during the course of the study. Ultimately, patients in StanC improved SPPB total score by 2 points; whereas Renal Rehab's SPPB total score decreased by 1 point from baseline to three-months ($p<0.05$). These data suggest that recruiting incident hemodialysis patients is difficult and that Renal Rehab does not improve physical function in the incident HD population. This thesis provides specific recommendations to inform further studies.

Dedication

To my sister Dana, who is the definition of unconditional love. You have always been one of my biggest cheerleaders and greatest teachers on this journey called life. I am so grateful for having you in my corner and so blessed to be your sister. A large part of me was taken the day you left. I wish I could have made things different. I love you beyond measure. I know you'd be so proud of me.

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Abbreviations

BREB - Biomedical Research Ethics Board

CES-D - Centre for Epidemiological Studies Depression Questionnaire

CDU – Central Dialysis Unit

CKD – chronic kidney disease

DSI – dialysis symptom index

ESRD – end stage renal disease

GFR – glomerular filtration rate

HAP – human activity profile

HAP-AAS - human activity profile-adjusted activity score

HAP-MAS - human activity profile-maximal activity score

HRQOL – health related quality of life

HD – hemodialysis

IPAQ – international physical activity questionnaire

KDIGO – Kidney Disease: Improving Global Outcomes

KDOQI – Kidney Disease Outcome Quality Initiative

Kt/V – K=dialyzer clearance of urea, t=dialysis time, **V**=volume of distribution of urea

MRP – Manitoba Renal Program

MVPA – moderate to vigorous physical activity

NYHA – New York Heart Association

RA – research assistant

PD – peritoneal dialysis

SCDU – Sherbrook Centre Dialysis Unit

SEE – self-efficacy for exercise survey

SODU – Seven Oaks Dialysis Unit

SPPB – short physical performance battery

SWT – shuttle walk test

TUAG – timed up and go

URR – urea reduction ratio

VO_{2peak} – peak oxygen consumption

6MWT – six minute walk test

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Chapter 1: Literature Review

Introduction

Chronic kidney disease (CKD) is a growing public health problem that spans the globe[1]. In Canada, an estimated 2.9 million people are at risk or have been diagnosed with this disease[2]. CKD is classified into five stages and is defined as damage to the kidneys, negatively impacting kidney function for a period of three months or more[3]. It poses a large financial burden on society and is associated with high morbidity and mortality rates[4]. According to Couser et al.[4], patients whose kidneys fail represent about 0.02-0.03% of the population but utilize 2-3% of the annual health care budget to treat. The United States medicare expenditures in 2007 exceeded $25 billion to treat patients in stage five CKD, otherwise known as end stage renal disease (ESRD)[4]. Patients in ESRD require dialysis or transplant in order to sustain life. In Canada, it can cost up to an estimated $83,000 per year to treat one hemodialysis patient in ESRD[5].

Prevalence of CKD

Approximately 36,251 Canadians were living with ESRD in 2015 which is 36% higher than the number recorded in 2006. Fifty-three percent of those Canadians were sixty-five years and older and an additional 41% were forty-five to sixty-four years of age[6]. Manitoba reports the highest total number of ESRD patients treated at a given point in time (i.e. prevalent; 1,707 per million population) and the second highest number of newly diagnosed patients (i.e. incident; 241 per million population) for ESRD in Canada[6]. Diabetes and renal vascular disease (including hypertension) are the leading causes of CKD and contribute to 38% and 14% of CKD prevalence, respectively[3].

Therefore people living with diabetes and hypertension, including members of certain ethnic groups who have a greater incidence of these diseases (e.g. Aboriginal and South Asian) have an increased risk of developing CKD. Older adults and those with a family history of CKD are also at higher risk[3,7].

Treatment of CKD

Chronic kidney disease develops gradually over time, resulting in permanent damage. It can be treated in attempt to slow the progression of the disease; however, there is no cure. CKD is classified into stages one to five (Table 1). These stages are based on the cause of CKD as well as glomerular filtration rate (GFR; how well the kidneys are filtering the blood) and albuminuria (the abnormal presence of the protein albumin in the urine). The risk of CKD progression increases towards stage five as the GFR declines and the protein levels in the urine rise. Therefore, declining kidney function in patients is assessed through blood and urine tests and is generally treated by controlling blood pressure, diabetes and decreasing protein in the urine.

Table 1. Prognosis of CKD by GFR and Albuminuria Categories

GFR Categories (ml/min/1.73 m²)			Albuminuria Categories		
			A1	**A2**	**A3**
			Normal to Mild Increase <30 mg/g <3 mg/mmol	Moderate Increase 30-300 mg/g 3-30 mg/mmol	Severe Increase >300 mg/g >30 mg/mmol
	G1	Normal or high (≥90)	low	moderate	high
	G2	Mild decrease (60-89)	low	moderate	high
	G3a	Mild to moderate decrease (45-59)	moderate	high	very high
	G3b	Moderate to severe decrease (30-44)	high	very high	very high
	G4	Severe decrease (15-29)	very high	very high	very high
	G5	Kidney failure (<15)	very high	very high	very high

Adapted from: Improving Global Outcomes (KDIGO) CKD Working Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International (Suppl.3): 1-150. Colour indicates level of risk, where green is low risk, yellow is moderate risk, orange is high risk and red is very high risk.

Kidney Disease: Improving Global Outcomes (KDIGO) is an organization that provides evidence-based clinical practice guidelines for the evaluation and management of CKD. KDIGO provides practitioners with best practice guidelines to aid them in the operation of their respective renal programs. In general, patients are medically managed by a team of professionals including a nephrologist, nurse, pharmacist and dietitian through the use of medications and diet restrictions[7]. If kidney damage progresses to kidney failure or ESRD, renal replacement therapies, namely, hemodialysis (HD), peritoneal dialysis (PD) or kidney transplant, would be implemented in order to sustain life. Of these modalities, HD is the most common[6]. Hemodialysis is a process by which blood is withdrawn from the body, cleaned through a special filter called a dialyzer and then is returned back to the body by a machine[7]. Approximately 4% of the blood is

outside the body at one time during dialysis. This treatment most often takes place in an outpatient unit of a hospital, three times a week for an average of four hours. Some patients with ESRD choose end of life care, which consists of physical and emotional support for the patient as the disease runs its natural course, ultimately resulting in death[3,7].

Included amongst KDIGO's CKD management guidelines is the recommendation that patients participate in physical activity, thirty minutes, five times per week. A similar organization; The National Kidney Foundation Kidney Disease Outcome Quality Initiative[8] (KDOQI; Table 2) echoes this guideline by recommending that physical activity be routinely encouraged as part of a patient's care plan[8]. Although this is the recommended practice, clinicians and the renal team do not routinely address physical activity with patients diagnosed with stage one to five CKD including those who have progressed to ESRD[9]. This is troubling as the majority of patients are physically inactive which negatively impacts their physical function and quality of life[10].

Table 2. Kidney Disease Outcome Quality Initiative (KDOQI) guidelines.

Guideline Title	Guideline Summary
Diabetes and CKD	Evaluation and classification of hemoglobin A1c (HbA1c) targets, treatments to lower low-density lipoprotein cholesterol (LDL-C) levels, use of angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin receptor blocker (ARB) treatment in diabetic patients with and without albuminuria.
Anemia in CKD	Evaluation of anemia in CKD regarding hemoglobin (Hb) range , erythropoieses stimulating agents (ESA), iron agents, pharmacological and nonpharmacological adjuvants to ESA treatment in HD-CKD, transfusion therapy as well as clinical practice recommendations for anemia in transplant recipients.
CKD: Evaluation, Classification, and Stratification	Definition and classification of stages of CKD, evaluation of laboratory measurements for clinical assessment of kidney disease, association of level of GFR with complications in adults, stratification of risk for progression of kidney disease and development of cardiovascular disease, recommendations for clinical performance measures.
Bone Metabolism and Disease in CKD	Evaluation of calcium and phosphorus metabolism, assessment and treatment of bone disease associated with CKD, evaluation of serum phosphorus levels, prevention and treatment of vitamin D insufficiency and vitamin D deficiency, dialysate calcium concentrations, $ß_2$-microglobulin amyloidosis, aluminum overload and toxicity, parathyroidectomy, metabolic acidosis, and bone disease in the kidney transplant recipient.
Bone Metabolism and Disease in Children with CKD	As above with addition of surgical management of osteodystrophy, management of dietary phosphorus intake in children with CKD, and recommendations for the use of growth hormone for children with CKD.

Hypertension and Antihypertensive Agents in CKD	Goals and use of antihypertensive therapy in CKD, evaluation of patients with CKD or hypertension, measurement of blood pressure, evaluation for renal artery disease, education on self-management behavior, dietary and other therapeutic lifestyle changes, pharmacological therapy, use of diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, special considerations in children and kidney transplant recipients.
Managing Dyslipidemia in CKD	Assessment and treatment of dyslipidemias in adults and adolescents**,** therapeutic lifestyle change including a diet for patients with CKD.
Nutrition in Children with CKD: 2008 Update	Evaluation of the growth and nutritional status, nutritional management and counseling, protein and energy requirements and therapy, vitamin and trace elements, bone mineral, electrolyte and vitamin D requirements and therapy, carnitine, nutritional management of transplant patients.
Nutrition in Chronic Renal Failure	Evaluation of protein-energy nutritional status, management of acid-base status, management of protein and energy intake, carnitine, and nutritional counseling and follow-up.
Hemodialysis Adequacy	Initiation of dialysis, methods for measuring and expressing the hemodialysis dose and post dialysis blood sampling, minimally adequate hemodialysis, control of volume and blood pressure, preservation of residual kidney function, quality improvement programs, and pediatric hemodialysis prescription and adequacy.
Peritoneal Dialysis Adequacy	Initiation of dialysis, peritoneal dialysis (PD) solute clearance targets and measurements, preservation of residual kidney function, quality improvement programs, recommended laboratory measurements for peritoneal membrane function and ultrafiltration volume, writing the PD prescription, pediatric PD.

Vascular Access	Patient preparation, selection and placement of a permanent hemodialysis access, cannulation of fistulae and grafts and accession of hemodialysis, catheters, detection of access dysfunction: monitoring, surveillance, and diagnostic testing, prevention and treatment of fistula, graft and catheter complications, and vascular access in pediatric patients.
Cardiovascular Disease in Dialysis Patients	Guidelines on evaluation and management of cardiovascular diseases (e.g. coronary artery disease, valvular heart disease, and peripheral vascular disease), cardiovascular risk factors (e.g. diabetes, blood pressure, smoking, and physical activity) as well as novel and controversial topics in cardiovascular diseases (e.g. intradialytic hypotension, inflammation, oxidative stress, nutritional and metabolic factors, body weight and management, and omega-3 fatty acids).

Mortality amongst the CKD population

Morbidity and mortality rates are high amongst the CKD population. The Canadian Organ Replacement Register[6] reports that overall, dialysis patients have a 45% survival rate at five years and that rate drops to 43% when specifically looking at HD. More concerning is the elevated death rate during the first six months of HD initiation with the mortality rate being the highest (80%) in the first and second months of starting dialysis therapy[11]

Physical inactivity is a known risk factor for increased mortality rates in the general population and in those with chronic disease[12-15]. CKD is no exception. O'Hare et al.[16] investigated whether inactivity was associated with decreased survival in HD and PD patients. Data was gathered from a study of 4,024 incident dialysis patients. Study participants considered physically inactive had lower physical function and quality of life scores as well as a higher death rate (11%) than those participants considered physically active (5%). After adjusting for variables associated with survival in this group including demographics, comorbidities, lab values, nutritional and socioeconomic status, inactive participants had a 62% increased risk for mortality over one year compared with the active participants. DeOreo et al.[17] also found that dialysis patients who were physically inactive had a higher risk of death. More specifically, in their analysis of 1000 HD patients they found that participants with a lower self-reported physical function score (<34), as measured by the SF-36, were twice as likely to die and 1.5 times more likely to be hospitalized. A total of 36 questions in eight sections makes up the SF-36 which is used as an indicator of overall health status. These findings were similar to those in a study by Knight et al.[18] who found that the mortality rate rose 1.2 to 2 times higher as

physical function scores decreased below 50. This theme seems to be consistent regardless of the stage of CKD. Roshanravan et al.[19] investigated the association between physical activity and mortality rates in 385 CKD patients in stages two to four. They found that when compared to the general population, those with CKD performed 30% lower in measurements of physical function (usual gait speed, timed up and go (TUAG) and six minute walk test (6MWT)). After adjustment for demographics and comorbidity, usual gait speed and TUAG were associated with all-cause mortality. More specifically, each 0.1m/s slower gait speed and each 1-second longer TUAG result was associated with an estimated 26% and 8% greater risk of death, respectively.

People with CKD are physically inactive

People with CKD are less active than healthy controls and are not reaching the levels of physical activity recommended by evidence based, best practice guidelines (Table 3). More specifically, Johansen et al.[20] found those in ESRD on HD to be 35% less active than healthy controls. Zamojska et al.[21] also found physical activity levels to be low. They assessed the physical activity levels in sixty HD patients via pedometry and found that participants took less than half of the steps taken by age matched healthy controls (6,896 ± 2,357 vs. 14,181 ± 5,383 per 48 hour, respectively). Similarly, Panaye et al.[22] found that in a cohort of 1,163 dialysis patients, 3,688 steps per day were taken on average with only 17% walking more than 7,500 steps per day. These numbers are well below the Canadian general population average of 9,500 daily steps for men and 8,400 daily steps for women as reported by Colley et al.[23]. According to Robinson-Cohen et al, patients with CKD spend 95% of their daily activities in sedentary to light activities, as

measured by accelerometer; whereas, less than 5% of wear time was spent performing moderate to vigorous physical activities (MVPA). Based on this data, only 6.5% of participants were classified as being physically active at the recommended physical activity guideline levels[24,25] (i.e. they performed moderate to vigorous activities for 30 minutes or more per day, five or more days per week, in 10 minute bouts)[26]. Fifteen percent of the general population is considered physically active according to evidence based, best practice guidelines[23].

People living with CKD not only show lower levels of physical activity when measured objectively, as compared to health controls, they also subjectively report lower physical activity levels and limitations in performing MVPA[20,27]. Stack et al.[27] analyzed 2,264 HD patients and found that more than half (56%) of the participants reported being physically active less than once a week. When participants were asked to rate the degree of limitation they had in performing MVPA, 42% of participants reported severe limitation in moderate activities and 75% in vigorous activities. Low physical activity levels are a problem because they are associated with low physical function, affecting activities of daily living and quality of life.

Table 3. Summary of research studies that have examined physical activity levels amongst CKD patient populations.

Author/Year	Purpose	Groups	Tools	Outcome	Summary
Robinson-Cohen et al., 2012	To measure physical activity levels using accelerometry	No control group n = 46 stage 1-4 CKD	ActiGraph GT3X accelerometer	95% of wear time was in sedentary to light activities	Physical activity levels are low amongst CKD – 6.5% were meeting recommended levels of physical activity.
Johansen et al., 2000	To measure physical activity levels using accelerometry	n = 114 n = 80 healthy controls n = 34 ESRD patients on HD	TriTrac-R3D accelerometer	35% of HD patients are less active than healthy controls	Patients on HD are less active than healthy controls.
Zamojska et al., 2006	To measure physical activity levels using pedometry	n = 76 n = 16 healthy controls n = 60 ESRD patients on HD	Oregon Scientific PE316CA pedometer	HD patients total steps (6,896 ± 2,357 per 48 h) were half of controls (14,181± 5,383 per 48 h)	HD patients take less steps and are therefore less active than healthy controls.
Stack et al., 2008	To describe patterns of physical activity using self-report questionnaire	No control group n = 2,264 ESRD patients on HD	KDQOL	56% reported exercising less than once a week, 42% and 75% reported severe limitations in moderate and vigorous activity respectively	HD patients report limitations in moderate and vigorous physical activity which contributes to inactivity.
Panaye et al., 2015	To evaluate physical	No control group n = 1,163 ESRD	PE317C pedometer	Median physical activity was 3,688	Dialysis patients present a very low

	activity levels using pedometry	patients on HD or PD		steps/day. Twenty percent walked between 5,000 and 7,500 steps and 17% walked more than 7,500 steps per day.	level of physical activity

CKD= chronic kidney disease; ESRD=end stage renal disease; HD= hemodialysis; KDQOL= Kidney Disease Quality of Life Short Form; N= total number of participants in study; n= number of participants in each group in the study.

Physical function is low in CKD

Physical function is an important aspect of health, independent living and quality of life and refers to the ability to perform activities of daily living such as getting up from a seated position or walking a short distance[28]. While renal replacement therapies (i.e. HD, PD and kidney transplant) keep patients alive longer, low levels of physical activity and high rates of functional impairment amongst CKD patients are linked to higher rates of hospitalization, morbidity and mortality in this population. Low physical activity also negatively impacts their ability to perform activities of daily living[24,29]. Measurements of physical function can range from self-reported questionnaires to specific tasks like performing a sit to stand or more vigorous laboratory measures such as a graded exercise test (e.g. VO_{2peak})[30]. Following the trend of physical activity, physical function also appears to be low in people living with CKD. According to Hiraki et al.[31] physical function deteriorates with the progressive loss of kidney function from stages two to five. When compared to age predicted norms, all measurements of physical function including the 6MWT, gait speed and sit to stand results were lower in those with CKD[32]. Walker et al.[33] found that 56% of CKD stage four to five patients, not yet on dialysis, had reduced physical function and Marcus et al.[34] concluded that when compared to a cohort of older adults (75±7 years) who did not have CKD, physical function was poorer in HD patients who were younger in age (49±16 years). Painter et al.[35] assessed physical function using a graded exercise test and found that HD patients achieved 19 ml O_2/kg/min which was 64% of the average VO_{2peak} values measured in the healthy population. Padilla et al.[32] found similar results when testing patients in CKD stages three to four (18 ml O_2/kg/min or 59% of age-predicted norms). Low VO_{2peak} in HD patients puts them at a higher rate

of mortality[36]. Specifically, patients with a median VO_{2peak} value above 17.5 ml O_2/kg/min had a lower mortality rate (5%) than those with a VO_{2peak} below this level (22%). As a comparison, a VO_{2peak} of 17.5 ml O_2/kg/min places HD patients at a fitness level similar to patients with cardiac and respiratory disease[36] (Table 4).

Table 4. Summary of research studies that have examined physical function levels amongst CKD patient populations.

Author/Year	Purpose	Groups	Tools	Outcome	Summary
Hiraki et al., 2012	To assess physical function in each stage of CKD	No control group n = 120 patients in CKD Stage 2, n = 17 Stage 3, n = 55 Stage 4, n = 25 Stage 5, n = 23	Handgrip strength	Stage 2 = 35 ± 9 kgf Stage 3 = 31 ± 10 kgf Stage 4 = 24 ± 10 kgf Stage 5 = 22 ± 8 kgf	Physical function decreases with progression of CKD.
			Knee extensor strength	Stage 2 = 0.66 ± 0.11 kgf/kg Stage 3 = 0.60 ± 0.13 kgf/kg Stage 4 = 0.51 ± 0.15 kgf/kg Stage 5 = 0.47 ± 0.16 kgf/kg	
			Single-leg stance time	Stage 2 = 58 ± 7 s Stage 3 = 51 ± 17 s Stage 4 = 32 ± 25 s Stage 5 = 2 ± 0.4 s	
			Maximum gait speed	Stage 2 = 2.2 ± 0.2 m/s Stage 3 = 2.1 ± 0.4 m/s Stage 4 = 1.7 ± 0.5 m/s Stage 5 = 1.7 ± 0.4 m/s	
Padilla et al., 2008	To assess physical function in pre-dialysis population	No control group n = 32 patients in CKD Stage 3, n = 19 Stage 4, n = 13	VO_{2peak} test	18 ± 7 ml/kg/min or 59% of age-predicted norms	All measures of physical functioning were reduced amongst Stage 3 & 4 CKD, as compared to age-predicted norms.
			Comfortable gait speed	124 ± 25 cm/s or 90% of age-predicted norms	
			Maximal gait speed	180 ± 38 cm/s or 85% of age-predicted norms	

			STS10	23 ± 9 s or 79% of age-predicted norms	
			6MWT	472 ± 102 m or 98% of age-predicted norms	
Painter et al., 1986	To assess functional capacity in ESRD patients	No control group n = 50 ESRD patients HD, n = 18 PD, n = 12 TX, n = 20	VO_{2peak} test	HD = 19 ± 6 ml/kg/min or 64% of healthy population	Functional capacity in ESRD patients is low compared to healthy population.
				PD = 21 ± 5 ml/kg/min or 62% of healthy population	
				TX = 32 ± 7 ml/kg/min or 93% of healthy population	
Sietsema et al., 2004	To use functional capacity to predict survival in ESRD patients on HD	No control group n = 175 ESRD patients on HD	VO_{2peak} test	All patients = 18.6 ± 7 ml/kg/min	Patients with >17.5 ml/kg/min had a 5% lower mortality rate than those with a VO_{2peak} below this level (22%). Functional capacity was a strong predictor of survival status.
				Survivors = 19.2 ± 7 ml/kg/min	
				Non-survivors = 14.9 ± 5 ml/kg/min	
Marcus et al., 2015	To determine if muscle wasting accounts for impaired physical function in	n = 122 elderly non-HD controls n = 108 ESRD patients on HD	6MWT	HD walked 86 m shorter distance in 6 minutes than non-HD elderly controls. Even with adjustments, HD had lower 6MWT distances (-117m).	When compared to elderly non-HD adults, HD patients had lower physical function despite younger age, not

	HD				explained by muscle mass or comorbid condition
Walker et al., 2015	To understand the clinical history of frailty and its association with worsening kidney function, adverse outcomes and dialysis modality decisions.	No control group N = 217 stage 4 or 5 CKD	baseline measure of SPPB	At baseline, 56% had reduced physical function and after adjustments, the risk of having reduced physical function was 7 fold higher for those with diabetes.	Identified a strong association between diabetes and frailty in people with CKD.

CKD= chronic kidney disease; ESRD=end stage renal disease; HD = hemodialysis; PD = peritoneal dialysis; TX = transplant; STS10 = sit to stand 10 times; 6MWT = six minute walk test; VO_{2peak} = peak oxygen consumption.

Frailty is high in CKD

Frailty is a clinical condition of low reserve and resistance to stressors as a result of cumulative declines across multiple physiologic systems. It causes vulnerability to adverse health outcomes including falls, hospitalization, institutionalization and death and is often associated with advanced age[37]. The most widely used screening tool for frailty came out of the Cardiovascular Health Study by Fried et al. [37]. This model, known as the frailty phenotype, characterizes frailty as the presence of three or more of the following five criteria: greater than 10 pounds of unintentional weight loss over one year, weak grip strength, self-report of exhaustion, slow gait speed and low physical activity. Another popular assessment tool was developed by Rockwood et al.[38]. This frailty model came out of the Canadian Study of Health and Aging and is referred to as the frailty index. It is a measure of frailty determined from a list of seventy clinical deficits that factors in clinical signs, symptoms, disabilities, disease and laboratory measurements. The greater the number of deficits an individual accumulates, the greater the likelihood frailty is present and is therefore an increased risk of adverse health outcomes. In addition, Rockwood et al.[38] developed the 7-point clinical frailty scale which is based on clinical judgement. It is highly correlated ($r = 0.80$) with the frailty index and has an advantage over other frailty models in its ease of use and capability to screen large numbers of patients. There are numerous other models of frailty; however, the majority are based on these basic approaches[39].

Shliplak et al.[40] used Fried et al.'s screening tool to look at the presence of frailty in a subset of the elderly population (≥ sixty-five years) with CKD. This cross-sectional analysis found that the participants with CKD had substantially greater prevalence of

frailty, and in fact, were more than twice as likely to be frail than participants who had normal renal function (15% versus 6%, respectively). In a similar study, Wilhelm-Leen et al.[41] also found the prevalence of frailty to be greater in individuals with CKD than those with normal kidney function and added that frailty not only increased as kidney function decreased (stage one and two = 6%, stage three b, four and five = 21%) but was independently associated with an increased risk of death. Johansen et al.[42] investigated frailty in both HD and PD patients and identified that 68% of the population met the study definition of frailty, which was independently associated with older age and being on HD as opposed to PD. However, although older age (74% aged sixty to seventy years and 78% aged seventy to eighty years) was strongly associated with frailty, they found that it was not only the elderly who were frail. Patients younger than forty years of age (44%) and those forty to fifty (61%) were also determined to be frail. Johansen et al.[42] also found that frailty was independently associated with a higher risk of death; frail patients were three times more likely to die within the first year of starting dialysis, as compared to patients who were not frail. Likewise, frail patients with CKD were more likely to have increased rates of death and hospitalization. In a study by McAdams-DeMarco et al.[43] 52% of HD patients had one or more hospitalizations in the first year of the study compared to 61% of HD patients who were frail. The three year mortality rate for frail participants was 40% as opposed to 16% for participants who were not frail. Frailty was associated with a 2.6 times higher risk of mortality and 1.4 times as many hospitalizations[43].

Exercise training interventions for CKD patients

A Cochrane Review by Heiwe and Jacobson [1], analyzed 1,863 participants in forty-five randomized controlled trials undertaken for eight weeks or more. The studies in this review included patients from any stage of CKD as well as ESRD and transplant; however the majority of studies tended to focus on ESRD-HD which were performed either during or outside of HD treatment. Various types of exercise training interventions were searched (i.e. aerobic, mixed aerobic plus resistance training, resistance training only and yoga). Aerobic exercise training programs were the most abundant amongst the studies analyzed with the majority prescribing exercise training three to five times a week. Based on the evidence, Heiwe and Jacobson concluded that regular exercise training improves physical function and fitness levels, blood pressure, some nutritional parameters such as albumin, as well as health related quality of life in people with CKD. The data indicated that both high and low intensity exercise training had a positive effect on aerobic capacity with a trend towards a greater increase in aerobic capacity with mixed aerobic plus resistance training compared to aerobic training alone. Heiwe et al. also found an improvement in muscle strength with resistance exercise training regardless of intensity[1]. Orcy et al.[44] found similar results in their HD exercise training intervention and concluded that the combination of aerobic and resistance training was more effective than resistance training alone. Other exercise interventions studies reported significant improvements in physical function and quality of life through exercise training programs incorporating both aerobic and resistance training exercises. Greenwood et al.[45] evaluated the feasibility and effectiveness of a twelve-week exercise and education program on functional capacity of patients in stages

of 3-4 CKD, ESRD-HD and transplant. The exercise program involved supervised exercise (i.e. warm-up, aerobic exercise, resistance training, cool down, balance and stretching) and education (e.g. self- management skills such as addressing barriers to lifestyle change, goal setting and problem solving) twice per week in addition to a home-based exercise program once per week. Results showed significant differences in all parameters from pre to post measures with improvements observed in physical function and mental health status as compared to baseline. Headley et al.[46] examined the effect of forty-eight weeks of moderate intensity exercise training in patients with stages two to four CKD. Twenty-one patients were matched at baseline according to their GFR and VO_{2peak} and were randomly assigned to receive standard care or standard care plus exercise training. By the completion of the study, the participants VO_{2peak} amongst the exercise group was significantly higher than the standard care group (20 ± 5 ml O_2/kg/min vs 17 ± 3 ml O_2/kg/min, respectively). Despite lower physical function and quality of life in ESRD patients, exercise training seems to have similar benefits as those seen in the earlier stages of CKD. A current systematic review of participants in ESRD by Barcellos et al.[47] is in agreement that exercise improves physical function, strength and quality of life and adds that although the evidence for the effect of exercise on mortality has not been demonstrated, the evidence is well established to support the inclusion of exercise as part of the regular treatment in dialysis units. (Table 5).

Table 5. Summary of research studies that have examined exercise training outcomes amongst CKD patient populations.

Author/Year	Purpose	Groups	Tools	Outcome	Summary
Heiwe et al., 2011	To assess the effect and design of exercise programs on CKD, ESRD and transplant patients.	Randomized controlled trials of CKD, ESRD or transplant patients undergoing exercise intervention for 8 weeks or more.	Cochrane systematic review and meta-analysis	Measured physical fitness, physical function, blood pressure, heart rate, nutritional parameters, inflammation, physical activity, depression, HRQOL, strength, lipids, cardiovascular dimensions, glucose metabolism, drop out and compliance, adverse events, mortality.	There is evidence for the beneficial effects of exercise on physical fitness, walking capacity, cardiovascular dimensions, HRQOL and some nutritional parameters in adults with CKD, ESRD and transplant.
Orcy et al., 2012	To compare the effects of resistance training with resistance and aerobic training on functional performance.	No control group n = 26 stage ESRD patients on HD Resistance & aerobic combined, n = 13 Resistance only, n = 13	6MWT	⇑ combined training group (40 ± 61 m).	The combination of aerobic and resistance training was more effective than resistance training alone to improve functional performance.

Greenwood et al., 2012	To explore if an exercise program could improve activities of daily living related to functional capacity in all stages CKD.	No control group n = 131 stage 3-4 CKD (n=32) ESRD-HD (n=29) Transplant (n=16)	DASI	⇑ 35%	A pragmatic, outpatient exercise program can improve physical function and mental well-being across the CKD/ESRD trajectory.
			SWT	⇑ 44%	
			TUAG	⇑ 25%	
			STS60	⇑ 21%	
			SCD	⇑ 28%	
			HAD	anxiety - ⇑ 16%; depression - ⇑ 28%	
Headley et al., 2012	To examine the effect of exercise training on kidney function and vascular parameters in CKD.	n = 21 Control group, n = 11 Stage 2-4 CKD, n =10	VO_{2peak} test	Control group = 44% ± 16% (ml/kg/min)	A 48 week exercise training program improved aerobic fitness as measured by VO_{2peak} test.
Barcellos et al., 2015	To critically appraise the effectiveness of exercise interventions among ESRD patients.	Randomized clinical trials comparing exercise with standard care on the health effects of ESRD patients mainly on HD. n = 59 articles	Systematic review	Measured HRQOL, physical fitness, lipids, inflammatory markers, muscular strength, body composition, CKD progression, cardiovascular dimensions.	Consistent evidence supports the positive effects of aerobic exercise on physical fitness, muscular strength and quality of life in ESRD patients.

CKD=chronic kidney disease; ESRD=end stage renal disease; HD=hemodialysis; DASI=duke activity status index; SWT=shuttle walk test; TUAG=timed up and go; STS60=sit to stand in 60 seconds; SCD=stair climb decent; HAD=hospital anxiety and depression score; ⇑=improvement; VO_{2peak} =peak oxygen consumption; 6MWT=six minute walk test.

Intradialytic vs extradialytic exercise

Studies have utilized both intradialytic (i.e. exercise during HD) and extradialytic (i.e. exercise outside of HD) venues to host exercise programs for individuals on HD. However, which is the most favorable with regards to functional improvements and adherence rates? According to Konstantinidou et al.[48]and Kouidi et al.[49], both have their merits. Each investigator compared supervised cycling and or resistance training during HD treatment to aerobic and resistance training programs done outside of HD, either at home or supervised in a facility. In both studies, intradialytic and extradialytic exercise programs showed improvements, specifically increases in exercise time (22-31% in intradialytic and 33-38% extradialytic[48,49]) and VO_{2peak} (24-36% intradialytic and 43-47% extradialytic[48,49]). However, in both studies, it was the extradialytic supervised exercise groups who experienced the greatest improvements. Unfortunately, despite attaining the best results, the extradialytic group also had the largest dropout rate at 24%[48]and 38%[49]. The reasons stated for those participants not completing the study were lack of time, transportation difficulties and medical reasons unrelated to exercise. Although the participants that exercised on non-dialysis days attained greater improvements in VO_{2peak}, adherence was poor. On the other hand, exercising during HD treatments was somewhat effective for improving VO_{2peak} and resulted in higher compliance. In addition, studies have found that physical activity, as measured by accelerometer, is lower on dialysis days as compared to non-dialysis days. Therefore incorporating exercise during HD treatment would help to combat this inactive time[50-52].

Intradialytic exercise and dialysis clearance

Another potential benefit to an intradialytic exercise program is the effect on the dialysis treatment itself. Uremia is a complication of CKD and occurs when urea and other waste products build up in the blood due to the kidney's inability to eliminate them. Dialysis removes these substances from the body that would otherwise become toxic. Kt/V and urea reduction ratio (URR) are two ways of assessing how effectively the dialysis treatment removes wastes from the body, specifically urea. This molecule is a good measure of HD adequacy as it is freely filtered across the HD membrane. It is hypothesized that exercise during dialysis may increase the efficiency of the dialysis treatment by increasing the blood flow to the muscles that in turn would increase the flux of urea from the tissue to the vascular compartment resulting in an increase in serum urea clearance. Giannaki et al.[53] studied intradialytic exercise and its effect on dialysis efficiency and found that cycling improved Kt/V and URR by 20% and 11% respectively. Parsons et al.[54] found an overall increase in Kt/V by 11% in their twenty-nine week intradialytic exercise program. In addition to Kt/V and URR, Kong et al.[55] investigated the effect of intradialytic cycling on the rebound of urea, creatinine and potassium levels following dialysis treatment. Rebound is a rebalancing of solutes that takes place between the intra and extracellular compartments minutes to hours after the dialysis treatment is complete. Dialysis reduces the serum solute levels but does not reduce intracellular levels efficiently. Potassium is an example of a molecule that is mainly located in the intracellular compartment and is associated with rebound in serum levels following hemodialysis. When a HD session with intradialytic cycling was compared to a HD treatment with no cycling they found that the proportion of rebound at

thirty minutes post-dialysis treatment was reduced for all three solutes with intradialytic exercise as compared with the HD session with no intradialytic exercise; urea decreased from 12% to 11% rebound, creatinine from 21% to 17% rebound and potassium from 62% to 44% rebound. They also found that Kt/V and URR increased; Kt/V urea from 1.00 to 1.15, URR from 0.63 to 0.68. Based on their findings, the authors concluded that exercise may increase the efficiency of dialysis equivalent to extending the dialysis time by fifteen to twenty minutes which could possibly result in a shortened dialysis treatment time or improvement in the HD treatment by improving removal of larger molecules that are harder to clear across the dialysis membrane. One such molecule is phosphate. Orcy et al.[56] did not find that exercise changed the removal of urea, creatinine or potassium but did see an improvement in the level of phosphate removal (5.6 mg/min in the exercise intervention group vs. 5.1 mg/min in the control group, $p=0.04$). The kidneys work to balance phosphorus and calcium levels in the blood. As kidney function declines, serum levels of phosphorus increase which binds to calcium, causing serum calcium to drop. The parathyroid gland detects low levels of calcium in the blood and releases parathyroid hormone, pulling calcium out of the bone to as it tries to bring it back into balance. Chronically, this can cause the bones to weaken and become brittle (renal osteodystrophy). The bound phosphorus and calcium can get deposited into soft tissue causing calcification in blood vessels such as the heart and lungs. Improved removal of phosphate with intradialytic exercise may help prevent this complication of CKD from developing.

Intradialytic exercise and cardiovascular health profiles

Cardiovascular disease is the leading cause of mortality in patients with CKD[57]. Intradialytic exercise is beneficial for physical function and quality of life[58]. However, less is known about the effects of intradialytic exercise on cardiac health. Momeni et al.[59] investigated the relationship between intradialytic exercise and echocardiographic findings among forty HD patients over a period of three months. The results showed that the exercise group experienced an increase in left ventricular ejection fraction (55 ± 3% to 59 ± 4%), a decrease in systolic pulmonary artery pressure (40 ± 19 mmHg to 33 ± 20 mmHg) and right ventricular size (3.43 ± 0.70 cm to 3.17± 0.54 cm) as well as an improvement in mitral valve velocity time integral (25.76 ± 7.91 to 22.66± 6.69) and mitral valve minimum pressure gradient (1.90 ± 0.96 to 2.26 ± 0.96). No change was found in the control group. Kouidi et al.[60] also found an increase in left ventricular ejection fraction (57 ± 11 % to 60 ± 13 %) as well as heart rate variability (101 ± 19 ms to 114 ± 11 ms) with no change in the control group. Rebouredo et al.[61] evaluated the effects of exercise training on blood pressure and in twenty-four weeks found that systolic and diastolic blood pressures decreased by 12 mm Hg and 5 mm Hg respectively. Afshar et al.[62] explored the effects of 8 weeks of aerobic and resistance training on inflammation status and lipid profiles in patients on HD. The major finding from this study was that inflammation status (i.e. hs-CRP; highly sensitive c-reactive protein) improved in both the aerobic (6 ± 3 mg/L to 1 ± 1 mg/L) and resistance training (7 ± 3 mg/L to 2 ± 2 mg/L) groups with no effect on the control group. Lipid profiles are an important aspect of cardiovascular health, as unhealthy levels are associated with an increased risk for coronary heart disease. Barcellos et al.[47] references twelve studies that

have measured lipid profile outcomes. Only one of the twelve studies found that physical activity, specifically yoga, had an effect on lipids. That study reported a 15% decrease in lipids.

Psychological effects of exercise and CKD

Psychological issues, such as anxiety, depression and decreased quality of life are common in ESRD patients[63]. According to Lacson et al.[64], depressive symptoms in incident HD patients are also associated with higher rates of hospitalization, dialysis withdrawal and mortality. Exercise has been found to have a positive effect on these issues in healthy populations as well as those with chronic disease such as CKD. Suh et al.[65] evaluated the effects of a twelve-week supervised extradialytic exercise program on anxiety, depression and quality of life and found that both anxiety and quality of life ratings improved post-intervention. Van Vilsteren et al.[66] examined whether an intradialytic cardiovascular and resistance training program could improve health-related quality of life in patients on HD. The exercise intervention showed improvements in vitality, general health perception and health change. Another intradialytic study by Ouzouni et al.[67] showed favorable effects of exercise on mental health status. Thirty-five HD patients (age 49 ± 14 years) were randomized into either a supervised cycling and resistance training program during their dialysis treatment or a control group for a total of ten months. The exercise group had a 39% improvement in depressive symptoms as well as improvements on measures of life satisfaction (18%) and quality of life (38%). Other randomized controlled trials looking at aerobic exercise in the HD population suggest that exercise has a positive effect on self-reported depressive symptoms[68-70]. Collectively, it

appears that exercise during HD enhances the psychological status and quality of life of participants.

Knowledge gaps in research literature

Based on the data presented in this literature review, it is evident that physical activity levels and functional status are low in people at all stages of CKD and particularly in those on HD. It appears that physical activity interventions improve physical activity levels, functional capacity, psychological status and quality of life amongst a cohort of HD patients. At the time when we conducted this thesis research, we were unaware of any other study examining the effectiveness of exercise training in the incident HD population; however, after conducting a literature search while writing this thesis document, I identified one paper by Parker et al.[71] who included incident HD participants in their report. That retrospective observational study looked at hospital admission and length of hospital stay in a cohort of prevalent (n=76) and incident (n=26) HD patients who participated in a six month intradialytic cycling program. . The incident time frame was defined from HD commencement to six months and the incident participants had been on HD for a median of three months (range: 0-5). Our definition included the first three months following dialysis initiation which is traditionally known as the incident HD time period. Although Parker et al. found an association between intradialytic cycling and a decreased in hospital admission and length of hospital stay in incident patients, that study did not address the declining physical status patients experience during HD initiation. The literature indicates that patients beginning HD face high mortality rates and declining physical function during the first year on HD which lead to poor outcomes.

Perhaps this decline could be prevented by intervening in the incident time period. Therefore, my thesis research examined the feasibility of implementing a twelve-week self-management and rehabilitation exercise program in incident HD patients. A second objective was to determine if the intervention influences health related outcomes. To our knowledge, a similar study has not been conducted.

Chapter 2: Study Design and Methods

Rationale, objectives and hypotheses

Based on the literature review presented, people on HD have low levels of physical activity and physical function and increased rates of functional impairment, frailty, hospitalization, morbidity and mortality as compared with the general population. Very little is known about the effectiveness of exercise therapy in incident dialysis patients and whether intervening at the beginning of dialysis initiation could prevent the decline in physical function. Therefore, we designed a randomized controlled pilot study to determine if implementation of a twelve-week exercise rehabilitation program consisting of structured lifestyle education, a home based resistance exercise program, plus cycle-exercise during HD improves physical function over a twelve-week period in incident HD patients compared to a cohort of incident dialysis patients who receive exercise education but no formal rehabilitation program. This pilot study was designed to test the feasibility of the approach in incident HD patients for the purpose of informing a future randomized controlled trial.

We hypothesize that:

1. Patients who complete a twelve-week self-management education and exercise rehabilitation program will have higher physical function scores, as measured by the Short Physical Performance Battery test (SPPB), than those patients who receive standard care.
2. Patients who complete a twelve-week self-management education and exercise rehabilitation program, as compared to standard care, will have; a) improvements in their health-related quality of life (HRQOL) as measured by the EQ5D-3L, EQ Visual

Analogue Scale (VAS); b) reduction in dialysis symptoms as measured by the Dialysis Symptom Index (DSI); c) improvements in frailty status as measured by the Modified Fried Criteria; d) improvements in physical fitness scores as measured by the shuttle walk test (SWT); e) improvements in physical activity behaviour patterns as measured by the Human Activity Profile (HAP), the International Physical Activity Questionnaire Short Version (IPAQ) and multi-directional accelerometry; and, f) improvements in self-efficacy for exercise as measured by the Self-Efficacy for Exercise Survey (SEE).

Ethics approval

The study protocol was approved by the University of Manitoba Biomedical Research Ethics Board (BREB; Appendix A). The study was supported by a grant from the Manitoba Medical Services Foundation (#8-2015-14) and the Winnipeg Foundation. We also had study site approval from Health Science Centre and Seven Oaks General Hospital. This study has been registered with ClinicalTrials.gov (NCT02259413).

Study population

All adults classified as incident CKD (i.e.; within the initial three months of HD) in any of the three in-centre HD units in Winnipeg, MB, Canada (i.e. Sherbrook Centre Dialysis Unit; SCDU, Central Dialysis Unit; CDU, and Seven Oaks Dialysis Unit; SODU) were eligible for enrollment.

Inclusion criteria: To be included in the study, patients had to be eighteen years and older, within ten weeks of beginning HD and not expected to recover renal function.

Patients who did not have plans to change HD modality or relocate outside of Winnipeg during intervention period (twelve-weeks), were able to communicate in English and were determined to be safe and appropriate to exercise by the dialysis unit nephrologist would be considered for the study. Patients were also required to be able to provide informed written consent to participate.

Exclusion criteria: Patients who were previously diagnosed with acute myocardial infarction within three months prior to enrollment, had crescendo or unstable angina, had unstable arrhythmias, symptomatic hypoglycemia greater than two times per week in the previous month or experienced shortness of breath at rest (New York Health Association Class 4) were excluded from the study.

Sample size: For this pilot study, we recruited five participants per treatment group, for a total of 10 participants. Based on previous clinical trials, a 30% dropout rate was anticipated with this particular population[72]. Therefore, fourteen participants were targeted per treatment arm for a total enrollment of twenty-eight participants.

Enrollment, randomization and initial assessment

The ethical guidelines and principles of the BREB and the Declaration of Helsinki were followed throughout the development and implementation of this research project. Individuals that met the inclusion/exclusion criteria were asked by the dialysis staff if they were interested in speaking with a member of the research team about the study. Those interested were approached by a member of the research team, at which time the research assistant (RA) provided further details of the study. Individuals who provided written consent were assessed by the unit nephrologist for medical clearance to exercise.

If that individual was deemed appropriate for the study, a baseline assessment appointment was arranged at the Manitoba Renal Program (MRP) Exercise Counseling Clinic approximately six to ten weeks after their first HD session.

At the baseline assessment appointment, in addition to usual procedures at the MRP Exercise Counseling Clinic (see description on page 36), the RA described study procedures and ensured that any questions were answered. Patients completed baseline testing for primary and secondary outcomes at this initial appointment as described below. The following demographic and clinical data were also collected from each patient's HD chart: age, sex, race, height, weight, cause of renal failure, type of HD access, mean dialysis adequacy as measured during each HD treatment by Kt/V (calculated the week before enrollment), blood pressure, hemoglobin, albumin, phosphate, calcium, potassium, parathyroid hormone, low density lipoproteins, total cholesterol, triglycerides, hemoglobin A1c, weekly erythropoietin dose, weekly intradialytic fluid gains (calculated the week before enrollment), comorbidities and medications.

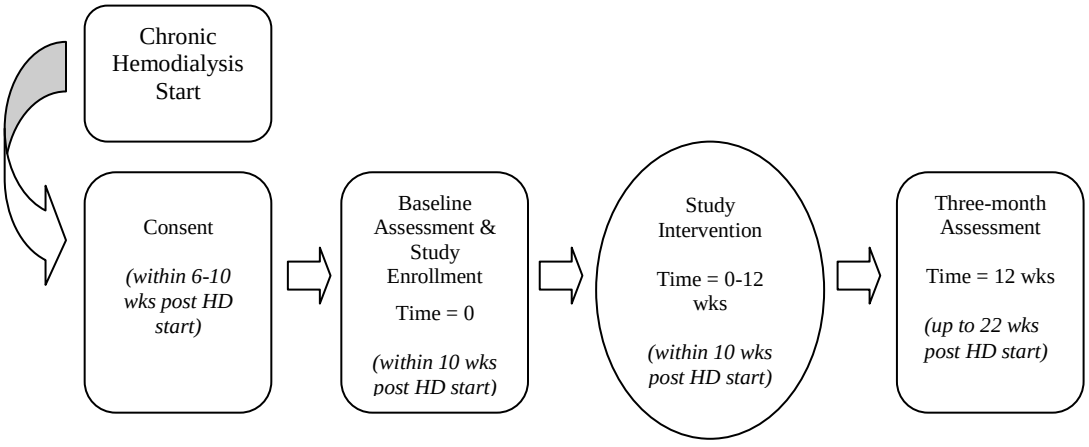
Randomization to control and intervention groups was accomplished by a third party using block randomization in blocks of four with allocation concealment to study investigators and RA. Following the baseline assessment, the study kinesiologist handed participants the next sequential, sealed envelope, which they opened to reveal their assigned study group. The individuals randomized to the intervention arm performed a maximal incremental cycle test at the Wellness Institute prior to exercise intervention commencement. This took take place in order to allow standardize prescription of exercise intensity during the study intervention. This test was supervised by an exercise

specialist to determine maximal workload achieved. Briefly, patients began cycling at a power output of 0 watts for one minute then increased their power output by 25 watts every two minutes until volitional fatigue, allowing us to determine maximal power output.

Data collection and assessments

Data was collected at baseline and twelve-week assessment appointments. Figure 1 illustrates the study timeline. The RA contacted patients in both the intervention and standard care group at each of these time points to arrange a meeting with the research team at the MRP Exercise Counseling Clinic. At these appointments, patients completed assessments for primary and secondary outcomes as described below. Assessments were performed by the same individual at each of the study time points to minimize observer bias. As well, all assessments were performed midweek on a non-dialysis day to minimize the effects of fluid overload and dialysis fatigue on outcome assessments.

Figure 1: Study timeline



Exercise Intervention

Control group:

Participants randomized to the standard care (control) group attended the MRP Exercise Counseling Clinic as part of their baseline assessment. This clinic runs as an ongoing clinical program and was implemented to provide efficient assessment of patient safety for exercise participation, baseline measures of physical function and to provide standardized exercise counseling to individuals with CKD in Manitoba. At the clinic, patients met with a nephrologist who provided medical clearance to exercise and identified any specific activity contraindications based on history and physical exam. Following this, patients underwent a brief battery of physical performance measures to assess current level of physical function. These included the SPPB, grip strength and the SWT. Patients then met with the clinic kinesiologist for one on one discussion about barriers, motivators and goals for exercise. This culminated in the prescription of an individualized exercise plan. Throughout the clinic, the importance and benefits of physical activity for overall health and well-being were emphasized.

Study participants in the control group did not undergo any formal exercise intervention, but were not prohibited from participation in exercise outside of the study protocol. Exercise activity outside of the prescribed program was tracked via self-report using exercise logbooks and objectively through accelerometry at study assessment time points.

Intervention group:

Participants randomized to the intervention group received usual standard care as above. In addition to standard care, participants in the intervention arm participated in a twelve-week exercise rehabilitation program incorporating the three following components:

1. Resistance training exercise program at home: Patients were taught about the importance of physical activity and how to exercise safely. Resistance training exercises were demonstrated and material (tubing, information packages and exercise logbook) was provided to the patient to allow for self-managed exercise at home. Patients began with 1 set of 10 repetitions (reps), 2 times per week at a Borg of 4-5 (somewhat hard to hard) on the 10-point scale. Resistance exercises included a chair squat, seated row, leg extension, chest press, calf raise, lateral raise, leg curl, and abdominals. Once 10 reps felt "easy or moderate" on the Borg scale, they were encouraged to increase to 12 reps. When 12 reps felt "easy or moderate" they were encouraged to increase to 15 reps. Once this became "easy or moderate", they were to add on a second set and drop back down to 10 reps. This progression continued until reaching 3 sets of 15 reps. Exercise activity outside of the prescribed program was tracked via self-report using exercise logbooks.
2. Intradialytic aerobic exercise on a cycle ergometer: Over the course of the twelve-week intervention, participants cycled three times weekly at their usual HD sessions at an intensity of 50-60% of maximal work load based on results from the baseline incremental cycle test. This exercise intensity has been modeled after

a study by Parsons et al.[73] and has been previously shown to elicit an increase in VO_{2peak} by 10% over a period of twelve weeks[65]. Individual cycling sessions involved sixty minutes of continuous cycling in the first half of each dialysis treatment using Therapy Trainer™ (Greely, CO) or Monark rehabilitation trainer 881E cycle ergometers modified for dialysis treatment in beds or chairs as per participant requirements. For patients who were unable to complete the prescribed sixty minutes of continuous exercise, rest periods were provided as needed. Exercise was only performed during the first half of the HD session to minimize the risk of hypotension that often occurs in patients during the second half of HD treatment and has been used successfully in previous studies[58,74,75].

During the initial three intradialytic exercise sessions, participants were assisted in ergometer set up and supervised closely during exercise by the study kinesiologist. Following three sessions (or more if required), once participants were comfortable with the exercise procedure, HD unit staff assisted with set up of the cycle ergometers and monitoring during exercise sessions. Duration of total exercise time and self-reported exercise intensity as measured by the Borg rate of perceived exertion scale[76] was recorded for each exercise session in participant logbooks. A Borg rate of 3-4 (moderate to somewhat hard) on the 10-point scale was the prescribed target while cycling. Logging exercise sessions was initially done by the kinesiologist but became the responsibility of the study participant after the first week of cycling. Patients were also responsible for increasing exercise intensity over the course of the study as instructed by the study kinesiologist. When the cycling intensity dropped to a 2 (easy) on the 10-

point scale, patients were encouraged to increase the watts so that it resumed a Borg of 3-4 (moderate to somewhat hard). The study kinesiologist checked in with each participant in the intervention group on a weekly basis to address problems and questions and ensure ongoing incremental intensity improvements were achieved.

In addition to routine dialysis monitoring (blood pressure and pulse before, after and every thirty minutes during HD and glucose pre and post HD in those who have diabetes), individuals had blood pressure, pulse and oxygen saturation measured at exercise initiation and every fifteen minutes until completion of their exercise session. Individuals who have diabetes also had glucose measured midway through each exercise session. Dialysis unit nurses, physicians and research study staff, monitored intradialytic exercise sessions for safety and intensity.

3. Bedside education sessions: These standardized sessions, intended to educate participants on how to safely incorporate exercise into their daily life, were completed in one-to-one format by the study kinesiologist during each participant's HD treatment. Topics included how to address common barriers to exercise participation, how to resume activity after a break or medical set back, and when one should not cycle during HD.

Adherence to the exercise intervention was measured in two ways. First the proportion of resistance and cycling exercise sessions logged as compared to total number of possible exercise sessions was calculated for each participant in this arm. In addition, the total number of minutes cycled over the course of the study was calculated

based on logbook records and the proportion of minutes achieved compared to total possible minutes were calculated for each individual.

Outcomes

1. Feasibility outcome: To demonstrate feasibility of the study protocol and rehabilitation intervention to inform the design of a larger clinical trial. Feasibility was assessed as the ability to recruit the specified number of patients over the allotted time frame, the number of participants withdrawing from the study and the participant adherence to the protocol. In addition, issues concerning recruitment, transportation and time, exclusion criteria, dialysis modality and location, equipment, patients and staff were addressed. Based on the data from Bohm et al. [72], we expected to see <30% proportion of study withdrawals and >70% protocol adherence.

2. Primary outcome: Change in physical function at twelve weeks as measured by SPPB. The SPPB (Appendix-C) is a composite score combining the results of gait speed, chair stand and balance tests. Scores range from 0 (worst) to 12 (best), and participants can be classified into severe (0-3), moderate (4-6), mild (7-9) or minimal (10-12) limitations in physical function based on their SPPB score[78]. An SPPB score below 9 has been strongly correlated with the frailty phenotype in elderly Canadians[79]. SPPB scores have been shown to have predictive validity for mortality, nursing home admission and disability in various populations including those with CKD[80]. A change in score by 1 point is considered clinically significant in the risk for future mortality and nursing home admissions[78].

3. Secondary outcomes:

a. Change in HRQOL: was assessed at twelve weeks using the EQ5D-3L™ and EQ VAS (Appendix D). This self-administered tool consists of a descriptive system containing five questions in three-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 VAS asks individuals to rate their current state of health from "worst imaginable" to "best imaginable" on a 100-point scale[81]EQ-5D-3L™ and has been extensively used and validated in various populations and disease states. Normative data for Canadians and the ESRD/CKD population available[82,83].

b. Change in dialysis-related symptoms: was assessed at twelve weeks using the Dialysis Symptom Index (DSI) (Appendix-B-3). Dialysis-related symptoms are an important component of HRQOL in ESRD and symptom burden is positively correlated with low physical activity and function[84]. The DSI is a thirty-item self-administered questionnaire with low administrative burden. It was developed to measure the presence (yes/no) and severity of common physical and emotional symptoms in individuals receiving maintenance HD[85]. The presence of symptoms is reported in the results section as "dialysis symptom score" and the severity as "dialysis symptom burden". A larger score denotes a greater presence and or severity of symptoms. The DSI is reliable and has been validated in multiple studies in the North American HD population[85-87].

c. Change in frailty status: was assessed at twelve weeks using the Modified Fried Criteria (Appendix E). Frailty is closely related to physical function, highly

prevalent in ESRD and confers a high risk for mortality and hospitalization[40,88-90]. The frailty phenotype was defined by the presence of three or more of the following characteristics:

1. Unintentional weight loss of > 4.5 kg in prior year
2. Grip strength weakness: ≤ 30 kilograms in strongest hand in males and ≤ 20 kilograms in strongest hand in females
3. Exhaustion: using two questions from Centre for Epidemiological Studies Depression (CES-D) Questionnaire: "I felt that everything is an effort" and "I could not get going". Answering moderate amount or most of the time to either question will receive a point for this criterion.
4. Slowness on four meter gait speed test (time > 4.82 seconds or unable to do test)
5. Low physical activity: men exerting ≤ 383 kilocalories per week and women exerting ≤ 270 kilocalories per week using IPAQ[37,90].

d. Change in physical fitness: was assessed using the SWT (Appendix F). This test has been used previously to show improvements in aerobic fitness following rehabilitation in patients with chronic disease[91]. This test was performed at baseline to assist in the prescription of exercise intensity throughout the duration of the study.

e. Change in physical activity behavior pattern: was characterized at twelve weeks subjectively using: i) HAP; Appendix G: the HAP is a ninety-four item self-reported physical activity questionnaire that has been well correlated with objective measures of physical activity and has been widely used and validated in

various populations, including those with ESRD on HD[92,93]. The questionnaire identifies activities that the individual is still doing and those that the individual has stopped doing to calculate a Maximal Activity Score (MAS) and Adjusted Activity Score (AAS). The HAP-MAS and HAP-AAS have been shown to have a correlation of 0.78 and 0.73 (respectively) with objectively measured physical activity using accelerometers in individuals on HD[94]. IPAQ; Appendix H: ii) IPAQ Short Version contains seven questions designed to elucidate type and duration of physical activity performed over the week preceding questionnaire administration. Scoring can produce categorical and continuous scores. Evidence for validity of this tool in the HD population exists[95]. The continuous IPAQ provides a measure of duration of physical activity performed. This information is not available from the HAP. The use of both tools above, more accurately and completely characterize the changes in physical activity behaviour over the duration of the study. In addition, change in physical activity behaviour was characterized objectively at twelve weeks using: iii) Multi-directional accelerometry: An Actical Physical Activity Monitor ™ (Appendix I) (Philips Respironics, Bend, OR) was worn for a period of seven days with fifteen second epochs, as this technique is considered the gold standard for physical activity assessment[96]. Participants were instructed to wear the accelerometer on their dominant hip during waking hours at each assessment period. During any cycling exercise, participants were asked to place the accelerometer on their dominant ankle as any movement during this activity cannot be picked up by the unit when worn on the hip.

f. Change in self-efficacy for exercise: was assessed at twelve weeks using the Self-Efficacy for Exercise questionnaire (SEE); Appendix J. This self-reported tool consists of nine questions in ten-point Likert scale format. The resultant summary score measures an individual's perception of how likely they are to successfully incorporate physical activity into their daily routine. This measure has been shown to be reliable and valid in predicting physical activity behaviour in elderly adults from various cultural backgrounds[97-99].

Statistical analysis

All outcome analyses were performed in an intention-to-treat manner on a case available basis. Baseline characteristics and demographics of the intervention and control groups were described using median (interquartile range) for continuous variables. Categorical variables were expressed as proportions. Comparison of descriptive and outcome variables between the StanC and Renal Rehab groups were performed using Mann Whitney U test for continuous variables and Fisher's Exact test for categorical variables, as appropriate. A p-value of ≤ 0.05 was considered statistically significant in our analysis.

Chapter 3: Results

Feasibility outcomes

Recruitment

Recruitment began on May 25, 2015. Based on previous clinical trials, a 30% dropout rate was anticipated with this particular population[72]. Therefore, fourteen participants per treatment arm were targeted for a total enrollment of twenty-eight participants. The first participant was enrolled on August 26, 2015. Even though the recruiting process was purposefully rolled out slowly, recruiting study patients was more challenging than expected. Amendments were therefore made to aid the recruiting process; explained below. The recruitment process concluded on December 31, 2016 with eleven patients enrolled in total (Figure 2). The following sections highlight the challenges encountered and amendments that followed.

For the first seven weeks of recruitment, patients were approached at the two-week time point in their HD process. During this time, twenty patients new to HD were approached and all declined participation in the study. Out of the twenty approached, fourteen patients reported that they were still adapting to and overwhelmed by the significant lifestyle changes and demands required of the HD process and were, therefore, declining participation in the study. Therefore, an amendment was made to postpone approaching patients from two to four weeks which, therefore, pushed study enrollment from four to six weeks post dialysis initiation. Although this change improved recruitment and contributed to the enrollment of the first two patients during weeks eight to fourteen, we found that recruiting and enrolling patients by the six-week time frame was too restrictive. Specifically, eleven patients were excluded from the study. Of these

eleven patients, nine patients were in the hospital and too ill to approach and two had low hemoglobin levels which did not meet the established patient safety criteria within the studies enrollment period. The recruitment challenges were reviewed with local clinicians and clinical trialists at the 2016 Nephrology Trials Network meeting[100]. Both of these groups felt that extending the period allowable for enrollment and commencement of the intervention to within ten weeks of HD initiation would allow for additional recruitment and still be within the window of what is traditionally considered incident hemodialysis. Both adjustments to the recruiting time frame had minimal impact, as overall recruitment into the study was still low.

Transportation and time barriers

Originally, study patients were asked to attend four weeks of group education and resistance training sessions at a medical fitness facility. Feedback from patients receiving chronic HD was that they had numerous demands on their time including attending HD sessions three times a week and multiple medical appointments. Because of this, patients stated they were reluctant to attend any other appointments and reported that additional sessions at a gym-centered facility were too difficult to manage. During our recruiting process, four patients said they would not come to extra appointments outside of dialysis, nine said that transportation was an issue and seven said they had no time. In addition, one of the two recruited patients did not show up for the scheduled education and resistance training sessions at the designated medical fitness facility. Therefore to ease barriers of time and transportation, patients were no longer required to travel to a fitness facility. It was arranged for patients to receive the four weeks of education and resistance

training sessions during their HD treatment in a one-to-one manner with the study kinesiologist.

Exclusion criteria limited recruitment

Exclusion criteria for participation in any research study is important for patient safety. Patients were originally not considered for this study if their hemoglobin levels were less than 95 g/L by six weeks after initiating dialysis. Specifically, two patients were excluded because of low hemoglobin levels however twenty-five people had low hemoglobin initially that eventually increased to meet target in the appropriate time frame. An amendment was made to lower the hemoglobin level from 95 g/L to 90 g/L but this had no impact on recruitment numbers. During the recruiting process, it was common for patients to experience low hemoglobin in the first ten weeks of beginning HD. Therefore, the scheduled recruitment approaches were regularly delayed until hemoglobin levels could reach the established minimum thresholds. Because it was impacting recruitment, it was an issue that was also brought up with the clinicians and clinical trailists at the 2016 Canadian Nephrology Trials Network meeting[100]. These experts felt that hemoglobin thresholds were not a patient safety risk for participating in the study. They recommended that hemoglobin be removed from the exclusion criteria and that the clinical nephrologists at each center use their judgment for patient safety. This advice was followed and there were no adverse outcomes related to hemoglobin levels since this criterion was removed. It was also suggested that other exclusion criteria, in addition to hemoglobin, be removed to enhance study enrollment. For example, planned elective surgery during the study period other than HD access creation

or repair, severe musculoskeletal injury or pain which would preclude participation in exercise classes or cycling during HD and unstable HD sessions with frequent hypotension or HD access issues (fistula blows/infiltration; poor catheter function with frequent alarms with change of position) were removed from the eligibility criteria. As of Dec 9, 2015, the following inclusion criteria was utilized: eighteen years and older, within ten weeks of commencing chronic HD, not expected to recover renal function, no expected change in dialysis modality or relocation outside of Winnipeg during the intervention period (twelve weeks), able to communicate in English, able to provide written informed consent and determined to be safe and appropriate to exercise by dialysis unit nephrologist. Exclusion criteria: acute myocardial infarction, crescendo or unstable angina within the past three months, unstable arrhythmia, symptomatic hypoglycemia greater than two times per week in previous week, shortness of breath at rest or on home oxygen (New York Heart Association Class four).

Change in dialysis modality or location

In total, Manitoba has four HD sites located in Winnipeg and sixteen rural dialysis units. All acute cases of renal failure are dealt with at three Winnipeg hospital units. To facilitate this, people living in rural areas relocate to Winnipeg for acute treatment. Many hope to continue their HD care at a unit closer to home once they are stable and well enough to travel. Although this thesis reports results from a three-month intervention, it is part of a larger twelve-month study. Therefore, some patients who anticipated a modality or location change reported that they felt that they were unable to commit to the twelve-month time period of the overall study. The time frame of a modality or location

change is dependent on many variables and may not take place for some time after starting dialysis. In many cases it is likely that although this change would take place within a year's time, it would not take place during the twelve-week intervention timeframe, allowing the patient to participate in the study if they wished. Therefore, the inclusion criterion was changed from no expected change in dialysis modality or relocation outside of Winnipeg “during the study period" to "during the twelve-week intervention period". Thirty patients were excluded from the study prior to the revision of this criterion due to changing units/modalities and eight patients declined participation in the study because of this issue. It was noted that six months later at least two of the eight patients who declined the study due to their expected change in location, were still dialyzing in the same unit.

Equipment, participants and staff

Patients receiving dialysis treatment typically dialyze in a bed at most units so a bike that could be pedaled while lying in bed was engineered in order for one particular unit to participate in the study. However, this customized bike had delays in production and was not yet complete at the time the first two study participants were enrolled and were both randomized to the intervention arm of the study. Therefore, it was arranged with management to bring in a dialysis chair for the participants to cycle during their treatment. Unfortunately, the first participant did not adhere to the one hour cycling limit but instead cycled forty minutes longer than prescribed and experienced a drop in blood pressure and blood glucose causing the nursing staff to intervene. During this event, staff found it difficult to manually recline the chair into the trendelenburg position which puts

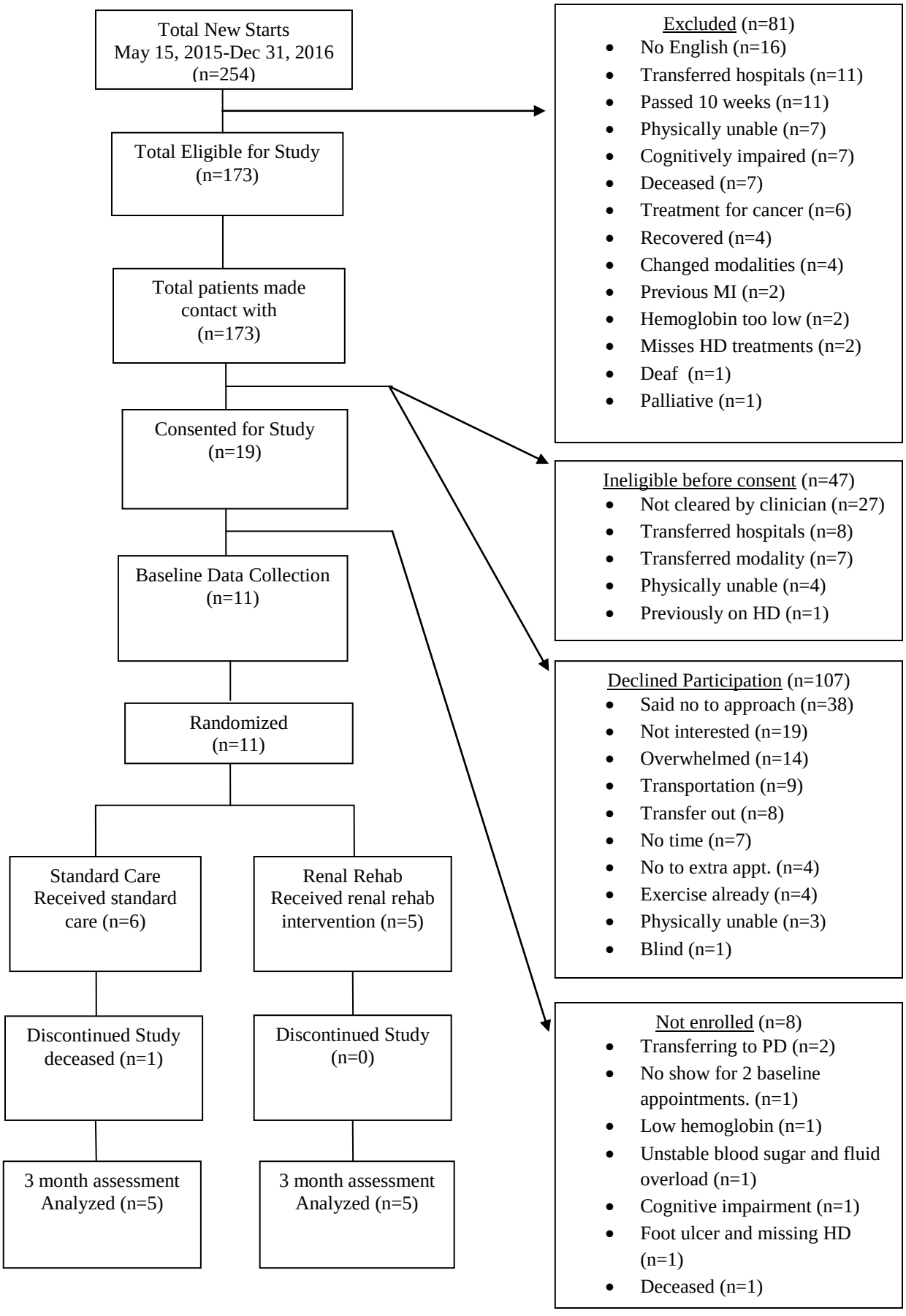
the participant in a head down, declined position. As a result of this incident, staff received demonstrations on how to successfully put the chair into the trendelenburg position and an information/instruction sheet was developed, fastened to the chair and emailed out to all dialysis staff. This issue was also discussed in the daily nurse report meeting. In addition, the study consent form was revised to better delineate possible risks of exercise participation to the patients, individuals with diabetes had their glucose checked at the beginning, end and midway points while they were cycling and standard orders were created and placed on each participants dialysis chart if they are randomized to the intervention arm, to ensure study protocol was followed.

Although education was provided to staff regarding safe use of the dialysis chair, staff were still not comfortable dialyzing a patient in it and a decision was made to no longer use the chair in that unit. The customized bed-bike was still not complete when the second participant at this unit was randomized to the intervention arm and because the dialysis chair was no longer being used, a bike, called a Moto Med, was acquired from Rehabilitation Services in the hospital to enable the second participant to bike during treatment.

Another issue related to this topic was staff involvement. As per study protocol, after three sessions and/or once participants were comfortable with the exercise procedure, HD unit staff were to assist participants with the set-up of the cycle ergometers and monitoring vitals such as oxygen saturation, during exercise sessions. Dialysis staff were made aware of this via daily nurse report meeting and were trained in the proper technique for lifting the dialysis bikes and securing them to the mechanical dialysis chair by the study kinesiologist, before the study began. A safe work procedure document was

also developed and attached to the cart that stored the bikes and on the wall where the bikes were stored. Although this was set in place, participants often did not bike if the study kinesiologist was not present. This impacted participants biking at one particular unit as participants were then not getting the bike set-up in order to pedal during their treatment.

Figure 2. Patient flow of recruitment.



Baseline characteristics

Medical chart reviews were conducted for study participants to collect baseline demographics and clinical data such as comorbidities, lab values, medications and dialysis treatment information (Table 6). Basic demographic data, including age, gender, height, weight, BMI, and smoking status did not differ between StanC and Renal Rehab groups. There were no differences in comorbidities, between study groups (Table 6). Likewise, no differences were observed in lab values, including hemoglobin and albumin between the two groups. Medication prescription was also similar between StanC and Renal Rehab. Type of HD access, dialysis adequacy, weekly intradialytic fluid gains and blood pressures were similar between study groups (Table 6).

Table 6. Comparison of baseline characteristics between StanC and Renal Rehab participants.

	StanC (n=6)	**Renal Rehab (n=5)**	**p-value**
Demographics			
Age (years)	57 (46.75-64.25)	58 (57-58)	0.93
Sex (male)	5 (83%)	4 (80%)	1.00
Height (cm)	171.35 (169-172.8)	167.9 (165.4-171.5)	0.47
Weight (kg)	84.3 (74.6-90.18)	76.4 (70.4-85)	0.52
BMI	29.35 (28.45-30.33)	25.2 (24.9-27.9)	0.32
Current Smoker	1 (17%)	0 (0%)	1.00
Quit Smoking	3 (50%)	3 (60%)	1.00
Comorbidities			
Ischemic heart disease	2 (33%)	1 (20%)	1.00
Valve	0 (0%)	0 (0%)	1.00
Chronic heart failure	0 (0%)	2 (40%)	0.18
Arrhythmias	1 (17%)	2 (40%)	0.55
Peripheral vascular disease	0 (0%)	1 (20%)	0.45
Below knee amputation	0 (0%)	0 (0%)	1.00
Cholesterol	3 (50%)	3 (60%)	1.00
Hypertension	6 (100%)	4 (80%)	0.45
Lung	0 (0%)	0 (0%)	1.00
Stroke	2 (33%)	1 (20%)	1.00
Diabetes mellitus	4 (67%)	3 (60%)	1.00

Cancer	1 (17%)	1 (20%)	1.00
Arthritis	1 (17%)	1 (20%)	1.00
Joint/bone surgery	0 (0%)	1 (20%)	0.45
Lab Values			
Hemoglobin (g/L)	96.5 (88-99.75)	96 (95-96)	0.93
Albumin (g/L)	31 (31-31)	30 (26-30)	0.32
Serum Phosphate	1.48 (1.25-1.58)	1.72 (1.27-1.75)	0.41
Calcium	2.27 (2.11-2.40)	2.38 (2.3-2.4)	0.65
Potassium	4.35 (4.3-4.85)	4.7 (4.4-5)	0.58
Parathyroid Hormone	298.15 (225.75-328.63)	367.5 (274-432)	0.52
Low Density Lipoprotein	1.7 (1.55-1.85)	1.4 (0.9-1.7)	0.41
Triglycerides	1.67 (1.67-1.71)	1.24 (1-1.35)	0.52
Total Cholesterol	3.25 (3.11-3.38)	3.22 (2.31-3.56)	0.79
Hemoglobin A1c (%)	5.65 (5.28-6.7)	6.2 (5.5-6.2)	1.00
Medications			
Erythropoietin	6 (100%)	5 (100%)	1.00
ASA	3 (50%)	3 (60%)	1.00
Plavix	1 (17%)	0 (0%)	1.00
Beta-blocker	3 (50%)	4 (80%)	0.55
Nitrates	1 (17%)	0 (0%)	1.00
ACE inhibitor	5 (83%)	3 (60%)	0.55
Other blood pressure meds	4 (67%)	2 (40%)	0.57
Cholesterol medication	4 (67%)	1 (20%)	0.24
Vitamin D	1 (17%)	0 (0%)	1.00
Anticoagulants	0 (0%)	0 (0%)	1.00
Quinine	0 (0%)	0 (0%)	1.00
Diabetes medication oral	1 (17%)	1 (20%)	1.00
Diabetes medication insulin	3 (50%)	3 (60%)	1.00
Other medications	1 (17%)	0 (0%)	1.00
Dialysis			
Hemodialysis access (CL)	5 (83%)	4 (80%)	1.00
Average dialysis adequacy (Kt/V)	1.49 (1.12-1.75)	1.44 (1.44-1.67)	0.86
Weekly Intradialytic fluid gains (kg)	6.45 (5.43-7.4)	7.8 (3.5-9.1)	0.65
Systolic blood pressure	154 (139-160)	127 (111-150)	0.23
Diastolic blood pressure	87.5 (80-95.75)	75 (70-79)	0.054

Continuous variables expressed as median and interquartile range. Statistical comparison between groups was performed using Fisher's Exact test for categorical variables and Mann-Whitney U test for continuous variables. BMI, body mass index; ACE, angiotensin converting enzyme; CL, central line.

Renal Rehab adherence data

Intervention adherence was recorded on a log sheet and was collected for all participants randomized to the Renal Rehab intervention (n=5; Table 7). Renal Rehab participants were enrolled in the intervention for a period of twelve weeks for a total of thirty-six cycling (12 weeks x 3 session per week) and twenty-two resistance training (11 weeks x 2 sessions per week) sessions. They completed an average of 45% of the cycling sessions and 67% of the resistance training sessions. The participants in the Renal Rehab group were required to cycle a total of 2,160 minutes through the thirty-six sessions. They completed an average of 34% of the cycling minutes (Table 8).

Table 7. Cycling and resistance training sessions completed by Renal Rehab group.

Participant Number	**Cycling Session Completed (/36)**	**Resistance Training Completed (/22)**
1	8 (22%)	0 (0%)
2	15 (42%)	13 (59%)
7	16 (44%)	18 (82%)
8	16 (44%)	21 (95%)
11	26 (72%)	22 (100%)

Table 8. Cycling minutes completed by Renal Rehab group.

Participant Number	**Total Minutes Cycled**	**% of Intervention Completed (total minutes cycled/2160 min)**
1	430	20%
2	590	27%
7	450	21%
8	855	40%
11	1326	61%

Primary outcome: physical function

The SPPB, which includes balance, gait speed and chair stand, was used to assess lower extremity physical function. SPPB total showed a significant median change of 1 in the StanC group and -1 in the Renal Rehab group from baseline to 12 weeks (p=0.04; Table 9). The balance, gait speed and chair stand did not show any significant differences individually. Table 10 looks at a comparison of physical function between StanC and Renal Rehab at baseline and three months detecting a change in SPPB ≥1 point. Statistical significance was not achieved due to a low sample size, however a clinically meaningful change with an improvement of 1 point or more was observed[101]. (Table 10).

Table 9. Comparison of physical function between StanC (n=5) and Renal Rehab (n=5) at baseline and three months.

	Baseline	**3 Months**	Δ	**p-value**
SPPB Total				
StanC	10 (10-11)	12 (11-12)	1 (0-1)	0.04*
Renal Rehab	10 (8-12)	9 (4-12)	-1 (-2-0)	
SPPB Balance				
StanC	4 (4-4)	4 (4-4)	0 (0-0)	0.70
Renal Rehab	3 (2-4)	3 (1-4)	0 (0-0)	
SPPB Gait Speed				
StanC	4 (4-4)	4 (4-4)	0 (0-0)	0.10
Renal Rehab	4 (4-4)	3 (3-4)	-1 (-1-0)	
SPPB Chair Stand				
StanC	2 (2-3)	4 (3-4)	1 (0-1)	0.10
Renal Rehab	3 (3-4)	3 (0-4)	0 (0-0)	

Continuous variables expressed as median and interquartile range. Δ was calculated as the difference between 3 month and baseline for individuals and presented as the median and interquartile range for the Standard Care or Renal Rehab groups. Statistical comparison between groups using the Δ data was performed using a Mann-Whitney U

test. SPPB, short physical performance battery. *=significant change between StanC and Renal Rehab.

Table 10. Comparison of physical function between StanC (n=5) and Renal Rehab (n=5) at baseline and three months detecting a change in SPPB ≥1 point.

	% Improved	p-value	% Worse	p-value
SPPB Total				
StanC	3 (60%)	0.20	0 (0%)	0.20
Renal Rehab	0 (0%)		3 (60%)	
SPPB Balance				
StanC	0 (0%)	1.00	0 (0%)	1.00
Renal Rehab	0 (0%)		1 (20%)	
SPPB Gait Speed				
StanC	0 (0%)	1.00	0 (0%)	0.20
Renal Rehab	0 (0%)		3 (60%)	
SPPB Chair Stand				
StanC	3 (60%)	0.20	0 (0%)	1.00
Renal Rehab	0 (0%)		1 (20%)	

% who improved and % who got worse were compared between StanC and Renal Rehab using a Fisher's Exact Test.

Secondary outcomes

Health related quality of life

Health related quality of life was measured using the EQ-5D. The EQ-5D is separated into a descriptive system comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, each with levels 1-3, with 1 indicating no problem and 3 indicating extreme problems. The EQ-5D includes a visual analogue scale (VAS). The proportion of participants indicating some or extreme problems (2 or 3) for each subdomain was compared between groups. No differences were observed between StanC

and Renal Rehab groups for any component of the EQ-5D at any time point (Table 11; Table 12).

Table 11. Comparison of EuroQol 5D-3L indicating some to extreme problems between StanC (n=5) and Renal Rehab (n=5) at baseline and three months.

	Baseline	3 month	% Improved	p-value	% Worse	p-value
EQ5D Mobility						
StanC	0 (0%)	1 (20%)	0 (0%)	1.00	1 (20%)	1.00
Renal Rehab	2 (40%)	2 (40%)	1 (20%)		1 (20%)	
EQ5D Self-care						
StanC	0 (0%)	0 (0%)	0 (0%)	1.00	0 (0%)	1.00
Renal Rehab	0 (0%)	1 (20%)	0 (0%)		1 (20%)	
EQ5D Usual Activities						
StanC	0 (0%)	2 (40%)	0 (0%)	0.40	2 (40%)	1.00
Renal Rehab	2 (40%)	1 (20%)	2 (40%)		1 (20%)	
EQ5D Pain/Discomfort						
StanC	1 (20%)	3 (60%)	0 (0%)	1.00	2 (40%)	0.40
Renal Rehab	1 (20%)	1 (20%)	0 (0%)		0 (0%)	
EQ5D Anxiety/Depression						
StanC	0 (0%)	3 (60%)	0 (0%)	1.00	3 (60%)	0.20
Renal Rehab	1 (20%)	0 (0%)	1 (20%)		0 (0%)	

Categorical variables expressed as proportion. % who improved and % who got worse were compared between StanC and Renal Rehab using a Fisher's Exact Test.

Table 12. Comparison of EuroQol 5D Visual Analogue Scale between StanC (n=5) and Renal Rehab (n=5) at baseline and three months.

	Baseline	3 month	Δ	p-value
EQ5D-VAS				
StanC	50 (45-60)	80 (55-80)	20 (10-20)	0.50
Renal Rehab	70 (50-75)	80 (70-80)	10 (0-20)	

Continuous variables expressed as median and interquartile range. Δ was calculated as the difference between 3 month and baseline for individuals and presented as the median and interquartile range for the Standard Care or Renal Rehab groups. Statistical comparison between groups using the Δ data was performed using a Mann-Whitney U test.

Dialysis-related symptoms

No differences were observed between StanC and Renal Rehab groups at any time point for either DSI parameter (Table 13).

Table 13. Comparison of Dialysis Symptom Index between StanC (n=5) and Renal Rehab (n=5) at baseline and three months.

	Baseline	**3 Months**	Δ	**p-value**
Dialysis Symptom Score				
StanC	4 (3-9)	9 (6-17)	0 (0-13)	0.80
Renal Rehab	4 (1-5)	9 (7-9)	5 (2-8)	
Dialysis Symptom Burden				
StanC	11 (6-26)	29 (16-47)	3 (0-36)	0.90
Renal Rehab	9 (2-12)	24 (22-26)	17 (12-20)	

Continuous variables expressed as median and interquartile range. Δ was calculated as the difference between 3 month and baseline for individuals and presented as the median and interquartile range for the Standard Care or Renal Rehab groups. Statistical comparison between groups using the Δ data was performed using a Mann-Whitney U test.

Frailty status

Frailty status was assessed using the Modified Fried Criteria. Frailty was defined by the presence of 3 or more characteristics including unintentional weight loss, hand grip weakness, exhaustion, gait speed slowness and low physical activity (Table 13). Based on the Modified Fried Criteria, one participant in the Renal Rehab group was determined to be frail at baseline; whereas two were determined to be frail at three months. No participants were deemed to be frail at either time point in the StanC group (Table 14).

Table 14. Number of StanC (n=5) and Renal Rehab (n=5) patients considered frail at baseline and three months according to the Modified Fried Criteria.

	Baseline	3 month	% Improved	p-value	% Worse	p-value
Total Frail						
StanC	0 (0%)	0 (0%)	0 (0%)	1.00	0 (0%)	1.00
Renal Rehab	1 (20%)	2 (40%)	0 (0%)		1 (20%)	
COMPONENTS						
Weight						
StanC	3 (60%)	1 (20%)	3 (60%)	1.70	1 (20%)	0.50
Renal Rehab	1 (20%)	1 (20%)	0 (0%)		0 (0%)	
Exhaustion						
StanC	0 (0%)	2 (40%)	0 (0%)	0.40	2 (40%)	0.40
Renal Rehab	3 (60%)	1 (20%)	2 (40%)		0 (0%)	
Hand Grip Strength						
StanC	1 (20%)	1 (20%)	1 (20%)	0.50	1 (20%)	1.00
Renal Rehab	2 (40%)	3 (60%)	0 (0%)		1 (20%)	
Gait Speed						
StanC	0 (0%)	0 (0%)	0 (0%)	1.00	0 (0%)	0.40
Renal Rehab	1 (20%)	3 (60%)	0 (0%)		2 (40%)	
Physical Activity						
StanC	0 (0%)	0 (0%)	0 (0%)	1.00	0 (0%)	1.00
Renal Rehab	2 (40%)	1 (20%)	1 (20%)		0 (0%)	

Categorical variables expressed as proportion. % who improved and % who got worse were compared between StanC and Renal Rehab using a Fisher's Exact Test.

Physical fitness

The Shuttle Walk Test was used to assess aerobic fitness. No differences were observed between StanC and Renal Rehab groups at any time point (Table 15).

Table 15. Comparison of Shuttle Walk distance between StanC (n=5) and Renal Rehab (n=5) at baseline and three months.

	Baseline	3 Months	Δ	p-value
Shuttle Walk Test				
StanC	200 (180-340)	330 (290-360)	50 (30-110)	0.20
Renal Rehab	120 (120-250)	80 (70-280)	0 (-40-0)	

Continuous variables expressed as median and interquartile range. Δ was calculated as the difference between 3 month and baseline for individuals and presented as the median and interquartile range for the Standard Care or Renal Rehab groups. Statistical comparison between groups using the Δ data was performed using a Mann-Whitney U test.

Physical activity behaviour patterns

Physical activity behavior patterns were assessed using the HAP (Table 16), IPAQ (Table 17), and multidirectional accelerometry (Table 18). No differences were observed between StanC and Renal Rehab groups, for HAP, IPAQ or multidirectional accelerometery at any time points. According to the IPAQ, at baseline, one participant was considered low active and four moderately active in the StanC group and two participants were low active and three moderately active in the Renal Rehab group. At three months, two participants were low active and three moderately active in the StanC group and one individual was low active and four were moderately active in the Renal Rehab group. In addition, one participant out of five was determined to have met the Canadian physical activity guidelines of 150 MVPA min/week in both groups at baseline. Two participants out of five met the guidelines in both groups at three months. Three or more days was considered valid wear time for analyzing the multidirectional accelerometers. Three (two StanC and one Renal Rehab) participants out of ten had valid days at baseline and five (three StanC and two Renal Rehab) participants out of ten had valid days at the three-month time point. However, all participants were included in the

analysis (Table 18). Statistical analysis was not run on the participants who had valid wear time at both time points because Renal Rehab only had one participant with valid data.

Table 16. Comparison of Human Activity Profile Questionnaire between StanC (n=5) and Renal Rehab (n=5) at baseline and three months.

	Baseline	3 Months	Δ	p-value
Maximum Activity Score				
StanC	76 (69-81)	64 (64-77)	-4 (-5-6)	0.50
Renal Rehab	77 (67-79)	58 (45-67)	-3 (-34-0)	
Adjusted Activity Score				
StanC	60 (53-65)	55 (49-74)	3 (-4-11)	0.30
Renal Rehab	46 (46-62)	42 (32-60)	-4 (-6- -2)	

Continuous variables expressed as median and interquartile range. Δ was calculated as the difference between 3 month and baseline for individuals and presented as the median and interquartile range for the Standard Care or Renal Rehab groups. Statistical comparison between groups using the Δ data was performed using a Mann-Whitney U test.

Table 17. Comparison of International Physical Activity Questionnaire between StanC (n=5) and Renal Rehab (n=5) at baseline and three months.

	Baseline	3 Months	Δ	p-value
Total Physical Activity Met Minutes/Week				
StanC	717 (495-2895)	1078 (924-1230)	-321 (-1817-429)	0.09
Renal Rehab	834 (10-1426)	1109 (1074-2892)	1002 (240-1109)	
Total Physical Activity Minutes/Week				
StanC	195 (150-630)	280 (260-325)	-75 (-370-130)	0.20
Renal Rehab	220 (3-430)	300 (285-720)	80 (0-285)	

Continuous variables expressed as median and interquartile range. Δ was calculated as the difference between 3 month and baseline for individuals and presented as the median and interquartile range for the Standard Care or Renal Rehab groups. Statistical comparison between groups using the Δ data was performed using a Mann-Whitney U test.

Table 18. Comparison of accelerometer physical activity between StanC (n=5) and Renal Rehab (n=5) at baseline and three months.

	Baseline	3 Months	Δ	p-value
Wear Minutes				
StanC	2603 (1841-4987)	2938 (2495-3086)	-868 (-932-483)	0.30
Renal Rehab	1310 (1036-1693)	1621 (520-2588)	-71 (-517-505)	
Sedentary Minutes				
StanC	2368 (1569-4387)	2287 (2124-2767)	-730 (-995- -82)	0.30
Renal Rehab	1022 (859-1541)	1294 (327-2064)	-246 (-533-347)	
Light Minutes				
StanC	223 (205-522)	306 (150-581)	83 (-100-203)	0.83
Renal Rehab	152 (150-232)	321 (109-449)	171 (-28-176)	
MVPA Minutes				
StanC	79 (55-141)	66 (38-218)	-33 (-77-17)	0.40
Renal Rehab	25 (11-32)	14 (10-75)	5 (-1-19)	

Continuous variables expressed as median and interquartile range. Δ was calculated as the difference between 3 month and baseline for individuals and presented as the median and interquartile range for the Standard Care or Renal Rehab groups. Statistical comparison between groups using the Δ data was performed using a Mann-Whitney U test. MVPA, moderate to vigorous physical activity.

Self-efficacy for exercise

Self-efficacy for exercise was assessed using the Self-Efficacy for Exercise survey. No differences were observed between StanC and Renal Rehab groups at any time point (Table 19).

Table 19. Comparison of Self-Efficacy for Exercise Questionnaire between StanC (n=5) and Renal Rehab (n=5) at baseline and three months.

	Baseline	3 Months	Δ	p-value
Self-Efficacy for Exercise				
StanC	42 (36-58)	48 (45-49)	-9 (-14-12)	0.30
Renal Rehab	56 (55-57)	38 (37-43)	-14 (-17-0)	

Continuous variables expressed as median and interquartile range. Δ was calculated as the difference between 3 month and baseline for individuals and presented as the median

and interquartile range for the Standard Care or Renal Rehab groups. Statistical comparison between groups using the Δ data was performed using a Mann-Whitney U test.

Patient safety and adverse events

The exercise intervention was generally well tolerated by the Renal Rehab group. Several adverse events did occur in both study groups. During the sixth cycling session, one participant in the exercise group developed hypotension and hypoglycemia after cycling for one-hundred minutes during HD even though he was instructed to not go beyond the sixty minute maximal time limit. Subsequently, after leaving HD feeling well, medically stable with no issues, he lost his balance while getting into a vehicle and fell. He was admitted to hospital with a fractured humerus and required surgical repair. He was also subsequently found to have bacteremia on the day of initial events which was treated with intravenous antibiotics and he recovered. A second participant in the exercise group had a transient ischemic attack related to a known pre-existing cerebral artery stenosis one day after his fourth cycling session which was a non-HD day. In the StanC Group, one participant passed away due to sepsis during a hospital admission for hip fracture following a fall. This event happened in the eleventh week of the study. Adverse events were reviewed by an independent nephrologist on service at the time of each event and not involved with the study. Adverse events were also reviewed by the study data and safety monitoring board (Dr. James Zacharias, Chair, MRP Standards). The participant who cycled for one-hundred minutes was deemed to be a serious adverse event as a result of the intervention. As a result of this incident, the consent form was revised to better delineate possible risks of exercise participation. In diabetic individuals, glucose was checked at the beginning, end and every thirty minutes

while cycling during HD and to ensure that study protocol was followed with respect to the cycling intervention, standard orders were created and placed on each participants dialysis chart randomized to the intervention arm. It was determined that the other two participant's incidents were not related to the study intervention.

Chapter 4: Discussion

People on HD experience higher mortality rates than the general population with a 43.3% survival rate at five years[6]. This death rate dramatically increases in the first six months of starting HD and is the highest (80%) in the first two months of beginning treatment[11]. Simple daily tasks become increasingly difficult and quality of life becomes negatively impacted. Contributing to the risk of mortality is the decreased level of physical activity and physical function experienced by individuals as CKD worsens. As a result there is an increased risk of disability, hospitalization and mortality[102].

Based on that literature, we implemented a self-management exercise rehabilitation program to address the physical decline during the first year on HD. Perhaps beginning an exercise intervention shortly after dialysis initiation could prevent the physical decline that contributes to poor outcomes. The hypothesis was that patients who complete a twelve-week self-management education and exercise rehabilitation program would have greater improvements in physical function and other measures, such as quality of life, than those patients who received standard care. However, we ran into many challenges along the way and in the end our data did not support our hypothesis. On the contrary, a significant difference was detected for our primary outcome of physical function in the standard care group. It was thought that if effective, the exercise intervention could slow or perhaps reverse the physical decline and thereby decrease rates of disability, hospitalization and mortality in the incident HD population. My data does not indicate that this is the case.

Feasibility of implementing exercise therapy for incident dialysis patients

According to Eldridge et al.[103] feasibility studies ask the following questions: *can and should a future trial be done and if so, how?* A pilot study, considered a subset of a feasibility study, asks the same questions and tests a specific research design similar to that which will be used in a larger trial, but on a smaller scale[103]. My thesis research is a randomized pilot study. Moving forward, there are indicators that a future trial of this sort could be done, however, future trials will be strengthened by the specific challenges experienced in my work. Therefore, this thesis includes specific recommendations to inform future trials.

The largest challenge we encountered was recruitment. We discovered that in the first three months of dialysis, patients were still adapting to and overwhelmed by the significant changes and demands of the HD process and as a result, felt unable to participate in the study. Other factors potentially contributing to this uncertain time include patient transfer between hospitals, switching dialysis modalities, recovering renal function and no longer requiring HD or just not showing up for HD treatment altogether. Some patients may have been feeling too ill or are admitted to hospital. Some are physically unable to pedal a bike or to sit in a chair for a full treatment. Others may not be able to communicate in English or may have cognition or auditory impairments. Lai et al.[104] have reported that psychosocial factors related to emotional distress, concerns about treatment and social support also contributed to this uncertain time. For these reasons, in order for patients to adjust to the HD schedule, treatment and individual needs, we suggest recruiting patients in a later time frame, the earliest being three to six months. This enrollment window was successful for Thompson et al.[77] who included

patients that were on HD for three months or more. They exceeded their recruitment goal of twenty-eight patients, enrolling thirty-one patients over twelve weeks.

Another factor identified by patients in our research that impacted recruitment was the burden of time and transportation. This barrier was also recognized by Bohm et al.[105]. Many patients were reluctant to attend any appointments related to the study outside of their HD unit and treatment time. Therefore, we suggest that future trials consolidate study appointments to take place at the patients HD unit. If this is not possible, arranging transportation for patients in the form of a bus pass, handi-transit or taxi cab may aid the recruiting process.

Recruitment was also inhibited by restrictive eligibility criteria, which were eventually modified in our study protocol following consultation with expert panels of clinicians and researchers familiar with CKD. A similar issue was reported by Roberts et al.[106]. They eventually made amendments to their eligibility criteria, which originally limited age and length of time on dialysis, in order to enhance recruitment. In the present study, hemoglobin levels and the limited window of time to enroll incident dialysis patients into the study impacted enrollment. Hemoglobin levels tended to be low upon initial contact with patients. In these cases, the research team followed up with the patient to determine if they met the hemoglobin inclusion criteria at a later time within the recruitment period. We questioned the relevance of the hemoglobin inclusion criteria after it was identified that this criteria was excluding a number of potential participants. Hemoglobin measures the oxygen carrying capacity of the red blood cells. The kidneys are responsible for producing a hormone called erythropoietin, which stimulates the bone marrow to produce red blood cells. Production of erythropoietin decreases with the decline of kidney

function, causing anemia. This can affect patients in the early stages of CKD and is very common in people on HD. Hemoglobin levels may be chronically low by the time a person would require dialysis and exercise with chronically low stable hemoglobin levels is not considered a safety risk in most patients on HD. We then searched the literature and identified only one study that listed hemoglobin as part of their eligibility criteria. Hemoglobin was not reported to have an impact on recruitment[72]. This could be because study participants were already in the prevalent stage of HD and by that time hemoglobin levels were stabilized. Therefore, in order to enhance recruitment, we suggest that the eligibility criteria remain safe but not needlessly restrictive. In addition, if recruitment began in the three to six month timeframe as suggested, issues such as hemoglobin would have time to increase and stabilize to target levels.

In addition to the recruitment challenges, we encountered logistical challenges related to equipment and staff involvement. Our first two participants randomized into the intervention group both dialyzed at a unit that was only equipped with beds. Due to a delay in arm design and production, the customized bed-bikes were not ready for use so a dialysis chair was brought in, in order for these participants to begin the cycling portion of the intervention. The dialysis staff had difficulty operating the chair when the first participant ran into issues and as a result, it was decided to no longer use the dialysis chair in this unit. This impacted the biking experience of the second participant randomized to the intervention at this same unit. Because of these issues, we would recommend to ensure all study equipment, including the dialysis chair, is trialed with standard operating procedures and ready for use prior to the study commencing. We falsely assumed dialysis staff knew how to operate the dialysis chair which is an

assumption that should be recognized and avoided in the future. We therefore suggest that all dialysis staff be trained in the operation and safety procedures of any equipment used in the study prior to the study beginning, namely the dialysis chair. The appropriate information sheet should be distributed to all staff and instructions for any equipment used in the study should be attached to the equipment and/or in a visible area where the equipment is stored.

Staff participation in a research study is another important issue to address when implementing a study of this nature as it requires nursing staff to have a role. According to the literature, staff report that participation in an intradialytic exercise program for patients adds to their workload and is outside their job description[107]. Therefore, it is important to have management and staff on board before starting the study[108]. An integrated knowledge translation approach brings all parties together to deliberate in the various stages of the research process and contribute to cultivating the relationship between all participants so that knowledge is created and applied in a meaningful way[109]. An integrated knowledge translation approach was taken in the development and design of this project with input from multiple stakeholders and staff. This project engaged in ongoing refinement based on the patient's needs as demonstrated in the multiple amendments made throughout the study. In addition, consistent engagement between the research team and clinical staff in the form of weekly scheduled meetings would be beneficial to stay abreast on study progress and or issues. Although we did not hold weekly scheduled meetings, the research team was in regular contact with dialysis staff and were able to address any issues on the spot. This allowed the team to refine the intervention and its implementation over time. Even so, further work to enhance the

implementation of such an integrated knowledge translation project, with additional strategies to increase staff "buy in" for example, is important to continually work towards.

Adherence to exercise training

Overall, adherence to the protocol was poor. Participants reported completing an average of sixteen out of thirty-six cycling sessions done during their HD treatment and fifteen out of twenty-two resistance training sessions done at home. This was much lower than reported in a study by Thompson et al.[77] who evaluated the efficacy of cycling, resistance training or both combined, during HD. Out of the three exercise groups, adherence rates were 83%, 89% and 90% respectively. It is important to note that this study included patients on HD for three months or greater. The mean time on HD was three years in that study. Issues contributing to our low adherence rates included patient health issues experienced either during HD or outside of treatment. Issues experienced during HD related to blood pressure, blood glucose, access site and general malaise. Issues experienced outside of HD included a fall leading to hospitalization and a transient ischemic attack. We also experienced equipment challenges due to the delay of the customized bed-bikes, staff not knowing how to put the dialysis chair in the trendelenberg position and staff not assisting with bikes during the weekend HD treatments. Incorporating additional behaviour change techniques, further to the motivational interviewing approach taken in the MRP Exercise Counseling Clinic, may help improve adherence to exercise[110].

Safety of exercise training in patients with CKD

With multiple comorbidities and a high prevalence of hypertension, diabetes and cardiovascular disease in the CKD population, the perceived negative risk of exercise has been highlighted by nephrologists and staff as a deterrent to promote exercise to patients [107]. The majority of exercise studies have confirmed that it is safe for patients in all stages of CKD to participate in aerobic and resistance training exercises safely, whether done during HD treatment or outside of receiving dialysis[1]. However, there have been a few cases of adverse events reported in the literature. Examples include tendon ruptures or fractures in participants with hyperparathyroidism as well as hypotension and hypoglycemia experienced during intradialytic cycling[1,105]. Another study identified a partial tear of a rotator cuff muscle, however, the participant continued the lower body exercises for the last six weeks of the intervention and completed the final assessment[111]. No cardiac events related to exercise have been reported in the literature. In addition, Parker et al.[71] cycled patients on HD as early as 1 month after beginning treatment and had no adverse events as a result of exercise. Our study and exercise protocol was designed with the potential risks in mind to ensure patient safety was at the forefront of all decisions. However, despite precautions taken to ensure the safety of the patients and staff in our research, one issue was encountered during the twelve-week intervention. A participant cycled forty minutes longer than prescribed and experienced a drop in blood pressure and blood glucose causing the nursing staff to intervene. It is important to note that the adverse effects occurred because the participant did not follow the sixty minute maximum cycling protocol. Other than this issue, no other health risks were reported as a result of the study. We suggest that research and dialysis staff communicate regularly to

ensure study protocol is understood and that participants be monitored by research or dialysis staff each dialysis session to be sure that the study protocol is being followed.

Renal Rehab did not improve physical function

Physical function is an important attribute of independent living and quality of life. A deterioration of physical function is associated with disability, increased hospitalizations and an increased risk of mortality in individuals undergoing hemodialysis[18]. Multiple research studies utilizing intradialytic exercise have shown an increase in physical function[1,47]. To our knowledge, with the exception of Parker et al.[71], all previous exercise interventions were conducted during HD with a cohort of prevalent HD patients. Our study is unique in that this exercise program delivery was conducted in the first three months from the start of dialysis, which is the incident stage of HD.

Our data showed a significant improvement in SPPB; however, it was in favor of the StanC group, which is contrary to our hypothesis. Specifically, patients in StanC increased their median total SPPB score from 10 at baseline to 12 at three months. Renal Rehab group's median SPPB total slipped from 10 at baseline to 9 at three months. Two Renal Rehab participants achieved the maximum score of 12 at both baseline and three-month time points. The SPPB, used to test lower extremity function, is predictive of disability, hospitalizations, morbidity and mortality[78]. An SPPB total score of 9 and under is indicative of poor health outcomes[78]. Based on this data, 3 out of the 5 patients in the intervention, whose SPPB scores decreased from 8,10 and 3 at baseline to 4, 9 and 1 at three months, are at risk of adverse health outcomes. Two-thirds of the participants in the intervention were already at risk of poor outcomes at the start of the study.

The improvement in physical function in StanC rather than those in Renal Rehab is contrary to what other research has shown. In an intradialytic exercise study of twenty-four HD patients, Liu et al.[112] found that a twelve-week cycling program significantly increased the 6MWT by 47 meters (p=0.002) and the sit-to-stand test by a mean of three repetitions (p=0.007). A randomized trial of forty-four HD patients compared intradialytic resistance training to a control group who stretched. They found that SPPB improved in the strength training group by 21% as compared to the controls[113]. Although it is surprising in the present study, that the improvement in physical function was found in StanC and not Renal Rehab, there may be several reasons that can explain this result.

To begin, the main reason the intervention was not successful could be due to the intervention not having been completed as intended. For example, the study experienced lower adherence to the intervention than planned. The intervention was designed so that participants would cycle for sixty minutes each HD session which equated to a total of 2160 cycling minutes; whereas, the Renal Rehab group completed from 430 minutes to 1326 minutes during the three-month intervention period.

As detailed in the results section, two out of the five participants in Renal Rehab experienced health issues that impacted their ability to complete the intervention. These two participants only completed eight and sixteen of the total thirty-six cycling sessions. Only one of the two participants engaged in the resistance training exercises and completed eighteen of the total twenty-two sessions. A third participant did not cycle at times due to low blood pressure and fistula issues, which is a common occurrence during HD treatment, however it contributed to his inability to complete all exercise sessions. Overall, he completed fifteen out of thirty-six cycling sessions and thirteen of the

possible twenty-two resistance training sessions. Because the Renal Rehab group included five individuals, the results were greatly impacted by the three individuals not being able to fully participate.

Another issue impacting the full participation of patients in Renal Rehab was related to equipment and staff. This impacted one participant in the study intervention who dialyzed on Tuesday, Thursdays and Saturdays. The study kinesiologist was not present Saturdays and therefore staff were asked to help set up the bike for this individual. Unfortunately, this never happened and was not identified as an issue until after the research ended. In reviewing the log sheets, outside of the initial three sessions, this participant never biked on a Saturday which could be attributed to this issue. This individual completed sixteen out of thirty-six cycling sessions, eleven of those not completed were Saturdays. This finding was similar to an intradialytic study done by Thompson et al.[107] who found that patients experienced difficulty obtaining exercise equipment from staff. Increased communication between the research team members and staff could have identified this issue sooner and prevented it from continuing.

The intensity level of biking may have also impacted the results. In order to determine the biking intensity during HD, a bike test was performed at the baseline assessment for any participant randomized to the intervention. All participants completed 50 watts of the bike test and based on the 50-60% protocol, participants were to set their intensity at 25 watts to begin. However, based on the log sheets, two participants felt they could not increase the intensity after individually reaching 15 watts and 20 watts. Another participant initially attained 25 watts however had health issues and could only work up to 12 watts after he resumed cycling. Parsons et al.[73] conducted a low intensity

intradialytic exercise program over twenty weeks and allowed the participants to choose their own exercise intensity. Although the participant's self-selected intensities were not mentioned, the study found improvements in dialysis clearance and functional performance. Many other intradialytic studies have based the exercise intensity on the Borg, instructing participants to cycle at a 12-13 (moderate to somewhat hard) on the scale, and have seen improvements in outcomes such as physical function and quality of life[56,114-119]. Fewer studies have utilized testing to determine cycling intensity while on HD. However, a study by Anding et al.[120] had participants perform a maximal incremental test on a cycle ergometer which began at a workload of 10 watts and increased by 10 watts every two minutes until muscular fatigue or were symptomatic. By the end of the study, participants were cycling at 20.8±2.6 watts. Storer et al.[121] found that participants increased their training intensity from 19±9 watts during the first week of training to 29±25 watts at the end of the ten week study. However, Storer noted that the initial training intensity of 19±9 watts was 66% of their target training intensity and the final intensity of 29±25 watts was 88% of their target. Despite the lower work rate, participants subjectively rated these intensities as "very hard" and "hard" using the Borg rate of perceived exertion scale. Participants in our study rated cycling sessions anywhere from "moderate" to "very hard".

Another possible explanation of StanC group improvement in physical function is that they may have been more physically active in their leisure time. According to the exercise log sheets this appears to be the case. StanC reported they did 10,049 minutes (n=4) of cardiovascular exercise compared to 4,850 minutes (n=5) in Renal Rehab group. Statistical analyses of the activity logs was not conducted. When Renal Rehab's leisure

time minutes were combined with their cycling minutes (3,651 min) they reached a total of 8,501 minutes of cardiovascular activity. It also appears that StanC was more physically capable at baseline than participants randomized to the intervention group. Specifically, no participants in the StanC group used any supports for walking; whereas, three of the five participants in Renal Rehab used either a cane or walker. Low accelerometer wear time in the Renal Rehab group and Renal Rehab participants not wearing the accelerometer on their ankle during cycling may have also misrepresented the amount of activity achieved in the Renal Rehab group as measured by accelerometer. Based on our experience perhaps a certain level of ability needs to be initially assessed so that the population is evenly matched. A larger sample size would be expected to mitigate the allocation issue, as individuals with diverse abilities would be randomized to both groups.

Another factor to consider is the volatility in health that occurs in the incident phase of dialysis. Perhaps it is possible that exercise negatively impacts physical function because of the stress it puts on an already taxed system in these first three months of treatment. It is also possible that patients are weakest when first starting dialysis and naturally regain physical function as they receive treatment. Walters et al.[122] analyzed 422 incident dialysis patients and found that their level of functioning was significantly impaired as compared to prevalent dialysis patients. Tamura et al.[123] also looked at functional status. They studied 3,702 nursing home residence (age 73±11 years) before and after the initiation of dialysis. After initiation of dialysis they found a significant decline in functional status. Furthermore, they reported that this decline accelerated during the three months prior to starting dialysis. Tamura et al. also found that functional status

stabilized between dialysis months one and four but then continued to decline out to one year. Due to the decline in physical function as CKD worsens, perhaps the time to make an impact on incident HD dysfunction would be in the early stages of CKD, before the initiation of dialysis. Starting an exercise program well before the initiation of dialysis could translate into better outcomes in the first three months of initiating dialysis treatment and may slow or halt the progression of CKD so that the trajectory to dialysis is lengthened[47,124].

Renal Rehab made no impact on secondary outcomes

The secondary study outcomes of HRQOL, dialysis symptoms, frailty, physical fitness, physical activity behavior patterns and self-efficacy to exercise were not found to be different between the two groups at any time point. This may have occurred for many of the reasons already discussed as well as because of our small sample size and lack of power to detect a clinically significant difference in any outcome.

Study limitations

It is important to acknowledge study limitations. First, this study was a pilot for feasibility purposes, so we did not expect to be powered to observe significant change in our primary outcome, physical function, as assessed by the SPPB. In addition, the SPPB has a ceiling score of 12 which may have limited the ability to detect changes. However, recruitment was more challenging than expected and less than half (n=11) the anticipated number of participants (n=28) were enrolled in the study. Recruitment of HD patients in clinical trials has also been shown to be difficult. Pipen et al.[125] ran into recruitment

issues and as a result modified their original recruitment goal from 250 to 90 patients. Roberts et al.[106] stopped recruitment after realizing that their planned sample size was unable to be attained in the time frame allotted. My pilot data will help inform future work and guide improvements in the delivery of exercise and education programming in this population.

Secondly, the original eligibility criteria utilized for safe study recruitment may have resulted in an overly restrictive selection bias. This selection bias may have prevented a true representative sample of incident HD patients from being chosen. Many of the inclusion and exclusion criteria were modified along the way to aid the recruiting process, never the less, this study's parameters excluded 128 patients, limiting us to 126 out of a possible 254 potential recruits (50% of the total incident HD population). We made contact with all 126 patients and only nineteen of them (15%) consented for the study. Eight of the patients consented were excluded due to missing baseline assessments or missing HD treatments, having unstable hemoglobin or blood sugar, being fluid overloaded, having a foot ulcer, being cognitively impaired or transferring to another modality. This left eleven of the consented patients (9%) who were enrolled in the study. The reasons for patients declining study participation were that they simply said no to being approached about the study or said they were not interested when approached. Many stated they were overwhelmed with everything going on in their life and others felt that transportation, time, or attending extra appointments was too much of a burden. Others were hoping to transfer to a different unit or modality and others either felt they would be physically unable to participate in the study and others felt like they were exercising enough already.

Selection bias could have also resulted from study recruitment procedures. There is a possibility that the patients recruited to participate in the study were more motivated to improve their health than those who declined to be approached or declined participation in the study. The multiple amendments to the study could also have resulted in bias and it is possible that selection bias played a role in the initial screen for patient's participation in the study, by the unit nephrologists, as outlined in the inclusion criteria. Although a full explanation of the study was scripted and delivered in the same manner each time and nephrologists were given an inclusion/exclusion criteria checklist to guide them in deciding if a patient was appropriate for the study, this may have led to a healthier sample of the HD population and we must acknowledge this is a limitation to the study.

A third limitation is related to study blinding. Although all research staff were blinded to group randomization at baseline, they were not blinded at the 3 month re-assessment time point. Study kinesiologists who performed the pre and post assessments were also responsible to guide the participants randomized to Renal Rehab through the intervention as well as acquire weekly log sheets from both groups on a weekly basis. Although a double blind study design would be ideal, it is not feasible to blind the participant or the clinical team to which group a participant is allocated to. This issue can be mitigated by the use of a blind assessor who is unaware of which group the participant is allocated to. It is also advised that the statistician responsible for analyzing the data be blinded.

A fourth study limitation relates to the use of accelerometers. Multi-directional accelerometers are considered the gold standard for physical activity assessment[96]; however, the devices fail to capture several common activities such as stationary cycling

and resistance training exercises. Participants in the Renal Rehab group were to wear the accelerometer on their ankle the week leading up to their three-month reassessment if they were cycling during HD. However, this did not happen because of patients failing to wear the accelerometer to their HD treatment or study kinesiologists forgetting to secure the accelerometer on to the patient's ankle while cycling. Regardless, there was not enough valid wear time recorded to analyze the accelerometers properly despite returning accelerometers to participants a second time if the original data did not look sufficient. Only three participants out of ten at baseline and five participants out of ten at three months had sufficient wear time. Huijnen et al.[126] excluded sixteen out of sixty-six participants due to invalid accelerometer data and 3% of participants in Uswatte et al.[127] study wear time was insufficient. In the future, specific strategies should be developed and identified to ensure the patient is wearing the device. In addition, other wearable devices that track exercise, such as a FitBit® or smart phone technology, should be explored to see if there are better options to capture objective activity data.

Future directions

My research adds valuable information to the literature about the feasibility of recruiting study participants from the incident HD population. This pilot trial did not support the primary or secondary hypothesis. Based on the results of this study, I recommend recruiting patients three to six months after HD initiation and in order to enhance enrollment, researchers should involve multi-centers to attain the desired number of participants, especially on a larger scale. As the incident phase of HD can be a turbulent time and the exact point at which patients are ready to participate in a study is unknown, future research may want to explore the point at which a patient's health

stabilizes medically in conjunction with when the patient is feeling ready to engage with a study both physically and mentally. Perhaps a patient-orientated research approach would be useful so that ultimately "the right patient receives the right intervention at the right time"[128]. This type of approach is important to ensure that patients are part of the conversation so that research questions and results are relevant to the population in question with the goal of improving healthcare systems and practices through application of the knowledge attained.

Conclusions

This study showed that Renal Rehab, although safe, is difficult to implement in the incident HD population. While our results do not support the hypothesis that Renal Rehab would improve physical function, quality of life and other secondary outcomes in incident HD participants more than StanC, several important recommendations were identified. As patients find the beginning months of HD overwhelming, we suggest waiting to three to six months before approaching a patient about exercise study participation. By this time, patients are mostly settled into HD life and their health is stabilized. It is also recommended to recognize the burden of transportation and time and address this burden by localizing all study appointments to the patients HD unit. Alternative strategies to reduce these burdens could also be implemented, such as providing transportation options in the form of a bus or taxi passes. While using safety as a key parameter, it is important that the eligibility criteria not be needlessly restrictive. It is also important that the participant is informed about the study and all it entails and is supported to make health behavior change. It is also important to integrate the dialysis

management and staff within the research paradigm so they have ownership of the research and its outcomes. Equipment should be trialed and ready to use when the study is rolled out and all staff and patients trained appropriately on its usage. Based on the low recruitment rate and the participant adherence to the protocol, future research should consider the merits of incorporating additional health behaviour change strategies to better support participants to exercise. Future research should continue utilizing an integrated knowledge translation approach and patient-orientated research paradigms when developing research questions, interventions and outcome measures.

Appendices

A) Biomedical Research Ethics Board
B) Short Physical Performance Battery
C) EuroQol 5 – Dimension 3 – Level Quality of Life and Visual Analogue Scale
D) Dialysis Symptom Index
E) Modified Fried Criteria
F) Shuttle Walk Test
G) Human Activity Profile
H) International Physical Activity Questionnaire
I) Accelerometer Sample File
J) Self-Efficacy for Exercise Survey
K) Written Consent Form

Appendix A – Biomedical Research Ethics Board

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS Research Ethics Board

P126 - 770 Bannatyne Avenue
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BIOMEDICAL RESEARCH ETHICS BOARD (BREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Full Board Review

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Dr. C. Bohm	HSC/Internal Medicine/Nephrology	B2014:088
BREB MEETING DATE:	**APPROVAL DATE:**	**EXPIRY DATE:**
August 25, 2014	September 11, 2014	August 25, 2015
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable):		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
NA	Effect of an Exercise Rehabilitation Program on Physical Function in Incident Hemodialysis Patients: A Randomized Controlled Pilot Study (Linked to B2005:153 and B2007:067)
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: Manitoba Medical Service Foundation	

Submission Date(s) of Investigator Documents:	REB Receipt Date(s) of Documents:
July 29 and September 10, 2014	July 31 and September 10, 2014

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date
Protocol:		
Proposal	V. 2	September 10, 2014
Consent and Assent Form(s):		
Research Participant Information and Consent Form	V. 2	September 10, 2014
Other:		
Appendix List - # 1-9, and #11	V. 1	23/07/2014

CERTIFICATION
The University of Manitoba (UM) Biomedical Research Board (BREB) has reviewed the research study/project named on this ***Certificate of Final Approval*** at the ***full board meeting*** date noted above and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM BREB.

BREB ATTESTATION
The University of Manitoba (UM) Biomedical Research Board (BREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the BREB complies with the membership requirements for Research Ethics Boards defined in

Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the REB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the BREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the REB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM BREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report.**

Sincerely,

Lindsay Nicolle, MD, FRCPC
Chair, Biomedical Research Ethics Board
Bannatyne Campus

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone:** (204) 789-3255/ **Fax:** (204) 789-3414

Appendix B – Short Physical Performance Battery

Balance Test [stand beside participant to supply support to prevent balance loss]

Side-by-side stand

"I want you to stand with your feet together side-by-side, for up to 10 seconds. Hold this position until I say stop… Ready begin."

Time: ***pre***: _____ s

Score: ***pre***: _____ pts

1 pt: ≥ 10 s
0 pts: < 10 s or unable

Semi-tandem stand [if side-by-side successful]

"I want you to stand with the side of your heel of one foot against the side of the big toe of the other foot, for up to 10 seconds. Hold this position until I say stop… Ready begin."

Time: ***pre***: _____ s

Score: ***pre***: _____ pts

1 pt: ≥ 10 s
0 pts: < 10 s or unable

Tandem stand [if semi-tandem successful]

"I want you to stand with your feet in a straight line, for up to 10 seconds. Hold this position until I say stop… Ready begin."

Time: ***pre***: _____ s

Score: ***pre***: _____ pts

Balance Test Scoring: 2 pt: ≥ 10 s
1 pt: 3-9.99 s
0 pt: < 3 s or unable

4m Gait Speed

Time taken to walk 4 m

Now I am going to observe how you normally walk. I want you to walk to the other end of the course at your usual speed, just as if you were walking down the street. Walk all the way past the tape before you stop… Ready, begin." [Repeat task]

Trial 1:_____ s

Trial 2:_____ s

Best of 2 trials:_____._____ s

Gait Speed Scoring : 4 pt: < 4.82 s
3 pt: 4.82-6.20 s
2 pt: 6.21-8.70s
1 pt: >8.7 s
0 pt: unable

SPPB Score: _____ pts

Was the test performed with a walking aid (e.g. cane or walker,)?

N 0 Y 1

Chair Stand Test

"Do you think you will be able to stand up from a chair without using your arms? First fold your arms across your chest and sit so that your feet are on the floor; then stand up keeping your arms folded across your chest. Please stand up as quickly as you are able five times. After standing up each time, sit down and then stand up again…Ready begin."

Able to stand up from chair five times without using arm rests? N 0 Y 1

Time: ***pre:*** _____ s

Score: ***pre:*** _____ pts

Chair Stand Scoring: 4 pt: ≤ 11.19 s
3 pt: 11.20-13.69 s
2 pt: 13.70-16.69 s
1 pt: ≥16.70 s
0 pt: > 60 s or unable

Appendix C – EuroQol 5-Dimension 3-Level Quality of Life and Visual Analogue Scale

EuroQol 5-Dimension 3-Level (EQ-5D-3L)

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

MOBILITY

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

SELF-CARE

I have no problems with self-care ❑

I have some 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 with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

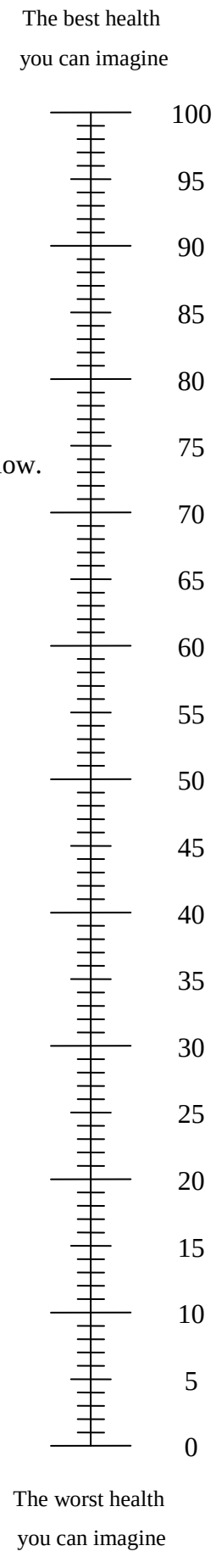
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

EuroQol Visual Analog Scale (EQ-VAS)

- 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.

YOUR HEALTH TODAY =



Appendix D – 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.

During the past week: Did you experience this symptom?		*If "yes": How much did it bother you?*				
		Not At All	**A Little Bit**	**Some-what**	**Quite a Bit**	**Very Much**
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

During the past week: Did you experience this symptom?		***If "yes": How much did it <u>bother</u> you?***				
		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?		***If "yes": How much did it bother you?***				
		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	NO YES →	1	2	3	4	**5**

Appendix E – Modified Fried Criteria

Nutrition

"*Have you unintentionally lost weight* (i.e. not due to dieting or exercise)*?"*
N 0 Y 1

If yes, "*How much weight have you lost in the last 12 months?* _____ kg

Weight loss conclusion N 0 Y 1

(Yes if > 4.5 kg (10 lbs) or > 5% in past 12 months)

Exhaustion [based on CES-D]

"*How often in the last week did you feel that everything was an effort?"*

Rarely or none of the time (< 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
0	1	2	3

"*How often in the last week did you feel that you could not 'get going'?"*

Rarely or none of the time (< 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
0	1	2	3

Exhausted conclusion N 0 Y 1

(Yes if answered "Occasionally..." or "Most..." to either question 1 or 2)

Handgrip Strength

Kilograms of handgrip strength (no decimals)

"For this exercise, I am going to use this instrument (Show Dynamometer) to test your arm strength. Hold the instrument in your hand with your forearm parallel to the floor. Now, when I say squeeze, squeeze as hard as you can until I tell you to stop. I will ask you to do this two times for each hand… Ready lets begin."

[Arm flat at side, do not rest arm on chair armrest or against body]
[Each squeeze should last at least 2-3 seconds]

Left hand

Trial 1: _____ kg

Trial 2: _____ kg

Right hand

Trial 1: _____ kg

Trial 2: _____ kg

Maximum value:_____ kg

Weak? *Pre-* N 0 Y 1

(Simplified cut-off: ♂: ≤ 30 kg ♀: ≤ 20 kg in the strongest hand)

Appendix F – Shuttle Walk Test

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).

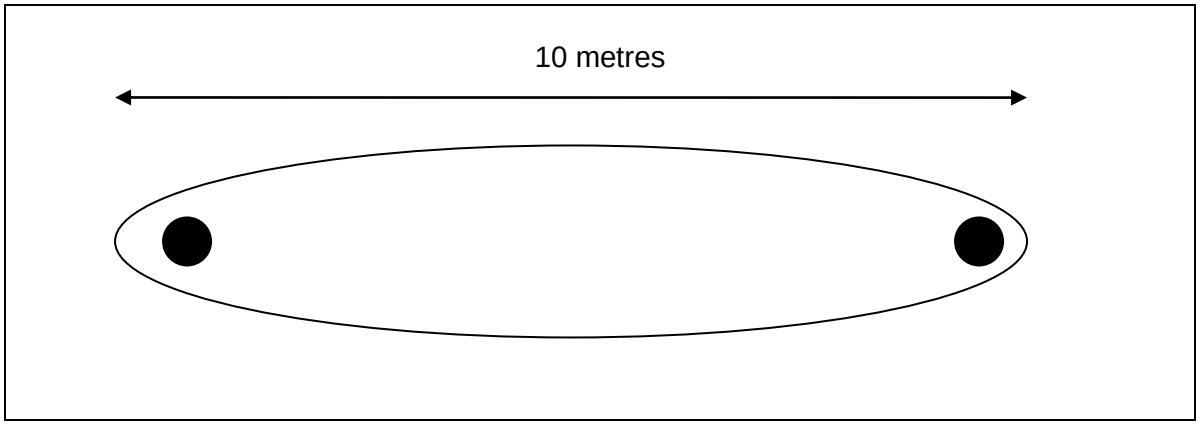


Figure 1 Plan of Shuttle Walk Test course

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

Table 2 - Shuttle Walking Test

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 3 - Endpoints for Sub Maximal 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

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

Table 4 - Equipment needed for Sub Maximal Shuttle Walking Test

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

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

Table 5 - Protocol for Sub Maximal Shuttle Walking Test

• 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
• Set marker cones 9 metres apart
• Fit patient with pulse oximeter
• Explain Borg ratings of breathlessness and perceived exertion (RPE) and ensure subjects understand how to use these
• Play the instructions on the CD to the patient
• Clarify the endpoints of the test with subject (See Table 3)
• Walk round with the patient for the first or two minutes to help them establish the

correct pace (starting pace is approximately 1 mph)
• Tell subject about an increase in walking speed just prior to the next triple bleep
• Discourage subjects from talking while they are doing the test
• Record total distance walked in metres, heart rate and oxygen saturation immediately once sitting
• Record reason for stopping 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.

References

Leger, L.A. and Lambert, J. (1982) 'A maximal multistage 20m shuttle run test to predict VO_2 max'. *European Journal of Applied Physiology* 49: 1-12.

Singh, S.J. et al. (1992) 'Developments of a shuttle walking test of disability in patients with chronic airways obstruction', *Thorax*, 47: 1019-24.

Singh, S.J. et al. (1994) 'Comparison of oxygen uptake during a conventional treadmill test and the shuttle walking test in chronic airflow limitation', *European Respir J* 7: 2016-2020.

Appendix G – Human Activity Profile

Human Activity Profile

Please place a tick in the appropriate box; until there are clearly no activities listed that you are able to do at the present time. If you are still doing an activity tick the first box, if you have stopped doing an activity tick the second box, if you have never done an activity tick the third box.

This questionnaire was constructed by A J Fix and DM Daughton and published in the *Human Activity Profile Professional Manual*, Psychological Assessment Resources Inc., 1988

		Still doing this activity	Have stopped doing this activity	Never did this activity
1	Getting in & out of chairs or bed without assistance….			
2	Listening to the radio……..			
3	Reading books, magazines or newspapers……			
4	Writing letters or notes……..			
5	Working at a desk or table……..			
6	Standing for more than 1 minute……..			
7	Standing for more than 5 minutes……..			
8	Dressing or undressing without assistance……			
9	Getting clothes from drawers or closets……			
10	Getting in and out of cars without assistance……			
11	Dining at a restaurant……			
12	Playing cards / table games……..			
13	Taking a bath without assistance……..			
14	Putting on shoes, stockings or socks, no rest or breaks required			
15	Attending a movie, play, church event or sports ……. activity			
16	Walking 30 yards / 27 meters……			
17	Walking 30 yards non-stop……			
18	Dressing / undressing, no rest or break needed……..			
19	Using public transport or driving a car 99 miles or less			
20	Using public transport or driving a car 100 miles or…. more			

		Still doing this activity	Have stopped doing this activity	Never did this activity
21	Cooking your own meals……..			
22	Washing or drying dishes……..			
23	Putting groceries on shelves……..			
24	Ironing or folding clothes……..			
25	Dusting / polishing furniture or polishing a car……			
26	Showering……..			
27	Climbing 6 steps……			
28	Climbing 6 steps non stop……			
29	Climbing 9 steps……			
30	Climbing 12 steps……..			
31	Walking ½ block on level ground……			
32	Walking ½ block on level ground non-stop……..			
33	Making a bed (not changing sheets)……			
34	Cleaning windows……			
35	Kneeling, squatting to do light work……			
36	Carrying a light load of groceries …… (milk bread)			
37	Climbing 9 steps non-stop……			
38	Climbing 12 steps non-stop……..			
39	Walking ½ city block uphill……..			
40	Walking ½ city block uphill non-stop……..			
41	Shopping by yourself……			
42	Washing clothes by yourself……			
43	Walking 1 city block on level ground……..			
44	Walking 2 city blocks on level ground……..			
45	Walking 1 city block on level ground non-stop……			
46	Walking 2 city block on level ground non-stop……			

		Still doing this activity	Have stopped doing this activity	Never did this activity
47	Scrubbing floors, walls or cars……..			
48	Making a bed, changing sheets……			
49	Sweeping……....			
50	Sweeping 5 minutes non-stop……			
51	Carrying a large suitcase or bowling 1 game……			
52	Vacuuming carpets……			
53	Vacuuming carpets 5 minutes non-stop……			
54	Painting interior / exterior……			
55	Walking 6 city blocks on level ground……..			
56	Walking 6 city blocks on level ground non-stop……..			
57	Taking out the garbage……..			
58	Carrying a heavy load of groceries……..			
59	Climbing 24 steps……			
60	Climbing 36 steps……			
61	Climbing 24 steps non-stop……..			
62	Climbing 36 steps non-stop……			
63	Walking 1 mile……			
64	Walking 1 mile non-stop……..			
65	Running 110 yards (100 m) or playing softball / baseball ….....			
66	Dancing (social)……			
67	Doing callisthenics or aerobic dancing …… (5 minutes non-stop)			
68	Mowing the lawn …… (power mower but not a ride on mower)			
69	Walking 2 miles……			
70	Walking 2 miles non-stop……			
71	Climbing 50 steps (2 ½ floors)……			

		Still doing this activity	Have stopped doing this activity	Never did this activity
72	Shovelling, digging or spading ……			
73	Shovelling, digging or spading 5 minutes non-stop…..			
74	Climbing 50 steps (2 ½ floors) non-stop……..			
75	Walking 3 miles or golfing 18 holes without golf cart..			
76	Walking 3 miles non stop……			
77	Swimming 25 yards……....			
78	Swimming 25 yards non-stop……			
79	Bicycling 1 mile…….....			
80	Bicycling 2 miles…….....			
81	Bicycling 1 mile non-stop……..			
82	Bicycling 2 miles non-stop……			
83	Running or jogging ¼ mile……			
84	Running or jogging ½ mile……...			
85	Playing tennis or racquetball……			
86	Playing basketball / soccer (game play)……			
87	Running or jogging ¼ mile non-stop……..			
88	Running or jogging ½ mile non-stop……..			
89	Running or jogging 1 mile……..……			
90	Running or jogging 2 miles……...			
91	Running or jogging 3 miles……...			
92	Running or jogging 1 mile in 12 minutes or less……..			
93	Running or jogging 2 miles in 20 minutes or less…….			
94	Running or jogging 3 miles in 30 minutes or less….....			

Maximum Activity Score (MAS) = highest ranking activity still being done
Adjusted Activity Score (AAS) = MAS – the number of items that have been stopped that fall **below** the MAS
Activities that were 'never done' are not counted

Appendix H – International Physical Activity Questionnaire

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

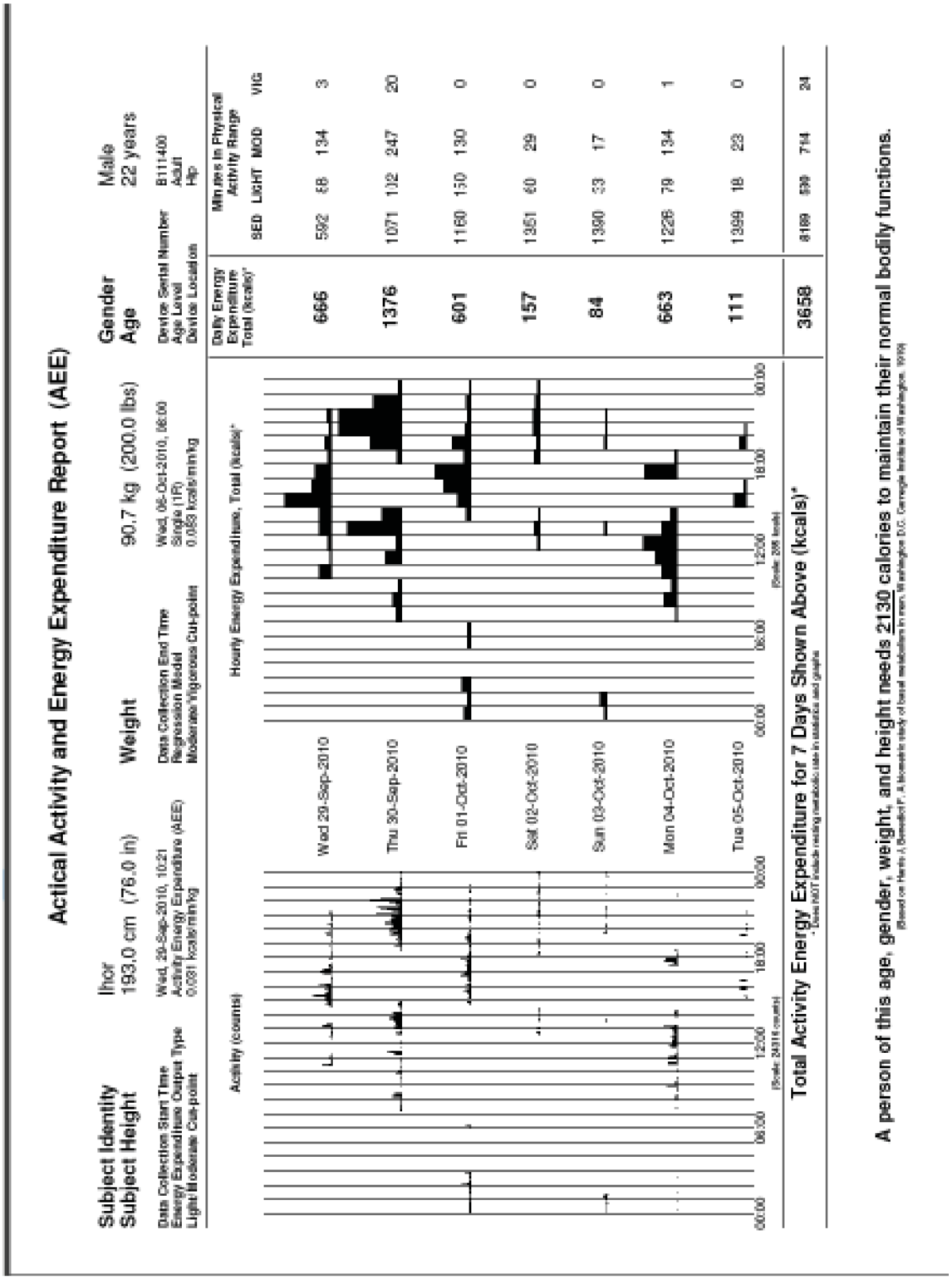
_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

Appendix I – Accelerometer Sample File



Appendix J – 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 K – Written Consent Form

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

Title of Study: Effect of an Exercise Rehabilitation Program on Physical Function and Quality of Life in Incident Hemodialysis Patients: A Randomized Controlled Trial.

Principal Investigator: **Dr. Clara Bohm BScH, MD, MPH, FRCPC**
Nephrologist, Manitoba Renal Program
Assistant Professor, University of Manitoba
Phone: (204) 787-3583

Co-Investigators:
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You are being asked to participate in a research study. Please take your time to review this consent form and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this study and you may discuss it with your friends, family or (if applicable) your doctor before you make your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information you do not clearly understand.

Purpose of the Study

This research study is being conducted to determine if a self-management education and exercise program that includes, home based resistance training, plus cycle-exercise during dialysis enhances physical function in incident hemodialysis patients.

Study Procedures

In this study, you will be randomized into one of the 2 study groups described below. Randomized means that you are put into a group by chance, like flipping a coin. You will have an equal chance of being placed in either group.

Standard Care Group Procedures:

If you are eligible for the 'current standard care' group, you will be asked to complete the following 4 appointments with the Research Assistant:

Appointment #1: The baseline appointment will take place at the Wellness Institute approximately 6-26 weeks after starting your dialysis treatment. Prior to this appointment, the Research Assistant will visit you during your dialysis treatment and describe the project procedures to you and ensure that any/all of your questions are answered. The Research Assistant will provide you with a study information sheet and ask you to provide written consent. The Research Assistant will give you a time and date to attend the baseline appointment and leave you with a series of questionnaires that you will fill out and bring with you to the baseline appointment. The Research Assistant will also provide you with a Physical Activity Monitor, which is a small device that is about the size of a watch and is worn on a belt. You will be asked to wear this monitor for a period of 7 consecutive days. This device measures the amount and intensity of physical activity that you complete on a daily basis. Given the small size and placement of the accelerometer at belt level, you will be able to participate in your normal daily routine without alteration. It is important to note that the monitor will only measure the amount of physical activity that you accumulate and does not store personal information. Therefore your privacy will not be adversely affected by wearing the unit. The monitor will be given to you by the research staff prior to each of the four appointments and you will be asked to bring the unit in with you to each of your appointments which will take place at the Wellness Institute. At this appointment, you will be asked to complete several physical tests. This appointment will take approximately 1 hour of your time.

Appointment #2: This appointment will occur approximately 12 weeks (3 months) after you have started the study. You can choose whether this appointment will occur at the Wellness Institute or your dialysis unit, depending on what is more convenient for you. Prior to this appointment, the Research Assistant will visit you during your dialysis treatment and give you a time and date to attend appointment #2. The Research Assistant will also leave you with a series of questionnaires to fill out and a Physical Activity Monitor to wear for 7 days. You will be asked to bring both the questionnaires and the Physical Activity Monitor to your appointment #2. At this appointment you will hand in all questionnaires and the Physical Activity Monitor as well as complete several physical tests. This appointment will take approximately 1 hour of your time.

Appointment #3: This appointment will occur approximately 26 weeks (6 months) after you have started the study. You can choose whether this appointment will occur at the Wellness Institute or your dialysis unit, depending on what is more convenient for you. Prior to this appointment, the Research Assistant will visit you during your dialysis treatment and give you a time and date to attend appointment #3. The Research Assistant will also leave you with a series of questionnaires to fill out and a Physical Activity Monitor to wear for 7 days. You will be asked to bring both the questionnaires and the Physical Activity Monitor to your appointment #3. At this appointment you will hand in all questionnaires and the Physical Activity Monitor as well as complete several physical tests. This appointment will take approximately 1 hour of your time.

Appointment #4: This appointment will occur at the Wellness Institute approximately 52 weeks (12 months) after you have started the study. Prior to this appointment, the Research Assistant will visit you during your dialysis treatment and give you a time and date to attend appointment #4. The Research Assistant will also leave you with a series of questionnaires to fill out and a Physical Activity Monitor to wear for 7 days. You will be asked to bring both the questionnaires and the Physical Activity Monitor to your appointment #4. At this appointment you will hand in all questionnaires and the Physical Activity Monitor as well as complete several physical tests. This appointment will take approximately 1 hour of your time.

As part of the standard care group you will also be asked to keep track of any exercise you do using an exercise log sheet that the study kinesiologist will collect weekly.

Intervention Group Procedures:

If you are randomized to the intervention group, you will be asked to complete the same 4 appointments outlined for the standard care group above and keep track of any physical activity you do outside of the structured program using an exercise log sheet that will be provided to you . In addition, you will be asked to participate in a structured exercise program specifically designed to increase your level of physical activity.

To help identify the intensity at which you should start exercising, during your first appointment at the Wellness Institute, you will be asked to exercise on a stationary bicycle with gradually increasing workload for as long as you can comfortably do so. This appointment will take approximately 30-60 minutes.

As part of the study, you will be required to participate in supervised exercise on a stationary bicycle during your dialysis treatments. The program itself will consist of 60 minutes of continuous cycling exercise at a pre-determined intensity. You will also receive standardized education and resistance training sessions either prior to or during your hemodialysis sessions during the first 4 weeks of the intervention. After this, you will be provided with materials to continue exercising at your home when it is convenient for you.

There will be NO cost to you for participating in the exercise programs, other than your time and your usual transportation costs to attend dialysis.

Risks and Discomforts

The risks of participating in this research are considered to be minimal. However, there is a certain degree of risk involved in the initiation of any exercise program. If you are randomized to the intervention group, you will be carefully assessed by dialysis unit physicians and staff prior to the initiation of the exercise program. Additionally, the symptom limited, graded program of exercise would be individualized according to your personal health status.

Monitored exercise is very low risk. Exercise has been shown to be safe in hemodialysis in other studies. However, when starting any exercise program it is possible that you could:

- **Have muscle or joint soreness after exercise, especially if you have not exercise recently**
- **Have low blood pressure on hemodialysis after exercising**
- **Develop or have worsening chest pain (angina) during or after exercise (low risk)**
- **Develop an irregular or fast heart rate rhythm during or after exercise (low risk)**
- **Develop a heart attack during or after exercise (low risk)**
- **Have low sugars during or after exercise if you have diabetes. It is important to monitor your sugars closely when starting any exercise program.**
- **There is a very small risk of death related to the above side effects if they occur**

Although the exercise instructions will be provided by certified and experienced instructors, if you have reason to believe that you would be at physical risk of harm/injury by participating in the program, you are asked to decline participation in this project. Additionally, trained healthcare personnel are also on site at all times. The researcher may decide to take you out of this study without your consent if your health status changes to prevent you from being able to continue to participate. Your participation in the study may also be discontinued upon the advice of a medical doctor.

Benefits

There may or may not be direct benefit to you from participating in this study. We intend to use the information learned from this study to benefit other incident hemodialysis patients and help them to become more physically active.

Costs

All procedures, which will be performed as part of this study, are provided at no cost to you. The indirect cost to you will be transportation to the assessment appointments. However, this cost will be subsidized at the amount of $20 per assessment.

Confidentiality

Information gathered in this research study may be published or presented in public forums, however your name and other identifying information will not be used or revealed. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Medical records that contain your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba.

Organizations that may inspect and/or copy your research for quality assurance and data analysis include groups such as: The University of Manitoba Biomedical Research Ethics Board.
All study related documents will bear only your assigned study number. All data will be entered into a computer and transmitted electronically to members of the research team only. All hard copy records will be kept in a secure area and only those persons identified will have access to these records. No information revealing any personal information such as your name, address or telephone number will leave the Health Sciences Centre or Seven Oaks General Hospital. If deemed necessary by the research staff, information regarding your health

Voluntary Participation/Withdrawal from the Study

Your decision to take part in this study is voluntary. You may refuse to participate or you may withdraw from the study at any time. However, if you decide to stop participating in the study, we encourage you to discuss this decision with the research study staff first. There are no consequences to withdrawing from the study. Your decision not to participate or to withdraw from the study will not affect your care at this centre. If the study staff feels that it is in your best interest to withdraw you from the study, they will remove you without your consent. We will tell you about any new information that may affect your health, welfare, or willingness to remain in this study.

Questions

You are free to ask any questions that you may have about your treatment and your rights as a research participant. If any questions come up during or after the study or if you have a research-related injury, contact Dr. Todd Duhamel at (204) 235-3589 or tduhamel@sbrc.ca.

For questions about your rights as a research participant, you may contact The University of Manitoba, Bannatyne Campus Research Ethics Board Office at (204) 789-3389. Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

Statement of Consent

I have read this information/consent form. I have had the opportunity to discuss this research study with Dr. Todd Duhamel and/or his staff. I have had my questions answered by them in a language I understand. This risks and benefits have been explained to me. I believe that I have not been unduly influenced by any study team member to participate in the research study by any statements or implied statements. Any relationship (such as employer, supervisor, or family member) I may have with the study team has not affected my decision to participate. I understand that I will be given a copy of this consent form after signing it. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that information regarding my personal identity will be kept confidential, but that confidentiality is not guaranteed. I authorize the inspection of any

of my records that relate to this study by The University of Manitoba Research Ethics Board and the St. Boniface Hospital Office of Clinical Research for quality assurance purposes.

By signing this consent form, I have not waived any of the legal rights that I have as a participant in a research study.

I agree to be contacted for future follow-up in relation to this study – YES____ NO____

I would like to receive a summary of the study findings - YES____ NO____

If YES, please provide mailing or e-mail address:

_____

Participant signature: _____ Date: _____
(day/month/year)

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent.

Printed Name: _____ Date:_____
(day/month/year)

Signature: _____ Role in the study: _____

ALL SIGNATORIES MUST DATE THEIR OWN SIGNATURE.

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