TITLE OF THE PROTOCOL:

Clinical value and cost-effectiveness of intra-dialytic exercise for the improvement of health-related quality of life in people with stage 5 chronic kidney disease undergoing maintenance haemodialysis.

Short title/Acronym:	**PrEscription of intra-Dialytic exercise to improve quAlity of Life in patients with chronic kidney disease (PEDAL)**
Sponsor:	**King's College Hospital NHS Foundation Trust**
Chief Investigator:	**Professor Iain Macdougall**
Trial Identifiers	
NCT number:	NCT02222402
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Chief Investigator Agreement Page

The clinical study as detailed within this research protocol **(Version 3.0, dated 02.11.2016)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

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The clinical study as detailed within this research protocol **(Version 3.0, dated 02.11.2016)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

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The clinical study as detailed within this research protocol **(Version 3.0 dated 02.11.2016)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

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STUDY SUMMARY/SYNOPSIS

Does intra-dialytic exercise improve health-related quality of life in maintenance haemodialysis patients?

TITLE	Clinical value and cost-effectiveness of intra-dialytic exercise for the improvement of quality of life in stage 5 chronic kidney disease patients receiving maintenance haemodialysis
SHORT TITLE	PEDAL Study
Protocol Version Number and Date	V2.0 17 July 2015
Methodology	Pragmatic, single-blind randomised controlled trial
Phase	IV
Study Duration	48 months
Study Centre	Multi-centre
Objectives	To determine, in comparison to usual care, whether usual care augmented by intra-dialytic exercise training improves health-related quality of life in stage 5 CKD patients receiving maintenance haemodialysis renal replacement therapy
Number of Subjects/Patients	380 participants
Diagnosis and Main Inclusion Criteria	Evaluation of the clinical value and cost-effectiveness of usual care augmented intra-dialytic exercise training in the management of 380 stage 5 chronic kidney disease patients receiving maintenance haemodialysis renal replacement therapy
Duration of intervention	9 months
Reference therapy	Usual care maintenance haemodialysis renal replacement therapy
Methodology and Analysis	Primary analysis will be ANCOVA comparison of 6 month outcomes, adjusted for baseline differences. Secondary analyses will be multivariate repeated measures analysis, adjusted for baseline differences

Glossary of Terms and Abbreviations

AE	Adverse Event
CI	Chief Investigator
CKD	Chronic Kidney Disease
CRO	Contract Research Organisation
CRP	C-Reactive Protein
DASI	Duke Activity Status Index
DSMC	Data Safety Monitoring Committee
eCRF	Electronic Case Report Form
EQ/ED-5D	Standardised instrument to measure health outcomes in health economic analyses
GCP	Good Clinical Practice
GCTU	Glasgow Clinical Trials Unit
HbA1c	Glycosylated Haemoglobin
HIC	Health Informatics Centre
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
ISF	Investigator Site File
ITT	Intention to Treat
KDQoL	Kidney Disease Quality of Life
KDQoL PCS	KDQoL Physical Composite Score6
KDQoL MCS	KDQoL Mental Composite Score
MCID	Minimum Clinically Important Difference
NHS R&D	National Health Service Research & Development
NRES	National Research Ethics Committee
PI	Principal Investigator
QC	Quality Control
PA	Physiotherapy Assistant
PIN	Participant / Patient Identification Number
PIS	Participant / Patient Information Sheet
RA/SC/RN	Research Assistant /Co-ordinator / Nurse
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SS60	Sit-to-Stand in 60 minutes
TMG	Trial Management Group
TMF	Trial Master File
TSC	Trial Steering Committee
TUG	Timed Up and Go test
WPD	Working Practice Document

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1. Introduction

1.1 Background

PEDAL is a pragmatic, multi-centre single-blind randomised controlled trial (RCT) designed to evaluate the clinical value and cost-effectiveness of intra-dialytic exercise training as a means to improve the health-related quality of life of people with stage 5 chronic kidney disease who are receiving maintenance haemodialysis renal replacement therapy.

We intend to recruit 380 prevalent adult renal outpatients (aged 18+), from those undergoing in-centre (hospital unit, satellite unit) renal replacement therapy via maintenance haemodialysis. Patients will be eligible if they have been dialysing for more than three months and are naive to intra-dialytic exercise. Eligible and consenting patients will then be randomly allocated to one of two treatment arms: usual care maintenance haemodialysis renal replacement therapy (UCHD) or usual care augmented by intra-dialytic exercise training (EXHD).

The primary clinical outcome for the study is the change in Kidney Disease Quality of Life (KDQOL) Physical Composite Score between baseline and 6 months. Additional important secondary outcomes will include change in peak aerobic capacity, physical fitness, arterial stiffness (pulse wave velocity) and blood pressure, other quality of life and symptom burden assessments (KDQOL-Mental Composite Score, EQ5D, , habitual physical activity levels and cost effectiveness. Participants will receive 9 months exposure to either their usual care therapy or the intra-dialytic exercise training augmented usual care. Outcomes of the intervention will be measured at entry to the study (0 months) and again after 6, 9 and 15 months.

The incidence of new patients accepted for renal replacement therapy in the UK has almost doubled in 10 years from 60 patients per million population (pmp) to 110pmp (1). Diabetes remains the single most common cause of the gradual loss of kidney function and in combination with cardiovascular disease (CVD), is responsible for the 10-30 times greater mortality rates of HD patients compared to the general population (2). Improved dialysis techniques and management of co-existing disease, have made HD more tolerable and many new patients can anticipate a longer life expectancy (3), although not always with a good quality of life. In part, this may reflect the increased age profile of incident patients with a median age of 65 years and the associated presence of the clinical syndrome of frailty (4). This syndrome is characterised by persistent fatigue, weight loss, muscle weakness, severe functional limitations and low physical activity (PA) levels many of which often deteriorate further with the initiation of HD (5). Both physical inactivity and impaired physical function are strongly associated with increased morbidity, mortality and reduced quality of life (QOL) in HD patients (6,7,8). QOL is also independently associated with mortality in HD patients with SF36QOL-Physical Composite scores (PCS) of less than 25 associated with a 93% increased risk of death and a 56% increased risk of hospitalisation, whilst a 10-point decrease in the PCS translated into a 25% increased risk of death within 2 years (8). Conversely, a 1-point increase in the PCS was associated with a 3.5% improvement in the odds of death (9). Resultantly, interventions designed to increase PA and reduce sedentary behaviour in HD patients might reduce CVD risk, improve physical functioning, reduce fatigue and in turn possibly lead to improved QOL. Evidence from three (10,11,12) systematic reviews indicates that a range of exercise training interventions show potential to

improve exercise capacity and some functional limitations in people with chronic kidney disease. The greatest effects were reported after 6 months of exercise and were associated with both supervised and higher intensities of exercise. However, most of the studies reviewed were small trials, many of which were not methodologically robust, and also included non-intra-dialytic interventions in the evidence synthesis. Few of the reviewed studies were appropriately powered to detect QOL outcomes and none included a cost effectiveness analysis. Older, comorbid individuals, with the additional burden and consequences of the HD process, represent a classic example of a frail population. Compared to adults without CKD, self-reported ability to participate in activities of daily living, such as climbing steps, walking short distances without stopping and daily self-care tasks, is extremely low in HD patients regardless of age (4,13,14). Within 1 year of initiating HD, frail patients were more likely to die or be hospitalised compared to non-frail patients (4,13) and only 5% of elderly HD patients (mean age: 75 years) were fully independent (14). In the HD population physical function and PA are strongly associated with overall quality of life, morbidity and mortality (6,7,8,9,15). Sietsema et al.(6) observed that exercise capacity was predictive of outcome in 175 ambulatory HD patients. Patients with a peak aerobic capacity above the median threshold of 17.5 mL/kg/min had a statistically lower rate of death during the 3.5 years follow-up period. Moreover, exercise capacity remained the strongest predictor of survival over the 3.5-year follow-up, even when corrected for other contributing variables. Analysis of data from the USRDS Dialysis Morbidity and Mortality Study indicated that patients classified as sedentary at study initiation showed a 62% greater risk of mortality over 1 year compared with non-sedentary patients even after adjustment for other variables associated with survival in this group (15). Recent systematic review evidence (11) suggests that, when compared to standard care, exercise interventions during dialysis can statistically improve physical fitness (peak aerobic capacity) by about 18%, or at least appear to limit the potential for the relentless deterioration of physical and psychosocial function observed across all stages of CKD. The Dialysis Outcomes and Practice Patterns study (DOPPS) observed that patients who exercised during dialysis more than twice a week had significantly better scores in the mental and physical components of the KDQoL-SF, physical function and quality of sleep, compared to patients who exercised less frequently (16). Regularly exercising patients were also 33% less likely to be hospitalised due to fractures. Interestingly, a 9% lower mortality risk was observed for each 10% increment in the number of patients exercising within a unit whilst mortality risk was reduced by 31% as patient exercise frequency increased from 1 to 6 or more times per week.

Fatiguability, defined as an overwhelming, debilitating, and sustained sense of exhaustion that decreases one's ability to carry out daily activities, is another prevalent and severe symptom experienced by patients in stage 5 CKD (17). The burden of this symptom is substantial, with patients reporting a severity of 3.1 units on a 1 (not at all bothersome) to 5 (bothers very much) scale (17). As a further indicator of the importance of this symptom, 94% of patients would accept longer haemodialysis if fatigue was reduced (18). Fatigue is also associated with CKD patient QOL and mortality (17,19). Furthermore, fatigue is a barrier to participating in physical activity (20). In CKD patients a recent Cochrane review discursively suggested that exercise can reduce feelings of fatigue (11). However, a meta-analysis on the influence on fatigue was not possible due to insufficient numbers of participants and moderate to severe risk of study bias. In other fatigued populations including chronic fatigue syndrome, exercise can reduce fatigue symptoms (21,22). Implementing an exercise programme is also likely to have a statistically significant

and clinically important improvement to patient reported fatigue, which then may encourage patients to sustain more physically active life styles in the longer term (20).

1.2 Rationale and Risks/Benefits

The rationale for intra-dialytic exercise is both intuitively and pragmatically appealing as the environment of unit-based HD provides an ideal platform for the implementation and potential sustainability of exercise rehabilitation programmes for, and thus the exercise behaviour of, HD patients. The pre-existing need for patients to attend thrice-weekly, 4 hour-long HD sessions, provides a practical opportunity to deliver a safely structured and supervised rehabilitation programme with an enhanced potential for participation, associated with a substantially reduced patient burden in terms of time, effort and travel costs. The importance of the patient inconvenience burden has been confirmed by a previous study that reported a lower drop out rate from intra-dialytic exercise training (17%) compared to an exercise training programme (25%) for HD patients conducted on non-dialysis days (23). Time spent on dialysis is also reported to be the most physically inactive period for HD patients (24) and thus an exercise intervention implemented during HD would directly address the important key PA guideline that recommends the reduction of prolonged periods of inactivity to the minimum (28). The K/DOQI Clinical Practice Guidelines for the management of CV disease risk factors in patients with CKD now include a separate guideline section (guideline 14) supporting physical activity promotion as an integral part of patients' care plans (25). Clear research recommendations are proposed to strengthen the evidence base on the best way to incorporate PA into the routine care of HD patients. This indicates a need for the resolution of what might, for HD patients, constitute the optimal exercise prescription for the delivery of health outcomes, including combatting frailty and reduction of cardiovascular risk. We believe that our study proposal, by addressing many of the methodological weaknesses of previous studies, will resolve some of the remaining issues around the efficacy of exercise training to deliver health-related benefits for HD patients. In addition, through the incorporation of the cost effectiveness analysis we believe that we will be in a position to offer a methodologically robust and long awaited insight in relation to an implementation strategy for long term adoption and sustainability of intra-dialytic exercise training in HD units across the UK and other countries.

Evidence explaining why this research is needed now

Recent clinical practice guidelines for Cardiovascular Disease (CVD) in CKD produced by the U.K Renal Association (26) suggest that exercise should be encouraged, and patients (including dialysis patients) should be enrolled on regular exercise programmes, exercising 3 to 5 times weekly either during dialysis or between dialysis sessions (Guideline 1.4-CVD: CVD risk factors). A major obstacle to the implementation of such exercise programmes in many UK NHS Renal Units is the lack of evidence from high quality randomised controlled trials of intra-dialytic exercise training. This is often required to justify the necessary costs of programme set-up and delivery. As a result, only a few renal units are able to provide this type of therapy resulting in an inequality of service provision that needs to be urgently addressed. A need for quality evidence remains despite the publication of the recent Cochrane Review (11) which indicated some potential for exercise training interventions in CKD patients. Most of the trials reviewed used inadequate randomisation procedures and/or failed to undertake intention-to-treat (ITT) analyses,

resulting in a moderate to high degree of bias being identified in 82% of the trials included in the meta-analysis. Taken together, these weaknesses can combine to exaggerate the impact of an intervention. There was also evidence of significant heterogeneity between trials indicating that results were not consistent across studies. This is perhaps understandable given the extremely wide remit applied by the authors of that review, covering the entire CKD disease trajectory and also many modes of exercise training, including non-intra-dialytic interventions. Only two studies using combined aerobic and muscular conditioning exercise interventions during dialysis were included and only two of the trials studied whether or not any benefits of an exercise intervention persisted beyond the intervention. Also, the vast majority of reported trials of exercise training with HD patients were underpowered to detect anything other than a massive treatment effect and none reported cost effectiveness data. Physical inactivity is a modifiable risk factor and exercise interventions designed to increase PA and reduce sedentary behaviour in patients on dialysis may improve health related outcomes and be cost effective in the longer term. However, there remains a pressing need for high-quality grade A evidence from randomised controlled trials in order to evaluate the clinical benefit and cost effectiveness of intra-dialytic exercise. It has been suggested also that a rigorously designed, and appropriately powered pragmatic, RCT study may also go some way towards addressing the issue of whether physical inactivity contributes to increased mortality in these patients or is just an indicator of poor general condition that increases mortality risk (27). The importance of this question can only increase in view of the rising prevalence of CKD.

2. Study Objectives and Design

2.1 Study Objectives

2.1.1 Primary Objective

To determine, in comparison to usual care, whether usual care augmented by intra-dialytic exercise training improves health-related quality of life in stage 5 CKD patients receiving maintenance haemodialysis renal replacement therapy

2.1.2 Secondary Objectives

i. To determine, in comparison to usual care, whether usual care augmented by intra-dialytic exercise training improves the physical function of stage 5 CKD patients receiving maintenance haemodialysis renal replacement therapy

ii. To compare the effect of usual care augmented intra-dialytic exercise training versus usual care on systemic and biochemical markers of vascular and cardio-metabolic health of stage 5 CKD patients receiving maintenance haemodialysis renal replacement therapy

iii. To assess, in comparison to usual care, whether usual care augmented by intra-dialytic exercise training is associated with an excess of adverse events in stage 5 CKD patients receiving maintenance haemodialysis renal replacement therapy

iv. To explore and document the views of participants and members of the renal care teams in relation to their experiences of usual care and intra-dialytic exercise-augmented usual care

v. To estimate the cost-effectiveness of augmenting, with intra-dialytic exercise training, the usual care stage of 5 CKD patients receiving maintenance haemodialysis renal replacement therapy

2.1.3 Primary Endpoint

The primary endpoint for this study will be the documented change in Kidney Disease QOL questionnaire Physical Composite Score (KDQOL-PCS) between baseline and 6 months. The KDQOL is a disease-specific quality of life measure.

2.1.4 Secondary Endpoint

Assessed at 6, 9 and 15 months. Change between baseline and follow-up for:

- KDQOL-PCS
- KDQOL-MCS
- KDQOL-Vitality subscale
- KDQOL- symptom burden subscale
- IPAQ
- Height (at screening visit only), Weight and anthropometric (BMI, waist to hip ratio)
- Peak aerobic capacity
- Duke Activity Status Index (self-report 12-item activity of daily living questionnaire)
- 10m Timed-up-and-go (composite test of leg strength, balance, coordination and gait speed)
- Sit-to-stand 60 (proxy measure of lower extremity muscular endurance)
- Tinetti Falls Efficacy Scale
- Habitual physical activity (a self-report assessment via International Physical Activity Questionnaire)
- Habitual physical activity (GT3X tri-axial accelerometer)
- Arterial stiffness (via pulse wave velocity and augmentation index)
- Blood pressure
- Hb
- ESAs
- Phosphate
- Parathyroid hormone (PTH)
- EQ-5D, a generic multi-attribute health related QOL questionnaire for use in cost utility analysis.
- Health Economic questionnaire regarding resource use
- All hospitalisations
- All-cause mortality
- Cardiovascular mortality
- Safety / Harms (SAE)

Qualitative Study and analysis

A constructivist phenomenological approach will be used to learn about views and perceptions of participants and build greater understanding of varied perspectives of both service users and providers (Crotty 1998; Grbich 1999). Focus groups and individual interviews will be used as most appropriate to the stage of the study and location of data collection. All participants in the pilot study and RCT will be eligible for inclusion in the qualitative sub-study. Purposive sampling will be used to ensure varied experiences and viewpoints are represented, for example, including service users and providers from different study regions, including people in both study arms, and aiming to include people with different participation rates and response to the intervention. Appropriate topic guides will be developed for pilot study and RCT, and for service users and providers; questions will be discussed within the project team and steering group.

Health Economic analysis

To maximise relevance to policy, the health economic evaluation will follow the guidelines recommended by NICE, including the use of cost-utility analysis and adopting an NHS costing perspective. Quality adjusted life years (QALYs) will be derived from utility scores generated using a standard UK algorithm from the EQ-5D. Resource use associated with physiotherapy assistant time and [training in use of equipment and delivery of personal exercise programmes per patient] time will be recorded prospectively using timesheets for the intervention group. Equipment costs will be calculated using the annuity method with discounting rates set as per NICE base case]. Other health care resource use will be captured through patient questionnaires administered monthly during dialysis sessions. Factors to be measured have been extracted from the literature and consultation with experts and include (but are not limited to): primary care consultations, nephrologists consultations, calls to NHS Direct/NHS24, accident and emergency visits, NHS provided devices and aids and Physiotherapy sessions. During the internal pilot phase a free format "other" category will be included to check for omitted items. Additionally, hospital admissions and medication use will be recorded (with consent) from nephrologists' records. Resource use estimates will then be combined with standard UK sources to estimate total NHS costs.

2.2 Study Design

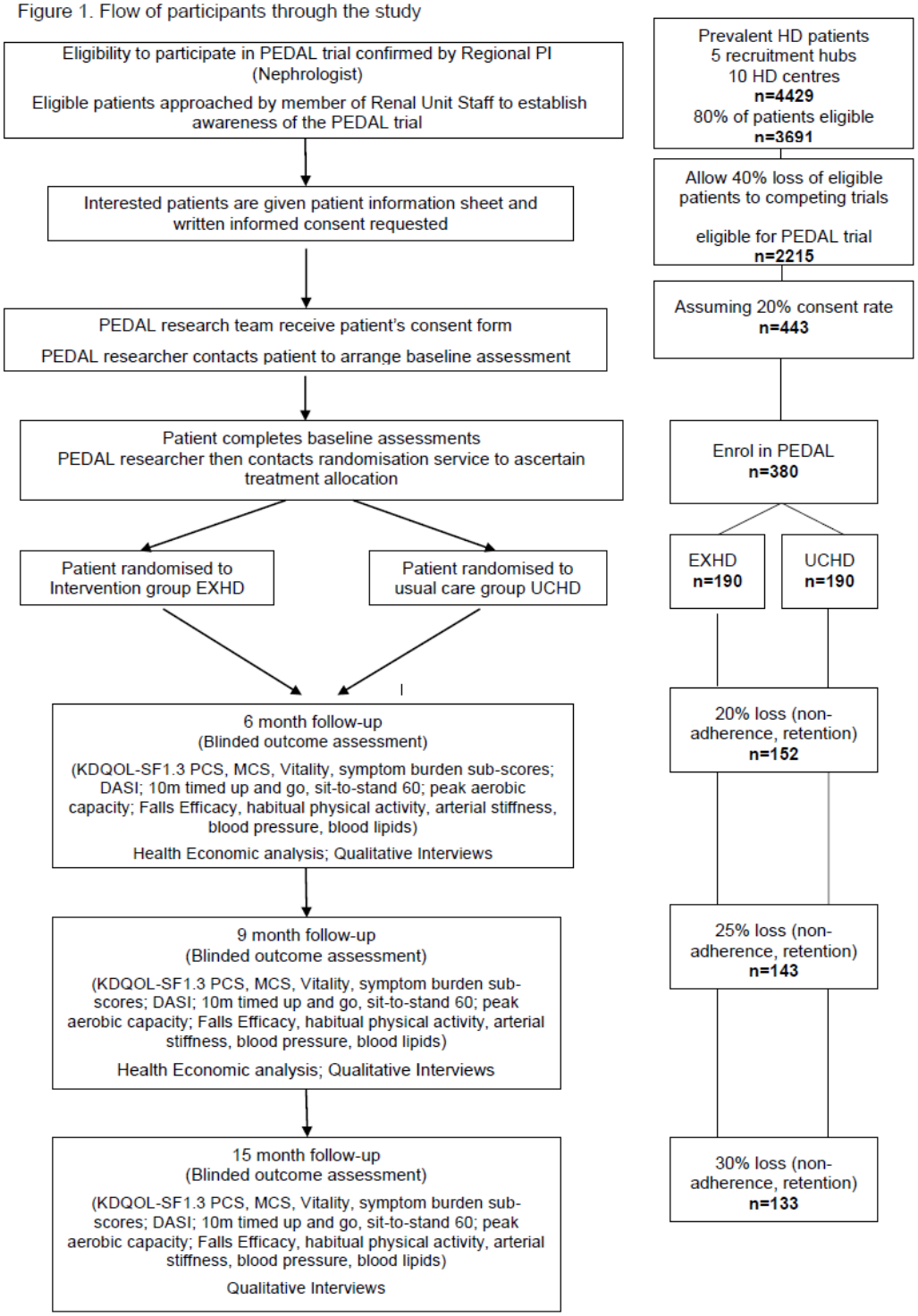
The PEDAL study is designed as a pragmatic, multicentre RCT (with an internal pilot study) with two treatment arms: intra-dialytic exercise training plus usual care maintenance haemodialysis (EXHD) versus usual care maintenance haemodialysis (UCHD). Participants' QOL and functional limitations will be assessed prior to treatment randomisation and after 6, 9 and 15 months. The primary endpoint will be after 6 months with additional follow-up at the end of the intervention (9 months) and again 6 months after the end of the intervention period. It will be impossible to blind the "treating" physiotherapy assistants or the participants and thus the study will undertake blinded outcome assessment and analysis. We propose to recruit participants to the PEDAL study from all eligible adult prevalent HD patients who have been receiving maintenance HD for more than 3 months. These will be recruited from UK (outpatient in-centre) HD units. Recruitment for the trial will take place over a 21-month period between November 2014 and July 2016 in HD units

based in 10 sites across 5 regions of the United Kingdom (London, Birmingham/West Midlands, East Midlands, North Wales & North West England, and Central Scotland)

2.3 Study Scheme Diagram

Flow diagram

Figure 1. Flow of participants through the study



3. Subject Selection

3.1 Number of Participants

The total study duration will be 48 months and will involve 380 participants; 190 of whom will be randomly allocated to receive usual care maintenance haemodialysis renal replacement therapy (as described in section 4.5.1) and 190 randomly allocated to receive usual care augmented by intra-dialytic exercise training (as described in section 4.5.2). Further details of sample characteristics and desired statistical power are described respectively in sections 4.1 and 6.6. Figure 1, above, summarises the estimated percentage proportions, and absolute recruitment numbers, for participant availability, eligibility and participant flow through the PEDAL study. The key milestones for this proposed study are outlined in Table 1.

Table 1. PEDAL Trial milestones

Month 0 -6	Recruitment of Staff
	Staff training (SOP for outcome assessments and exercise training, eCRF)
	Outstanding Ethics amendments/approvals and R & D approval
	Finalising the set-up of research sites
Month 7	Recruitment of first participants
Month 13	Follow-up assessments begin
Month 13	Submission of protocol paper for publication
Month 18	Internal pilot data evaluation
Month 19	Report to Steering Committee and DMC for interim review
Month 28	Recruitment ends
Month 42	End of follow-up
Month 42	Production of Qualitative study Report
Month 42	Closure of all databases
Month 48	Draft report and Draft papers submitted

3.2 Inclusion Criteria

- Prevalent Stage 5 CKD patients (GFR <15 mL/min) receiving maintenance haemodialysis therapy for more than 3 months
- Male or female
- Aged >18 years
- Able to provide written informed consent

3.3 Exclusion Criteria

- Patients unlikely to be on HD for > 6 months (this includes cachectic patients, those with severe heart failure, patients in whom dialysis withdrawal is being considered, and patients likely to receive a live-donor transplant or transfer to PD in that period of time)
- Less than 3 months after the initiation of haemodialysis (patients in this time-frame are generally less clinically stable, many having vascular access procedures performed, and rates of inter-current events, including death and hospitalisation, are very much higher in the first 3 months after commencement of chronic haemodialysis)
- Deemed to be clinically unstable by treating physician
- Bilateral lower limb amputees
- Dementia or severe cognitive impairment (as will be unable to give consent and/or complete questionnaire assessments)
- Severe psychiatric disorders – except treated stable
- Pregnancy

4. Study Procedures

4.1 Identifying Participants

Prevalent adult patients (aged 18+), treated as outpatients, undergoing in-centre (hospital unit, satellite unit) renal replacement therapy via maintenance haemodialysis. Patients who are naive to intra-dialytic exercise will be recruited from HD units across the five participating "regions". A number of exclusion criteria apply, and these are listed in section 3.3 above. The majority of potential participants for the PEDAL study will be identified during routine haemodialysis management consultations and concurrent evaluation of patient (clinical) notes to confirm eligibility for participation. Patients already established on haemodialysis for more than 3 months will be eligible and are easily identified from hospital databases and dialysis logs. If considered potentially eligible for the study, they will be approached by a member of the renal care team who will discuss the study with them and leave them a Patient Information Sheet (PIS) to read with further details.

The sample will be obtained from ~10 recruitment sites organized into five "regions" spread across the UK. The research sites selected are considered broadly representative of contemporary UK haemodialysis units and geographically cover a wide range of the UK (Glasgow/Lanarkshire, Salford/North Wales, Derby/Nottingham, Birmingham/Heart of England Trust, London). These centres have been selected as they also provide access to large numbers of prevalent HD patients. Figure 1 summarises participant flow through the study. Using UK Renal Registry data from

2010 (1) we estimate there to be approximately 3800 eligible prevalent patients for this study. We are allowing for the potential loss of approximately 40% of these eligible patients due to their enrolment in other clinical trials with potentially confounding effects upon study outcomes in the PEDAL trial. In addition, we have conservatively employed a 20% consent/participation rate in all of our sample estimates leaving a potentially recruitable sample pool of around 440 prevalent patients. We intend to recruit 380 patients to meet the study objectives with a target rate of 18 participants per month entering the trial across the 21 month recruitment period.

4.2 Informed Consent Procedures

After allowing the patient a minimum of 24 hours to read and digest the information in the PIS, and to consult with family members, the research team will approach the patient (usually during the next dialysis session) and be available to answer any questions. If the patient is happy to proceed, an appointment will be made for familiarisation and baseline outcome assessment sessions. Informed consent may be obtained by any member of the research team, including the Principal Investigator, sub-investigator, research nurse, research assistant, research coordinator, or physiotherapy assistant.

4.3 Screening for Eligibility

After informed consent is obtained and eligibility by all the criteria (protocol sections 3.2 & 3.3) confirmed, study assessments as outlined in section 4.6 will be performed.

4.4 Randomisation and Treatment Allocation

Randomisation will be via a centrally controlled web-based GCP compliant randomisation system, run by Glasgow Clinical Trials Unit (GCTU). To ensure balanced assignment across critical variables, a minimisation algorithm will be employed, using baseline age, sex and diabetic status.

Participants will be allowed to continue all their usual medication throughout.

4.5 Reference Therapy (Usual Care) and Intervention Treatment

4.5.1 Usual Care: Haemodialysis Renal Replacement Therapy

Haemodialysis is the most common dialysis (renal replacement) treatment for kidney failure, usually involving three dialysis sessions a week, and each lasting around 4 hours. In addition to the dialysis procedure itself, patients receive a number of management interventions, including blood pressure control, treatment of anaemia, phosphate control, and cardiovascular risk mitigation strategies. They may also receive dietary advice, counselling, input from social workers, and other forms of educational support. Many of the patients take renin-angiotensin blockers which are believed to afford cardiovascular protection. Aspirin and/or cholesterol-lowering therapies may be prescribed in an attempt to further reduce cardiovascular risk. Anaemia is treated by the use of erythropoietin replacement therapy and intravenous iron supplementation. Phosphate control is achieved by both dietary advice and the use of phosphate binders. For the purposes of this trial, we suggest that usual care, in both arms of the trial, should allow all of these other treatments so that we are

investigating any additional benefit of the intra-dialytic exercise training intervention to usual care.

4.5.2 Planned Intervention: Intra-dialytic Exercise Training

The intra-dialytic exercise prescription will be based on current Physical Activity (PA) guidelines for the elderly (28) and for people with diabetes (29) and cardiovascular disease (30). These recommend a minimum target amount of 1000 kcal per week be expended in PA for health benefits with optimal benefits associated with weekly target PA accumulation of 1500 to 2000 kcal. As opportunity for structured prescribed exercise is largely restricted to patients' three haemodialysis days the eventual aim is for the patients to accumulate as great a proportion of this minimum threshold level of 1000 kcal per week via intra-dialytic exercise. Peak aerobic capacity assessment will be conducted to derive and individualise the exercise prescription. Using a modified cycle ergometer, aerobic exercise will be performed in a semi-recumbent position, 3 times per week during the first two hours of haemodialysis. The initial prescription will be set in the moderate intensity range of 40-60% of peak aerobic capacity, progressing to 75% level by the end of the intervention. This exercise adoption phase aims to support patients in achieving the "average" target daily PA level within each intra-dialytic exercise session (21 minutes, continuous cycling, moderate intensity range or ~140 kcal/cycling session) and approximating 42% of the minimum weekly PA target. The exercise prescription will be individually increased through three additional phases of progression (months 2-4), behaviour development (months 5-6); and maintenance (months 7-9). The aim is for patients to increase exercise duration and intensity to expend around 185, 230, and 250 kcal per intra-dialytic exercise session respectively in each phase. Exercise duration and intensity will be regularly adjusted via ratings of perceived exertion, to ensure that the planned initial target volume of exercise (kcal per week) is "achieved" by all patients. These energy expenditure goals are deliverable via an increase in intra-dialytic cycling from 21 to 40 minutes, at moderate/vigorous exercise intensity, and will result in 55%, 69% and 75% respectively, of target weekly minimum PA volume being achieved. Twice per week, patients will also complete lower extremity muscular conditioning exercise, using ankle weights, after the aerobic cycling exercise. Drop-out rates for similar exercise training studies ranges from 17% to 25% (23) however all patients enrolled in the trial will be followed up to allow an intention to treat analysis.

We propose to employ physiotherapy assistants (PA, band 4 technical Instructors) in each region to deliver the intra-dialytic intervention. All PAs will be trained by the joint PI and regional coordinators, on how to standardise the delivery of the exercise prescription as well as how to record exercise prescription milestones, compliance behaviours, and any adverse outcomes. The proposed exercise intervention delivered this way would ensure appropriate and consistently applied progression of both the duration and intensity of the exercise training. Recent evidence from the British Renal Society Symposium revealed that successful patient compliance with and the effectiveness of intra-dialytic exercise training was enhanced by the involvement of a physiotherapy assistant in programme delivery (34). This role, supervised and quality assured by the regional coordinator, involves the technical implementation of the exercise prescription and associated protocols produced by the regional Research Assistant who will be blinded to treatment allocation.

4.6 Schedule of Assessment for each visit

Table 2. The range and phasing of PEDAL study assessment procedures

ASSESSMENT PROCEDURES	Timeline ± 1 week				
	Screening	Baseline	6 months	9 months	15 months
Informed Consent	X				
Inclusion/Exclusion Criteria	X				
Medical History/Demographics	X				
Adverse Events Recorded		X	X	X	X
Review/Record Medication		X			
Anthropometric Measurements					
Height		X	X	X	X
Weight		X	X	X	X
Body Mass Index		X	X	X	X
Waist-to-Hip ratio		X	X	X	X
Quality of Life (and symptom burden) Assessments)					
* KDQOL		X	X	X	X
* EQ5D		X	X	X	X
Cardiovascular Assessments					
Resting Heart Rate		X	X	X	X
Resting Blood Pressure		X	X	X	X
Pulse Wave Velocity		X	X	X	X
Augmentation Index		X	X	X	X
Functional Capacity Measurements					
Peak Aerobic Capacity (VO_2 peak and/or Peak power output)		X	X	X	X
Sit-to-Stand 60		X	X	X	X
Functional Mobility (10mTUG)		X	X	X	X
* DASI questionnaire		X	X	X	X
* Tenetti Falls Efficacy Scale		X	X	X	X
Habitual Physical Activity					
GT3X Accelerometer		X	X	X	X
International Physical Activity Questionnaire		X	X	X	X
Routine Clinical Chemistry					
URR(5)		X			
Blood lipid levels (LDL, HDL, triglyceride levels)		X			
Hb (and ESAs)		X	X	X	X
HBA1c		X			
CRP		X			
Bicarbonate		X			
Phosphate		X	X	X	X
Parathyroid hormone		X	X	X	X
Note: * denotes patient-reported outcome.					

4.7 End of Study Definition

The end of study is defined as the last participant's last visit (LPLV). The Sponsor, CI and/or the trial steering committee have the right at any time to terminate the study for clinical or administrative reasons. The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved. A summary report of the study will be provided to the Sponsor and the REC within 1 year of the end of the study.

4.7.1 Continuation of Intervention following the end of study

The study intervention will not be provided to participants routinely at the end of the study. Physicians caring for the study participant will make the decision whether or not to prescribe intra-dialytic exercise therapy to participants after their trial participation ends.

4.8 Subject Withdrawal

Any physician involved in the usual care of patients may withdraw patients from randomised treatment using their clinical judgment. This might occur due to the occurrence of an AE and the onset of symptoms that limit exercise tolerance. Patients withdrawn from randomised treatment will remain in the study for safety follow-up and subsequent events will be included in the ITT analysis but will be censored in the per-protocol analyses. If withdrawal is due to an AE it will be logged as such on the eCRF. All reasons for withdrawal will be noted in the participant's CRF and medical case notes.

4.8.1 Withdrawal of Consent to Follow-up

If at any time the patient formally withdraws his/her consent for future participation and disclosure of future information, no further evaluations will be performed and no additional data should be collected. Data collected before such withdrawal will be retained and used in the study analysis (with consent.)

4.8.2 Patient Retention

We will attempt to minimise the loss to follow-up in this study by (i) emphasising to participants the importance of their attendance at follow-up assessments even if they are no longer compliant with the intervention, (ii) reducing outcome assessment appointments to a maximum of four non-dialysis day visits, (iii) using a reminder protocol for non-dialysis day assessment appointments that utilises prompts via the dialysis unit staff, letters and telephone contact, (iii) providing travel remuneration (including, where necessary, taxi costs); (v) provision of training in issues related to compliance for all study staff who come in contact with the participants.

5.0 Safety

5.1 Definitions

Unexpected events that have not been defined as endpoints should be classified as either an SAE or AE depending on their severity. There is no requirement to report AE's. All SAEs must be recorded from the time at which the randomisation of the participant has occurred until the last study visit. The member of the research team should ask about the occurrence of SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant should be used to enquire about AE/SAE occurrence. Participants should also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an SAE, the event should be recorded. However, common symptoms in dialysis patients such as headache, nausea, itching etc., as well as infections not requiring hospitalisation, will not be recorded. Each initial SAE will be considered for severity, causality or expectedness and may be reclassified as a serious event or reaction based on prevailing circumstances.

A serious adverse event (SAE) is any AE that:

- results in death;
- is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect.

5.2 Unexpected Serious Adverse Events

SAEs should be reported to the Clinical Trials Unit within 7 days. The report should include an assessment of causality by the Principal Investigator at each site (see section 5.4). The Chief Investigator will be responsible for the prompt notification of findings that could adversely affect the health of subjects or impact on the conduct of the trial. Notification of confirmed unexpected SAEs will be to the Sponsor, the Research Ethics Committee and the Data and Safety Monitoring Committee (DSMC).

5.3 Reporting Unexpected Serious Adverse Events

Investigators will make their reports of all unexpected adverse events, whether serious or not, to the Glasgow Clinical Trials Unit.

5.3.1 Assessment of intensity

Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning; the subject is unable to carry out usual activities and/or the subject's life is at risk from the event

5.3.2 Assessment of causality

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the adverse event and the exercise intervention.

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the adverse event and the exercise intervention.

Unlikely: A causal relationship is improbable and another documented cause of the adverse event is most plausible.

Unrelated: A causal relationship can definitely be excluded and another documented cause of the adverse event is most plausible.

6. Statistical Considerations

Analysis and reporting of this trial will be based on Consolidated Standards of Reporting Trials (CONSORT) guidelines with the analyses conducted on an intention-to-treat basis. Descriptive statistics of clinical and socio-demographic variables at baseline will be presented. All treatment comparisons will be adjusted for the minimisation variables (diabetic status, age and gender).

6.1 Primary Outcome

KDQOL PCS: The control (UCHD) and intervention (EXHD) groups will be compared on the primary outcome measure (change from baseline to 6 months in KDQOL-SF 1.3 PCS) using a normal linear model adjusting for baseline KDQOL-SF 1.3 PCS. The findings will be presented as the (adjusted) mean difference (95% confidence interval) between the treatment groups

6.1 Secondary Outcomes

Other continuous outcomes will be analysed as for the primary outcome. Binary secondary outcomes will be compared between treatment arms using multiple logistic regression. The results will be presented as the adjusted odds-ratio for intervention versus control and its 95% confidence interval. Time to event secondary outcomes will be analysed using the Cox proportional hazards model to determine the adjusted hazard-ratio (95% confidence interval) for intervention versus control.

6.3 Exploratory Analysis

Each continuous outcome measured at multiple time points during the course of the trial (e.g. KDQOL PCS) will be analysed using a normal linear mixed model to evaluate how it evolves in the two arms over the course of the trial.

6.4 Safety Analyses

Discontinuations from the intervention and permanent study withdrawals and their reasons will be tabulated as will adherence to the intervention. Serious adverse events will be tabulated by system organ class and body system.

6.5 Interim Analysis

No formal interim analyses will be conducted. Unblinded safety data will be reviewed by an independent data monitoring committee to ensure the ongoing safety of participants.

6.6 Sample Size Calculation

A total of 380 patients will be randomised equally in the 5 centres to either UCHD or EXHD, giving 190 per treatment arm. Based on evidence from phase II trials (23) we expect 17-25% of patients to discontinue the exercise programme due to transplant, death or personal choice over the 9 month intervention period. A similar discontinuation rate will occur in the UCHD group, leading to 133 patients per group completing the study. Based on the PCS variability seen in Painter et al (31) and comparing 6-month KDQOL PCS between groups by two sample t-test (two-sided 5% significance level), this sample size would give 83% power to detect a mean difference of 4 points in KDQOL PCS. Greater power would be achieved in the final trial analysis through adjustment for baseline KDQOLPCS using analysis of covariance (ANCOVA). The 4 point effect size is of clinical relevance: as there is an established relationship between each 1 point increase in PCS and reduced mortality and hospitalisation (8,9). Such effect sizes have been reported for HD patients with a 7-point increase in the mean PCS of low functioning patients observed after an exercise training intervention (33).

7. Data Handling & Record Keeping

It is the responsibility of the PI (in conjunction with the Research Coordinator and RA) to ensure the accuracy of all data entered and recorded in the electronic CRFs and the database. The Delegation of Responsibilities Log will identify all trial personnel responsible for data collection, entry, handling and managing the database. The data will be collected by the RA (who will be blinded to the treatment allocation) and/or the RC, either directly onto a paper CRF with subsequent transcription to the eCRF, or direct data entry onto the web based eCRF. Where there is electronic storage of non-identifiable data it will be on a password protected device and/or database.

The study questionnaires (e.g KDQOL and EQ-5D) will be completed at each assessment visit by the patient with the assistance of the research assistant, directly onto a paper format with subsequent transcription to the eCRF.If the participant does not attend the assessment, the questionnaires will be given to the participant during dialysis, and collected back by the physiotherapy assistant.

NHS laboratory derived blood tests will be held on local NHS clinical systems databases in an identifiable format and for an indefinite time frame which can be assessed by primary and secondary care practitioners for future health care of patients. All research data and data established from the NHS tests will be stored in an unidentifiable format on password protected disaster recovery formatted database on the Glasgow Clinical Trial Unit server. Quality control of data will be maintained by

the Data Monitoring Committee. Patients will be informed of data storage and consent will be sought.

All research blood samples (link-anonymised) will be processed at each site and transported to the relevant laboratory for analysis. Depending upon volume and composition of each blood sample, additional blood serum/plasma samples will be stored (with consent.) and transported at the end of the study to the clinical laboratory at King's College Hospital under the custodianship of the CI for future research which will be scientifically and ethically reviewed. The medical notes will act as source data for past medical history, subsequent medical conditions, hospital admissions, diagnostic reports, and blood and urine results.

7.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, or the REC. The CI and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

7.2 Data Management System

A data management system will be provided by GCTU. The study system will be based on the protocol and electronic CRF for the study and individual requirements of the investigators. Development and validation of the study database; and QC and extraction of data will be done according to GCTU procedures. Extracts for analysis will be based on the dummy data tables provided by the study team.

7.3 Record Retention and Archiving

To enable monitoring and/or audits from the Sponsor REC, the investigators agree to keep records, including the identity of all participating patients (sufficient information to link records, all original signed informed consent forms, serious adverse event forms, source documents, and detailed records of treatment disposition.) The records should be retained by the study site coordinators and investigator for a period of 15 years and archived in accordance with KCH SOP.

7.4 Inspection of Records

Principal Investigators and institutions involved in the study will permit trial related monitoring, audits, REC review, and regulatory inspection(s). In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor or regulatory authorities direct access to all study records and source documentation.

7.5 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians, investigators and research nurses treating the participants.
Computers used to collate the data will have limited access measures via user names and passwords. The data will be transferred to a study specific secure server. The data with have no personal identifiers beyond the Patient Identification Number. Published results will not contain any personal data that could allow identification of individual participants.

8.0 Quality Control and Quality Assurance

8.1 Risk Assessment

A pre-Sponsorship study risk assessment will be carried out by the KCH Research Governance Manager prior to Sponsorship approval being granted.

8.1.1 Potential Risks

Potential adverse reactions to exercise tolerance and functional capacity assessments and exercise training will be described in patient information sheets and explained to all potential participants. The patients will be expected to attend on non-dialysis days for 4 assessments visits and will undergo functional capacity testing. The patient group have an underlying pathology and many will be elderly and may have many co-morbidities.

8.1.2 Minimising Risk

Careful monitoring of patients throughout the trial with dedicated care and adverse event monitoring will be undertaken as required. Patients will receive a card containing all study staff contact details to enable patients to contact staff with any concerns. All patients will have access to taxi transport for each assessment visit to aid accessibility and comfort. Risks of exercise tolerance assessments and venepuncture will be discussed with the patients with access to staff if required.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP.) A favourable ethical opinion will be obtained from the appropriate REC and local NHS R&D approval will be obtained prior to commencement of the study.

8.3 Protocol Amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by the CI.

Amendments to the protocol must be submitted in writing to the Sponsor and then to the appropriate REC as appropriate and local R&D Offices for approval prior to participants being enrolled into an amended protocol. A copy of all approved amendments will be sent to study's funder (the HTA).

8.4 Protocol Violations and Deviations

PIs should not implement any deviation from the protocol without agreement from the CI, Sponsor, REC as appropriate except where necessary to eliminate an immediate hazard to trial participants. In the event that an Investigator needs to deviate from the protocol, the nature of and reasons for the deviation should be recorded as per Sponsor KCH SOP on the Protocol Violation/Deviations and Serious Breaches (KCH) If this necessitates a subsequent protocol amendment, this should be submitted to the Sponsor/NHS R&D Office for approval, and then to the REC for review and approval if appropriate. Any Protocol Deviations, Violations, Potential Serious Breaches and Urgent Safety Measures must be recorded using the KCH Serious Breach Log available from the sponsor website. An up-to-date copy will be filed in the ISF.

8.5 Investigator Responsibilities

The CI is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of GCP, the following areas listed in this section are also the responsibility of the CI. Responsibilities may be delegated to an appropriate member of study site staff. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list.

8.5.1 Informed Consent

The PI is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved. Participants must receive adequate oral and written information – as appropriate. Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant should be performed by the Investigator or designated person, and must cover all the elements specified in the Participant Information Leaflet /Informed Consent form. The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled. The participant should be informed and agree to their medical records being inspected by regulatory authorities and appropriate TASC staff but understand that their name will not be disclosed outside the hospital.
The PI or delegated member of the trial team and the participant should sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant should receive a copy of this document and a copy should be filed in the TMF and ISFs and a copy in the patient's medical records. Informed consent may be obtained by any member of the research

team, including the Principal Investigator, sub-investigator, research nurse, research assistant, research coordinator, or physiotherapy assistant

8.5.2 Study Site Staff

The PI must be familiar with the protocol and the study requirements. It is the PI's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial-related duties.

8.5.3 Investigator Documentation

Prior to beginning the study, each PI will be asked to provide particular essential documents to the Sponsor, including but not limited to: Curriculum vitae (CV), signed and dated by the PI indicating that it is accurate and current. The CI, with the agreement of the Sponsor, will ensure all other documents required for compliance with the principles of GCP are retained in a TMF and that appropriate documentation is available in local ISFs.

8.6 Summary Monitoring Plan

Most of the monitoring will be conducted by the Remote Statistical Monitoring Plan instigated by the Glasgow Clinical Trial Unit. Where there are concerns regarding the conduct/integrity of the study, on-site monitoring visits will be conducted by representatives of the Sponsor.

9. Trial Management and Oversight Arrangements

9.1 Project Management Group

The trial will be coordinated by a Trial Management Group, consisting of the Chief Investigator, GCTU Assistant Director and Senior Clinical Trial Manager, Study Trial Manager and a statistician.

9.2 Trial Management

A Trial Manager will oversee and coordinate the study and will be accountable to the CI. The PI at each site will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team. A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

9.3 Central Trial Office

The Central Trial Office (KCH & Glasgow Clinical Trials Unit) will provide support to each site. The office will be responsible for randomisation, collection of data in collaboration with the RA/RN/RC, data processing and analysis. Publication and dissemination of the study results will be coordinated by the Trial Office in collaboration with the Chief Investigator and Investigators.

9.4 Trial Steering Committee

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The study's funder, HTA will formally appoint the chair and members after the nominations from the TMG. The charter will be drawn up to describe membership, roles and responsibilities of the Trial Steering Committee.

9.5 Data Monitoring Committee

An independent data monitoring committee (DMC) will be constituted and a charter will be drawn up to describe membership, roles and responsibilities. The study's funder, HTA will formally appoint the chair and members after the nominations from the TMG. This committee will receive unblinded data and will have the power to recommend to the steering committee modifications to study conduct including early discontinuation of the study based on a risk/benefit assessment of the study data. Formal stopping rules will be defined in the DMC charter. However, thresholds for early stopping will require a high level of evidence (overwhelming evidence of difference between the two treatment groups for the primary and/or secondary endpoints) and a small number of times at which early stopping can be recommended such that there will be no meaningful impact on the study power calculations.

10. Reporting, Publications and Notification of Results.

10.1 Progress Reports

Regular progress reports will be sought by the funder as outlined in its programme policy. Advice on the scheduled dates will be provided by HTA.

10.2 Authorship Policy

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared. Authorship eligibility for each manuscript arising from this study will be determined according to the criteria laid out in the Working Practice Document on Authorship filed in the Study Operations Manual.

10.3 Publication

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

10.4 Peer Review

This trial has undergone peer review by external peer reviewers, commissioned by the funder. In addition, the final publication of the study will be peer-reviewed by the referees of the journal to which the paper (and its protocol) will be submitted.

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12. Appendices

Appendix 1 - Estimated time required to conduct principal study outcome assessments

Appendix 2: PEDAL Sub-study - Examining the presence and patterns of Frailty and Falls risk before and after an intra-dialytic exercise programme

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Appendix 6: PEDAL Sub-study – A pilot study to determine the influence of exercise on cardiac electrical and structural function in dialysis patients

Appendix 7: PEDAL Sub-study – A pilot study to determine the impact of exercise on cognitive function in haemodialysis patients

Appendix 1 - Estimated time required to conduct principal study outcome assessments

Estimated time required to conduct principal study outcome assessments	Estimated time (mins)	When outcome is to be measured ± 1 week			
		Baseline	6 months	9 months	15 months
Anthropometric Measurements (height, weight, BMI, waist:hip)	5	X	X	X	X
BP and resting heart rate Arterial stiffness (PWV &AI)	30	X	X	X	X
Functional mobility (10mTUG)	5	X	X	X	X
DASI questionnaire	5	X	X	X	X
Sit-to-stand 60	5	X	X	X	X
Tinetti Falls Efficacy Scale	10	X	X	X	X
Quality of Life (KDQOL)	20	X	X	X	X
EQ5D	10	X	X	X	X
Peak Aerobic capacity (Vo2 peak and/or peak power output) from graded exercise test	30	X	X	X	X
Physical activity measured by GT3X accelerometry	7 days	X	X	X	X
Routine clinical; chemistry – Hb, phosphate, PTH	during study period				

Appendix 2: PEDAL Sub-study

Examining the presence and patterns of Frailty and Falls risk before and after an intra-dialytic exercise programme

1.0 Aim

To establish a frailty phenotype for this group of patients and examine whether an intra-dialytic exercise programme can positively impact on frailty and associated clinical outcomes such as falls risk. Frailty will be defined according to the Fried's frailty criteria (Fried et al. 2001) as the presence of 3 or more frailty risk factors (muscle weakness, exhaustion/fatigability, unintentional weight loss of more than 4.5 kg, low physical activity, and slow walking speed. This frailty phenotype has been associated to a three-fold higher risk of falling in patients on haemodialysis (McAdams-DeMarco et al., 2013). Three of these outcomes are already collected as part of the PEDAL study secondary outcomes (exhaustion, fatigability, monitoring of weight changes, physical activity levels).
The PEDAL study constitutes an ideal opportunity to pursue the above research question which is relatively unexplored in people on haemodialysis, despite the fact that falls and frailty are highly prevalent in this group of people. The frailty score is also an important predictor of future morbidity and mortality in many different people with chronic conditions and the elderly, including people with CKD. Therefore, it would be a meaningful additional outcome for the PEDAL study.

2.0 Sub-study assessment / monitoring outcomes

i. Prospective monitoring of falls incidence using a customised self-reported diary.

   Patients will be given a diary booklet where they will be asked to record any fall events they experience and the circumstances around the event (i.e. location, symptoms, trigger and consequences. Although hospitalisations is a stated PEDAL study outcome and a fall may be a cause for hospitalisation, not all falls result in serious injury that require hospitalisation. As part of this sub-study, all circumstances and causes of falls will be reported and will augment any information already recorded as part of the main study. Patients will be asked to maintain a falls-diary each month.

ii. STS-5 as an indicator of lower extremity muscle power/strength.

   STS60 is a secondary outcome of PEDAL. We are proposing to record the time it takes to complete the first 5 STS transfers during the STS-60 test execution. We will use this measurement as an index of lower limb strength. Established cut-off criteria that reflect severe muscle weakness which also relate to future clinical adverse events currently exist. No additional patient assessment procedure will be required and this information will be extracted from an assessment that patients perform as part of the main study.

iii. Gait speed over 4 m.

This outcome will be extracted from the TUG-10 test which is undertaken as part of the main PEDAL study. Two markers will be placed on the floor between 3 and 7 metres of the walking course and the time it takes to walk from 3-7 m will be used to reflect gait speed over 4 meters. Established cut-off criteria for gait speed over 4 m exist for inclusion in the Frailty phenotype.

3.0 Sub-study procedures

Sub-study data will be recorded by the Research Assistant during the patient assessment visits at baseline, 6 months, 9 months and 15 months.
Physiotherapy assistants or the Research Co-ordinator will collect the patient reported falls diary each month.

Appendix 3: PEDAL Sub-study

Establishing the validity of the IPAQ-LS in accurately describing physical activity levels in people receiving haemodialysis therapy.

1.0 Aim

To establish the accuracy of the self-reported long form International Physical Activity Questionnaire (IPAQ) in estimating the type and quantity of Physical activity (PA) levels as well as time spent in sedentary activities vs. objectively measured PA data and sedentary time using GT3X accelerometers.

The IPAQ is a validated questionnaire across a range of ages and populations with different demographical/clinical characteristics (Strath et al. 2013), but its validity against objectively recorded PA data has not been reported in patients with CKD. The IPAQ is concerned with type and amount of PA performed over a short recall-period of the previous 7 days. Although, a range of short recall PA questionnaires have been used in the CKD population to characterise PA behaviour, none have been validated against objectively measured data and thus no best recommendations exist on a PA assessment tool. This area of research is still very much under active development and therefore, this sub-study can significantly contribute to extremely limited literature about the clinical and research accuracy of this tool to characterise PA behaviour vs. uni-axial and tri-axial derived accelerometry and inclinometry as captured by the GT3X device.

2.0 Additional data to be recorded

Uni-axial and tri-axial based accelerations over 7 days will be recorded in order to establish the level of agreement between the IPAQ-LS derived data and GT3X recorded data.

Comparison outcomes will include the following, plus any other deemed necessary upon examination of data;

i) Total time (min) per week in walking
ii) Total time (min) per week in moderate intensity activities
iii) Total time (min) week in low intensity activities
iv) Total time (min) per week in vigorous activities
v) Total time (min) per week in all activities
vi) Classification of PA behaviour as meeting or not meeting existing PA guidelines (>150 min/week at moderate intensity)
vii) Total time (min) per week in sedentary activities

3.0 Sub-study procedures

The patient assessment procedure for the sub-study is as per main PEDAL study GTX3 Accelerometer assessment.
Patients will be required to complete the IPAQ questionnaire upon return of the GT3X device, and not on the day that the GT3X device will be given to the patient, so that data reported on IPAQ reflects PA data recorded by the GT3X device over the previous 7 days
Data will be reported and analysed using records which will be separate to the eCRF.

Appendix 4: PEDAL Sub-study

The effect of an intra-dialytic exercise programme on submaximal work and metabolic efficiency and on recovery from exercise

1.0 Aim

To determine the effect of an intradialytic exercise programme on indices reflecting work and metabolic efficiency at submaximal levels of exercise and cardiac parasympathetic system re-activation following recovery from maximal exercise.

Peak indices of exercise tolerance such as peak power output and peak VO2, are the most commonly reported outcomes in the renal exercise literature, and VO2 peak as measured during incremental exercise testing is a significant and independent predictor of future all-cause mortality and morbidity in CKD and in other chronic conditions. However, VO2 peak may be underestimated in patients with CKD and may not reflect the true level of impairment in work/metabolic efficiency and functional reserve, as incremental tests are often terminated by patients before they reach criteria indicative of maximal or near maximal levels of exercise. Thus, it has been proposed that submaximal indices of physiological function, such as VO2 at pre-selected absolute power outputs or at percentages of peak power outputs may be better indicators of underlying physiological metabolic and cardiovascular efficiency (Koufaki and Kouidi 2010). Furthermore, recovery indices from maximal exercise such as HR and BP, have been linked to morbidity and mortality outcomes in people with diabetes and cardiovascular disease (Cole et al. 1999, Lipinski 2004) but have never been examined in people with CKD. Therefore, this sub-study would help fully evaluate the effectiveness of the proposed PEDAL intervention on a range of outcomes reflecting physical function efficiency at intensities that better correspond to daily living activities and are not influenced partly by tolerance of local fatigue symptoms, personal motivation and familiarity with exercise testing procedures and confidence.

2.0 Sub-study assessment / monitoring outcomes

i. VO2, power output, HR, BP, VO2/HR, pulse pressure, ventilation and any other derived indices from gas exchange analysis at ventilatory threshold and at 70% of peak values.
ii. HR/BP recovery at 1, 2, 3, 4 minutes during active recovery from peak exercise.

3.0 Sub-study procedures

No additional patient assessments are required for the sub-study.
The data that will be used for the sub-study is routinely recorded as part of the set-up and safe monitoring of patients who undertake incremental exercise testing.
Data will be reported and analysed using records which will be separate to the eCRF.

Appendix 5: PEDAL Sub-study

Does intra-dialytic exercise improve lean tissue mass in stage 5 CKD patients receiving maintenance haemodialysis?

1.0 Background

Unlike in the general population, body mass index (BMI) is inversely associated with survival in haemodialysis (HD) patients[1]. However, the relative contribution of lean tissue mass (LTM) and fat tissue mass (FTM) in affording this protection is not clearly defined. A recent study by the Monitoring Dialysis Outcomes (MONDO) initiative using bio-impedance spectroscopy (BIS) measured lean tissue index (LTI) and fat tissue index (FTI) in 37,345 prevalent HD patients suggests that both LTI and FTI within the normal range (10th to 90th percentile) are associated with best survival[2]. Using a large international HD database, we recently examined the impact of LTI and FTI on survival in incident HD patients (n=31,955). Survival progressively reduced from the highest to the lowest quartile of LTI[3]. Separation of the survival curves was much narrower for FTI. Studies with surrogate markers of LTM and FTM also suggest that LTM is more protective than FTM[4,5]. However, patients with end stage renal disease who are on HD progressively lose lean tissue mass due to several catabolic factors and impairment of anabolic factors that operate in this group of patients[6-10]. Therefore, there is need for effective nutrition and exercise strategies to protect LTM.

2.0 Aim

To assess whether intra-dialytic exercise is able to improve LTM.

3.0 Primary objective

To determine, in comparison to usual care, whether usual care augmented by intra-dialytic exercise training improves BIS measured LTI in stage 5 CKD patients receiving maintenance haemodialysis renal replacement therapy.

4.0 Inclusion and Exclusion Criteria for Sub-study

As per main study.

5.0 Sub-study procedure

The sub-study will be carried out at participating PEDAL sites which have available the Body Composition Monitor (BCM, Fresenius Medical Care).

Patient assessment visits are as per main PEDAL study (baseline, 6 months, 9 months and 15months. BCM measurements will be done during the patient assessment visits.

The following will be measured and recorded;
LTM, FTM and over hydration index (OH).
LTI and FTI will be derived by dividing fat and lean tissue mass by height squared.
LTI, FTI and OH will be compared between the groups.

6.0 Primary endpoint

Change in BIS measured LTI at 6 months.

7.0 Secondary endpoint

Change in BIS measured LTI at 9 and 15 months.
Change in BIS measured FTI at 6, 9 and 15 months
Change in fluid overload (OH) at 6, 9 and 15 months.
Association between LTI and QOL.
Association between FTI and QOL.

LTI, FTI and OH will be compared between the groups.

8.0 Participants

Eligible patients will be invited to join the sub-study in addition to their participation in the main trial. Participation in this sub-study is entirely optional. An additional Patient Information Sheet and Consent Form will be provided to and completed by all interested patients prior to participation in the sub-study.

9.0 Statistical analysis

Primary analysis will be ANCOVA comparison of 6 month outcomes, adjusted for baseline differences. Secondary analyses will be multivariate repeated measures analysis, adjusted for baseline differences.

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Appendix 6: PEDAL Sub-study

A pilot study to determine the influence of exercise on cardiac electrical and structural function in dialysis patients

1.0 Background

Mortality in haemodialysis patients is extremely high and predominantly due to cardiac causes and in particular sudden cardiac death (1,2,3). It is postulated that uraemic cardiomyopathy and autonomic imbalance, commonly present in haemodialysis patients (2), contribute decisively to the heightened cardiovascular risk. Novel electrocardiographic and echocardiographic techniques have emerged that showing promising results in characterising high risk autonomic (4), repolarisation (5,6,7) and echocardiographic profiles (8). Physical exercise has been shown to be associated with decreased cardiac risk in patients with atherosclerotic cardiovascular disease (9) and is known to improve cardiac autonomic modulation (10,11) and promote physiological cardiac remodelling (12). The PEDAL study provides an investigation opportunity to test prospectively in a randomised fashion the impact of exercise on electrophysiologic and electrocardiographic risks profiles.

2.0 Aim

The aim of this sub-study is to test the impact of regular intradialytic exercise programme on:

I. Three-dimensional repolarisation descriptors calculated from 12 lead ECG monitoring (QRS-T angle cosine or TCRT, T Wave Morphology Dispersion, T wave Residua) and cardiac autonomic modulation indices assessed by Heart Rate Variability (HRV) parameters (spectral HRV parameters LF, HF, LF/HF) at rest, following postural provocations and intradialytic electrolyte challenge, and non-linear measures (Heart Rate Turbulence) measured over a 24 hour period by ECG Holter monitoring equipment.

II. Selected echocardiographic parameters from speckle tracking strain analysis (peak global longitudinal strain, peak systolic and late diastolic longitudinal strain rates, circumferential early diastolic strain rate), LV mass, LV dimensions, E/A ratio, Ejection fraction, left atrial dimensions (diameter and volume)

3.0 Sub-study procedures

The electrocardiographic assessment measurements will be performed at baseline, 6, 9, and 15 months post-randomisation and standardised echocardiograms will be performed at baseline and 9 months post randomisation. Subjects will be invited to attend in the morning before their scheduled haemodialysis session. Patients will be instructed to avoid heavy meal, abstain from smoking, caffeine containing beverages and alcohol, and avoid demanding physical activity for at least two hours before measurements. After 5 minutes resting in quite temperature controlled room the brachial BP and pulse rate will be measured with a BP device at sitting and standing position. After 10 minutes of rest in supine position the Holter 12 lead ECG recording will be initiated by a research nurse or physiotherapist using Mason-Likar electrode placement, using the CardioMem® CM 3000-12 Holter device. The skin over the

chest will be cleaned with special fine sandpaper before attaching the leads and the hair over the chest may need to be shaved before placing the leads.
Participants will be asked to perform the following standardized postural changes: Resting supine for 7 minutes followed by sitting for 7 minutes followed by unsupported standing for 7 minutes. The recorder will then remain attached to the patient for a total period of 24 hours and will be detached by the nurse/physiotherapists on the following non-dialysis day during the scheduled evaluation visit.
The attending nurse/physiotherapists will record the following time points: start of the recording, sitting, standing, end of standing, start of haemodialysis treatment and end of haemodialysis treatment (denoted as time points 0,1,2,3,4,5,6 respectively). Standard analysis of heart rate variability (HRV) will be performed using the commercial software of the analyser. Advanced analysis of ECG-based parameters of ventricular repolarization will be performed with custom written software.
Standardised echocardiograms will be performed by an experienced cardiologist during the scheduled baseline and 9 month evaluation visits, which occur on non-dialysis days. Speckle tracking software will be applied on the acquired images at baseline and at 9 months from randomisation.

4.0 Participants

Participants will be recruited from Salford Royal NHS Foundation Trust and King's College Hospital NHS Foundation Trust. The study population will consist of 80 haemodialysis patients participating in the PEDAL trial, 40 patients in the exercise programme and 40 controls. The inclusion and exclusion criteria are as per main study.

5.0 Statistical Analysis

After the calculation of the measurements of the repolarisation, HRV and echocardiographic strain patterns has been completed, the results will be linked to the database of clinical and outcome characteristics for statistical analyses. The population distribution of the measured indices is expected to be potentially non-normal. Therefore nonparametric statistics will be used to compare the values of the indices between patients treated subjects and controls. We are not aware of any studies examining the impact of intradialytic exercise on the selected parameters. Based on reported power calculations assessing HRV changes in dialysis patients following pharmacological intervention (16) a total of 60 subjects could power the study to detect 20% or larger reduction in LF:HF. The suggested number takes into consideration an expected drop-out rate of 17-25%.

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Appendix 7: PEDAL Sub-study

A pilot study to determine the impact of exercise on cognitive function in haemodialysis patients

Background:
End Stage Renal Disease (ESRD) affects 60,000 people in the UK and the median age of people receiving renal replacement therapy is increasing(1). Cognitive impairment (CI) affects two thirds of patients over 55 years old on dialysis(2) which is more than double the prevalence of CI in age matched cohorts(3). It is independently associated with mortality(2), frailty(4), depression(5) and poor quality of life(2). An ageing population and in particular an ageing dialysis population signifies that the burden of patients with renal disease and CI will increase. Furthermore CI is underdiagnosed in renal patients(6) and diagnostic apathy impacts on their treatment and management.

A recent systematic review has highlighted the beneficial effect of exercise in patients with CI in the general population(7) although no study has evaluated the effect of exercise in renal patients. The PEDAL study is a UK multicentre randomised control trial evaluating the clinical utility and cost effectiveness of a 9-month intradialytic exercise programme but no cognitive outcome measures are being analysed.

The neuropathology of CI is unknown but several studies suggest that vascular disease plays a prominent causative role(8,9). Novel MRI techniques have revealed subtle brain changes following exercise intervention, for example increased hippocampal volume using high resolution T1-weighted imaging(10) and increased blood flow using arterial spin labelling (ASL)(11). Diffusion-weighted MRI (DW-MRI) demonstrates subtle changes to both grey and white matter microstructure following a variety of interventions(12) and in particular following interventions to the dialysis prescription(13).

Aim:
This pilot study will inform the development of a definitive fully powered randomised trial to assess the impact of exercise on the cognitive function and MRI brain images of dialysis patients.

Primary Objective:
Determine the feasibility of obtaining sensitive measures of cognition and MRI image changes (including high resolution T1w images for volumetric analysis, ASL, DW-MRI and T2w FLAIR) in patients undergoing a 9-month exercise intervention.

Secondary Objectives
1. Determine the incidence and progression of cognitive impairment in a cohort of patients willing to undergo an exercise based intervention.
2. Determine the nature and extent of the cognitive impairment in this cohort e.g. language, memory, executive function etc.
3. Determine the nature of MRI changes and the sensitivity of each MRI metric to detect change.
4. Measure recruitment and attrition rates to inform the design of a future larger trial
5. To record reasons for non-recruitment and attrition to inform the future design of a larger study
6. To assess the acceptability, administration and suitability of the chosen neurocognitive battery

7. To qualitatively explore the impact of the diagnosis of cognitive impairment on the patient and their family

Design:
20 patients enrolled into the third wave of the PEDAL study at SRFT, irrespective of their enrolment into the control or treatment arm, will be approached for cognitive assessment. A nested cohort will also undergo MR brain imaging at baseline and at 9 months.

Procedures:
All patients will undergo a 2-hour battery of neurocognitive tests at baseline and at 9 months. In addition, a nested cohort of 10 of these patients will undergo an MRI scan at baseline and at 9 months. The Principal Investigator will conduct a qualitative analysis on the effect that a diagnosis of cognitive impairment has on those patients newly diagnosed. The exercise component will adhere to PEDAL's protocol.

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