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The GFR-Exercise feasibility study

Submission date	Recruitment status	[_] Prospectively registered
24/09/2018	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
01/10/2018	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
06/04/2021	Urological and Genital Diseases	[_] Record updated in last year

Plain English summary of protocol

Background and study aims
There are many causes of Chronic Kidney Disease (CKD) and it has been recognised for many years that kidney dysfunction often progresses to total kidney failure. People with CKD have about 50% of the exercise capacity of normal sedentary individuals and are unable to participate in the same activities as healthy people. Physical inactivity doubles the risk of developing heart disease but, unlike people with other long-term conditions, people with kidney disease are not generally offered exercise rehabilitation. Physiotherapists are best placed to initiate prescribed exercise for this patient population. The main aim of this study is to determine if it feasible to recruit, randomise and retain participants in a study that uses the gold standard measure of kidney function (mGFR), to explore whether a 12-month exercise training intervention can slow down the progression of kidney disease for patients who haven't yet reached the stage where they require regular haemodialysis – which is very restrictive, debilitating and costly. If this study shows exercise results in improved or preserved kidney function, delaying or preventing progression to kidney failure, haemodialysis and kidney transplantation, this would give an additional treatment option that would have a major impact on individual's health, quality of life and long-term prognosis. This study team hopes to use the results of this study to plan a larger study examining the effectiveness of exercise training to slow CKD progression.

Who can participate?
CKD patients aged over 18 years

What does the study involve?
Participants are randomly allocated into the intervention group or the control group. Participants in the intervention group receive a 12-month supervised exercise intervention, provided by a physiotherapy assistant, in addition to usual care. The control group receives usual care, which includes 3 yearly attendances at hospital general nephrology clinics. The progression of kidney disease is assessed with measured glomerular filtration rate clearance (kidney function measurement). The main objective of this study is to determine if it is feasible to recruit, randomise and retain participants in this type of study.

What are the possible benefits and risks of participating?
The main benefit is to help improve care for future patients. The risk of a serious illness from

participating in this study is very low. There have been no cases reported of chromium-51 labeled ethylenediamine tetraacetic acid (51Cr-EDTA) causing kidney damage at the low dose which will be used in the study (this is used to measure mGFR).

Where is the study run from?
1. King's College Hospital NHS Foundation Trust (UK)
2. Betsi Cadwaladr University Health Board (UK)

When is the study starting and how long is it expected to run for?
September 2018 to April 2021 (updated 18/10/2019, previously: September 2019)

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
38499

Study information

Scientific Title
Exercise training and progression of chronic kidney disease: a randomised controlled feasibility study. The GFR-Exercise feasibility study (GFR-Ex)

Acronym
GFR-Ex

Study objectives
This trial is a feasibility study for a planned multi-centre randomised controlled trial that will examine the efficacy of exercise training as a means to retard progression of CKD in pre-dialysis patients with declining kidney function.

The main aim of this study is to determine if it is feasible to recruit, randomise and retain participants in a study that utlises the gold standard measured glomerular filtration rate (mGFR), with chromium-51 labeled ethylenediamine tetraacetic acid (51Cr-EDTA) or Inulin, to explore whether an exercise training intervention has the potential to retard kidney function decline in patients with progressive stage 3 to 4 CKD.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London - Camden & Kings Cross Research Ethics Committee, 09/08/2018, ref: 18/LO/0852

Primary study design
Interventional

Study design
Randomised; Both; Design type: Treatment, Process of Care, Psychological & Behavioural, Complex Intervention, Physical, Rehabilitation, Qualitative

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Chronic kidney disease

Interventions
STUDY DESIGN: A feasibility randomised controlled trial with a nested qualitative study to explore participants experiences.

ESTIMATED TRIAL DURATION PER PARTICIPANT: 12 months

SAMPLE AND RECRUITMENT JUSTIFICATION:
The aim is to recruit 50 participants at Kings and 40 participants at Betsi Cadwaladr University Health Board (BCUHB) to this feasibility RCT study. It isn't necessary to calculate a sample size for a feasibility study, although a justification of the chosen sample size is helpful. In total 90 participants with progressive CKD will be recruited over 12 months. This will allow the rate of potential participant recruitment, actual rate of recruitment, retention, and ease of data collection to be assessed adequately and efficiently, yet in a large enough sample to inform the definitive study power calculation.

Potential trial participants will be approached during routine nephrology clinic at King’s College Hospital or Betsi Cadwaladr University Health Board (BCUHB). Members of the site staff will screen for potential eligible study participants using the inclusion/exclusion criteria. Patients who fulfil the inclusion criteria will have their eligibility confirmed by the research team. After confirming eligibility, eligible patients will be approached by an appropriately trained member of the clinic team to ascertain interest in entering the study. This individual (likely to be either the

PI or research nurse) will give a comprehensive verbal explanation of the trial (explaining both the investigational and standard treatment options and highlighting any possible benefits or risks relating to participation). Time for questions throughout the discussion will be given and questions adequately addressed. Potential participants will also be given a written information sheet about the trial and be given sufficient time (providing they have received the patient information sheet and had at least 24 hours to read and fully understand the implications of the trial) to consider the study information prior to deciding whether to take part. Participants that agree to enter the study will then be asked to consent to undergo study assessments. If the participant is willing to take part then they will be asked to sign the consent form with a member of the research team countersigning.

STUDY SCHEDULE:
Testing will occur at the same time of day (early morning) for each study visit at baseline, 6 and 12 months. Blinded randomisation will be done via direct web randomisation hosted at the King' s Clinical Trials Unit (KCTU). Participants will be allocated into intervention or control group using a 1:1 allocation ratio. The study nurse and the fellow collecting other outcome measures will be blinded to treatment allocation. Participants will be asked to not reveal their group allocation. For full details on outcome collection please refer to study protocol.

a) Baseline /randomisation visit
The baseline/randomisation visit must occur no more than 4 weeks after the patient has successfully passed a screening visit. These assessments may be split over 2 visits if the participant prefers.

Data to be collected: informed consent and registration, medical history, height, weight, blood pressure, pulse rate, medications, waist and hip circumference, blood test for kidney function using chromium-51 labeled ethylenediamine tetraacetic acid (51Cr-EDTA) or inulin, urine test (albumin to creatinine ratio and protein to creatinine ratio), pulse wave velocity, flow mediated dilatation, carotid intima-media thickness, bioelectrical impedance analysis, peak and submaximal cardiorespiratory fitness, International Physical Activity Questionnaire and GTX accelerometer, short-form 12 questionnaire, knee extension muscle strength assessment, contrast enhanced ultrasound of the kidneys.

b) 6-month visit
The 6-month visit must occur within the period of time 2 weeks either side of the scheduled 6-month assessment date. These assessments may be split over 2 visits if the participant prefers. The data must be collected for all required procedures performed during the baseline /randomisation visit, with the exception of the contrast enhanced ultrasound of the kidney which will be performed at 12 months only.

d) 12-month visit
The 12-month visit must occur within the period of time 2 weeks either side of the scheduled 12-month assessment date. These assessments may be split over 2 visits if the participant prefers. The data must be collected for all required procedures performed during the baseline /randomisation visit.

In addition to these outcomes, a selection of participants (up to 20) will be invited to individual semi-structured interviews to record qualitative data of their experiences during the study.

THE INTERVENTION GROUP:
Participants randomised to the active treatment arm of the study will receive a 12-month supervised exercise intervention, provided by a physiotherapy assistant, in addition to usual

care. The individualised exercise plan will be based on objective assessment of cardiorespiratory fitness during an incremental cycling exercise protocol. The exercise plan will consist of aerobic and strength training components as per established physical activity guidelines. Exercise intensity for the aerobic training will be set at moderate intensity 40-70% of VO2 reserve (VO2R) or heart rate reserve (HRR) and will be delivered in 10 minute bouts. The aim for patients will be to accumulate 40 minutes of moderate intensity exercise 4 x/week (3 supervised, 1 unsupervised) (160 min/week) after 6 months of training and to sustain this level for the final 6 months. Duration of aerobic training component will range from 20-40 minutes, depending on individual fitness and exercise plan. The strength training will consist of a range of 6-8 exercises targeting large multi-joint muscle groups in order to improve core strength and balance, as well as functional mobility and strength. Initial level of external load will be maximum weight that will still allow patients to perform 10 to 15 repetitions with correct technique. The strength training will last between 10-20 minutes and will be performed in between or at the end of the aerobic training bouts. The intervention will be delivered by physiotherapy assistants in a hospital-gym setting, in groups of up to 6 participants.

THE USUAL CARE GROUP:
Usual care for patients with stages 3-4 CKD includes 3 yearly attendances at hospital general nephrology clinics. They 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, aspirin and/or lipid lowering agents in an attempt to reduce cardiovascular risk. Patients do not receive formal physical activity or exercise recommendations as part of usual care. They will be assessed at 0, 6, and 12 months.

STATISTICAL ANALYSIS:
This will be conducted by the Principal Investigator and collaborators, supported by Fiona Reid, Senior Statistician, King's College London.
a) Number and percentages of potential participants identified for screening for recruitment, recruited and retained in the study for up to 12 months:
• Number screened per month
• Number recruited per month (aim > 15% of invitees)
• Number retained per month (aim > 80% at 6 and 12 months)
• Percentage of study visits / intervention sessions completed in full and mean duration of baseline and follow up visits
• Proportion of planned data collection visits that are completed in full
• Proportion of exercise sessions (supervised and unsupervised) completed in full
• Length of time for study visits
b) Calculate the dosage of exercise training delivered in the intervention (aerobic and resistance training) to assist with the production of a training manual (for intervention fidelity) for the future definitive study
c) Mean differences and standard deviations between rate of change in kidney function (measured GFR, serum creatinine, eGFR, PCR, and ACR) values for exercising and non-exercising participants will be explored for the definitive study. The effect sizes of the difference in rate of change in measured GFR between the groups will be calculated for each variable
d) The relationship between the rate of change in kidney function, exercise training, weight change and renal perfusion (measured with contrast enhanced ultrasound of the kidney) measures over time using simple linear regression (Pearson/Spearman correlation coefficient) and with exercise training as a categorical variable with ANOVA (note: not powered to detect statistical difference) will be described
e) Interviews will be transcribed and analysed using inductive thematic analysis (Braun & Clarke,

2006), informed by techniques from grounded theory, including line-by-line open coding grounded in data and constant comparison of all instances of codes

Intervention Type
Behavioural

Primary outcome(s)
Feasibility:
1. Number of participants screened per month, measured using a screening log monthly
2. Number recruited per month, measured using an enrolment log monthly
3. Proportions of eligible people unwilling to participate with reasons given (e.g. live too far away etc), measured using a screening log monthly
4. Number retained per month, measured using an enrolment log monthly
5. Proportion of planned data collection visits that are completed in full length of time for study visits
6. Adherence to planned supervised exercise training schedule (number of sessions attended) of >80%, measured using Trust Database (PiMS) Clinic Attendance Log
7. Completion of unsupervised exercise diaries of >80%

Key secondary outcome(s)
KIDNEY FUNCTION measured through blood tests and urine sample at baseline, 6-month and 12-month visits:
1. Measured glomerular filtration rate (mGFR) using chromium-51 labeled ethylenediamine tetraacetic acid (51Cr-EDTA) or Inulin
2. Estimated GFR (eGFR) by CKD-EPI equations; using lab determined serum creatinine and cystatin C
3. Urinary albuminuria (albumin to creatinine ratio) and proteinuria (protein to creatinine ratio)

KIDNEY VASCULAR HEALTH measured at baseline and 12-month visits:
1. Contrast enhanced kidney ultrasound at baseline and 12 months
2. Pulse Wave Velocity: arterial stiffness assessed at the systemic region (carotid-femoral PWV) using the Vicorder system (Skidmore Medical Ltd) - equipment already secured
3. Flow mediated dilatation
4. Carotid Intima-Media Thickness (CIMT)
5. Blood pressure
6. Heart rate

PHYSICAL FUNCTION OUTCOMES measured at baseline, 6-month and 12-month visits
1. Peak cardiorespiratory fitness: VO2peak determined during an incremental recumbent cycling exercise tolerance protocol using the MetaLyzer 3B cardiopulmonary exercise testing system (Cortex)
2. Habitual physical activity, measured using long form International Physical Activity Questionnaire (IPAQ) and GTX accelerometers
3. Knee muscle strength measured by a Biodex dynamometer (3 times to the left and right leg)

BODY COMPOSITION and anthropometric measures, measured at baseline, 6-month and 12-month visits:
1. Body composition by bioelectrical impedance (Fresenius BCM)
2. Waist: hip ratio

3. Body mass (kg)
4. Body height (cm)
5. Body mass index

SAFETY measured at baseline, 6-month and 12-month visits:
1. No. of hospital admissions
2. Expected and unexpected harms

Completion date
30/11/2022

Eligibility

Key inclusion criteria
1. Stages 3-4 CKD patients defined by the following criteria:
1.1. GFR 15-60mL/min from local lab CKD-EPI determined eGFR
1.2. Minimum decline= 5mL/min/year over previous 12-24 months, as meausured by linear regression analysis (minimum of 3 measurments of eGFR over 12 months)
2. Male or female
3. Age > 18 years
4. Declining CKD with no likelihood of reversibility

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Age < 18 years
2. Pregnancy
3. Have a history of untoward reactions to iodinated contrast media
4. Have a recent history (last six months) episode of acute kidney injury or have sickle cell disease
5. Requires support for ambulation less than 20 meters
6. Psychosis, bi-polar, eating disorders, any other cognitive/neurological related issues
7. Infection or course of antibiotics within the last month
8. Enrolled in supervised exercise training in previous 3 months

Date of first enrolment
14/09/2018

Date of final enrolment
30/11/2021

Locations

Countries of recruitment
United Kingdom

England

Wales

Study participating centre
King’s College Hospital NHS Foundation Trust (lead site)
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Betsi Cadwaladr University Health Board
Ysbyty Gwynedd
Penrhosgarnedd
Bangor
United Kingdom
LL57 2PW

Sponsor information

Organisation
King's College Hospital NHS Foundation Trust

ROR
https://ror.org/01n0k5m85

Funder(s)

Funder type
Government

Funder Name
NIHR Trainees Co-ordinating Centre (TCC); Grant Codes: ICA-CL-2017-03-020

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	version V1	08/01/2018	01/10/2018	No	Yes