ISRCTN49033491 https://doi.org/10.1186/ISRCTN49033491

Should we disconnect haemodialysis fistulas in kidney failure patients after they have received a successful kidney transplant?

Submission date 10/12/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 04/02/2022	**Overall study status** Completed	
Last Edited 14/11/2023	**Condition category** Circulatory System	

Plain English summary of protocol

Background and Study Aims
Kidney transplantation is the best form of treatment for most patients with kidney failure. Although outcomes from transplantation are very good, people with a working transplant do not live as long as the general population, with a fifth of transplant patients dying from heart disease.

Before they receive a transplant, patients often require a period of haemodialysis, whereby the blood is cleansed by regularly attaching the patient to an artificial kidney machine. For this, patients often have an operation to create an arteriovenous fistula, which involves joining a vein in the arm directly onto a nearby artery. Once created, the fistula vein expands and the blood flow through the vein increases markedly. While this is ideal for providing access for haemodialysis, the increased blood flow means that the heart must work harder, and studies have shown that the heart becomes bigger and its muscle thicker. Although not proven, it seems likely that these changes to the heart may contribute to the extra deaths from heart disease.

This study will examine whether an operation to disconnect the fistula vein from the artery improves heart function in kidney transplant patients. As preliminary work for a much larger study, we will recruit forty consenting patients with good, stable kidney transplant function, and who still have a working fistula.

Who can participate?
Adult kidney transplant recipients with stable transplant function a working arteriovenous fistula.

What does the study involve?
Participants will be asked to undergo a series of baseline tests and assessments:
1. An ultrasound scan of their arteriovenous fistula
2. A cardiopulmonary exercise test

3. A blood test to measure their levels of NT-proBNP
4. Two quality of life questionnaires
5. Wear a wrist-worn accelerometer for 7 days

Participants will be allocated to one of two groups, with an equal chance of being in either group (like tossing a coin), to receive either standard care or the intervention (surgical disconnection of their arteriovenous fistula). If they are randomised to the intervention group, they will undergo the surgery and then have a post-surgery check-up. If they are randomised to the standard care group, their arteriovenous fistula will be left in place unless their doctors decide it must be disconnected for clinical reasons.

All participants will be asked to repeat the tests and assessments (as listed above) 6 months later. All participants will be asked whether they would be happy to have an interview with a qualitative researcher to discuss their experience of being invited to join the study and their participation. Approximately 20 - 30 participants will be interviewed after they complete the COBALT study.

A small number of patients who decline to take part in the study will also be asked for consent to take part in an interview to discuss their experience of being invited to take part in COBALT and their reasons for declining.

Approximately 20 health care professionals will also be invited to an interview to explore their experience of the study.

What are the possible benefits and risks of participating?
There is not yet enough evidence to support disconnection of arteriovenous fistulae, in kidney transplant recipients, and so we cannot say whether any participants will benefit personally from taking part in the trial. The potential benefit will be for kidney transplant patients in the future, as COBALT and the proposed large trial, should improve the evidence base for clinical care.

For participants who receive the intervention and have their fistula disconnected, there is a possibility of kidney transplant failure in the future, which could require a return to haemodialysis. In this scenario, patients might need to have a new fistula created via a surgical procedure.

Those participants who undergo the disconnection surgery may experience surgical complications. These include discomfort and redness related to clotting occurring in the draining fistula vein (occurs in approximately 20% of patients); bleeding (occurs in 1% of patients); wound infection (occurs in 1% of patients); numbness at the surgical site due to cutaneous nerve damage (occurs in 2% of patients); development of poor blood flow in the fingers or limb from interruption of distal arterial flow. Infection, blood clotting, and bleeding may impact negatively on the cosmetic appearance of the arm.

Undergoing a Cardiopulmonary Exercise Test carries the same risk as moderate exercise, and the test is carried out in a hospital with appropriate medical supervision to deal with any adverse events that occur. The number of patients who develop problems during the test is low, but occasionally people do develop problems such as abnormal blood pressure, abnormal heart rhythm, fainting, or chest pain.

Where is the study run from?
Cambridge University Hospitals NHS Foundation Trust (UK) and the University of Cambridge (UK) are sponsoring the study. NHS Blood and Transplant Clinical Trials Unit (UK) is managing the study.

When is the study starting and how long is it expected to run for?
September 2021 to December 2023

Who is funding the study?
The National Institute for Health Research (NIHR) Research for Patient Benefit Programme (UK), Addenbrooke's Kidney Patient Association (UK), and Cambridge University Hospitals NHS Foundation Trust (UK)

Who is the main contact?
1. Gavin Pettigrew (Scientific)
2. Anna Sidders (Public), COBALT@nhsbt.nhs.uk

Contact information

Type(s)
Scientific

Contact name
Prof Gavin Pettigrew

ORCID ID
https://orcid.org/0000-0003-3724-9945

Contact details
Department of Surgery
University of Cambridge
Addenbrooke's Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ
+44 (0)1223 245151
gjp25@cam.ac.uk

Type(s)
Public

Contact name
Ms Anna Sidders

Contact details
NHS Blood and Transplant
Clinical Trials Unit
Cambridge Blood Centre
Long Road
Cambridge

United Kingdom
CB2 0PT
+44 (0)1223 588915
cobalt@nhsbt.nhs.uk

Additional identifiers

Integrated Research Application System (IRAS)
305610

Central Portfolio Management System (CPMS)
51565

Study information

Scientific Title
Should we ligate haemodialysis fistulas in patients after they have been transplanted successfully: the COBALT feasibility study (Cardiorespiratory Optimisation By AVF Ligation after Transplantation).

Acronym
COBALT

Study objectives
1. To conduct a feasibility study involving six centres that mirrors a proposed RCT, but that uses pre-defined cut-offs with regards to patient recruitment and retention rates to justify progression to the RCT. The proposed RCT hypothesis is that in stable renal transplant patients, fistula disconnection improves cardiorespiratory fitness, thereby increasing patients' activity levels and improving quality of life.
2. To understand patients' and clinicians' perceived acceptability of the proposed trial design and processes, with a view to planning strategies to optimise recruitment and retention for the main RCT.
3. To assess feasibility and acceptability of CPET in the kidney transplant population, as judged by the proportion of participants who successfully complete both tests.
4. To assess patient compliance with wearing a wrist accelerometer (activity sensor).

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 02/02/2022, East Midlands - Derby Research Ethics Committee (Equinox House, Nottingham, NG2 4LA, United Kingdom; +44 (0)207 1048211; derby.rec@hra.nhs.uk), ref: 22/EM/0002

Approved 02/02/2022, East Midlands - Derby REC (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 (0)207 1048211; derby.rec@hra.nhs.uk), ref: 22/EM/0002

Primary study design
Interventional

Study design
Randomized, open-label, interventional feasibility study

Study type(s)
Quality of life

Health condition(s) or problem(s) studied
Cardiorespiratory fitness in adult kidney transplant recipients with stable transplant function and a patent arteriovenous fistula (AVF).

Interventions
The intervention in COBALT is surgical disconnection of an arteriovenous fistula. This involves either surgically dividing and oversewing the fistula vein at the site of the original anastomosis onto the artery, or disconnecting the fistula vein entirely from the artery at the anastomotic site and repairing the arterial defect with a vein 'patch'. The operation may also include excision of the venous outflow segment if particularly enlarged or aneurysmal.
The control is standard of care; continued conservative management, with fistula disconnection only performed if clinically indicated.
Participants will be randomised to either the intervention or standard care in a 1:1 ratio, using a web-based randomisation service.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Feasibility measured using the proportion of approached patients who complete the study (defined as the proportion of all approached patients, who consent to participate, receive the allocated intervention, and complete both cardiopulmonary exercise tests without withdrawing) between recruitment and 6 months

Key secondary outcome(s)
1. Feasibility measured using the following:
1.1. Proportion of approached patients who consent to participation measured at recruitment
1.2. Proportion of participants who receive the allocated intervention measured at 0 days
1.3. Proportion of participants who complete both cardiopulmonary exercise tests (CPETs) measured at baseline and 6 months
1.4. Proportion of participants who did not withdraw measured over the 6-month study period
1.5. Proportion of participants who received the allocated intervention and completed both CPETs without withdrawing measured over the 6-month study period
1.6. Proportion of participants who were compliant with wearing wrist accelerometers measured for both 7 day periods at baseline and 6 months
1.7. Rate of patient recruitment at each trial centre measured at recruitment
1.8. Time (days) from providing consent to the first CPET and from CPET to fistula disconnection measured over the 6-month study period
1.9. Patient and clinician perceived acceptability of trial design and processes through qualitative interviews at 6 months
2. Cardiopulmonary fitness measured using peak maximal oxygen consumption (VO2) at baseline and 6 months
3. Physical functioning measured using the physical functioning domain of SF-36 Quality of Life questionnaire score at baseline and 6 months
4. Activity levels measured as mean daily Euclidean norm minus one (ENMO) using accelerometry

data.at baseline and 6 months
5. NT-proBNP levels measured using serum NT-proBNP value at baseline and 6 months
6. Blood pressure measured using office blood pressure sphygmomanometer at baseline and 6 months
7. Cardiopulmonary capacity measured using the ventilatory anaerobic threshold (VAT), endurance time, peak workload, O2 pulse, O2 uptake/ work rate slope (VO2/WR), minute ventilation/ CO2 output slope (VE/VCO2), heart rate/ VO2 slope (HR/VO2), and perceived exertion rating (Borg scale) during CPET at baseline and 6 months
8. Kidney transplant function measured using eGFR by CKD-EPI estimation at baseline and 6 months
9. Fistula-related symptoms measured using the VASQOL questionnaire for all participants at enrolment, and at 6 months for participants allocated to standard care
10. Proportion of participants with at least one major adverse cardiovascular event (MACE) measured using the incidence of cardiovascular death, ischaemic cardiovascular event (myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft), or hospitalisation for heart failure at any time during the 6-month study period
11. Safety measured using the following at any time during the 6-month study period:
11.1. Surgical complications from fistula disconnection (number in each Clavien-Dindo classification)
11.2. Fistula-related complications in the standard care group
11.3. Transplant failure (return to permanent dialysis or re-transplantation)
11.4. Hospitalisation (number of hospitalisations and cumulative days in hospital)
11.5. Patient death (all-cause)
12. Health status measured using the SF-36 scores from the role functioning/emotional, emotional well-being, social functioning, pain, general health, and health change domains at baseline and 6 months

Completion date
31/12/2023

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 04/02/2022:
1. The participant is an adult, aged 16 years or older
2. The participant is at least one year from kidney transplant and with a patent AVF
3. The participant has stable transplant function (eGFR >35 ml/min/1.73m² and without recent rejection episode or recent decline in graft function)
4. The participant has adequate English to understand the study information by verbal explanation and the written participant information sheet
5. The participant provides full informed consent

Previous participant inclusion criteria:
1. Aged ≥16 years
2. ≥1 year from kidney transplant and with a patent AVF
3. Stable transplant function (eGFR >35 ml/min/1.73m² and without recent rejection episode or recent decline in graft function)
4. Capacity to provide full informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
40

Key exclusion criteria
1. Lacking capacity
2. CPET is contraindicated
3. Considered to have no further first-line options for AVF creation at their wrist or elbow
4. AVF disconnection is required on clinical grounds

Date of first enrolment
01/03/2022

Date of final enrolment
31/05/2023

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Addenbrooke's Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Oxford University Hospitals NHS Foundation Trust
Churchill Hospital
Old Road
Headington

Oxford
United Kingdom
OX3 7LE

Study participating centre
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

Study participating centre
Queen Elizabeth University Hospital
1345 Govan Road
Glasgow
United Kingdom
G51 4TF

Study participating centre
University Hospital Coventry
Clifford Bridge Road
Coventry
United Kingdom
CV2 2DX

Study participating centre
Freeman Hospital
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust

ROR
https://ror.org/04v54gj93

Organisation
University of Cambridge

ROR
https://ror.org/013meh722

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Addenbrooke's Kidney Patient Association

Funder Name
Cambridge University Hospitals

Alternative Name(s)
CUH

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and analysed during the current study will be available upon request from Prof. Gavin Pettigrew (gjp25@cam.ac.uk) after the trial results have been published (expected September 2024) and should continue to be available for 4 years, until approximately September 2028. Data will be available in relation to the trial described above (i.e. demographic, clinical and laboratory). Requests should be sent to Prof. Pettigrew and reasonable requests with an acceptable scientific case will be considered. Transfer of data will require a Data Transfer Agreement (DTA), with the signature of the requester and a legal representative of the institution. The DTA will specify all conditions of the agreement and the scope of the work. Participant identifiers will not be included in the data sent and researchers will be required to provide a commitment to refrain from using the data to try and identify participants. All participants have provided their written informed consent for their data to be used in this way.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		09/02/2023	10/02/2023	Yes	No
HRA research summary			28/06/2023	No	No