

Should we ligate haemodialysis fistulas in patients once they have been transplanted successfully: a randomised feasibility study for a parallel randomised controlled trial

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Abstract

Background

Although considered the best means of providing haemodialysis, arteriovenous fistulas (AVFs) may increase long-term cardiovascular morbidity and mortality because of the low peripheral resistance and high cardiac output that develops. We assessed whether a randomised controlled trial (RCT) examining the cardiovascular impact of AVF ligation in stable renal transplant patients was feasible.

Methods

A parallel two-arm, non-blinded, feasibility trial enrolled forty consenting adult kidney recipients with a patent AVF and with good transplant function (estimated Glomerular Filtration Rate > 35 mL/min/1.73m²) from six UK centres. At baseline, each had maximal oxygen consumption (peak VO₂) quantified by cardiopulmonary exercise testing (CPET), and activity levels and other quality of life (QoL) domains assessed by wrist accelerometry and Short Form-36 questionnaire responses. Participants were randomised by a web response system in a 1:1 ratio to surgical disconnection of their AVF (intervention) or to continued conservative management (standard care), stratified according to AVF site (wrist or elbow) and AVF volume flow (low or high). The assessments were repeated six months later.

The primary outcome measure was the proportion of approached patients who completed the study, with pre-determined red-amber-green criteria determining progression to the main study. Secondary non-blinded clinical outcome measures included: peak VO₂; physical functioning (SF-36 score); total activity levels (mg/day); N-terminal pro B-type natriuretic peptide (NT-proBNP – higher values indicating myocardial overstretch).

Key findings

The target 40 patients were recruited to the trial and randomised. However, only 27 (67.5%) received the allocated intervention and completed both CPETs, with 7 of 20 (35%) randomised to AVF disconnection not undergoing surgery, below the predetermined completion rate required for trial progression. Compliance to wearing the wrist accelerometers was generally much better.

With regards secondary outcome measures, neither peak VO₂ (the proposed primary end-point for the main RCT) nor accelerometry activity levels were increased following AVF disconnection. There were, however, apparent improvements in 6-monthly NT-proBNP levels and physical functioning scores.

Conclusions

Although based on small numbers of participants, AVF ligation may be associated with improvements in physical functioning and NT-proBNP values. However, the much higher rates of participant drop-out than anticipated (particularly for the intervention group) would make successful delivery of the proposed RCT extremely challenging, with impractically large numbers of participants required. Alternative study designs should be considered.

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Background

Transplantation is the best form of treatment for people with end-stage kidney disease (ESKD), offering clear survival, Quality of Life (QoL), and cost benefits over the alternative option of continued dialysis ^{1–4}.

Nevertheless, for those with a working transplant, life expectancy remains poorer than the age-matched general population ^{5, 6}. Life-long immunosuppression is associated with increased mortality from infection and malignancy, but most strikingly, cardiovascular disease (CVD) is five times more prevalent in kidney transplant patients than the age-matched general population ⁷, and accounts for 21% of deaths in the UK renal transplant population, compared to 14% in the general population ^{8, 9}. CVD is now

the most frequent cause of death in US kidney transplant patients¹⁰. Many of the conditions responsible for ESKD (most notably diabetes and hypertension) have well documented cardiac sequelae, and additional factors related to the transplant (such as the metabolic consequences of immunosuppression) may also increase cardiovascular risk. There is, however, increasing focus on whether arteriovenous fistulas (AVFs) also contribute to long-term cardiac morbidity and mortality.

For patients with ESKD, AVFs are considered the optimal vascular access for providing haemodialysis. Other modalities, such as a central venous catheter or a synthetic arteriovenous graft, have higher failure rates and increased risks of infection: thus AVFs are associated with improved QoL^{11,12} and a lower incidence of sepsis-related deaths^{13,14}. National guidelines thus recommend AVFs as the primary choice for haemodialysis access¹⁵.

Notwithstanding, AVFs induce marked haemodynamic and cardiac changes in the individual. The blood flow through an AVF increases massively as it 'matures', with fistula flow rates of over 2 litres/minute common^{16,17}. As the fistula vein dilates, the systemic vascular resistance drops, which triggers neurohormonal responses aimed at increasing cardiac contractility and circulating volume. This increases ventricular preload, stroke volume and cardiac output, resulting in left ventricular (LV) hypertrophy and dilatation, which in severe cases may manifest as high-output cardiac failure¹⁸⁻²⁰. There is growing concern that, even in relatively fit individuals, this ventricular remodelling after AVF formation may increase cardiovascular risk^{21,22}.

Recent discussions have therefore focused on whether AVFs should be disconnected after successful kidney transplantation. This remains contentious, because although disconnection results in beneficial cardiac remodelling and reversal of LV hypertrophy²³, it is not yet clear if this reduces CVD burden. The only randomised controlled trial (RCT) to date²⁴ reported a reduction in LV mass (as measured by Magnetic Resonance Imaging) upon AVF ligation, but LV mass does not necessarily reflect functional capacity and the trial has not yet prompted a change in clinical practice. This may partly reflect ingrained attitudes of transplant patients and their clinicians towards preserving their AVF in case it is required again once their kidney transplant fails.

Stronger evidence is therefore needed to better inform patients about management of their AVF after transplantation and to decide whether AVF disconnection should become routine. To provide this evidence, we aimed to perform a multicentre RCT that combined rigorous assessment of cardiorespiratory fitness with activity monitoring and QoL assessment to determine how AVF disconnection impacts on the individual's physical capacity and their general well-being. This trial would thus test our main hypothesis:

'In stable renal transplant patients, fistula disconnection improves cardiorespiratory fitness, thereby increasing patients' activity levels and improving quality of life'.

Initial public and patient engagement highlighted, however, several possible issues regarding the practicalities of the trial. With two diametrically different trial arms - AVF disconnection involving a reasonably major operation versus AVF preservation with no additional treatment required - concerns were voiced that a lack of neutrality by potential participants or their clinicians over the best management of their AVF may hamper recruitment. The trial team were also unsure whether participants would manage to achieve the intensity of exercise required (to exhaustion at ventilatory anaerobic threshold) to successfully complete cardiopulmonary exercise testing (CPET). An initial randomised feasibility trial was therefore proposed that focused upon participant recruitment and retention rates. This approach further enabled us to gauge the suitability of using less invasive assessments of physical functioning as potential trial end-points, as well as incorporating formal qualitative testing of patient and clinician views on trial participation.

The objectives for the feasibility study were thus:

1. To conduct a feasibility study involving six centres, that mirrors a proposed full-scale RCT, with predefined cut-offs with regards patient recruitment and retention rates to justify progression to the larger RCT.
2. To assess feasibility and acceptability of CPET in the kidney transplant population, as judged by the proportion of participants who successfully complete both tests.
3. To understand patients' and healthcare professionals' perceived acceptability of the proposed trial design and processes.
4. To assess patient compliance with wearing a wrist-worn accelerometer (physical activity measurement).

Here, we report the feasibility study's findings.

Methods

The study design, performance and subsequent analysis of trial data proceeded according to the original funding application, without changes from the original published trial protocol ²⁵.

Study design and setting

The feasibility study mirrored the proposed RCT to examine the potential cardiorespiratory benefit of disconnecting the AVF in renal transplant recipients with stable kidney graft function. Briefly, an interventional, multicentre (6 UK hospitals), non-blinded, feasibility study randomised 40 patients in a 1:1 ratio to the intervention (AVF disconnection) or to continued standard care (preservation of AVF, with intervention only if clinically indicated), stratified by AVF site (wrist or elbow) and AVF flow rate (high or low). The study ran from 1st September 2021 until 23rd November 2023, with recruitment taking place between 1st April 2022 until 30th December 2022.

The overall study design is outlined in Fig. 1. At baseline, participants' fistula flow rates were measured by doppler ultrasound. Participants then underwent CPET and calculation of peak maximal oxygen consumption (peak VO_2) – the proposed primary endpoint for the main RCT. Participants' daily activity levels were assessed by wearing a wrist accelerometer for 7 days continuously, and blood sampled for N-terminal pro B-type natriuretic peptide assay (NT-proBNP – higher values indicating myocardial overstretch ²⁶). Participants were asked to complete short-form 36 (SF-36 ²⁷) and Vascular Access Specific QoL (VASQoL ²⁸) questionnaires. These tests were repeated 6 months later after randomisation or surgery.

Participant eligibility

Eligible potential participants were identified by the local clinical team from the inclusion and exclusion criteria below.

Inclusion criteria

1. Kidney transplant recipient aged 16 years or older
2. At least one year from kidney transplantation and with a patent AVF.
3. Stable kidney transplant function (estimated glomerular filtration rate (eGFR) $> 35\text{mL/min/1.73m}^2$ (calculated by CKD-EPI estimation ²⁹)) and without recent rejection episodes or recent decline in kidney function).
4. Adequate English to understand the study information by verbal explanation and the written participant information sheet.
5. Capacity to provide full informed consent.

Exclusion criteria

1. Patients lacking capacity.
2. Those in whom CPET is contraindicated, as per national guidance.
3. Those considered to have no further first-line options for AVF creation at their wrist or elbow, as assessed by a vascular access specialist.
4. Patients in whom AVF disconnection is indicated on clinical grounds.

Intervention

The standard care / control arm involved continued conservative management and preservation of the AVF, with intervention only performed if clinically indicated. In the intervention arm, the fistula vein was surgically divided and oversewn at the site of the original anastomosis onto the artery. The draining venous fistula outflow segment was also possibly excised, particularly if enlarged or aneurysmal. The procedure was performed under local, regional, or general anaesthesia, generally as a day-case.

Randomisation and blinding

The allocation sequence was produced by the trial statistician using SAS statistical software. The allocation sequence had varying undisclosed block sizes and was stratified by fistula site (wrist or elbow) and the binary variable fistula flow rate category (low (≤ 800 mL/min for wrist AVF, ≤ 1400 mL/min for elbow AVF) or high (> 800 mL/min for wrist AVF, > 1400 mL/min for elbow AVF). Participants were allocated at a 1:1 ratio to the trial intervention (surgical disconnection of their AVF) versus control (continued conservation management group). Allocation was conducted using Sealed Envelope (a centralised web-based randomisation system), with the randomisation list only accessible to the trial statisticians and Sealed Envelope.

It was not possible to blind this trial. The clinical care team, researchers, participants and clinical trial unit team members knew which arm of the trial was assigned at randomisation.

Outcomes

The primary outcome for the feasibility study was the proportion of approached patients who completed the study, defined as: 'the proportion of eligible, approached patients who consented, received the allocation intervention, and completed both CPET tests (achieving maximal exercise capacity) without withdrawing.'

Secondary outcome measures were grouped into: those related to the practicalities of trial delivery; clinical indices anticipated to be altered following AVF disconnection; safety outcome measures.

Feasibility outcome Measures:

1. Proportion of eligible approached patients who consent to participation
2. Proportion of participants who receive the allocated intervention
3. Proportion of participants who complete both CPETs
4. Proportion of participants who did not withdraw
5. Proportion of participants who received the allocated intervention and completed both CPETs without withdrawing
6. Proportion of participants who were compliant with wearing wrist accelerometers
7. Rate of patient recruitment at each trial centre
8. Time (days) from providing consent to first CPET and from CPET to fistula disconnection
9. Patient and healthcare professional perceived acceptability of trial design and processes (qualitative assessment carried out by interviews)

Clinical outcome measures:

1. Peak VO_2 as measured during incremental CPET on a cycle ergometer
2. Physical functioning domain score of Short Form-36 Quality of Life questionnaire ²⁷
3. Activity levels (mean daily Euclidean norm minus one (ENMO)) as calculated from accelerometry data collected from wrist accelerometer device worn over seven-day period at baseline and following six-month assessment
4. Serum N-terminal pro B-type natriuretic peptide (NT-proBNP) value
5. Office blood pressure

6. Additional CPET indices: ventilatory anaerobic threshold, endurance time, peak workload, O₂ pulse, VO₂/ work rate slope, minute ventilation/ CO₂ output slope, heart rate/VO₂ slope, perceived exertion rating (Borg scale)
7. Additional domain scores of the Short Form-36 QoL questionnaire ²⁷: physical role limitation, emotional role limitation, energy/ fatigue, emotional wellbeing, social functioning, pain, general health, perceived health change
8. Kidney transplant function (eGFR by CKD-EPI estimation ²⁹)
9. Fistula-related symptoms reported in modified VASQoL questionnaire ²⁸ (for all participants at enrolment, and at six months for cohort randomised to standard care)
10. Proportion of participants with at least one major adverse cardiovascular event (MACE) ³⁰: cardiovascular death; ischaemic cardiovascular event (myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft); hospitalisation for heart failure at any time during the six-month study period

Safety outcome measures:

1. Surgical complications from fistula disconnection (number in each Clavien-Dindo classification ³¹)
2. Fistula-related complications in the standard care group
3. Transplant failure (return to permanent dialysis or re-transplantation)
4. Hospitalisation (number of hospitalisations and cumulative days in hospital)
5. Patient death (all-cause)

Progression to the main RCT

Progression to the main trial was determined by pre-defined cut-offs related to recruitment and retention rates, with the following traffic light approach adopted:

Patient participation

- Green: > 40% of eligible approached patients consent to trial participation
- Amber: Between 30% and 40% of eligible approached patients consent
- Red: < 30% of patients consent

Adherence to randomisation and study completion

- Green: > 85% of enrolled participants received the allocated intervention and completed both CPETs without withdrawing
- Amber: Between 75% and 85% completion rate
- Red: < 75% completion rate

Statistical Analyses

The primary outcome (presented as n/N (%) along with the exact binomial 95% confidence interval (CI)) is the proportion of approached patients who completed the study, as defined above. Those whose allograft failed, died, or were lost to follow-up were considered as not completing the study successfully. The component proportions for calculating the primary outcome are presented (plus 95% CI) as secondary feasibility outcome. Compliance with wearing the wrist accelerometer (presented by study arm at baseline and 6 months) with wearing the wrist accelerometer was defined as a wear time of 96 hours, with a minimum of 20 hours in each quadrant of the 24-hour period to ensure activity levels were representative of the full 24-hour period.

Descriptive statistics of the secondary clinical outcomes are presented for each arm separately, at baseline, the six-month assessment, and the average change over time, with 95% CI. Peak VO₂ is presented by AVF site and according to pre-specified dichotomised (high or low) AVF flow rate categories. As the potential primary end-point for the main RCT, further mixed linear regression was used to examine any difference in peak VO₂ at six months between the two treatment arms, with adjustment for fistula site, flow rate, baseline peak VO₂ and random effect for centre. Participants with missing data for any of these variables were excluded. Hypothesis testing was not conducted for the other secondary clinical outcome data. Fistula-related symptoms were assessed using the modified VASQoL questionnaire for all participants at enrolment and at six months for the standard care arm and compared where applicable. Physical functioning was assessed by calculating the mean of the participants' responses to the 10 questions of the physical functioning domain of the SF-36 QoL questionnaire. The proportion of participants who experienced at least one MACE by six months was calculated (alongside 95% CI), and details of all reported MACEs collected. Summaries of all secondary safety outcomes are reported by arm.

Sample size calculation

As a feasibility, study a formal sample size calculation was not performed. However, if 85% of participants completed the study, 40 patients would give a 95% CI of 70.2% to 94.3%.

Qualitative Assessment of participant and clinician trial engagement

Integrated qualitative research aimed to identify issues (such as recruitment / informed consent, the acceptability of the interventions, and the suitability of the outcome measures) that may hamper the success of the proposed main RCT. Semi-structured interviews with healthcare professionals and with patients who accepted and declined trial participation across all six sites were performed, with the following specific objectives:

1. Investigate healthcare professionals' perspectives on the trial design, including perceptions of equipoise, views on the eligibility criteria, relevance of the primary and secondary outcomes, and approaches to measuring these.
2. Understand the acceptability of randomisation from patients' perspectives, with a focus on reasons for accepting/declining trial participation and factors that influenced these decisions.
3. Explore patients' experiences of trial participation, including perceived acceptability of being in the intervention/control arms and undergoing outcome assessments (e.g. CPET, wearing accelerometers).

Results

The trial consort diagram is attached (Fig. 2) and details that enrolment and randomisation of the target forty participants was reached within the scheduled study window, with all six participating renal transplant centres contributing, but with 37.5% recruited at Cambridge (Table 1). Participant demographics are detailed in Table 2, with the majority male and with a median age of 56 years. Notably, almost a quarter (22.5%) were diabetic, and the majority (85%) were prescribed antihypertensive medication. Wrist AVFs had been created in 67.5%, with the remainder elbow.

Table 1
Recruitment by centre

Centre	No. approached	% potentially eligible from approached	% consented and eligible from potentially eligible	% randomised from consented and eligible	No. randomised
Cambridge	24	95.8%	65.2%	100.0%	15
Glasgow	21	66.7%	35.7%	100.0%	5
Oxford	12	75.0%	55.6%	80.0%	4
London	13	100.0%	53.8%	100.0%	7
Coventry	19	73.7%	35.7%	100.0%	5
Newcastle	5	100.0%	80.0%	100.0%	4
Overall	94	83.0%	52.6%	97.6%	40

Table 2
Participant baseline characteristics

Participant characteristics	Standard care (n = 20)	Fistula ligation (n = 20)	Total (n = 40)
Age (Years)	52 (49–62)	60 (49–66)	56 (49–65)
Male	11 (55.0)	13 (65.0)	24 (60.0)
AVF side			
Left	16 (80.0)	17 (85.0)	33 (82.5)
Right	4 (20.0)	3 (15.0)	7 (17.5)
AVF site			
Elbow	7 (35.0)	6 (30.0)	13 (32.5)
Wrist	13 (65.0)	14 (70.0)	27 (67.5)
AVF flow rate			
High	15 (75.0)	14 (70.0)	29 (72.5)
Low	5 (25.0)	6 (30.0)	11 (27.5)
Mean brachial artery volume flow (ml/min)	1393 (1039–1977)	1457 (1035–2164)	1408 (1035–2042)
Mean brachial artery resistance index	0.43 (0.40–0.54)	0.48 (0.39–0.56)	0.46 (0.40–0.55)
Representative outflow vein diameter (mm)	10 (8–13)	10 (8–12)	10 (8–12)
Systolic blood pressure (mmHg)	126 (114–140)	136 (122–148)	129 (115–147)
Diastolic blood pressure (mmHg)	73 (68–80)	79 (71–87)	76 (69–85)
eGFR value (ml/min/1.73m ²)	56 (51–70)	57 (43–84)	57 (49–74)
Time between transplant and approach (Years)	4.0 (2.5–7.4)	4.9 (3.7–7.7)	4.8 (3.1–7.5)
Cardiovascular Risk Factors			
Ischaemic heart disease	0 (0.0)	3 (15.0)	3 (7.5)
Diabetes	6 (30.0)	3 (15.0)	9 (22.5)
Congestive heart failure	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	17 (85.0)	17 (85.0)	34 (85.0)
Smoker	1 (5.0)	1 (5.0)	2 (5.0)
Hyperlipidaemia	3 (15.0)	4 (20.0)	7 (17.5)
Prior Cerebrovascular accident	0 (0.0)	3 (15.0)	3 (7.5)
Medication			
ACE Inhibitors	2 (10.0)	4 (20.0)	6 (15.0)
Angiotensin Receptor Blockers	3 (15.0)	1 (5.0)	4 (10.0)
Beta blockers	9 (45.0)	8 (40.0)	17 (42.5)
Calcium Channel Blockers	12 (60.0)	11 (55.0)	23 (57.5)
Mineralocorticoid receptor antagonists	0 (0.0)	0 (0.0)	0 (0.0)
Diuretics	0 (0.0)	2 (10.0)	2 (5.0)

Participant characteristics	Standard care	Fistula ligation	Total
	(n = 20)	(n = 20)	(n = 40)
Statins	7 (35.0)	12 (60.0)	19 (47.5)
<i>Summary of missing data: None</i>			
<i>Data are number (%) for categorical variables, and median (IQR) for continuous variables</i>			

Study Primary Endpoint

Seven patients withdrew after randomisation, and notably, 7 of the 20 randomised to the intervention arm (AVF disconnection) did not undergo surgery, and 13 of 40 participants did not complete both CPETs; a requirement for completion of the study. Thus only 27 (67.5%) of participants received the designated intervention and completed the assessments required. This is below the minimum 75% completion rate prespecified as necessary for progression to the main RCT (Fig. 3, Table s1). Moreover, of the 37 (92.5%) participants who attended for the first, baseline CPET, only 22 (59.5%) reached maximal effort (required for accurate peak VO_2 quantification). Similarly, of the 27 (67.5%) who attended for the 6-month CPET, 18 (66.7%) achieved maximal effort.

Compliance with wearing wrist accelerometer

In contrast to successfully completing the CPET, participants appeared to find wearing the wrist accelerometers more acceptable, with 36 (90.0%) compliant with wearing the monitor at baseline (defined as a wear time of 96 hours, with 20 hours in each quadrant of the 24-hour period), and with 25 of the 33 (75.8%) participants who had not withdrawn from the study compliant in wearing the accelerometer at 6 months.

Analysis of Clinical Secondary Outcomes

As a feasibility exercise, the study was not powered to detect a difference in the assessed clinical endpoints that would perhaps be modified by AVF ligation. The baseline and six-month values of these clinical indices are depicted in Table 3. The principal clinical endpoint, peak maximal oxygen consumption (peak VO_2) – the proposed primary endpoint for the main RCT – did not increase upon AVF ligation, with a mean (SD) value at baseline and at 6-months in the intervention group of 22.1 (9.3) and 22.7 (9.8) mL/kg/min, respectively (Table 3 and Fig. 4a). A paired analysis (Table 3 and Fig. 4b) revealed that the average percentage change from baseline to 6-month peak VO_2 value each participant in the intervention arm was + 1.6% (95% CI: -3.0% to + 6.1%; which would not be considered clinically meaningful. In comparison, there was an average reduction of 6.7% (95% CI: -11.5 to -2.0%) in peak VO_2 values from baseline to 6 months in the standard care (AVF preservation) arm (Table 3). A subsequent sensitivity analyses of all CPETs performed (including the non-maximal tests) reaching similar findings. Secondary analysis of various other CPET indices, such as: ventilatory anaerobic threshold; endurance time; O_2 uptake / work rate slope; minute ventilation / CO_2 output slope; and perceived exertion rating at peak exercise (Borg scale) likewise did not suggest a clinical improvement following AVF disconnection (Table s3). The accelerometry activity levels, as quantified by ENMO values, were also not dramatically different at 6 months from baseline in either the standard care or AVF ligation groups (% change (95%CI): -0.9% (-10.1% to 8.4%) standard care and + 2.8% (-7.3% to 12.9%) intervention group; Table 3).

Table 3
Clinical outcomes at baseline, at 6 months and the average percentage change

Outcome	Standard care (n = 20)			Fistula ligation (n = 20)			Total (n = 40)		
	Baseline	6- months	Average % change (95% CI)	Baseline	6- months	Average % change (95% CI)	Baseline	6- months	Average % change (95% CI)
Peak maximal oxygen consumption (VO_{2peak} ml/kg/min) – N	10	9	8	12	9	9	22	18	17
Mean (sd)	20.2 (4.5)	18.9 (4.8)	-6.7% (-11.5% - -2.0%)	22.1 (9.3)	22.7 (9.8)	+ 1.6% (-3.0% - +6.1%)	21.2 (7.4)	20.8 (7.7)	-2.3% (-6.0% - +1.3%)
Mean ENMO (mG) - N	18	14	13	18	11	11	36	25	24
Median (IQR) ¹	26 (20– 30)	24 (23– 28)	-0.9% (-10.1% - +8.4%)	20 (17– 26)	18 (16– 28)	+ 2.8% (-7.3% - +12.9%)	23 (17– 29)	23 (17– 28)	+ 0.8% (-5.5% - +7.1%)
Physical functioning domain of SF-36 score – N	20	17	17	19	13	13	39	30	30
Median (IQR)	70 (50– 90)	70 (45– 95)	-12.6% (-31.8% - +6.7%)	65 (50– 95)	95 (55– 100)	+ 29.2% (-5.9% - +64.2%)	65 (50– 95)	75 (45– 95)	+ 5.5% (-13.6% - +24.6%)
Serum NT-proBNP value (Ng/L) – N	20	17	17	20	13	13	40	30	30
Median (IQR)	307 (162– 480)	263 (192– 538)	+ 38.5% (9.1% - 68.0%)	328 (105– 579)	178 (53– 252)	-28.5% (-52.6% - -4.4%)	328 (148– 494)	246 (136– 436)	+ 9.5% (-12.9% - 31.9%)
Kidney function, eGFR(ml/min/1.73m ²) – N	20	17	17	20	13	13	40	30	30
Median (IQR)	56 (51– 70)	63 (51– 72)	+ 2.1% (-4.4% - 8.6%)	57 (43– 84)	67 (50– 90)	+ 6.6% (0.9% - 12.2%)	57 (49– 74)	65 (50– 77)	+ 4.0% (-0.2% - 8.3%)
Systolic blood pressure (mmHg) – N	20	17	17	20	13	13	40	30	30
Median (IQR)	73 (68– 80)	79 (67– 83)	3.6% (-2.4% - 9.6%)	79 (71– 87)	83 (80– 92)	12.4% (-2.7% - 27.5%)	76 (69– 85)	81 (72– 85)	7.4% (0.4% - 14.4%)
Diastolic blood pressure (mmHg) – N	20	17	17	20	13	13	40	30	30
Median (IQR)	126 (114– 140)	133 (124– 143)	5.5% (-3.9% - 14.4%)	136 (122– 148)	133 (122– 149)	5.9% (-8.8% - 20.6%)	129 (115– 147)	133 (122– 148)	5.7% (-2.1% - 14.4%)

Outcome	Standard care			Fistula ligation			Total		
	(n = 20)			(n = 20)			(n = 40)		
	Baseline	6-months	Average % change (95% CI)	Baseline	6-months	Average % change (95% CI)	Baseline	6-months	Average % change (95% CI)
			14.9%)			20.7%)			13.4%)
The % average change represents the mean of the percentage increase (+) or decrease (-) in a parameter's value from baseline to 6 months for each participant; N represents the number of participants included who had values at both time points. Only maximal CPET results are presented. ENMO, Euclidean norm minus one, measures participants' daily activity levels through a wrist accelerometer. Only results where the participant was compliant with wearing the wrist monitor (as defined in the protocol) are included. eGFR is estimated using CKD-EPI estimation.									

The number of participants prevent definitive conclusions, but there may, in contrast, be a clinical difference in 6-month physical functioning scores and serum NT-proBNP values in the AVF ligation group (Table 3). Whereas the median physical functioning domain score was not different at 6 months from baseline in the standard care arm, it increased from 65 to 95 in the intervention (AVF disconnection) arm (Table 3 and Fig. 5a). A paired comparison of the individual participant's baseline and 6-month values (Table 3 and Fig. 5b) also suggests a clinical improvement in physical activity following AVF disconnection; there was an average percentage decrease of 12.6% (95% CI: -31.8 - +6.7%) in physical functioning at 6 months from baseline in the standard care arm, compared with an increase of 29.2% (95%CI: -5.9 - +64.2%) in the intervention group, although this difference did not reach statistical significance. A similar paired analysis (Table 3 and Figs. 6a & 6b) also found that serum NT-proBNP values (a marker of myocardial overstretch) fell in the intervention group at 6 months (% average (95%CI) decrease for each participant: 28.5% (-52.6% to -4.4%)), and if anything increased in the standard care group (% average increase per participant: +38.5% (9.1% - 68.0%)). Again, numbers are too small to make firm conclusions, but there is possibly a correlation between the improvements in physical functioning and fall in NT-proBNP levels, in that, of the 9 of 13 participants in the intervention arm that had a > 25% decrease in NT-proBNP levels, six had increases in their physical function score, with the other three unchanged.

Safety events

One participant experienced an adverse event during the CPET, necessitating termination of the test. Five participants undergoing AVF ligation experienced surgical complications relating to: thrombophlebitis of the disconnected vein, wound collection; wound infection and cellulitis. These were reported as mild and did not require hospitalisation. One participant developed hand weakness and altered sensation a month after AVF disconnection. This was initially reported as a SUSAR (Suspected Unexpected Serious Adverse Reaction), but improved spontaneously and was subsequently downgraded to an Adverse Event, although it remains unclear if these symptoms were related to the surgery. Two participants in the standard care group experienced AVF-related complications in the 6-month study period. No participants in either study arm suffered a MACE during the study period, nor did any participant's kidney fail.

Qualitative Assessment of participant and clinician trial engagement.

The participant and clinician perspectives on their involvement in the trial were assessed by integrated formal qualitative assessment. A series of interviews with participants (both consenting and those who declined participation (n = 24) and their responsible clinicians (n = 17) were performed. The importance of the research question was universally acknowledged, with clinicians admitting to ongoing uncertainty as to how to best manage the AVF in successfully transplanted renal patients. Several consistent themes were identified at interview. Despite enthusiasm for the trial, clinicians found identification of suitable patients to approach challenging, largely because centres did not keep records of transplant patients who still had patent AVFs. Moreover, clinicians found that potential participants often had strong opinions about how to manage their AVF, with relatively few open-minded about whether to have ligation or continue conservative treatment; a sentiment echoed in the interviews with participants.

Consequently, all clinicians thought that recruiting sufficient numbers to the proposed main RCT would not be possible, with several mentioning that the publicity of the trial paradoxically increased referrals for AVF ligation, but not for trial participation. It was also evident that clinicians often held strong views about managing the AVF of particular patients and would set additional criteria for participation that excluded patients who were otherwise eligible for trial inclusion. Finally, the relatively high rate of patients not receiving the intervention after randomisation was explored, but no common theme was identified, other than participants having second thoughts as the prospects of undergoing a relatively major operation became a reality.

Discussion

The study protocol specified traffic-light stop-go criteria for progression to the main trial, with a red signal of either patient participation < 30% or study completion rate < 75% indicating abandonment. We confirmed that it is possible to consent patients into the trial, with 53% of eligible approached patients having consented to participate in the trial. However, as only 68% of randomised participants adhered to the randomisation and completed the study, we are not planning to apply for further funding to hold the main RCT. Delivering the multicentre RCT as originally envisaged would be extremely challenging, with recruitment of the required 500 patients who complete the trial and adhere to randomisation highly likely to be unsuccessful. Patients and clinicians were very supportive and felt the trial addressed an important question, but all centres found patient recruitment much more demanding than initially envisaged, and the trial clinicians concurred that the trial should not proceed.

The embedded qualitative assessment found several possible explanations for the problems encountered in recruitment and completion:

- Centres had no ready means of identifying potential participants (transplant recipients with stable function and with a patent AVF) other than approaching all patients at transplant follow-up clinic.
- Potential recipients and their clinicians were rarely neutral about how to manage their AVF and preferred one trial arm.
- Participants randomised to AVF disconnection frequently decided against surgery as the date for their operation approached.

In addition, a relatively large proportion of participants did not manage to achieve maximal effort on the CPET; a requirement for calculating peak VO_2 . Furthermore, analysis of the peak VO_2 values obtained (the proposed primary endpoint for the main RCT) did not suggest an improvement following AVF ligation in the intervention group, although a signal may not have been detected due to the small number of participants. Similarly, the wrist accelerometry exercise values did not appear to be improved by AVF ligation. In contrast, analysis of NT-proBNP values suggested there was possibly an improvement (decrease) in circulating NT-proBNP levels following AVF ligation, particularly when considering the paired analysis of individuals' baseline and 6-monthly values, with, moreover, perhaps a correlation between a fall in NT-proBNP and an increase in reported physical functioning.

Conclusions

Despite some clinical indices suggesting that cardiovascular function and physical activity may be improved in the six months following AVF ligation, the initial feasibility study highlighted obstacles relating to participant identification, randomisation and retention that would prevent successful completion of the proposed multicentre RCT. Some of these, such as the lack of patient and participant equipoise, but particularly the nature of a surgical trial in which the two arms impose dramatically differently upon the recipient, appear intractable, and it is difficult to envisage how, even after redesign, a formal randomised trial could be run successfully.

Abbreviations

AVF	Arteriovenous Fistula
CVD	Cardiovascular Disease
CPET	Cardiopulmonary Exercise Testing

eGFR	estimated glomerular filtration rate
ENMO	mean daily Euclidean norm minus one
ESKD	end-stage kidney disease
LV	Left Ventricular
MACE	Major Adverse Cardiac Events
NT-proBNP	N-terminal pro B-type natriuretic peptide
Peak VO ₂	Maximal oxygen consumption
QoL	Quality of Life
VASQoL	Vascular Access Specific Quality of Life

Declarations

Ethics approval and consent to participate

This study was approved by the East Midlands – Derby Research Ethics Committee (22/EM/0002) and the Health Research Authority. Written informed consent was obtained from the participants by a suitably qualified member of the clinical/research team who has received trial training. The patient's right to refuse participation in the trial and withdraw from the study at any time and without reason was respected, without prejudicing their further treatment

Consent for publication

Not applicable

Availability of data and materials

Access to the final dataset is available upon request from Prof Gavin Pettigrew, gjp25@cam.ac.uk, after publication of trial results, and will be available for four years. No identifiable data will be shared. All participants have provided written informed consent for their data to be used in this way.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Contributions to the various aspects of the study are as detailed below. All authors had full access to the data in the study and take responsibility for the decision to submit for publication.

The trial statisticians SS, CH, JP, AN and JB had access to, and verified, the underlying data. GJP recommended submission to Pilot and Feasibility Studies with support from all coauthors.

Conceptualisation: VS, RM, DMS, SK, GJP.

Data curation: SS, CH, JM, SL, JB.

Formal Analysis: SS, CH, JP, AN and JB.

Funding application: VS, EA, PBM, RM, JPH, AA, DMA, KLR, LR, LW, MG, CH, AS, SK, GJP.

Investigation: SP, SS, EA< PBM, RM, JPH, AA, DMS, KLR, LR, LW, MG, KS, CH, MS, MB, SK, GJP.

Methodology: VS, SS, CH, DMS, RM, EA, SK, LR, GJP.

Project Administration: AS.

Validation: SS, CH, and JB.

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Writing review and editing: All authors.

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Tables

Table 1 Recruitment by centre

Centre	No. approached	% potentially eligible from approached	% consented and eligible from potentially eligible	% randomised from consented and eligible	No. randomised
Cambridge	24	95.8%	65.2%	100.0%	15
Glasgow	21	66.7%	35.7%	100.0%	5
Oxford	12	75.0%	55.6%	80.0%	4
London	13	100.0%	53.8%	100.0%	7
Coventry	19	73.7%	35.7%	100.0%	5
Newcastle	5	100.0%	80.0%	100.0%	4
Overall	94	83.0%	52.6%	97.6%	40

Table 2: Participant baseline characteristics

Participant characteristics	Standard care (n=20)	Fistula ligation (n=20)	Total (n=40)
Age (Years)	52 (49-62)	60 (49-66)	56 (49-65)
Male	11 (55.0)	13 (65.0)	24 (60.0)
AVF side			
Left	16 (80.0)	17 (85.0)	33 (82.5)
Right	4 (20.0)	3 (15.0)	7 (17.5)
AVF site			
Elbow	7 (35.0)	6 (30.0)	13 (32.5)
Wrist	13 (65.0)	14 (70.0)	27 (67.5)
AVF flow rate			
High	15 (75.0)	14 (70.0)	29 (72.5)
Low	5 (25.0)	6 (30.0)	11 (27.5)
Mean brachial artery volume flow (ml/min)	1393 (1039-1977)	1457 (1035-2164)	1408 (1035-2042)
Mean brachial artery resistance index	0.43 (0.40-0.54)	0.48 (0.39-0.56)	0.46 (0.40-0.55)
Representative outflow vein diameter (mm)	10 (8-13)	10 (8-12)	10 (8-12)
Systolic blood pressure (mmHg)	126 (114-140)	136 (122-148)	129 (115-147)
Diastolic blood pressure (mmHg)	73 (68-80)	79 (71-87)	76 (69-85)
eGFR value (ml/min/1.73m ²)	56 (51-70)	57 (43-84)	57 (49-74)
Time between transplant and approach (Years)	4.0 (2.5-7.4)	4.9 (3.7-7.7)	4.8 (3.1-7.5)
Cardiovascular Risk Factors			
Ischaemic heart disease	0 (0.0)	3 (15.0)	3 (7.5)
Diabetes	6 (30.0)	3 (15.0)	9 (22.5)
Congestive heart failure	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	17 (85.0)	17 (85.0)	34 (85.0)
Smoker	1 (5.0)	1 (5.0)	2 (5.0)
Hyperlipidaemia	3 (15.0)	4 (20.0)	7 (17.5)
Prior Cerebrovascular accident	0 (0.0)	3 (15.0)	3 (7.5)
Medication			
ACE Inhibitors	2 (10.0)	4 (20.0)	6 (15.0)
Angiotensin Receptor Blockers	3 (15.0)	1 (5.0)	4 (10.0)
Beta blockers	9 (45.0)	8 (40.0)	17 (42.5)
Calcium Channel Blockers	12 (60.0)	11 (55.0)	23 (57.5)
Mineralocorticoid receptor antagonists	0 (0.0)	0 (0.0)	0 (0.0)
Diuretics	0 (0.0)	2 (10.0)	2 (5.0)
Statins	7 (35.0)	12 (60.0)	19 (47.5)

Summary of missing data: None

Data are number (%) for categorical variables, and median (IQR) for continuous variables

Table 3: Clinical outcomes at baseline, at 6 months and the average percentage change

Outcome	Standard care (n=20)			Fistula ligation (n=20)			Total (n=40)		
	Baseline	6- months	Average % change (95% CI)	Baseline	6- months	Average % change (95% CI)	Baseline	6- months	Average % change (95% CI)
Peak maximal oxygen consumption (VO _{2peak} ml/kg/min) – N	10	9	8	12	9	9	22	18	17
Mean (sd)	20.2 (4.5)	18.9 (4.8)	-6.7% (-11.5% - -2.0%)	22.1 (9.3)	22.7 (9.8)	+1.6% (-3.0% - +6.1%)	21.2 (7.4)	20.8 (7.7)	-2.3% (-6.0% - +1.3%)
Mean ENMO (mG) - N	18	14	13	18	11	11	36	25	24
Median (IQR) ¹	26 (20-30)	24 (23-28)	-0.9% (-10.1% - +8.4%)	20 (17-26)	18 (16-28)	+2.8% (-7.3% - +12.9%)	23 (17-29)	23 (17-28)	+0.8% (-5.5% - +7.1%)
Physical functioning domain of SF-36 score – N	20	17	17	19	13	13	39	30	30
Median (IQR)	70 (50-90)	70 (45-95)	-12.6% (-31.8% - +6.7%)	65 (50-95)	95 (55-100)	+29.2% (-5.9% - +64.2%)	65 (50-95)	75 (45-95)	+5.5% (-13.6% - +24.6%)
Serum NT-proBNP value (Ng/L) – N	20	17	17	20	13	13	40	30	30
Median (IQR)	307 (162-480)	263 (192-538)	+38.5% (9.1% - 68.0%)	328 (105-579)	178 (53-252)	-28.5% (-52.6% - -4.4%)	328 (148-494)	246 (136-436)	+9.5% (-12.9% - 31.9%)
Kidney function, eGFR(ml/min/1.73m ²) – N	20	17	17	20	13	13	40	30	30
Median (IQR)	56 (51-70)	63 (51-72)	+2.1% (-4.4% - 8.6%)	57 (43-84)	67 (50-90)	+6.6% (0.9% - 12.2%)	57 (49-74)	65 (50-77)	+4.0% (-0.2% - 8.3%)
Systolic blood pressure (mmHg) – N	20	17	17	20	13	13	40	30	30
Median (IQR)	73 (68-80)	79 (67-83)	3.6% (-2.4% - 9.6%)	79 (71-87)	83 (80-92)	12.4% (-2.7% - 27.5%)	76 (69-85)	81 (72-85)	7.4% (0.4% - 14.4%)
Diastolic blood pressure (mmHg) – N	20	17	17	20	13	13	40	30	30
Median (IQR)	126 (114-140)	133 (124-143)	5.5% (-3.9% - 14.9%)	136 (122-148)	133 (122-149)	5.9% (-8.8% - 20.7%)	129 (115-147)	133 (122-148)	5.7% (-2.1% - 13.4%)
The % average change represents the mean of the percentage increase (+) or decrease (-) in a parameter's value from baseline to 6 months for each participant; N represents the number of participants included who had values at both time points.									

Outcome	Standard care (n=20)			Fistula ligation (n=20)			Total (n=40)		
	Baseline	6- months	Average % change (95% CI)	Baseline	6- months	Average % change (95% CI)	Baseline	6- months	Average % change (95% CI)

Only maximal CPET results are presented.

ENMO, Euclidean norm minus one, measures participants' daily activity levels through a wrist accelerometer. Only results where the participant was compliant with wearing the wrist monitor (as defined in the protocol) are included.

eGFR is estimated using CKD-EPI estimation.

Figures

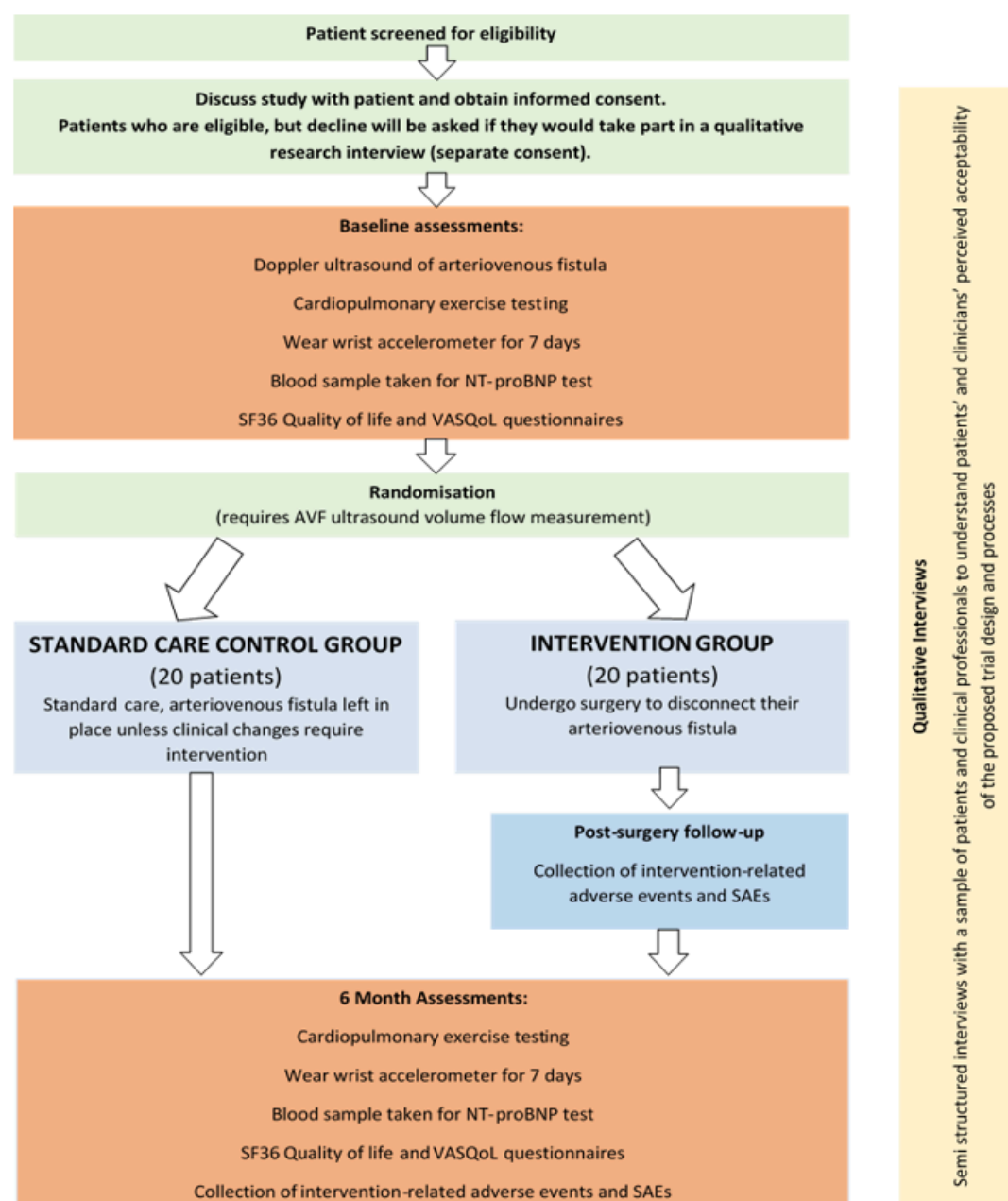


Figure 1

Design of Cardiorespiratory Optimisation By Arteriovenous fistula Ligation after renal Transplantation (COBALT) study.
AVF, arteriovenous fistula; CPET, cardiopulmonary exercise test; NT pro-BNP, N-terminal pro-B-type natriuretic peptide; SF-36, Short Form 36; VASQoL, Vascular Access Specific Quality of Life. Reproduced from ²⁵.

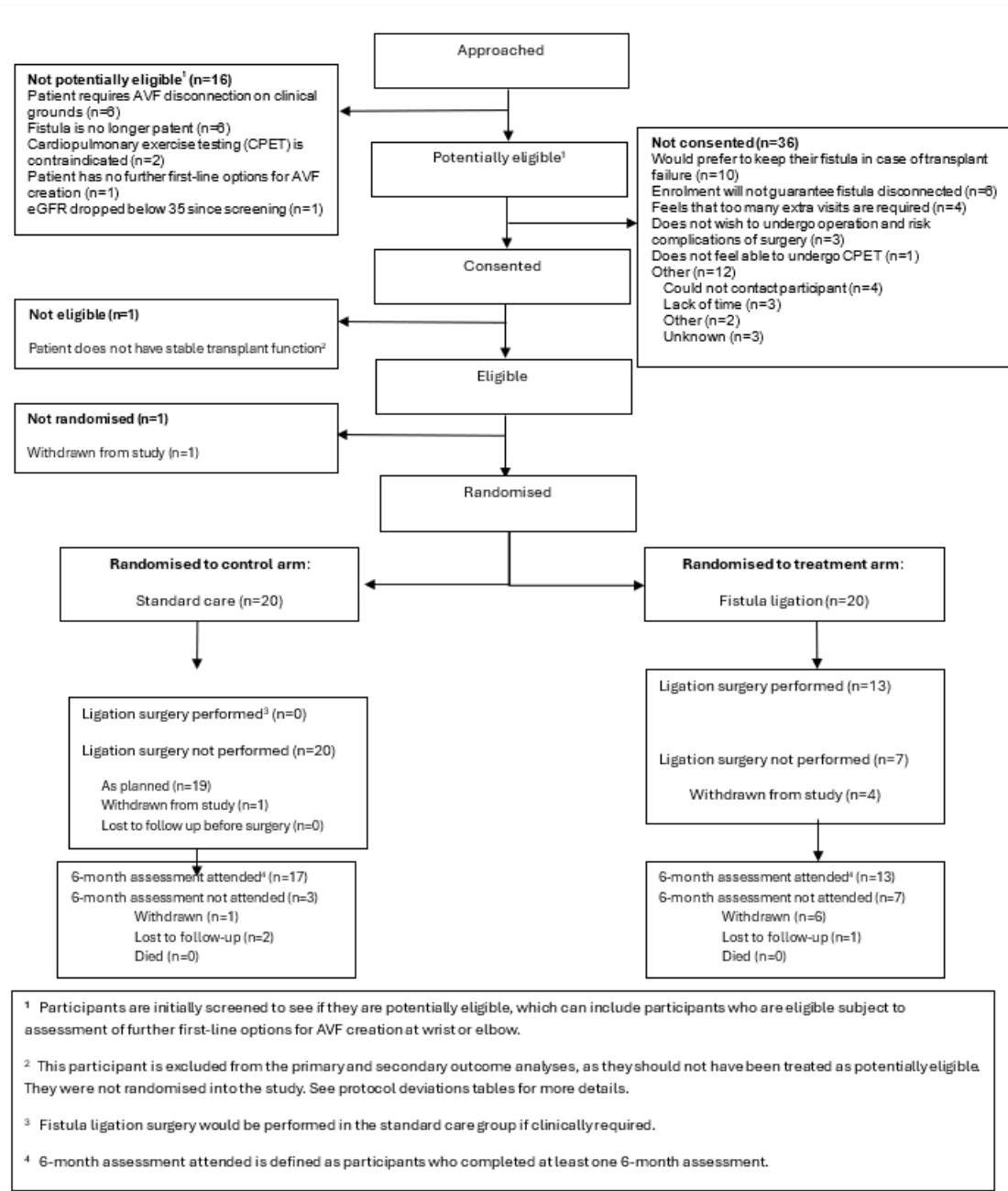


Figure 2

Participant Flow chart (CONSORT diagram)

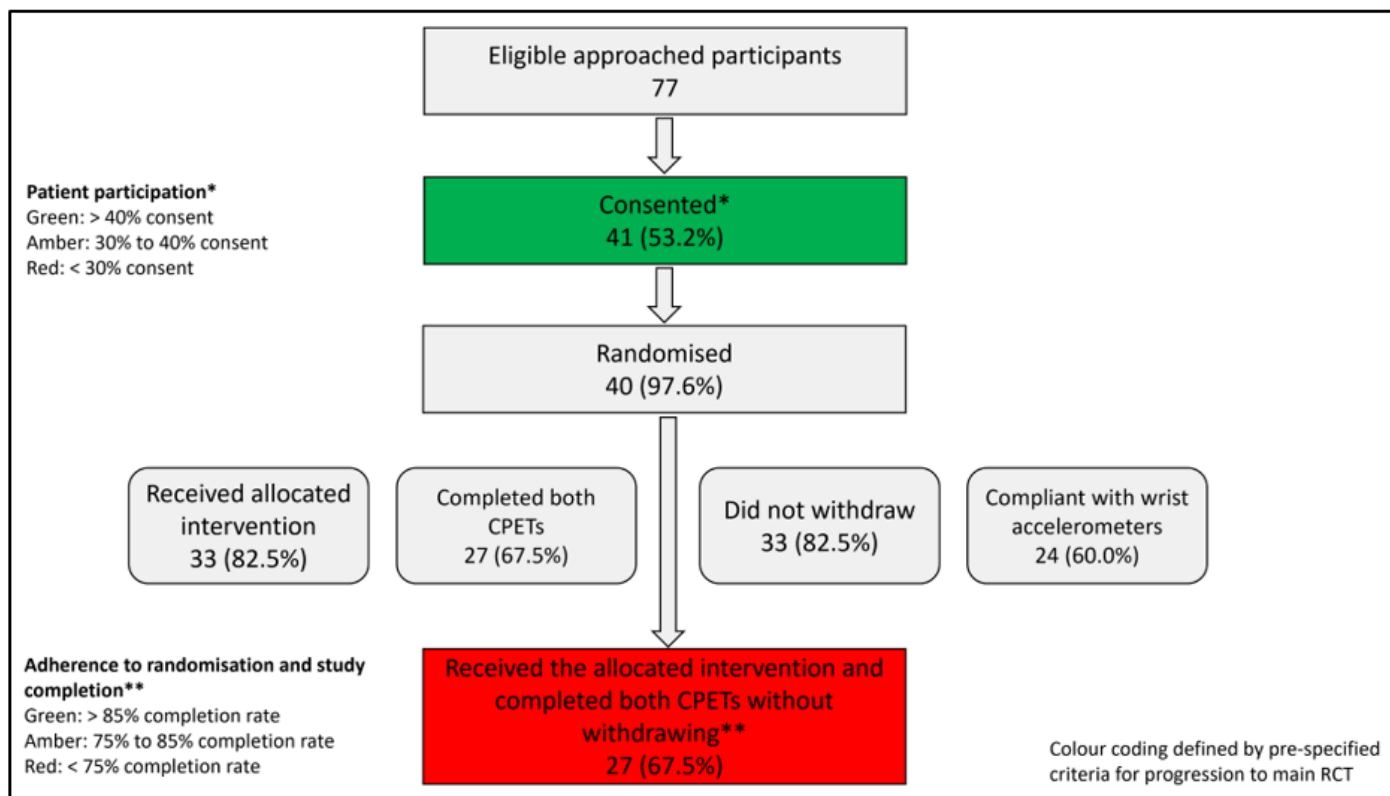


Figure 3

Flow chart illustrating status for progression to a larger efficacy trial

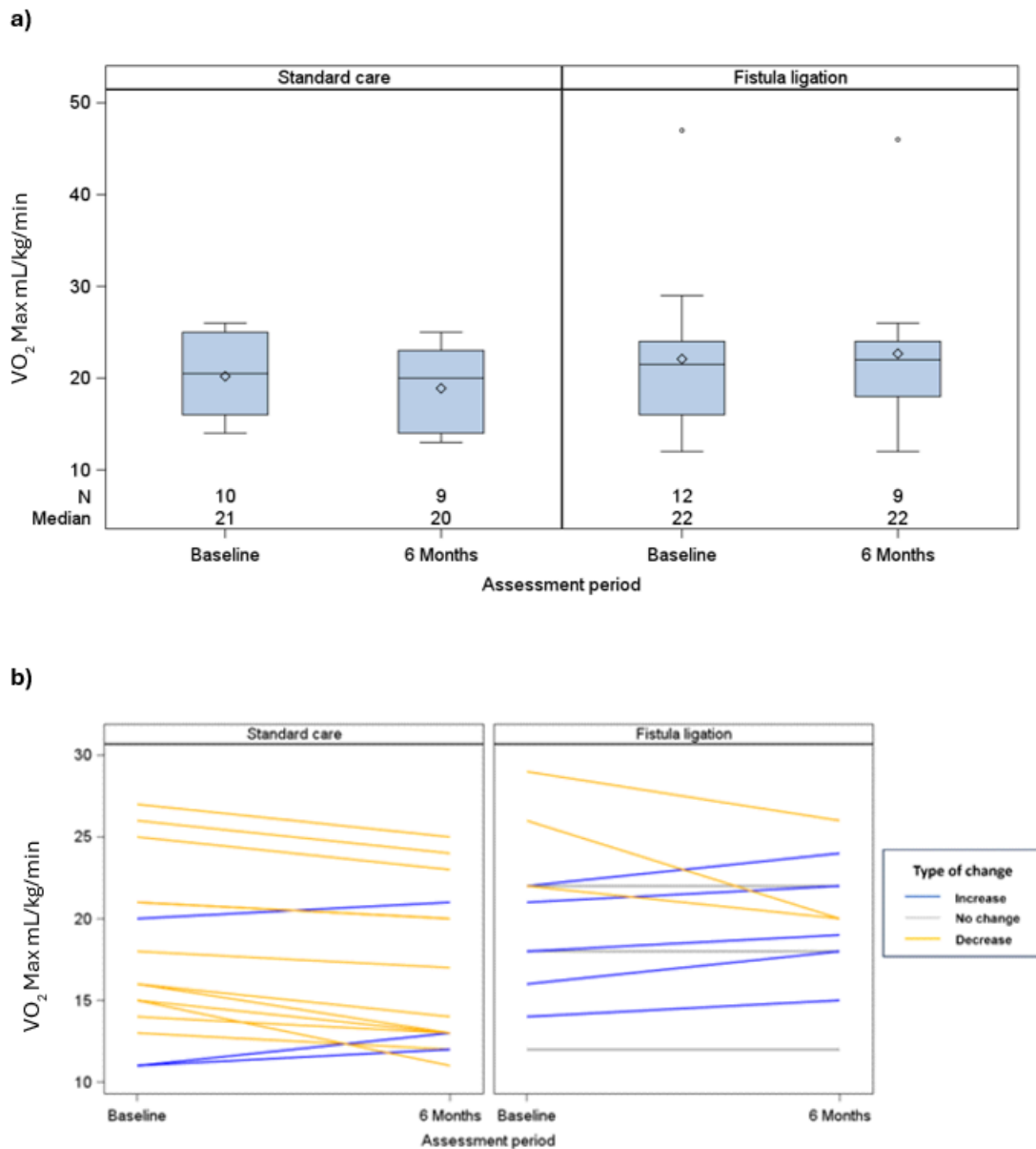
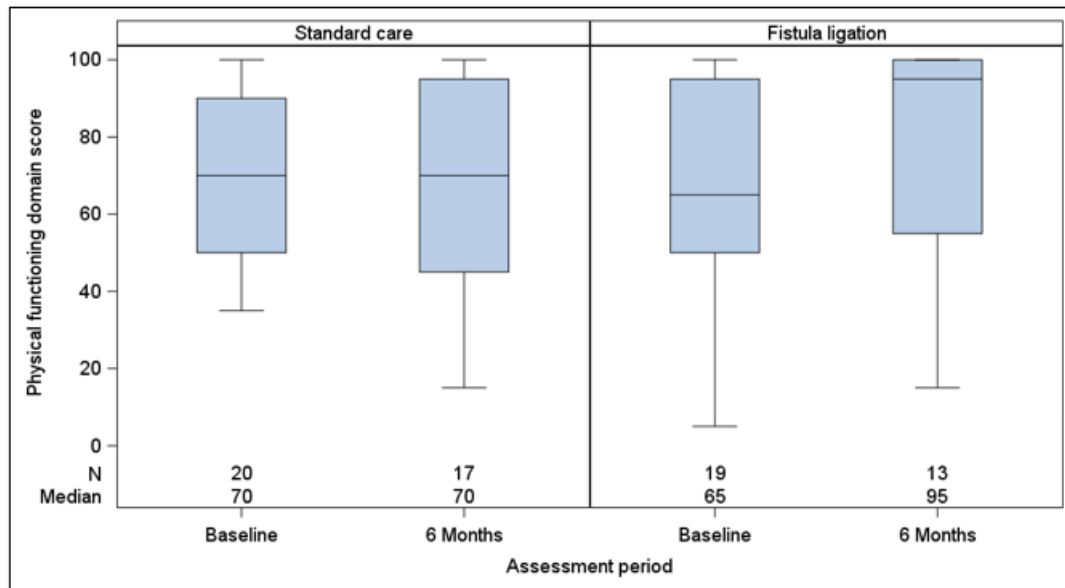


Figure 4

Peak VO₂ results by arm and assessment period.

a) Boxplot of VO₂ max results from all maximal CPET tests, by arm and at baseline and six months. **b)** Peak VO₂ max results by arm and at baseline and six months, but depicting individual participants' results. Values >30 mL/kg/min are omitted to improve readability.

a)



b)

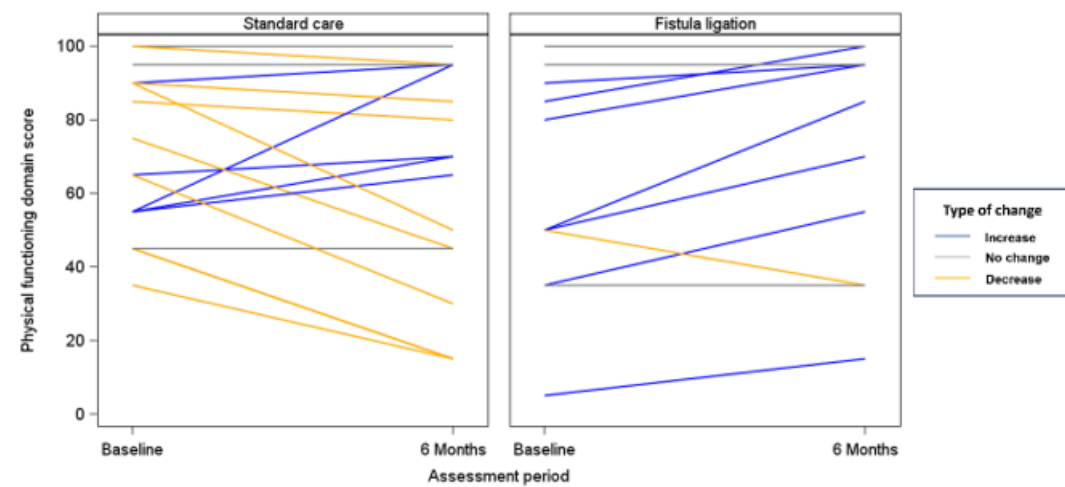
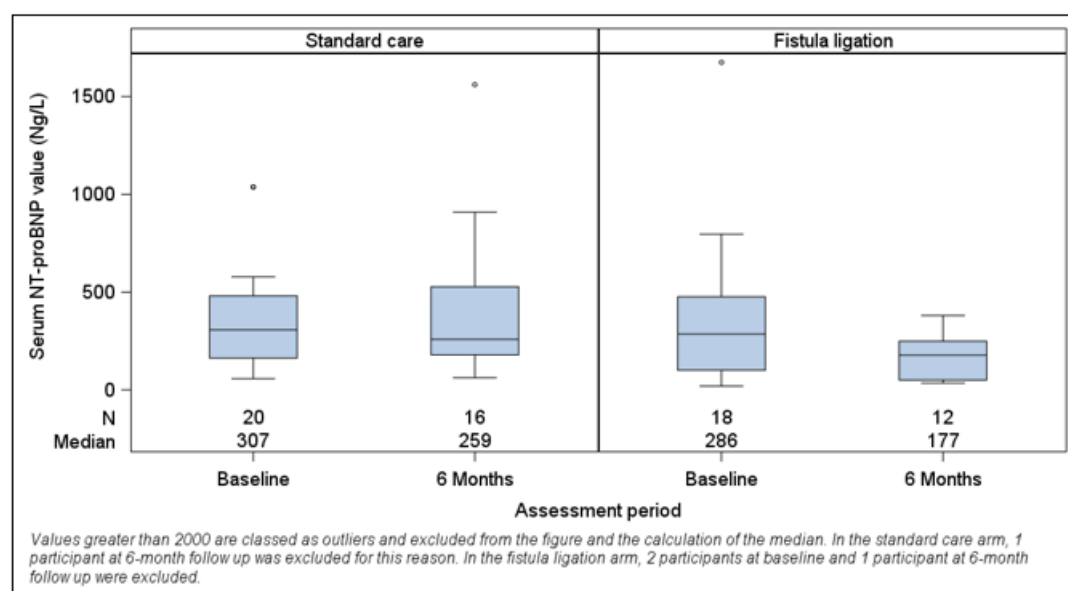


Figure 5

Reported activity levels following AVF disconnection. Activity levels were quantified by summing the responses to the ten physical functioning domains of the short-form 36 Quality of Life questionnaire. **a)** Boxplot depiction of median values at baseline and at 6 months, presented by study arm. **b)** Paired analysis of physical functioning domain scores, depicting changes in the individual's score from baseline to 6 months.

a)



b)

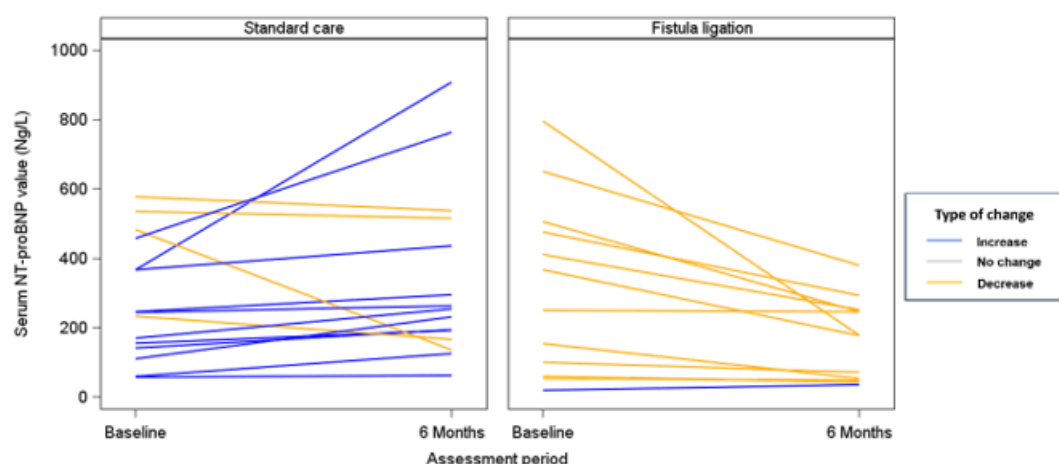


Figure 6

Serum NT-proBNP values at baseline and at six months. a) Boxplot presentation of median NT-proBNP serum values for all participants at baseline and six months according to trial arm. Values greater than 2000 Ng/L were classed as outliers and excluded from the figure and calculation of the median (in standard care arm: 1 participant at 6-month follow-up, and in intervention arm: 2 participants at baseline and 1 participant at 6-month follow-up). **b)** Paired depiction of individual participants' NT-proBNP values at baseline and six months, according to study arm. Values >1000 Ng/L are excluded from the figure to improve legibility.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplementarytables.docx](#)