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Complete List of Authors:	Tew, Garry; Sheffield Hallam University, Centre for Sport and Exercise Science Weston, Matthew; Teesside University, School of Social Sciences & Law Kothmann, Elke; James Cook University Hospital, Department of Academic Anaesthesia Batterham, Alan; Teesside University, Health and Social Care Institute Gray, Joanne; Northumbria University, Faculty of Health & Life Sciences Kerr, Karen; Northern General Hospital, Department of Anaesthesia Martin, Denis; Teesside University, Health and Social Care Institute Nawaz, Shah; Northern General Hospital, Sheffield Vascular Institute Yates, David; York Hospital, Department of Anaesthesia Danjoux, Gerard; James Cook University Hospital, Department of Academic Anaesthesia
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High-intensity Interval exercise Training before Abdominal Aortic Aneurysm repair (HIT-AAA): protocol for a randomised controlled feasibility trial

Garry A Tew[1]
Email: g.tew@shu.ac.uk

Matthew Weston[2]
Email: m.weston@tees.ac.uk

Elke Kothmann[3]
Email: elke.kothmann@stees.nhs.uk

Alan M Batterham[4]
Email: a.batterham@tees.ac.uk

Joanne Gray[5]
Email: joanne3.gray@northumbria.ac.uk

Karen Kerr[6]
Email: Karen.Kerr2@sth.nhs.uk

Denis Martin[4]
Email: d.martin@tees.ac.uk

Shah Nawaz[7]
Email: Shah.Nawaz@sth.nhs.uk

David Yates[8]
Email: david.yates@york.nhs.uk

Gerard Danjoux[3]*
* Corresponding author
Email: Gerard.danjoux@stees.nhs.uk

1 Centre for Sport and Exercise Science, Sheffield Hallam University, Sheffield S10 2BP, UK

2 School of Social Sciences & Law, Teesside University, Middlesbrough, TS1 3BA, UK

3 Department of Academic Anaesthesia, James Cook University Hospital, Middlesbrough, TS4 3BW, UK

4 Health and Social Care Institute, Teesside University, Middlesbrough, TS1 3BA, UK

5 Faculty of Health & Life Sciences, Northumbria University, Benton, Newcastle-Upon-Tyne, NE7 7XA, UK

6 Department of Anaesthesia, Northern General Hospital, Sheffield Teaching Hospitals Foundation Trust, Sheffield, S5 7AU, UK

7 Sheffield Vascular Institute, Northern General Hospital, Sheffield, UK, S5 7AU, UK

8 Department of Anaesthesia, York Hospital, York, YO31 8HE, UK

Abstract

Introduction

In patients with large abdominal aortic aneurysm (AAA), open surgical or endovascular aneurysm repair procedures are often used to minimise the risk of aneurysm-related rupture and death; however, aneurysm repair itself carries high risk. Low cardiopulmonary fitness is associated with an increased risk of early post-operative complications and death following elective AAA repair. Therefore, fitness should be enhanced before aneurysm repair. High-intensity interval exercise training (HIT) is a potent, time-efficient strategy for enhancing cardiopulmonary fitness. Here, we describe a feasibility study for a definitive trial of a pre-operative HIT intervention to improve post-operative outcomes in patients undergoing elective AAA repair.

Methods and analysis

A minimum of fifty patients awaiting elective repair of a 5.5-7.0 cm infra-renal AAA will be allocated by minimisation to HIT or usual care control in a 1:1 ratio. Patients allocated to HIT will complete three hospital-based exercise sessions per week, for 4 weeks. Each session will include 2 or 4 minutes of high-intensity stationary cycling followed by the same duration of easy cycling or passive recovery, repeated until a total of 16 minutes of high-intensity exercise is accumulated. Outcomes to be assessed before randomisation and 24 to 48 hours before aneurysm repair include cardiopulmonary fitness, maximum AAA diameter, and health-related quality of life. In the post-operative period, we will record destination (ward or critical care unit), organ-specific morbidity, mortality, and the durations of critical care and hospital stay. Twelve weeks after discharge, participants will be interviewed to re-assess quality of life and determine post-discharge healthcare utilisation. The costs associated with the exercise intervention and healthcare utilisation will be calculated.

Ethics and dissemination

Ethics approval was secured through Sunderland Research Ethics Committee. The findings of the trial will be disseminated through peer-reviewed journals, and national and international presentations.

Trial registration: Current Controlled Trials ISRCTN09433624

Keywords

Aortic aneurysm, abdominal; Vascular diseases; Exercise; Rehabilitation; Physical fitness; Feasibility studies

Article summary

Article focus

- Rates of morbidity and mortality following abdominal aortic aneurysm repair are high. Pre-operative exercise training to improve cardiopulmonary fitness might improve post-operative outcomes.

- The aims of this randomised controlled feasibility trial are (1) to explore potential primary outcomes for a subsequent definitive trial, (2) to examine the suitability of a high-intensity interval exercise training (HIT) programme for improving cardiopulmonary fitness pre-operatively, and (3) to examine the willingness of patients to be randomised and explore potential patient preferences.

Key messages

- Here we describe the protocol for a feasibility trial of a pre-operative HIT intervention versus usual care to improve post-operative outcomes in patients undergoing elective AAA repair.

- This preliminary trial will be used to inform a subsequent definitive trial.

Strengths and limitations of this study

- Appropriate allocation and analysis procedures will be used.

- A broad range of assessment methods will be used to comprehensively evaluate the feasibility, acceptability and efficacy of the pre-operative exercise intervention.

- The sample size is too small to provide accurate data on clinical and cost effectiveness; however, it is sufficiently large to inform the design of a subsequent definitive trial.

Introduction

Major non-cardiac surgery is associated with substantial peri-operative risk; the overall mortality rate appears low (c. 1-2%), but the number of operations performed (c. 250 million per annum worldwide) results in a large absolute number of deaths.[1] Moreover, post-operative complications occur up to 5 times as frequently,[1] with survivors experiencing physical limitations and reduced life expectancy.[2,3] Identification of individuals in this 'at risk' group for death and complications creates a significant challenge to clinicians in the pre-operative period. Objective assessment of cardiopulmonary fitness in the pre-operative period utilising cardiopulmonary exercise testing (CPET) is the established gold standard across the UK. It has a developing evidence base in predicting adverse outcome across a variety of high-risk surgical procedures,[4] and this has contributed substantially to clinicians' understanding of the impact of poor cardiopulmonary fitness.

There is a convincing physiological rationale linking improved cardiopulmonary fitness to a reduction in adverse outcome following surgery. The surgical stress response involves neuroendocrine, metabolic and inflammatory effects leading to a catabolic state and increased basal metabolic rate (up to three times pre-operative values[5,6]). A patient with adequate cardiopulmonary fitness is able meet these extra demands post-operatively, but patients with inadequate fitness levels might be unable to cope, leading to tissue hypoxia and peri-operative complications. Approximately half of patients presenting for intra-abdominal surgery do not have the pre-requisite fitness, on objective exercise testing, to be deemed 'low risk' for peri-operative complications.[7] It is intuitive that improving fitness levels in the pre-operative period will translate to reduced death and complications following major surgery.

Little is known about the impact of pre-operative exercise training on post-operative outcomes. In a recent systematic review,[8] the authors concluded that pre-operative exercise therapy prior to cardiac or abdominal surgery results in a reduced hospital length of stay and reduced post-operative morbidity, but that more research is required on the impact and long-term benefits. However, of the five studies identified that focused on cardiac and abdominal surgery, four involved inspiratory muscle training with pulmonary complications as the primary outcome. Clearly, this intervention improves respiratory muscle function, which might reduce post-operative pulmonary morbidity. However, this form of training is unlikely to favourably influence the wider range of sequelae of the surgical stress response. Only one study focused on the effect of a more general pre-surgery exercise training intervention. Arthur *et al*.[9] reported a reduction in median hospital length of stay of 1-day (vs. usual care control) following coronary artery bypass graft surgery with an 8-10 week exercise training programme plus education reinforcement and social support. The intervention involved 30 minutes of aerobic interval training, performed twice a week at 40-70% of functional capacity.

We believe that a programme of research is needed now to evaluate the benefits of pre-operative exercise training in patients undergoing elective non-cardiothoracic surgery. Abdominal aortic aneurysm (AAA) is a frequently lethal disease occurring in ~5% of males aged 50-79 years.[10] Annually 5,000-6,000 surgical repairs are performed across the UK,[11] making this an ideal homogenous high-risk target

population. The incidence of co-morbid disease is higher than other age-matched surgical populations: cardiac disease 60-70%, respiratory disease 40-50%, long-term smoking 50-80%, renal disease 10-12% and diabetes 10-12%.[12] Anecdotal observation from >1000 CPETs confirms that this population is also substantially less fit than other age-matched surgical populations. Findings from two recent publications also support the adverse impact of poor fitness on outcome in patients undergoing AAA repair.[13,14]

Intervention for AAA can be performed by either open or endovascular repair (EVAR), with a current ratio nationally of 55:45 in favour of EVAR.[11] 30-day mortality for open surgery in the UK in 2008 was 7-8%.[12] Earlier studies from the USA[15] and the Netherlands[16] reported major post-operative morbidity of 30-40%. Endovascular treatment is less invasive, with mortality and cardio-respiratory morbidity rates of 2-3%[11,12] and 10-15%,[15,16] respectively. For open surgery the UK mortality rate was higher than expected with respect to comparable countries, prompting the publication of a Quality Improvement Programme document with the explicit remit of standardising management to improve outcome.[11] Encouragingly such standardisation has brought about a significant 30-day mortality benefit for both procedures in the Vascular Society's most recent publication: 4.3% and 0.9% for open AAA and EVAR respectively.[17] Despite this there remains significant room for improvement. No information is routinely available on non-fatal complications, which are up to five times more prevalent than mortality and known to affect patient quality of life and overall life expectancy on hospital discharge. In addition, a key omission from the guidance is evidence or advice in relation to improving preoperative fitness, despite the fact that one of the main conclusions of the EVAR-2 study was that vascular teams should be focusing on techniques to improve patient fitness preoperatively.[18]

The proposed benefits of exercise "prehabilitation" are mediated by increases in cardiopulmonary fitness. Two pilot randomised controlled trials undertaken by our research team have documented improvements in cardiopulmonary fitness following moderate-intensity endurance exercise training in patients under surveillance for a small AAA. Kothmann *et al*.[19] reported a 10% increase in the oxygen consumption at the ventilatory threshold (a sub-maximal marker of cardiopulmonary fitness of prognostic significance) after 6 weeks of moderate-intensity cycling exercise performed for 30 minutes twice weekly. Tew *et al*.[20] observed a 2.5 $mL \cdot kg^{-1} \cdot min^{-1}$ (~20%) improvement in the ventilatory threshold after 12 weeks of moderate-intensity cycling and treadmill walking exercise performed for 35-45 minutes thrice weekly. A recent review of preoperative exercise training proposed a research agenda,[21] with future directions including the role of prehabilitation in improving fitness levels prior to major surgery, the use of robust study designs with appropriate outcome measures, and evaluations of the effects of high-intensity interval exercise training (HIT) as a model for which there is extensive evidence of benefit in other subject groups, including heart failure patients.[22] A recent literature review by Giraud in cardiac rehabilitation concluded that when compared to moderate intensity training,[23] HIT has a similar safety profile (low absolute risk) and produces greater and more time-efficient improvements in fitness. For the current proposal HIT therefore represents a particularly attractive approach, as the time-window for intervention once a patient has been identified for aneurysm repair might be as short

as 4-6 weeks.[11] Therefore, an intervention with the potential for more rapid fitness benefits is preferable.

Our programme of work is aligned to the Medical Research Council's guidance for developing and evaluating complex interventions.[24] Given the limited extent of the evidence base, a feasibility study is clearly required to inform a subsequent definitive trial. The MRC guidance stresses that crucial feasibility work is often absent or insufficient, with 'definitive' trials undermined by acceptability, adherence, and delivery of the intervention, recruitment and retention issues, and smaller than expected effect sizes.

We are conducting a feasibility study to explore the potential benefits of a 4-week HIT programme, delivered prior to surgery for AAA repair. This will be stationary cycle-based, in-hospital and undertaken 3 times per week.

Aims

1. Explore potential primary outcomes for a subsequent definitive randomised controlled trial (RCT)
The physiological rationale suggests a causal pathway between adaptations consequent to exercise training and reduced mortality and morbidity. Potential primary outcomes for a definitive trial therefore include 30-day mortality, morbidity [Post-Operative Morbidity Survey (POMS) score], health-related quality of life (HRQOL), hospital length of stay, costs and cost-effectiveness

2. Examine the suitability of the exercise training for a subsequent definitive RCT
High-intensity interval training shows much promise as an efficacious, time-efficient and also enjoyable intervention for improving fitness. However, it has not been employed with AAA patients awaiting repair.

3. Examine the willingness of patients to be randomised and explore potential patient preferences
In RCTs, patients might have strong treatment preferences resulting in a refusal to be randomised, affecting the generalisability of results. Or, they might agree to be randomised but suffer from 'resentful demoralisation' if they end up in the non-preferred arm of the trial, leading to poor adherence. This issue requires examination in a feasibility study, as the preference effects for exercise vs. control in this patient population are unknown. Theoretically, patients might have a preference for the exercise arm due to a belief in the benefits. Notwithstanding the patient information provided, others might be fearful of engaging in high-intensity exercise prior to surgery and therefore might exhibit a preference for the control arm. These issues could affect the success of a definitive trial.

Objectives

(Aim 1)
Define the characteristics of the potential outcome measures. Specifically,
1. Define the distribution (e.g. log-normal, Poisson etc. for, e.g., length of hospital stay) and estimate the variability for the potential primary outcome measures to inform sample size planning for a subsequent definitive trial.

2. Estimate the effect size (intervention minus control) for each potential outcome variable (point estimate and its uncertainty). This information reflects the effectiveness of the intervention and the 'noise' in the measurement (precision of the measure) and together with the other information will inform the choice of primary outcome for a subsequent trial.
3. Assess the ease of data collection for each potential primary outcome (including participant and clinician burden, assessed via qualitative data).

(Aim 2)
This will specifically include; objective fitness changes, safety, enjoyment, delivery and adherence of the exercise intervention

(Aim 3)
Examine the strength of patient preferences for either the intervention or control arms (qualitative data). These data will be elicited from all patients assessed as eligible, to determine the extent to which preferences affect both recruitment and adherence.

Methods and analysis

Study Design

Three-centre, two-arm, parallel-group, randomised, controlled feasibility study. The study flowchart is shown in Figure 1.

Figure 1 Flowchart of the study
AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair; POMS, post-operative morbidity survey

Study Population and Recruitment Routes

Patients being assessed for surgery for a 5.5-7.0 cm AAA will be approached via vascular surgical or preoperative assessment clinics at recruiting institutions. Potential recruits will be approached at this stage by a study investigator and, if interested, provided a study information sheet. Where an investigator is not available, a study information letter will be sent to the patient requesting permission to contact them about the study.

Sample Size

The sample size for a feasibility study should be adequate to estimate critical parameters with sufficient precision. Herein, the critical outcome is adherence to the exercise intervention. A patient will be deemed compliant if they complete ≥75% of the scheduled sessions; i.e. 9/12 sessions for a 4-week intervention, plus all once-weekly maintenance sessions if surgery is delayed. We define success with respect to adherence as a lower limit of 0.67 (c. 2/3 of the population) for the 90% confidence interval for the proportion of the exercise group complying with the intervention. We estimate that ≥85% of the exercise group will be 'compliers' based

on our pilot studies in small AAA patients.[19,20] A 90% confidence interval for a single proportion around a value of 0.85 is 0.68 to 0.95 with n=25 patients. Using a 1:1 allocation ratio we require 25 patients per trial arm, 50 in total.

A minimum of 50 participants will therefore be recruited to the study.

Approximately 150 repairs of AAA <7.0 cm are performed across our three clinical institutions annually. Assuming 30% attrition for specialist referral and lack of pre-requisite fitness, approximately 176 potential patients will be available in our 21-month recruitment time-window.

Clinical Assessment

The clinical assessment processes described are based on routine practice at the recruiting institutions. All patients who are being considered for an elective AAA repair will attend a preoperative assessment clinic. Here, an individual's clinical risk profile for surgery will be established using history of relevant co-morbidities, physical examination and CPET. Evidence-based optimisation of medication will be performed at this stage.

After risk profiling, a patient's treatment options are discussed in a vascular multidisciplinary team meeting comprising input from surgery, anaesthesia and radiology. A risk-benefit assessment is undertaken based on a nationally agreed care pathway.[11] There are three possible outcomes: open aneurysm repair, EVAR or conservative management (i.e. when surgical risk is deemed too great or the patient elects not to proceed). The most appropriate postoperative care facility is also determined.

Eligibility criteria – see figure 1

Recruitment

Patients who express an interest at clinic, or who are sent a study information letter, will be contacted by telephone inviting participation (if no exclusion criteria). With verbal consent, the baseline assessment will be scheduled.

Baseline assessment

Written informed consent will be obtained. Participants will confirm their medical history and current medication and undergo a physical examination. Baseline measurements will then be recorded, including:

- Patient characteristics (sex, stature, body mass, body mass index)
- Resting pulse, blood pressure and oxygen saturations
- Maximum AAA diameter via trans-abdominal ultrasound (not if an ultrasound scan has been performed within the previous 8 weeks)
- Cardiopulmonary fitness via CPET – methods and recorded variables are described above. The CPET data will be used to identify the intensity at which the patients in the exercise group will initiate training. We have previously demonstrated the reliability of CPET in AAA patients.[25] Testing will be

performed according to an agreed protocol across all recruiting sites (available on request).

- HRQOL using the Medical Outcomes Study SF-36 version 2 questionnaire and the EuroQol EQ-5D-5L questionnaire, both of which have been used previously in AAA patients.[18,26,27]
- Participant preference for 'exercise' training or 'usual care' – prior to randomisation to explore patient preferences and subsequent changes in attitude consequent to the intervention. This design permits the exploration of the effects of preference in the analysis.[28]

Randomisation

After baseline assessment, patients will be randomly allocated 1:1 to exercise or usual care control (no supervised exercise), using minimisation to ensure balance across trial arms for important prognostic factors. We do not list these factors here, to avoid any risk of the staff recruiting patients being able to decipher the allocation sequence. Full details of the minimisation process will be published in a separate document with restricted access. The study statistician (AB) will conduct the minimisation process remotely via e-mail.

Exercise Intervention (weeks 1-4)

The exercise intervention period will be for 4 weeks leading up to surgery. Where possible, participants (exercise and control) will have a surgical date booked for the following week (week 5).

The exercise programme is broadly based on that which has been shown to be safe and effective for improving cardiopulmonary fitness in patients undergoing cardiac rehabilitation.[22,29-31] Patients allocated to the exercise group will complete three sessions of hospital-based HIT per week, throughout the 4-week pre-operative period. Exercise will be stationary cycling (Optibike Med, Ergoline, Germany), which has been reported to be a preferred mode for vascular patients (unpublished observations). Each session will begin and end with 10 and 5 minutes of unloaded cycling, respectively. In the first week of training, the main body of each session will involve eight 2-minute bouts of cycling, interspersed with 2-minute periods of unloaded cycling or "off-the-bike" slow walking, depending on patient preference. All of the "work" bouts during the very first session will be performed at the power output associated with ventilatory threshold determined on baseline CPET (i.e. the demarcation between moderate and heavy exercise intensity domains[32]). In subsequent sessions, power output will be gradually manipulated until the patient reports a perceived exertion of 6-7 on Borg's CR-10 scale[33] (i.e. hard to very hard) at the end of each work interval. However, for safety reasons, the intensity of exercise will be made easier if systolic blood pressure exceeds 180 mm Hg[34] or if heart rate exceeds 95% of the maximum observed on baseline CPET. In weeks 2-4, and for variety, the patient will be allowed to choose between doing four 4-minute work bouts or eight 2-minute bouts as the main body of each exercise session, both with a 1:1 work-to-rest ratio. Thus, each session will last ~45 minutes regardless of patient choice, which will include 16 minutes of high-intensity exercise. An experienced physiotherapist will supervise each session and record power output, perceived exertion, and blood pressure (manual sphygmomanometer) at the end of each work

interval. Heart rate will be recorded continuously at 5-s intervals through the entire exercise session (Polar RS400, Kempele, Finland). The collection of such data will permit a detailed quantification of the exercise intervention. Patients who do not undergo surgery in week 5 will complete one HIT session per week up until surgery to maintain fitness.[35] All adverse events will be recorded.

Information in relation to *participant's perceived enjoyment of exercise* is important to monitor. This is of relevance in adherence to the programme, whilst providing valuable information for planning a definitive study. We therefore plan to assess:

1. Changes in enjoyment of exercise both within sessions and throughout the programme. Perceived or likely enjoyment can change prior, during and after exercise as a consequence of a variety of factors e.g. anxiety, enjoyment, fatigue. We therefore plan to ask participants to assess enjoyment/perceived enjoyment of exercise prior to commencing, during and 20 minutes after exercise using a simple validated rating scale.[36] This will take <30 seconds to administer on each occasion and will be done during the first (baseline), 3rd, 6th, 9th and 12th sessions to track changes consequent to the programme.
2. Overall enjoyment of the exercise programme will be assessed during the week 5 assessment, using the validated multi-dimensional physical activity enjoyment scale (PACES).[37] This will be 2-3 days following completion of the overall programme, allowing participants reflection and evaluation time (see week 5 assessment below).

Two experienced exercise scientists will be responsible for ensuring treatment fidelity of the exercise programme (GT, MW).

Safety Considerations

There are two main safety considerations regarding running a programme of HIT in patients with AAA disease:

1. Cardiac risk – as previously outlined 60-70% of individuals with AAA disease suffer from comorbid cardiac disease. The baseline assessment of clinical risk profile and CPET will be instrumental in assessing this risk in detail, under the stress of exercise, at the outset. A recent review by Guiraud *et al*.[23] highlights the safety of HIT in patients with underlying coronary disease, heart failure and patients at risk of cardiovascular disease. We are reassured by their conclusion which states "there is growing scientific evidence that HIT presents little danger for selected stable cardiac patients, provided that the prescribed protocols are respected".

   In the event of an adverse cardiac event we will have the following in place:
   - Staff experienced and Intermediate Life Support-trained
   - Resuscitation equipment and oxygen immediately available
   - Hospital cardiac arrest team fully informed of time and place of training sessions
   - Participants requiring further assessment will be transferred to the Accident and Emergency Unit within the relevant hospital.

   All institutions have Cardiology expertise immediately available on site.

2. Risk of AAA expansion or rupture – an intuitive concern regarding exercise testing and training in patients with aneurysms is of excessive rises in double-product (systolic blood pressure × heart rate) evoking aneurysm expansion and rupture. However, the available evidence suggests that these concerns are unfounded. For example, no aneurysm ruptures or excessive aneurysm growth rates were reported in any of the three studies of moderate-intensity exercise training in patients with early AAA disease (from >4000 exercise sessions[19,20,38]), two of which were conducted at our institutions.[19,20] Further unpublished data from our institutions indicate no ruptures from >1300 maximal exercise tests in patients with large asymptomatic AAA being considered for elective aneurysm repair. Moreover, through national networked connections, and other relevant publications, we believe this position of safety to be correct for >5000 maximal exercise tests. This position is also supported by the European guidelines for the management of AAA disease, which state that physical activity is not associated with AAA growth,[39] as well as the ACC/AHA Practice Guidelines for the Management of Patients with Peripheral Vascular Disease,[40] which suggest that AAA patients should not be fearful of vigorous activity. The only reported adverse event we are aware of came from the patient series of Best *et al*.[41] where a rupture occurred 12 hours after maximal exercise testing in a patient with a 6.1 cm AAA, yielding a rupture rate for this study of 0.4%. However, the causal relationship between exercise and rupture is difficult to establish given the 12-hour intervening period.

   It would therefore appear that the risk of AAA growth or rupture is very low in the context of exercise training for individuals with both small and large aneurysmal disease. This risk would appear to be <1:5,000. When balanced against national perioperative mortality/morbidity figures available for surgery in the UK at present, we feel that this represents clear benefit in favour of undertaking the preoperative exercise as set out.

   In the event of a suspected AAA rupture patients would immediately be transferred to the Accident and Emergency department for prompt further evaluation. All clinical institutions have on-site vascular teams able to immediately respond to such a situation.

Despite this we see risk minimisation in this context as our primary concern and will implement the following control measures:

- Thorough pre-participation screening
- Exclusion of high-risk patients
- Hospital-based exercise testing and training
- Exercise sessions supervised by experienced cardiac physiotherapists trained in Intermediate Life Support
- Exercise sessions performed >3 hours after waking given the higher frequency of cardiovascular events during the morning hours[42]
- Prompt evaluation of prodromal symptoms
- Resuscitation equipment and oxygen immediately available
- Exercise termination if a patient has signs/symptoms suggestive of distress, cardiac or AAA adverse event

- Reduction in exercise intensity if a patient has systolic blood pressure rise to >180 mm Hg, or heart rate >95% of their maximum (from baseline CPET)

Safety Governance

In line with Medical Research Council guidance we have developed the following safety governance structure for the study:

- Data Monitoring and Ethics Committee (DMEC) – the DMEC comprises three academics/clinicians with appropriate expertise who are independent from the running of the study. Any serious adverse events will be reported to and fully investigated by the DMEC. The DMEC will make recommendations to the Trial Steering Committee with regards to any ethical or safety concerns they may have.
- Trial Steering Committee (TSC) – this committee is led by the Chief Investigator (CI), with representation from all collaborating clinical and academic institutions. A lay representative will be approached to sit on the committee. The TSC will meet 3 times per year to discuss all elements of study progress and conduct.
- TSC Safety Committee – a formal study safety committee has been established and comprises 3 study investigators, including the CI. This group has the remit of ensuring all appropriate safety standards are in place prior to study commencement, and during the course of the research.

All adverse and serious adverse events will be managed within the strict governance arrangements of the study sponsor and participating clinical institutions.

Week 5 assessments

During week 5 it is anticipated that participants will undergo AAA repair. In the same week, but 1-2 days prior to surgery, assessments will be performed in all participants. The outcomes, which are primarily aimed at investigating the safety and effectiveness of the exercise intervention compared with usual care, will include:

- Cardiopulmonary fitness via CPET (to assess fitness changes from baseline)
- Maximum AAA diameter via trans-abdominal ultrasound (to establish safety of exercise in relation to aneurysm growth)
- HRQOL questionnaires
- PACES assessment for overall exercise programme enjoyment (exercise intervention group only)

Due to logistical reasons it is anticipated that not all participants will undergo surgery in week 5. This will mainly be due to a temporary lack of hospital beds for admission preoperatively, or critical care post-operatively. In this situation, surgery will be rescheduled, where possible, within 4 weeks. A repeat CPET will be undertaken in patients whose surgery is delayed >4 weeks, to ensure we have an accurate assessment of pre-operative fitness in all patients. A CPET assessment of those patients who have performed one high-intensity training session per week from week 5 onwards will provide further valuable information of the dose-response nature of high-intensity training in this population.

An overview of data to be collected for this aspect of the study can be seen on the study Case Report Form (see Additional file 1).

Perioperative period

Participants will undergo open or endovascular aneurysm repair as determined at the multidisciplinary team meeting. All perioperative care will be at the discretion of the vascular teams (as per usual practice) who will be blinded to group allocation. Perioperative data will be collected as seen in Additional file 1.

Post-operatively an investigator blinded to group allocation will determine the following:

- Destination – ward or critical care unit
- Postoperative Morbidity Survey Score (POMS) – a validated tool used to assess organ-specific morbidity in the post-operative period.[43,44] Scores will be collected daily.
- Mortality
- Length of critical care and hospital stay

Post-discharge follow-up

At hospital discharge patients will be asked to keep a service receipt inventory to record treatment/care requirements for a 12-week period to inform the resource utilisation analysis. Participants will be interviewed via telephone at 6 weeks, with a follow-up appointment at 12 weeks after discharge to assess:

- HRQOL
- Resource utilisation
- Hospital readmissions, with diagnosis, within 12 weeks of initial discharge

Analysis Plan of Quantitative Study

Adherence with the exercise intervention will be analysed as described in the sample size justification, above, via the confidence interval for a single proportion. For the potential primary outcomes for a subsequent definitive trial, the likely effect of the exercise intervention will be estimated via standard intervention minus control comparisons (accounting for the type of variable and its distributional properties). We will examine the disposition of the 90% confidence interval for the observed effect to the minimum clinically important difference for each variable. Inasmuch as this is a feasibility study, these comparisons are exploratory and are intended to inform the subsequent trial. Data management will be performed according to the governance arrangements of the institutions involved in the project.

Analysis of Health Economics and Cost Effectiveness

A prospective economic evaluation will be rehearsed to develop and refine methods for a subsequent definitive trial. The main focus will be on how to accurately identify, quantify and value the additional costs of delivering the intervention and the potential resource implications versus usual care post-operatively and post-discharge. The costing approach will incorporate a broad analytical perspective (National Health Service and Social Services), which will help to detect cost-shifting between sectors. Resources utilised in the exercise group will be identified in terms of capital equipment and staff time. A staff-reported health economics questionnaire has been

developed to facilitate this (available upon request). Post-operative resource use will also be explored for all participants in terms of bed days (including critical care bed days). Post-discharge resource use for all treatment/care related to AAA surgery will be assessed retrospectively for 12 weeks by piloting the use of a self-report Service Receipt Inventory (patient diary). This will facilitate the development of a reliable and valid tool to capture resource use. Appropriate unit costs to be applied to resource use will be identified. These will be sourced from a combination of local costings and national databases.[45,46] All costs will be combined to rehearse the methods for total health and social care cost estimation in a subsequent definitive trial.

The methods to estimate an incremental cost-effectiveness ratio for exercise versus usual care in terms of Quality Adjusted Life Years will be rehearsed (using EQ-5D 5L administered at baseline and 12 weeks post discharge). In particular, issues relevant for sensitivity analysis will be explored to help understand how best to deal with statistical imprecision and other uncertainties in the full trial. For example, data will be bootstrapped to account for the expected skewness evident in economic cost data. The data collected as part of this feasibility study could be used to inform subsequent pre-trial modelling.

Analysis of Participant Interviews

We aim to explore participants' post-discharge experience. From a critical realism perspective, semi-structured interviews will cover quality of life, function and attitudes to exercise including fear.

Sixteen participants will be recruited using purposive sampling and the following criteria: men and women; a range of ages; both study groups; both forms of aneurysm repair; and a range of experiences post-discharge. The interviews (1 hour with a research nurse; audio-recorded and transcribed) will take place in the hospital at the 12-week post-discharge visit. Transcripts will be analysed thematically using quantitative and diary data for triangulation.

Qualitative data (brief interview) will also be collected from all participants (and from clinical outcome assessors where relevant) to assess the ease of data collection for each potential primary outcome (participant and clinician burden), to evaluate the perceived enjoyment of the exercise intervention, and to examine the strength of patient preferences for either the intervention or control arms. These data will be elicited from all patients assessed as eligible, to help determine the extent to which preferences affect both recruitment and adherence.

Criteria for success

A subsequent definitive RCT will be deemed feasible if:
1. An appropriate primary outcome variable is defined;
2. The lower limit of the 90% confidence interval for the proportion of the exercise intervention group complying with the intervention is ≥67%. A patient is defined as having complied with the intervention if he completes ≥75% of the scheduled sessions;
3. Patient preferences are not so strong that they result in the conclusion that an RCT is not a feasible design.

Ethics and dissemination

Ethics approval was secured through Sunderland Research Ethics Committee (reference 13/NE/0116) in May 2013.

The dissemination strategy for this research will be to inform a wide range of local, national and international audiences about the results and conclusions. It must however be remembered as part of this strategy that the current proposal is for preliminary work aimed at defining a subsequent definitive clinical trial.
1. Health professionals – we aim to publish our research in journals that cover the relevant medical specialties and with preference for those that deposit publications in open access databases to increase free dissemination. In addition, we aim to present this research at appropriate national and international conferences.
2. Users – from this perspective we aim in the first instance to collaborate with our patient representatives (from advisory and steering groups) and local experts in patient and public involvement to best facilitate user dissemination. We plan to write a specific news piece that will be forwarded to appropriate groups and organisations.
3. Service managers – as an exploratory study it is unlikely that results from this study will directly influence commissioning processes in the short term. More we will engage with appropriate primary and secondary care groups to discuss support for our proposed definitive study leading on from this research.

Trial status

Start date: 1 August 2013

Expected end date: 30 May 2015

Expected publication date: 1 January 2016

Status at time of submission of this article: recruiting

Funder: UK National Institute of Health Research - Research for Patient Benefit Programme (PB-PG-1111-26068)

List of abbreviations used

AAA	abdominal aortic aneurysm
CPET	cardiopulmonary exercise testing
EVAR	endovascular aneurysm repair
HIT	high-intensity interval exercise training
HRQOL	health-related quality of life
PACES	physical activity enjoyment scale
POMS	post-operative morbidity survey
RCT	randomised controlled trial

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

GT drafted the manuscript and contributed to the design of the study. Original study concept was by GD and AB. All co-authors contributed to the design of the study. GD is Chief Investigator for the project. EK is Principal Investigator (PI) at James Cook University Hospital (South Tees), SN is PI at Northern General Hospital (Sheffield) and DY is PI at York Hospital. All authors contributed to the critical revision of the manuscript for important intellectual content and read and approved the final manuscript.

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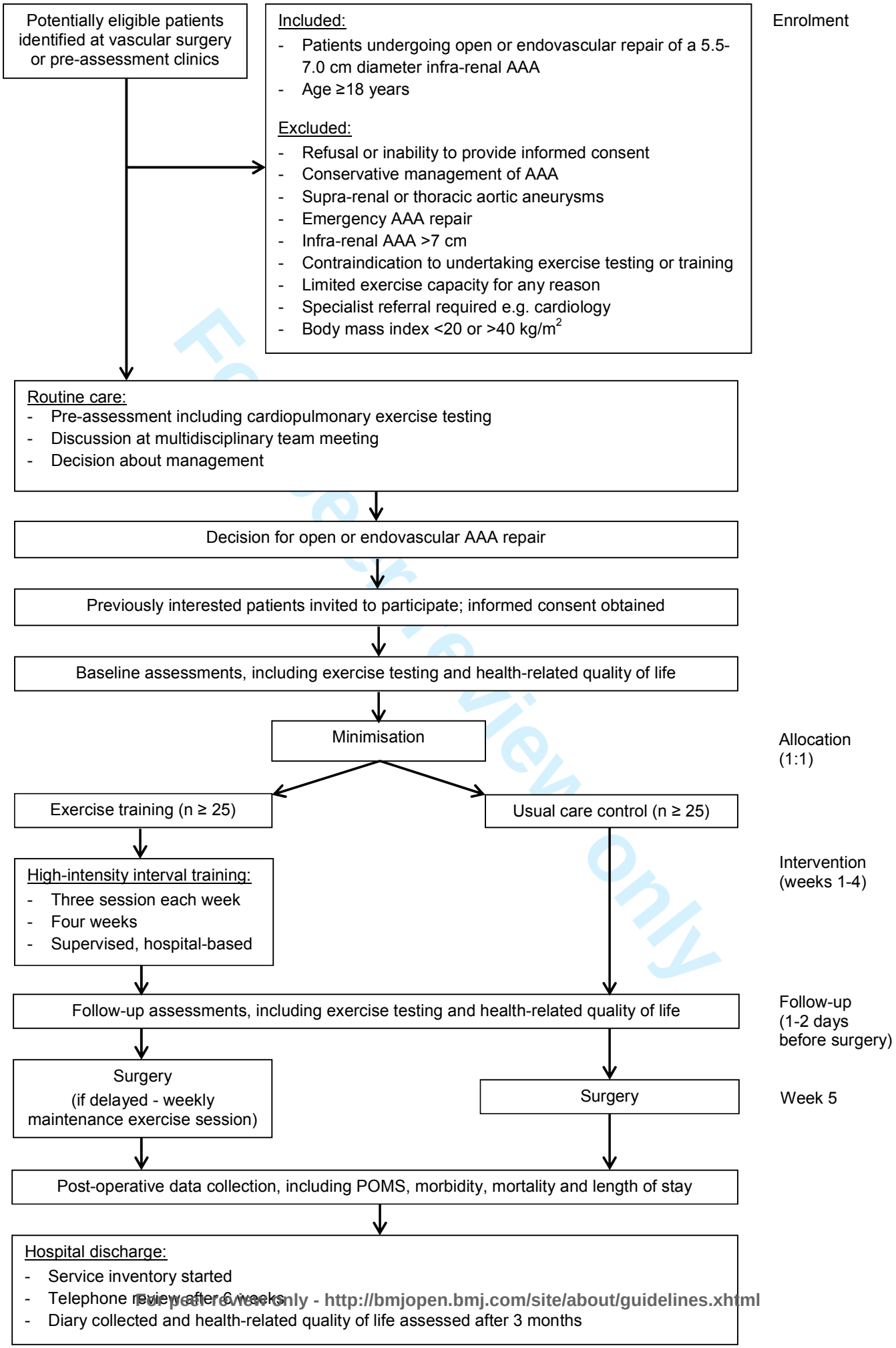
Figure legends

Figure 1 Study flowchart



HIT-AAA: Study Data Collection Form (Case Report Form)

Participant study number: _____ Participant initials: _____

Site: South Tees / York / Sheffield

Paperwork checklist (please tick):

- Written informed consent provided? [ ]
- Patient information sheet and copy of consent to patient [ ]
- Patient information sheet and copy of consent in medical notes [ ]
- Place study sticker in patient's notes [ ]
- Complete GP letters informing of patient's entry into study [ ]

1. Baseline data (week 0) **Date……**

Age	years	**Body mass**	kg
Sex		**Stature**	cm
Body mass index	kg/m^2	**Size of AAA**	cm
Baseline observations	BP:	RHR:	Sats: %
Date of vascular pre-assessment clinic			
METs score			
ASA score			
Modified revised cardiac risk index (answer yes or no)			
	Ischaemic heart disease		
	Congestive cardiac failure		
	Cerebrovascular disease		
	Insulin for diabetes mellitus		
	Creatinine > 177 µmol/l		
	Age >70 years		
	Abnormal electrocardiogram		
	Rhythm (other than sinus)		
Quantify abnormality			
	Uncontrolled blood pressure (systolic >160 mmHg, diastolic >90 mmHg)		
Other co-morbidities	Chronic obstructive pulmonary disease		
	Asthma		
	Other respiratory disease		
	Smoker (also tick if quit within 6 months)		
	Diabetes mellitus		
	Peripheral arterial disease		
	Gastrointestinal disease		
	Other (free text):		
Baseline creatinine (µmol/l)			
Baseline eGFR (ml/min)			
Baseline haemoglobin (mg/dL)			
Medications (please circle)	ACE inhibitor	Statin	Beta-blocker
	Calcium channel blocker	Antiplatelet A C D	Angiotensin II receptor antagonist
	NSAIDs	Diuretic	Insulin
	Warfarin	Oral hypoglycaemics	

A, aspirin; AAA, abdominal aortic aneurysm; ACE, angiotensin converting enzyme; ASA, American Society of Anesthesiologists; BP, blood pressure; C, clopidogrel; D, dypiridamole; eGMR, estimated glomerular filtration rate; MET, metabolic equivalents; NSAID, non-steroidal anti-inflammatory drug; RHR, resting heart rate.

Preference for exercise group (before randomisation) Yes / No

2. Baseline cardiopulmonary exercise test data (week 0)

Date……

Data	**Results or comment**	
Body mass		kg
Resting blood pressure		mmHg
Resting heart rate		beats/min
VO_2 at rest : Indexed		ml/kg/min
Absolute		ml/min
Anaerobic threshold Indexed		ml/kg/min
Absolute		ml/min
Power output at anaerobic threshold		W
Anaerobic threshold achieved (please circle)	Yes	No
VE/VCO_2 at anaerobic threshold		
VO_2 peak Indexed		ml/kg/min
Absolute		ml/min
Power output at VO_2 peak		W
O_2 pulse at the start of exercise		ml/beat
Peak O_2 pulse		ml/beat
Peak heart rate		beats/min
Peak blood pressure		mmHg
VE at rest		l/min
Peak VE		l/min
Inducible ischaemia (please circle)	Yes	No
Heart rate at ischaemia onset		beats/min
Ischaemia before / after anaerobic threshold (please circle)	Before	After
Oscillatory breathing pattern? (please circle)	Yes	No
Lowest exercise O_2 saturation		%
Oxygen Uptake Efficiency Slope (VO_2 ml/min / log VE l/min)		
Peak rating of perceived exertion		
Peak respiratory exchange ratio		
Reason for termination		

VCO_2, carbon dioxide production; VE, volume of expired air; VO_2, oxygen consumption.

3. Multi-disciplinary team data

Date…….

Type of surgery:	Open	EVAR	
Complexity of EVAR:	Complex	Non-complex	
Post-op destination:	Ward	HDU	ITU
Dated for surgery?	Yes	No	

Date if known: _____

4. Week 5 cardiopulmonary exercise test data

Date……

Data	**Results or comment**	
Body mass		kg
Resting blood pressure		mmHg
Resting heart rate		beats/min
VO_2 at rest : Indexed		ml/kg/min
Absolute		ml/min
Anaerobic threshold Indexed		ml/kg/min
Absolute		ml/min
Power output at anaerobic threshold		W
Anaerobic threshold achieved (please circle)	Yes	No
VE/VCO_2 at anaerobic threshold		
VO_2 peak Indexed		ml/kg/min
Absolute		ml/min
Power output at VO_2 peak		W
O_2 pulse at the start of exercise		ml/beat
Peak O_2 pulse		ml/beat
Peak heart rate		beats/min
Peak blood pressure		mmHg
VE at rest		l/min
Peak VE		l/min
Inducible ischaemia (please circle)	Yes	No
Heart rate at ischaemia onset		beats/min
Ischaemia before / after anaerobic threshold (please circle)	Before	After
Oscillatory breathing pattern? (please circle)	Yes	No
Lowest exercise O_2 saturation		%
Oxygen Uptake Efficiency Slope (VO_2 ml/min / log VE l/min)		
Peak rating of perceived exertion		
Peak respiratory exchange ratio		
Reason for termination		

VCO_2, carbon dioxide production; VE, volume of expired air; VO_2, oxygen consumption.

Preference for exercise group (following intervention) Yes / No

Week 5 Size of AAA (exercise group only) cm

If surgery delayed by >4 weeks please complete repeat exercise test sheet (p. 9)

5. Intra-operative data

Date of admission: _____

Date of intervention: _____

Days since last exercise test: _____ Test number: **1** **2** **3**

Intra-operative details

Type of repair (circle)	Open repair	EVAR
Open repair only:		
Surgical data	Aortic cross-clamp time	min
	Use of supra-renal clamp (please circle)	Yes / No min
Incision type (please circle)	Vertical / Transverse	
Other information (please circle)	Hostile abdomen Bi-iliac graft Inflammatory aneurysm	
Anaesthetic data for open repair or EVAR		
Type of anaesthetic Tick or comment as appropriate	General anaesthetic	
	Spinal	
	Spinal catheter	
	Epidural	Lumbar/Thoracic Intraop/ postop
	Combined spinal epidural anaesthesia	
	Local anaesthesia alone	
Estimated blood loss		ml
Urine output		ml
Intra-operative fluids	Crystalloids	ml
	Colloids	ml
	Cell salvaged blood	ml
	Packed cells	Units
	Fresh frozen plasma	Units
	Platelets	pools
	Cryoprecipitate	Units
Any intraoperative CVS support (circle)	Bolus	Infusion
Any intraoperative vasodilators (circle)	Bolus	Infusion
Requirement for CVS support at end of operation	Yes / No	Comment:
Post-operative care facility (circle)	Ward / HDU / ITU	

CVS, cardiovascular system; EVAR, endovascular aneurysm repair; HDU, high-dependency unit; ITU, intensive treatment unit.

Any intraoperative adverse events:

_____
_____
_____

Any adverse events between operation and midnight on day 0:

_____
_____
_____

Any other comments:

_____
_____
_____

Signature of intraoperative data collector: _____

6. Postoperative Morbidity (free text below) – including date

(a) Cardiac event

(b) Respiratory event

(c) Other event

Post-operative Morbidity Survey (POMS) data to be collected from end of surgery until discharge from hospital

7. Discharge Data

Date of discharge: _____

Date of death (write NA if not applicable): _____

Cause of death (write NA if not applicable): _____

Total hospital length of stay (nearest half day): _____

Days on ITU (write NA if not applicable): _____

Days on HDU (write NA if not applicable): _____

Date when POMS = 0: _____

8. Additional cardiopulmonary exercise test data

Date……

Data	Results or comment	
Body mass Resting blood pressure Resting heart rate		kg mmHg beats/min
VO_2 at rest : Indexed Absolute		ml/kg/min ml/min
Anaerobic threshold Indexed Absolute		ml/kg/min ml/min
Power output at anaerobic threshold		W
Anaerobic threshold achieved (please circle)	Yes	No
VE/VCO_2 at anaerobic threshold		
VO_2 peak Indexed Absolute		ml/kg/min ml/min
Power output at VO_2 peak		W
O_2 pulse at the start of exercise		ml/beat
Peak O_2 pulse		ml/beat
Peak heart rate Peak blood pressure		beats/min mmHg
VE at rest		l/min
Peak VE		l/min
Inducible ischaemia (please circle)	Yes	No
Heart rate at ischaemia onset		beats/min
Ischaemia before / after anaerobic threshold (please circle)	Before	After
Oscillatory breathing pattern? (please circle)	Yes	No
Lowest exercise O_2 saturation		%
Oxygen Uptake Efficiency Slope (VO_2 ml/min / log VE l/min)		
Peak rating of perceived exertion		
Peak respiratory exchange ratio		
Reason for termination		

VCO_2, carbon dioxide production; VE, volume of expired air; VO_2, oxygen consumption.

Postop day (0 = day of operation) Days run from 0000 – 2359	1	2	3	4	5	6	7
Put a tick in the box for each system if any criteria are fulfilled. *All criteria are changes in comparison with preoperative status.* **Level of care (1 / 2 / 3)**							
Pulmonary: New requirement for supplemental oxygen or other respiratory support. *(Include even if institutional practise or preventative for initial postoperative period)*							
Infectious: Currently on antibiotics or temperature >38 °C in the last 24 hr. *(Include antibiotic prophylaxis)*							
Renal: Presence of oliguria (500 ml/24 hr), OR increased serum creatinine (>30% from pre-op level) [baseline Cr x 1.3 = _____ µmol/L] OR urinary catheter in place.							
Gastro-intestinal: Unable to tolerate an enteral diet for any reason, including nausea, vomiting, and abdominal distension, or use of antiemetic.							
Cardiovascular system: Diagnostic tests or therapy within the last 24 h for any of the following: New myocardial infarction or ischaemia, Hypotension (requiring pharmacological therapy or fluid therapy >200 ml/hr), Atrial or ventricular arrhythmias, Cardiogenic pulmonary oedema, Thrombotic event (requiring anticoagulation).							
Central nervous system: Presence of new focal deficit, confusion, delirium or coma.							
Wound: Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound.							
Haematological: Requirement for any of the following within the last 24 hr: packed erythrocytes, platelets, fresh-frozen plasma, or cryoprecipitate.							
Pain: New postoperative pain significant enough to require strong opioids or regional analgesia. (*score until epidural is removed, strong opioids are IV morphine or oxycodone/oxycontin)*							
Data collector initials							

Please provide comments overleaf detailing:
- Any significant morbidity not described above.
- Reasons why patient still in hospital if no morbidity described above.

If patient discharged, please complete discharge data on page eight of this form

Day	Post-operative comments (include initials of data collector)
……	……
……	……
……	……
……	……
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……	……
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High-intensity Interval exercise Training before Abdominal Aortic Aneurysm repair (HIT-AAA): protocol for a randomised controlled feasibility trial

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004094.R1
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Complete List of Authors:	Tew, Garry; University of York, Department of Health Sciences Weston, Matthew; Teesside University, School of Social Sciences & Law Kothmann, Elke; James Cook University Hospital, Department of Academic Anaesthesia Batterham, Alan; Teesside University, Health and Social Care Institute Gray, Joanne; Northumbria University, Faculty of Health & Life Sciences Kerr, Karen; Northern General Hospital, Department of Anaesthesia Martin, Denis; Teesside University, Health and Social Care Institute Nawaz, Shah; Northern General Hospital, Sheffield Vascular Institute Yates, David; York Hospital, Department of Anaesthesia Danjoux, Gerard; James Cook University Hospital, Department of Academic Anaesthesia
Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Anaesthesia, Cardiovascular medicine, Health services research, Rehabilitation medicine
Keywords:	Aortic aneurysm, abdominal, Vascular diseases, Exercise, Rehabilitation, Physical fitness, Feasibility studies

High-intensity Interval exercise Training before Abdominal Aortic Aneurysm repair (HIT-AAA): protocol for a randomised controlled feasibility trial

Garry A Tew[1]
Email: garry.tew@york.ac.uk

Matthew Weston[2]
Email: m.weston@tees.ac.uk

Elke Kothmann[3]
Email: elke.kothmann@stees.nhs.uk

Alan M Batterham[4]
Email: a.batterham@tees.ac.uk

Joanne Gray[5]
Email: joanne3.gray@northumbria.ac.uk

Karen Kerr[6]
Email: Karen.Kerr2@sth.nhs.uk

Denis Martin[4]
Email: d.martin@tees.ac.uk

Shah Nawaz[7]
Email: Shah.Nawaz@sth.nhs.uk

David Yates[8]
Email: david.yates@york.nhs.uk

Gerard Danjoux[3]*
* Corresponding author
Email: Gerard.danjoux@stees.nhs.uk

1 York Trials Unit, Department of Health Sciences, University of York, York, YO10 5DD, UK

2 School of Social Sciences & Law, Teesside University, Middlesbrough, TS1 3BA, UK

3 Department of Academic Anaesthesia, James Cook University Hospital, Middlesbrough, TS4 3BW, UK

4 Health and Social Care Institute, Teesside University, Middlesbrough, TS1 3BA, UK

5 Faculty of Health & Life Sciences, Northumbria University, Benton, Newcastle-Upon-Tyne, NE7 7XA, UK

6 Department of Anaesthesia, Northern General Hospital, Sheffield Teaching Hospitals Foundation Trust, Sheffield, S5 7AU, UK

7 Sheffield Vascular Institute, Northern General Hospital, Sheffield, UK, S5 7AU, UK

8 Department of Anaesthesia, York Hospital, York, YO31 8HE, UK

Keywords

Aortic aneurysm, abdominal; Vascular diseases; Exercise; Rehabilitation; Physical fitness; Feasibility studies; Randomized controlled trial

Abstract: 298

Abstract

Introduction

In patients with large abdominal aortic aneurysm (AAA), open surgical or endovascular aneurysm repair procedures are often used to minimise the risk of aneurysm-related rupture and death; however, aneurysm repair itself carries high risk. Low cardiopulmonary fitness is associated with an increased risk of early post-operative complications and death following elective AAA repair. Therefore, fitness should be enhanced before aneurysm repair. High-intensity interval exercise training (HIT) is a potent, time-efficient strategy for enhancing cardiopulmonary fitness. Here, we describe a feasibility study for a definitive trial of a pre-operative HIT intervention to improve post-operative outcomes in patients undergoing elective AAA repair.

Methods and analysis

A minimum of fifty patients awaiting elective repair of a 5.5-7.0 cm infra-renal AAA will be allocated by minimisation to HIT or usual care control in a 1:1 ratio. Patients allocated to HIT will complete three hospital-based exercise sessions per week, for 4 weeks. Each session will include 2 or 4 minutes of high-intensity stationary cycling followed by the same duration of easy cycling or passive recovery, repeated until a total of 16 minutes of high-intensity exercise is accumulated. Outcomes to be assessed before randomisation and 24 to 48 hours before aneurysm repair include cardiopulmonary fitness, maximum AAA diameter, and health-related quality of life. In the post-operative period, we will record destination (ward or critical care unit), organ-specific morbidity, mortality, and the durations of critical care and hospital stay. Twelve weeks after discharge, participants will be interviewed to re-assess quality of life and determine post-discharge healthcare utilisation. The costs associated with the exercise intervention and healthcare utilisation will be calculated.

Ethics and dissemination

Ethics approval was secured through Sunderland Research Ethics Committee. The findings of the trial will be disseminated through peer-reviewed journals, and national and international presentations.

Trial registration: Current Controlled Trials ISRCTN09433624

Background

Major non-cardiac surgery is associated with substantial peri-operative risk; the overall mortality rate appears low (c. 1-2%), but the number of operations performed (c. 250 million per annum worldwide) results in a large absolute number of deaths [1]. Moreover, post-operative complications occur up to 5 times as frequently [1], with survivors experiencing physical limitations and reduced life expectancy [2, 3]. Identification of individuals in this 'at risk' group for death and complications creates a significant challenge to clinicians in the pre-operative period. Objective assessment of cardiopulmonary fitness in the pre-operative period utilising cardiopulmonary exercise testing (CPET) is the established gold standard across the UK. It has a developing evidence base in predicting adverse outcome across a variety of high-risk surgical procedures [4], and this has contributed substantially to clinicians' understanding of the impact of poor cardiopulmonary fitness.

There is a convincing physiological rationale linking improved cardiopulmonary fitness to a reduction in adverse outcome following surgery. The surgical stress response involves neuroendocrine, metabolic and inflammatory effects leading to a catabolic state and increased basal metabolic rate (up to three times pre-operative values [5, 6]). A patient with adequate cardiopulmonary fitness is able meet these extra demands post-operatively, but patients with inadequate fitness levels might be unable to cope, leading to tissue hypoxia and peri-operative complications. Approximately half of patients presenting for intra-abdominal surgery do not have the pre-requisite fitness, on objective exercise testing, to be deemed 'low risk' for peri-operative complications [7]. It is intuitive that improving fitness levels in the pre-operative period will translate to reduced death and complications following major surgery.

Little is known about the impact of pre-operative exercise training on post-operative outcomes. In a recent systematic review [8], the authors concluded that pre-operative exercise therapy prior to cardiac or abdominal surgery results in a reduced hospital length of stay and reduced post-operative morbidity, but that more research is required on the impact and long-term benefits. However, of the five studies identified that focused on cardiac and abdominal surgery, four involved inspiratory muscle training with pulmonary complications as the primary outcome. Clearly, this intervention improves respiratory muscle function, which might reduce post-operative pulmonary morbidity. However, this form of training is unlikely to favourably influence the wider range of sequelae of the surgical stress response. Only one study focused on the effect of a more general pre-surgery exercise training intervention. Arthur *et al*. [9] reported a reduction in median hospital length of stay of 1-day (vs. usual care control) following coronary artery bypass graft surgery with an 8-10 week exercise training programme plus education reinforcement and social support. The intervention involved 30 minutes of aerobic interval training, performed twice a week at 40-70% of functional capacity.

We believe that a programme of research is needed now to evaluate the benefits of pre-operative exercise training in patients undergoing elective non-cardiothoracic surgery. Abdominal aortic aneurysm (AAA) is a frequently lethal disease occurring in ~5% of males aged 50-79 years [10]. Annually 5,000-6,000 surgical repairs are performed across the UK [11], making this an ideal homogenous high-risk target

population. The incidence of co-morbid disease is higher than other age-matched surgical populations: cardiac disease 60-70%, respiratory disease 40-50%, long-term smoking 50-80%, renal disease 10-12% and diabetes 10-12% [12]. Anecdotal observation from >1000 CPETs confirms that this population is also substantially less fit than other age-matched surgical populations. Findings from two recent publications also support the adverse impact of poor fitness on outcome in patients undergoing AAA repair [13, 14].

Intervention for AAA can be performed by either open or endovascular repair (EVAR), with a current ratio nationally of 55:45 in favour of EVAR [11]. 30-day mortality for open surgery in the UK in 2008 was 7-8% [12]. Earlier studies from the USA [15] and the Netherlands [16] reported major post-operative morbidity of 30-40%. Endovascular treatment is less invasive, with mortality and cardio-respiratory morbidity rates of 2-3% [11, 12] and 10-15% [15, 16], respectively. For open surgery the UK mortality rate was higher than expected with respect to comparable countries, prompting the publication of a Quality Improvement Programme document with the explicit remit of standardising management to improve outcome [11]. Encouragingly such standardisation has brought about a significant 30-day mortality benefit for both procedures in the Vascular Society's most recent publication: 4.3% and 0.9% for open AAA and EVAR respectively [17]. Despite this there remains significant room for improvement. No information is routinely available on non-fatal complications, which are up to five times more prevalent than mortality and known to affect patient quality of life and overall life expectancy on hospital discharge. In addition, a key omission from the guidance is evidence or advice in relation to improving preoperative fitness, despite the fact that one of the main conclusions of the EVAR-2 study was that vascular teams should be focusing on techniques to improve patient fitness preoperatively [18].

The proposed benefits of exercise "prehabilitation" are mediated by increases in cardiopulmonary fitness. Two pilot randomised controlled trials undertaken by our research team have documented improvements in cardiopulmonary fitness following moderate-intensity endurance exercise training in patients under surveillance for a small AAA. Kothmann *et al*. [19] reported a 10% increase in the oxygen consumption at the ventilatory threshold (a sub-maximal marker of cardiopulmonary fitness of prognostic significance) after 6 weeks of moderate-intensity cycling exercise performed for 30 minutes twice weekly. Tew *et al*. [20] observed a 2.5 $mL \cdot kg^{-1} \cdot min^{-1}$ (~20%) improvement in the ventilatory threshold after 12 weeks of moderate-intensity cycling and treadmill walking exercise performed for 35-45 minutes thrice weekly. A recent review of preoperative exercise training [21] proposed a research agenda, with future directions including the role of prehabilitation in improving fitness levels prior to major surgery, the use of robust study designs with appropriate outcome measures, and evaluations of the effects of high-intensity interval exercise training (HIT) as a model for which there is extensive evidence of benefit in other subject groups, including heart failure patients [22]. A recent literature review by Giraud in cardiac rehabilitation [23] concluded that when compared to moderate intensity training, HIT has a similar safety profile (low absolute risk) and produces greater and more time-efficient improvements in fitness. For the current proposal HIT therefore represents a particularly attractive approach, as the time-window for intervention once a patient has been identified for aneurysm repair might be as short

as 4-6 weeks [11]. Therefore, an intervention with the potential for more rapid fitness benefits is preferable.

Our programme of work is aligned to the Medical Research Council's guidance for developing and evaluating complex interventions [24]. Given the limited extent of the evidence base, a feasibility study is clearly required to inform a subsequent definitive trial. The MRC guidance stresses that crucial feasibility work is often absent or insufficient, with 'definitive' trials undermined by acceptability, adherence, and delivery of the intervention, recruitment and retention issues, and smaller than expected effect sizes.

We are conducting a feasibility study to explore the potential benefits of a 4-week HIT programme, delivered prior to surgery for AAA repair. This will be stationary cycle-based, in-hospital and undertaken 3 times per week.

Aims

1. Explore potential primary outcomes for a subsequent definitive randomised controlled trial (RCT)
The physiological rationale suggests a causal pathway between adaptations consequent to exercise training and reduced mortality and morbidity. Potential primary outcomes for a definitive trial therefore include 30-day mortality, morbidity [Post-Operative Morbidity Survey (POMS) score], health-related quality of life (HRQOL), hospital length of stay, costs and cost-effectiveness

2. Examine the suitability of the exercise training for a subsequent definitive RCT
High-intensity interval training shows much promise as an efficacious, time-efficient and also enjoyable intervention for improving fitness. However, it has not been employed with AAA patients awaiting repair.

3. Examine the willingness of patients to be randomised and explore potential patient preferences
In RCTs, patients might have strong treatment preferences resulting in a refusal to be randomised, affecting the generalisability of results. Or, they might agree to be randomised but suffer from 'resentful demoralisation' if they end up in the non-preferred arm of the trial, leading to poor adherence. This issue requires examination in a feasibility study, as the preference effects for exercise vs. control in this patient population are unknown. Theoretically, patients might have a preference for the exercise arm due to a belief in the benefits. Notwithstanding the patient information provided, others might be fearful of engaging in high-intensity exercise prior to surgery and therefore might exhibit a preference for the control arm. These issues could affect the success of a definitive trial.

Objectives

(Aim 1)
Define the characteristics of the potential outcome measures. Specifically,
1. Define the distribution (e.g. log-normal, Poisson etc. for, e.g., length of hospital stay) and estimate the variability for the potential primary outcome measures to inform sample size planning for a subsequent definitive trial.

2. Estimate the effect size (intervention minus control) for each potential outcome variable (point estimate and its uncertainty). This information reflects the effectiveness of the intervention and the 'noise' in the measurement (precision of the measure) and together with the other information will inform the choice of primary outcome for a subsequent trial.
3. Assess the ease of data collection for each potential primary outcome (including participant and clinician burden, assessed via qualitative data).

(Aim 2)
This will specifically include; objective fitness changes, safety, enjoyment, delivery and adherence of the exercise intervention

(Aim 3)
Examine the strength of patient preferences for either the intervention or control arms (qualitative data). These data will be elicited from all patients assessed as eligible, to determine the extent to which preferences affect both recruitment and adherence.

Methods/Design

Study Design

Three-centre, two-arm, parallel-group, randomised, controlled feasibility study. The study flowchart is shown in Figure 1. Ethics approval was secured through Sunderland Research Ethics Committee (reference 13/NE/0116) in May 2013.

Figure 1 Flowchart of the study
AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair; POMS, post-operative morbidity survey

Study Population and Recruitment Routes

Patients being assessed for surgery for a 5.5-7.0 cm AAA will be approached via vascular surgical or preoperative assessment clinics at recruiting institutions. Potential recruits will be approached at this stage by a study investigator and, if interested, provided a study information sheet. Where an investigator is not available, a study information letter will be sent to the patient requesting permission to contact them about the study.

Sample Size

The sample size for a feasibility study should be adequate to estimate critical parameters with sufficient precision. Herein, the critical outcome is adherence to the exercise intervention. A patient will be deemed compliant if they complete ≥75% of the scheduled sessions; i.e. 9/12 sessions for a 4-week intervention, plus all once-weekly maintenance sessions if surgery is delayed. We define success with respect to adherence as a lower limit of 0.67 (c. 2/3 of the population) for the 90%

confidence interval for the proportion of the exercise group complying with the intervention. We estimate that ≥85% of the exercise group will be 'compliers' based on our pilot studies in small AAA patients [19, 20]. A 90% confidence interval for a single proportion around a value of 0.85 is 0.68 to 0.95 with n=25 patients. Using a 1:1 allocation ratio we require 25 patients per trial arm, 50 in total.

A minimum of 50 participants will therefore be recruited to the study.

Approximately 150 repairs of AAA <7.0 cm are performed across our three clinical institutions annually. Assuming 30% attrition for specialist referral and lack of pre-requisite fitness, approximately 176 potential patients will be available in our 21-month recruitment time-window.

Clinical Assessment

The clinical assessment processes described are based on routine practice at the recruiting institutions. All patients who are being considered for an elective AAA repair will attend a preoperative assessment clinic. Here, an individual's clinical risk profile for surgery will be established using history of relevant co-morbidities, physical examination and CPET. Evidence-based optimisation of medication will be performed at this stage.

After risk profiling, a patient's treatment options are discussed in a vascular multidisciplinary team meeting comprising input from surgery, anaesthesia and radiology. A risk-benefit assessment is undertaken based on a nationally agreed care pathway [11]. There are three possible outcomes: open aneurysm repair, EVAR or conservative management (i.e. when surgical risk is deemed too great or the patient elects not to proceed). The most appropriate postoperative care facility is also determined.

Eligibility criteria – see figure 1

Recruitment

Patients who express an interest at clinic, or who are sent a study information letter, will be contacted by telephone inviting participation (if no exclusion criteria). With verbal consent, the baseline assessment will be scheduled.

Baseline assessment

Written informed consent will be obtained. Participants will confirm their medical history and current medication and undergo a physical examination. Baseline measurements will then be recorded, including:

- Patient characteristics (sex, stature, body mass, body mass index)
- Resting pulse, blood pressure and oxygen saturations
- Maximum AAA diameter via trans-abdominal ultrasound (not if an ultrasound scan has been performed within the previous 8 weeks)
- Cardiopulmonary fitness via CPET. The CPET data will be used to identify the intensity at which the patients in the exercise group will initiate training. We have previously demonstrated the reliability of CPET in AAA patients [25].

Testing will be performed according to an agreed protocol across all recruiting sites (available on request).

- HRQOL using the Medical Outcomes Study SF-36 version 2 questionnaire and the EuroQol EQ-5D-5L questionnaire, both of which have been used previously in AAA patients [18, 26, 27].
- Participant preference for 'exercise' training or 'usual care' – prior to randomisation to explore patient preferences and subsequent changes in attitude consequent to the intervention. This design permits the exploration of the effects of preference in the analysis [28].

Randomisation

After baseline assessment, patients will be randomly allocated 1:1 to exercise or usual care control (no supervised exercise), using minimisation to ensure balance across trial arms for important prognostic factors. We do not list these factors here, to avoid any risk of the staff recruiting patients being able to decipher the allocation sequence. Full details of the minimisation process will be published in a separate document with restricted access. The study statistician (AB) will conduct the minimisation process remotely via e-mail.

Exercise Intervention (weeks 1-4)

The exercise intervention period will be for 4 weeks leading up to surgery. Where possible, participants (exercise and control) will have a surgical date booked for the following week (week 5).

The exercise programme is broadly based on that which has been shown to be safe and effective for improving cardiopulmonary fitness in patients undergoing cardiac rehabilitation [22, 29-31]. Patients allocated to the exercise group will complete three sessions of hospital-based HIT per week, throughout the 4-week pre-operative period. Exercise will be stationary cycling (Optibike Med, Ergoline, Germany), which has been reported to be a preferred mode for vascular patients (unpublished observations). Each session will begin and end with 10 and 5 minutes of unloaded cycling, respectively. In the first week of training, the main body of each session will involve eight 2-minute bouts of cycling, interspersed with 2-minute periods of unloaded cycling or "off-the-bike" slow walking, depending on patient preference. All of the "work" bouts during the very first session will be performed at the power output associated with ventilatory threshold determined on baseline CPET (i.e. the demarcation between moderate and heavy exercise intensity domains [32]). In subsequent sessions, power output will be gradually manipulated until the patient reports a perceived exertion of 6-7 on Borg's CR-10 scale [33] (i.e. hard to very hard) at the end of each work interval. However, for safety reasons, the intensity of exercise will be made easier if systolic blood pressure exceeds 180 mm Hg [34] or if heart rate exceeds 95% of the maximum observed on baseline CPET. In weeks 2-4, and for variety, the patient will be allowed to choose between doing four 4-minute work bouts or eight 2-minute bouts as the main body of each exercise session, both with a 1:1 work-to-rest ratio. Thus, each session will last ~45 minutes regardless of patient choice, which will include 16 minutes of high-intensity exercise. An experienced physiotherapist will supervise each session and record power output, perceived exertion, and blood pressure (manual sphygmomanometer) at the end of

each work interval. Heart rate will be recorded continuously at 5 s intervals through the entire exercise session (Polar RS400, Kempele, Finland). The collection of such data will permit a detailed quantification of the exercise intervention. Patients who do not undergo surgery in week 5 will complete one HIT session per week up until surgery to maintain fitness [35]. All adverse events will be recorded.

Information in relation to *participant's perceived enjoyment of exercise* is important to monitor. This is of relevance in adherence to the programme, whilst providing valuable information for planning a definitive study. We therefore plan to assess:

1. Changes in enjoyment of exercise both within sessions and throughout the programme. Perceived or likely enjoyment can change prior, during and after exercise as a consequence of a variety of factors e.g. anxiety, enjoyment, fatigue. We therefore plan to ask participants to assess enjoyment/perceived enjoyment of exercise prior to commencing, during and 20 minutes after exercise using a simple validated rating scale [36]. This will take <30 seconds to administer on each occasion and will be done during the first (baseline), 3rd, 6th, 9th and 12th sessions to track changes consequent to the programme.
2. Overall enjoyment of the exercise programme will be assessed during the week 5 assessment, using the validated multi-dimensional physical activity enjoyment scale (PACES) [37]. This will be 2-3 days following completion of the overall programme, allowing participants reflection and evaluation time (see week 5 assessment below).

Two experienced exercise scientists will be responsible for ensuring treatment fidelity of the exercise programme (GT, MW).

Safety Considerations

There are two main safety considerations regarding running a programme of HIT in patients with AAA disease:

1. Cardiac risk – as previously outlined 60-70% of individuals with AAA disease suffer from comorbid cardiac disease. The baseline assessment of clinical risk profile and CPET will be instrumental in assessing this risk in detail, under the stress of exercise, at the outset. A recent review by Guiraud *et al*. [23] highlights the safety of HIT in patients with underlying coronary disease, heart failure and patients at risk of cardiovascular disease. We are reassured by their conclusion which states "there is growing scientific evidence that HIT presents little danger for selected stable cardiac patients, provided that the prescribed protocols are respected".

   In the event of an adverse cardiac event we will have the following in place:
   - Staff experienced and Intermediate Life Support-trained
   - Resuscitation equipment and oxygen immediately available
   - Hospital cardiac arrest team fully informed of time and place of training sessions
   - Participants requiring further assessment will be transferred to the Accident and Emergency Unit within the relevant hospital.

   All institutions have Cardiology expertise immediately available on site.

2. Risk of AAA expansion or rupture – an intuitive concern regarding exercise testing and training in patients with aneurysms is of excessive rises in double-product (systolic blood pressure × heart rate) evoking aneurysm expansion and rupture. However, the available evidence suggests that these concerns are unfounded. For example, no aneurysm ruptures or excessive aneurysm growth rates were reported in any of the three studies of moderate-intensity exercise training in patients with early AAA disease (from >4000 exercise sessions; [19, 20, 38]), two of which were conducted at our institutions [19, 20]. Further unpublished data from our institutions indicate no ruptures from >1300 maximal exercise tests in patients with large asymptomatic AAA being considered for elective aneurysm repair. Moreover, through national networked connections, and other relevant publications, we believe this position of safety to be correct for >5000 maximal exercise tests. This position is also supported by the European guidelines for the management of AAA disease, which state that physical activity is not associated with AAA growth [39], as well as the ACC/AHA Practice Guidelines for the Management of Patients with Peripheral Vascular Disease [40], which suggest that AAA patients should not be fearful of vigorous activity. The only reported adverse event we are aware of came from the patient series of Best *et al*. [41] where a rupture occurred 12 hours after maximal exercise testing in a patient with a 6.1 cm AAA, yielding a rupture rate for this study of 0.4%. However, the causal relationship between exercise and rupture is difficult to establish given the 12-hour intervening period.

   It would therefore appear that the risk of AAA growth or rupture is very low in the context of exercise training for individuals with both small and large aneurysmal disease. This risk would appear to be <1:5,000. When balanced against national perioperative mortality/morbidity figures available for surgery in the UK at present, we feel that this represents clear benefit in favour of undertaking the preoperative exercise as set out.

   In the event of a suspected AAA rupture patients would immediately be transferred to the Accident and Emergency department for prompt further evaluation. All clinical institutions have on-site vascular teams able to immediately respond to such a situation.

Despite this we see risk minimisation in this context as our primary concern and will implement the following control measures:

- Thorough pre-participation screening
- Exclusion of high-risk patients
- Hospital-based exercise testing and training
- Exercise sessions supervised by experienced cardiac physiotherapists trained in Intermediate Life Support
- Exercise sessions performed >3 hours after waking given the higher frequency of cardiovascular events during the morning hours [42]
- Prompt evaluation of prodromal symptoms
- Resuscitation equipment and oxygen immediately available
- Exercise termination if a patient has signs/symptoms suggestive of distress, cardiac or AAA adverse event

- Reduction in exercise intensity if a patient has systolic blood pressure rise to >180 mm Hg, or heart rate >95% of their maximum (from baseline CPET)

Safety Governance

In line with Medical Research Council guidance we have developed the following safety governance structure for the study:

- Data Monitoring and Ethics Committee (DMEC) – the DMEC comprises three academics/clinicians with appropriate expertise who are independent from the running of the study. Any serious adverse events will be reported to and fully investigated by the DMEC. The DMEC will make recommendations to the Trial Steering Committee with regards to any ethical or safety concerns they may have.
- Trial Steering Committee (TSC) – this committee is led by the Chief Investigator (CI), with representation from all collaborating clinical and academic institutions. A lay representative will be approached to sit on the committee. The TSC will meet 3 times per year to discuss all elements of study progress and conduct.
- TSC Safety Committee – a formal study safety committee has been established and comprises 3 study investigators, including the CI. This group has the remit of ensuring all appropriate safety standards are in place prior to study commencement, and during the course of the research.

All adverse and serious adverse events will be managed within the strict governance arrangements of the study sponsor and participating clinical institutions.

Week 5 assessments

During week 5 it is anticipated that participants will undergo AAA repair. In the same week, but 1-2 days prior to surgery, assessments will be performed in all participants. The outcomes, which are primarily aimed at investigating the safety and effectiveness of the exercise intervention compared with usual care, will include:

- Cardiopulmonary fitness via CPET (to assess fitness changes from baseline)
- Maximum AAA diameter via trans-abdominal ultrasound (to establish safety of exercise in relation to aneurysm growth)
- HRQOL questionnaires
- PACES assessment for overall exercise programme enjoyment (exercise intervention group only)

Due to logistical reasons it is anticipated that not all participants will undergo surgery in week 5. This will mainly be due to a temporary lack of hospital beds for admission preoperatively, or critical care post-operatively. In this situation, surgery will be rescheduled, where possible, within 4 weeks. A repeat CPET will be undertaken in patients whose surgery is delayed >4 weeks, to ensure we have an accurate assessment of pre-operative fitness in all patients. A CPET assessment of those patients who have performed one high-intensity training session per week from week 5 onwards will provide further valuable information of the dose-response nature of high-intensity training in this population.

An overview of data to be collected for this aspect of the study can be seen on the study Case Report Form (see Additional file 1).

Perioperative period

Participants will undergo open or endovascular aneurysm repair as determined at the multidisciplinary team meeting. All perioperative care will be at the discretion of the vascular teams (as per usual practice) who will be blinded to group allocation. Perioperative data will be collected as seen in Additional file 1.

Post-operatively an investigator blinded to group allocation will determine the following:

- Destination – ward or critical care unit
- Postoperative Morbidity Survey Score (POMS) – a validated tool used to assess organ-specific morbidity in the post-operative period [43, 44]. Scores will be collected daily.
- Mortality
- Length of critical care and hospital stay

Post-discharge follow-up

At hospital discharge patients will be asked to keep a service receipt inventory to record treatment/care requirements for a 12-week period to inform the resource utilisation analysis. Participants will be interviewed via telephone at 6 weeks, with a follow-up appointment at 12 weeks after discharge to assess:

- HRQOL
- Resource utilisation
- Hospital readmissions, with diagnosis, within 12 weeks of initial discharge

Analysis Plan of Quantitative Study

Adherence with the exercise intervention will be analysed as described in the sample size justification, above, via the confidence interval for a single proportion. For the potential primary outcomes for a subsequent definitive trial, the likely effect of the exercise intervention will be estimated via standard intervention minus control comparisons (accounting for the type of variable and its distributional properties). We will examine the disposition of the 90% confidence interval for the observed effect to the minimum clinically important difference for each variable. Inasmuch as this is a feasibility study, these comparisons are exploratory and are intended to inform the subsequent trial. Data management will be performed according to the governance arrangements of the institutions involved in the project.

Analysis of Health Economics and Cost Effectiveness

A prospective economic evaluation will be rehearsed to develop and refine methods for a subsequent definitive trial. The main focus will be on how to accurately identify, quantify and value the additional costs of delivering the intervention and the potential resource implications versus usual care post-operatively and post-discharge. The costing approach will incorporate a broad analytical perspective (National Health Service and Social Services), which will help to detect cost-shifting between sectors. Resources utilised in the exercise group will be identified in terms of capital equipment and staff time. A staff-reported health economics questionnaire has been

developed to facilitate this (available upon request). Post-operative resource use will also be explored for all participants in terms of bed days (including critical care bed days). Post-discharge resource use for all treatment/care related to AAA surgery will be assessed retrospectively for 12 weeks by piloting the use of a self-report Service Receipt Inventory (patient diary). This will facilitate the development of a reliable and valid tool to capture resource use. Appropriate unit costs to be applied to resource use will be identified. These will be sourced from a combination of local costings and national databases [45, 46]. All costs will be combined to rehearse the methods for total health and social care cost estimation in a subsequent definitive trial.

The methods to estimate an incremental cost-effectiveness ratio for exercise versus usual care in terms of Quality Adjusted Life Years will be rehearsed (using EQ-5D 5L administered at baseline and 12 weeks post discharge). In particular, issues relevant for sensitivity analysis will be explored to help understand how best to deal with statistical imprecision and other uncertainties in the full trial. For example, data will be bootstrapped to account for the expected skewness evident in economic cost data. The data collected as part of this feasibility study could be used to inform subsequent pre-trial modelling.

Analysis of Participant Interviews

We aim to explore participants' post-discharge experience. From a critical realism perspective, semi-structured interviews will cover quality of life, function and attitudes to exercise including fear.

Sixteen participants will be recruited using purposive sampling and the following criteria: men and women; a range of ages; both study groups; both forms of aneurysm repair; and a range of experiences post-discharge. The interviews (1 hour with a research nurse; audio-recorded and transcribed) will take place in the hospital at the 12-week post-discharge visit. Transcripts will be analysed thematically using quantitative and diary data for triangulation.

Qualitative data (brief interview) will also be collected from all participants (and from clinical outcome assessors where relevant) to assess the ease of data collection for each potential primary outcome (participant and clinician burden), to evaluate the perceived enjoyment of the exercise intervention, and to examine the strength of patient preferences for either the intervention or control arms. These data will be elicited from all patients assessed as eligible, to help determine the extent to which preferences affect both recruitment and adherence.

Criteria for success

A subsequent definitive RCT will be deemed feasible if:
1. An appropriate primary outcome variable is defined;
2. The lower limit of the 90% confidence interval for the proportion of the exercise intervention group complying with the intervention is ≥67%. A patient is defined as having complied with the intervention if he completes ≥75% of the scheduled sessions;
3. Patient preferences are not so strong that they result in the conclusion that an RCT is not a feasible design.

Dissemination strategy

The dissemination strategy for this research will be to inform a wide range of local, national and international audiences about the results and conclusions. It must however be remembered as part of this strategy that the current proposal is for preliminary work aimed at defining a subsequent definitive clinical trial.
1. Health professionals – we aim to publish our research in journals that cover the relevant medical specialties and with preference for those that deposit publications in open access databases to increase free dissemination. In addition, we aim to present this research at appropriate national and international conferences.
2. Users – from this perspective we aim in the first instance to collaborate with our patient representatives (from advisory and steering groups) and local experts in patient and public involvement to best facilitate user dissemination. We plan to write a specific news piece that will be forwarded to appropriate groups and organisations.
3. Service managers – as an exploratory study it is unlikely that results from this study will directly influence commissioning processes in the short term. More we will engage with appropriate primary and secondary care groups to discuss support for our proposed definitive study leading on from this research.

Trial status

Start date: 1 August 2013

Expected end date: 30 May 2015

Expected publication date: 1 January 2016

Status at time of submission of this article: approvals obtained, but not yet recruiting

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List of abbreviations used (if any)

AAA	abdominal aortic aneurysm
CPET	cardiopulmonary exercise testing
EVAR	endovascular aneurysm repair
HIT	high-intensity interval exercise training
HRQOL	health-related quality of life
PACES	physical activity enjoyment scale
POMS	post-operative morbidity survey
RCT	randomised controlled trial

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Authors' contributions

GT drafted the manuscript and contributed to the design of the study. Original study concept was by GD and AB. All co-authors contributed to the design of the study. GD is Chief Investigator for the project. EK is Principal Investigator (PI) at James Cook University Hospital (South Tees), SN is PI at Northern General Hospital (Sheffield) and DY is PI at York Hospital. All authors contributed to the critical revision of the manuscript for important intellectual content and read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Figure legends

Figure 1 Study flowchart

High-intensity Interval exercise Training before Abdominal Aortic Aneurysm repair (HIT-AAA): protocol for a randomised controlled feasibility trial

Garry A Tew[1]
Email: ~~g.tew@shu.ac.uk~~garry.tew@york.ac.uk

Matthew Weston[2]
Email: m.weston@tees.ac.uk

Elke Kothmann[3]
Email: elke.kothmann@stees.nhs.uk

Alan M Batterham[4]
Email: a.batterham@tees.ac.uk

Joanne Gray[5]
Email: joanne3.gray@northumbria.ac.uk

Karen Kerr[6]
Email: Karen.Kerr2@sth.nhs.uk

Denis Martin[4]
Email: d.martin@tees.ac.uk

Shah Nawaz[7]
Email: Shah.Nawaz@sth.nhs.uk

David Yates[8]
Email: david.yates@york.nhs.uk

Gerard Danjoux[3]*
* Corresponding author
Email: Gerard.danjoux@stees.nhs.uk

1 York Trials Unit, Department of Health Sciences, University of York, York, YO10 5DD, UK~~Centre for Sport and Exercise Science, Sheffield Hallam University, Sheffield S10 2BP, UK~~

2 School of Social Sciences & Law, Teesside University, Middlesbrough, TS1 3BA, UK

3 Department of Academic Anaesthesia, James Cook University Hospital, Middlesbrough, TS4 3BW, UK

4 Health and Social Care Institute, Teesside University, Middlesbrough, TS1 3BA, UK

5 Faculty of Health & Life Sciences, Northumbria University, Benton, Newcastle-Upon-Tyne, NE7 7XA, UK

6 Department of Anaesthesia, Northern General Hospital, Sheffield Teaching Hospitals Foundation Trust, Sheffield, S5 7AU, UK

7 Sheffield Vascular Institute, Northern General Hospital, Sheffield, UK, S5 7AU, UK

8 Department of Anaesthesia, York Hospital, York, YO31 8HE, UK

Abstract

Background

Abdominal aortic aneurysm (AAA) is a frequently lethal disease affecting ~5% of men aged 50-79 years. In patients with large AAA (diameter >5.5 cm), mechanical intervention (i.e., open surgical or endovascular aneurysm repair) is often used to minimise the risk of aneurysm-related rupture and death; however, aneurysm repair itself carries high risk.

Low cardiopulmonary fitness is associated with an increased risk of early post-operative complications and death following elective AAA repair. Therefore, fitness should be enhanced before aneurysm repair. High-intensity interval exercise training (HIT) is a potent, time-efficient strategy for enhancing cardiopulmonary fitness. However, the feasibility, safety and effectiveness of HIT in patients awaiting AAA repair is unknown.

Here, we describe a feasibility study for a definitive trial of a pre-operative HIT intervention to improve post-operative outcomes in patients undergoing elective AAA repair. The main aim is to identify the primary outcome and estimated sample size for a definitive trial. A secondary aim is to investigate the suitability of HIT, primarily in terms of adherence, safety, acceptability, and its potential impact on cardiopulmonary fitness and post-surgery outcomes.

Methods/Design

This is a two-arm randomised controlled trial. A minimum of fifty patients awaiting elective repair of a 5.5 to 7.0 cm infra-renal AAA will be allocated by minimisation to HIT or usual care control in a 1:1 ratio. Patients allocated to HIT will complete three hospital-based exercise sessions per week, for 4 weeks. Each session will include 2 or 4 minutes of high-intensity stationary cycling followed by the same duration of easy cycling or passive recovery, repeated until a total of 16 minutes of high-intensity exercise is accumulated. Outcomes to be assessed before randomisation and 24 to 48 hours before aneurysm repair (week 5 where possible) include cardiopulmonary fitness, maximum AAA diameter, and health-related quality of life. In the post-operative period, we will record destination (ward or critical care unit), organ-specific morbidity, mortality, and the durations of critical care and hospital stay. Twelve weeks after discharge, participants will be interviewed to re-assess quality of life and determine post-discharge healthcare utilisation. The costs associated with the exercise intervention and healthcare utilisation will be calculated.

Trial registration

Current Controlled Trials ISRCTN09433624

Keywords

Aortic aneurysm, abdominal; Vascular diseases; Exercise; Rehabilitation; Physical fitness; Feasibility studies; Randomized controlled trial

Background

Major non-cardiac surgery is associated with substantial peri-operative risk; the overall mortality rate appears low (c. 1-2%), but the number of operations performed (c. 250 million per annum worldwide) results in a large absolute number of deaths [1]. Moreover, post-operative complications occur up to 5 times as frequently [1], with survivors experiencing physical limitations and reduced life expectancy [2, 3]. Identification of individuals in this 'at risk' group for death and complications creates a significant challenge to clinicians in the pre-operative period. Objective assessment of cardiopulmonary fitness in the pre-operative period utilising cardiopulmonary exercise testing (CPET) is the established gold standard across the UK. It has a developing evidence base in predicting adverse outcome across a variety of high-risk surgical procedures [4], and this has contributed substantially to clinicians' understanding of the impact of poor cardiopulmonary fitness.

There is a convincing physiological rationale linking improved cardiopulmonary fitness to a reduction in adverse outcome following surgery. The surgical stress response involves neuroendocrine, metabolic and inflammatory effects leading to a catabolic state and increased basal metabolic rate (up to three times pre-operative values [5, 6]). A patient with adequate cardiopulmonary fitness is able meet these extra demands post-operatively, but patients with inadequate fitness levels might be unable to cope, leading to tissue hypoxia and peri-operative complications. Approximately half of patients presenting for intra-abdominal surgery do not have the pre-requisite fitness, on objective exercise testing, to be deemed 'low risk' for peri-operative complications [7]. It is intuitive that improving fitness levels in the pre-operative period will translate to reduced death and complications following major surgery.

Little is known about the impact of pre-operative exercise training on post-operative outcomes. In a recent systematic review [8], the authors concluded that pre-operative exercise therapy prior to cardiac or abdominal surgery results in a reduced hospital length of stay and reduced post-operative morbidity, but that more research is required on the impact and long-term benefits. However, of the five studies identified that focused on cardiac and abdominal surgery, four involved inspiratory muscle training with pulmonary complications as the primary outcome. Clearly, this intervention improves respiratory muscle function, which might reduce post-operative pulmonary morbidity. However, this form of training is unlikely to favourably influence the wider range of sequelae of the surgical stress response. Only one study focused on the effect of a more general pre-surgery exercise training intervention. Arthur *et al*. [9] reported a reduction in median hospital length of stay of 1-day (vs. usual care control) following coronary artery bypass graft surgery with an 8-10 week exercise training programme plus education reinforcement and social support. The intervention involved 30 minutes of aerobic interval training, performed twice a week at 40-70% of functional capacity.

We believe that a programme of research is needed now to evaluate the benefits of pre-operative exercise training in patients undergoing elective non-cardiothoracic surgery. Abdominal aortic aneurysm (AAA) is a frequently lethal disease occurring in ~5% of males aged 50-79 years [10]. Annually 5,000-6,000 surgical repairs are performed across the UK [11], making this an ideal homogenous high-risk target

population. The incidence of co-morbid disease is higher than other age-matched surgical populations: cardiac disease 60-70%, respiratory disease 40-50%, long-term smoking 50-80%, renal disease 10-12% and diabetes 10-12% [12]. Anecdotal observation from >1000 CPETs confirms that this population is also substantially less fit than other age-matched surgical populations. Findings from two recent publications also support the adverse impact of poor fitness on outcome in patients undergoing AAA repair [13, 14].

Intervention for AAA can be performed by either open or endovascular repair (EVAR), with a current ratio nationally of 55:45 in favour of EVAR [11]. 30-day mortality for open surgery in the UK in 2008 was 7-8% [12]. Earlier studies from the USA [15] and the Netherlands [16] reported major post-operative morbidity of 30-40%. Endovascular treatment is less invasive, with mortality and cardio-respiratory morbidity rates of 2-3% [11, 12] and 10-15% [15, 16], respectively. For open surgery the UK mortality rate was higher than expected with respect to comparable countries, prompting the publication of a Quality Improvement Programme document with the explicit remit of standardising management to improve outcome [11]. Encouragingly such standardisation has brought about a significant 30-day mortality benefit for both procedures in the Vascular Society's most recent publication: 4.3% and 0.9% for open AAA and EVAR respectively [17]. Despite this there remains significant room for improvement. No information is routinely available on non-fatal complications, which are up to five times more prevalent than mortality and known to affect patient quality of life and overall life expectancy on hospital discharge. In addition, a key omission from the guidance is evidence or advice in relation to improving preoperative fitness, despite the fact that one of the main conclusions of the EVAR-2 study was that vascular teams should be focusing on techniques to improve patient fitness preoperatively [18].

The proposed benefits of exercise "prehabilitation" are mediated by increases in cardiopulmonary fitness. Two pilot randomised controlled trials undertaken by our research team have documented improvements in cardiopulmonary fitness following moderate-intensity endurance exercise training in patients under surveillance for a small AAA. Kothmann *et al*. [19] reported a 10% increase in the oxygen consumption at the ventilatory threshold (a sub-maximal marker of cardiopulmonary fitness of prognostic significance) after 6 weeks of moderate-intensity cycling exercise performed for 30 minutes twice weekly. Tew *et al*. [20] observed a 2.5 $mL \cdot kg^{-1} \cdot min^{-1}$ (~20%) improvement in the ventilatory threshold after 12 weeks of moderate-intensity cycling and treadmill walking exercise performed for 35-45 minutes thrice weekly. A recent review of preoperative exercise training [21] proposed a research agenda, with future directions including the role of prehabilitation in improving fitness levels prior to major surgery, the use of robust study designs with appropriate outcome measures, and evaluations of the effects of high-intensity interval exercise training (HIT) as a model for which there is extensive evidence of benefit in other subject groups, including heart failure patients [22]. A recent literature review by Giraud in cardiac rehabilitation [23] concluded that when compared to moderate intensity training, HIT has a similar safety profile (low absolute risk) and produces greater and more time-efficient improvements in fitness. For the current proposal HIT therefore represents a particularly attractive approach, as the time-window for intervention once a patient has been identified for aneurysm repair might be as short

as 4-6 weeks [11]. Therefore, an intervention with the potential for more rapid fitness benefits is preferable.

Our programme of work is aligned to the Medical Research Council's guidance for developing and evaluating complex interventions [24]. Given the limited extent of the evidence base, a feasibility study is clearly required to inform a subsequent definitive trial. The MRC guidance stresses that crucial feasibility work is often absent or insufficient, with 'definitive' trials undermined by acceptability, adherence, and delivery of the intervention, recruitment and retention issues, and smaller than expected effect sizes.

We are conducting a feasibility study to explore the potential benefits of a 4-week HIT programme, delivered prior to surgery for AAA repair. This will be stationary cycle-based, in-hospital and undertaken 3 times per week.

Aims

1. Explore potential primary outcomes for a subsequent definitive randomised controlled trial (RCT)
The physiological rationale suggests a causal pathway between adaptations consequent to exercise training and reduced mortality and morbidity. Potential primary outcomes for a definitive trial therefore include 30-day mortality, morbidity [Post-Operative Morbidity Survey (POMS) score], health-related quality of life (HRQOL), hospital length of stay, costs and cost-effectiveness

2. Examine the suitability of the exercise training for a subsequent definitive RCT
High-intensity interval training shows much promise as an efficacious, time-efficient and also enjoyable intervention for improving fitness. However, it has not been employed with AAA patients awaiting repair.

3. Examine the willingness of patients to be randomised and explore potential patient preferences
In RCTs, patients might have strong treatment preferences resulting in a refusal to be randomised, affecting the generalisability of results. Or, they might agree to be randomised but suffer from 'resentful demoralisation' if they end up in the non-preferred arm of the trial, leading to poor adherence. This issue requires examination in a feasibility study, as the preference effects for exercise vs. control in this patient population are unknown. Theoretically, patients might have a preference for the exercise arm due to a belief in the benefits. Notwithstanding the patient information provided, others might be fearful of engaging in high-intensity exercise prior to surgery and therefore might exhibit a preference for the control arm. These issues could affect the success of a definitive trial.

Objectives

(Aim 1)
Define the characteristics of the potential outcome measures. Specifically,
1. Define the distribution (e.g. log-normal, Poisson etc. for, e.g., length of hospital stay) and estimate the variability for the potential primary outcome measures to inform sample size planning for a subsequent definitive trial.

2. Estimate the effect size (intervention minus control) for each potential outcome variable (point estimate and its uncertainty). This information reflects the effectiveness of the intervention and the 'noise' in the measurement (precision of the measure) and together with the other information will inform the choice of primary outcome for a subsequent trial.
3. Assess the ease of data collection for each potential primary outcome (including participant and clinician burden, assessed via qualitative data).

(Aim 2)
This will specifically include; objective fitness changes, safety, enjoyment, delivery and adherence of the exercise intervention

(Aim 3)
Examine the strength of patient preferences for either the intervention or control arms (qualitative data). These data will be elicited from all patients assessed as eligible, to determine the extent to which preferences affect both recruitment and adherence.

Methods/Design

Study Design

Three-centre, two-arm, parallel-group, randomised, controlled feasibility study. The study flowchart is shown in Figure 1. Ethics approval was secured through Sunderland Research Ethics Committee (reference 13/NE/0116) in May 2013.

Figure 1 Flowchart of the study
AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair; POMS, post-operative morbidity survey

Study Population and Recruitment Routes

Patients being assessed for surgery for a 5.5-7.0 cm AAA will be approached via vascular surgical or preoperative assessment clinics at recruiting institutions. Potential recruits will be approached at this stage by a study investigator and, if interested, provided a study information sheet. Where an investigator is not available, a study information letter will be sent to the patient requesting permission to contact them about the study.

Sample Size

The sample size for a feasibility study should be adequate to estimate critical parameters with sufficient precision. Herein, the critical outcome is adherence to the exercise intervention. A patient will be deemed compliant if they complete ≥75% of the scheduled sessions; i.e. 9/12 sessions for a 4-week intervention, plus all once-weekly maintenance sessions if surgery is delayed. We define success with respect to adherence as a lower limit of 0.67 (c. 2/3 of the population) for the 90%

confidence interval for the proportion of the exercise group complying with the intervention. We estimate that ≥85% of the exercise group will be 'compliers' based on our pilot studies in small AAA patients [19, 20]. A 90% confidence interval for a single proportion around a value of 0.85 is 0.68 to 0.95 with n=25 patients. Using a 1:1 allocation ratio we require 25 patients per trial arm, 50 in total.

A minimum of 50 participants will therefore be recruited to the study.

Approximately 150 repairs of AAA <7.0 cm are performed across our three clinical institutions annually. Assuming 30% attrition for specialist referral and lack of pre-requisite fitness, approximately 176 potential patients will be available in our 21-month recruitment time-window.

Clinical Assessment

The clinical assessment processes described are based on routine practice at the recruiting institutions. All patients who are being considered for an elective AAA repair will attend a preoperative assessment clinic. Here, an individual's clinical risk profile for surgery will be established using history of relevant co-morbidities, physical examination and CPET. Evidence-based optimisation of medication will be performed at this stage.

After risk profiling, a patient's treatment options are discussed in a vascular multidisciplinary team meeting comprising input from surgery, anaesthesia and radiology. A risk-benefit assessment is undertaken based on a nationally agreed care pathway [11]. There are three possible outcomes: open aneurysm repair, EVAR or conservative management (i.e. when surgical risk is deemed too great or the patient elects not to proceed). The most appropriate postoperative care facility is also determined.

Eligibility criteria – see figure 1

Recruitment

Patients who express an interest at clinic, or who are sent a study information letter, will be contacted by telephone inviting participation (if no exclusion criteria). With verbal consent, the baseline assessment will be scheduled.

Baseline assessment

Written informed consent will be obtained. Participants will confirm their medical history and current medication and undergo a physical examination. Baseline measurements will then be recorded, including:

- Patient characteristics (sex, stature, body mass, body mass index)
- Resting pulse, blood pressure and oxygen saturations
- Maximum AAA diameter via trans-abdominal ultrasound (not if an ultrasound scan has been performed within the previous 8 weeks)
- Cardiopulmonary fitness via CPET ~~– methods and recorded variables are described above~~. The CPET data will be used to identify the intensity at which the patients in the exercise group will initiate training. We have previously

demonstrated the reliability of CPET in AAA patients [25]. Testing will be performed according to an agreed protocol across all recruiting sites (available on request).

- HRQOL using the Medical Outcomes Study SF-36 version 2 questionnaire and the EuroQol EQ-5D-5L questionnaire, both of which have been used previously in AAA patients [18, 26, 27].
- Participant preference for 'exercise' training or 'usual care' – prior to randomisation to explore patient preferences and subsequent changes in attitude consequent to the intervention. This design permits the exploration of the effects of preference in the analysis [28].

Randomisation

After baseline assessment, patients will be randomly allocated 1:1 to exercise or usual care control (no supervised exercise), using minimisation to ensure balance across trial arms for important prognostic factors. We do not list these factors here, to avoid any risk of the staff recruiting patients being able to decipher the allocation sequence. Full details of the minimisation process will be published in a separate document with restricted access. The study statistician (AB) will conduct the minimisation process remotely via e-mail.

Exercise Intervention (weeks 1-4)

The exercise intervention period will be for 4 weeks leading up to surgery. Where possible, participants (exercise and control) will have a surgical date booked for the following week (week 5).

The exercise programme is broadly based on that which has been shown to be safe and effective for improving cardiopulmonary fitness in patients undergoing cardiac rehabilitation [22, 29-31]. Patients allocated to the exercise group will complete three sessions of hospital-based HIT per week, throughout the 4-week pre-operative period. Exercise will be stationary cycling (Optibike Med, Ergoline, Germany), which has been reported to be a preferred mode for vascular patients (unpublished observations). Each session will begin and end with 10 and 5 minutes of unloaded cycling, respectively. In the first week of training, the main body of each session will involve eight 2-minute bouts of cycling, interspersed with 2-minute periods of unloaded cycling or "off-the-bike" slow walking, depending on patient preference. All of the "work" bouts during the very first session will be performed at the power output associated with ventilatory threshold determined on baseline CPET (i.e. the demarcation between moderate and heavy exercise intensity domains [32]). In subsequent sessions, power output will be gradually manipulated until the patient reports a perceived exertion of 6-7 on Borg's CR-10 scale [33] (i.e. hard to very hard) at the end of each work interval. However, for safety reasons, the intensity of exercise will be made easier if systolic blood pressure exceeds 180 mm Hg [34] or if heart rate exceeds 95% of the maximum observed on baseline CPET. In weeks 2-4, and for variety, the patient will be allowed to choose between doing four 4-minute work bouts or eight 2-minute bouts as the main body of each exercise session, both with a 1:1 work-to-rest ratio. Thus, each session will last ~45 minutes regardless of patient choice, which will include 16 minutes of high-intensity exercise. An experienced physiotherapist will supervise each session and record power output,

perceived exertion, and blood pressure (manual sphygmomanometer) at the end of each work interval. Heart rate will be recorded continuously at 5 s intervals through the entire exercise session (Polar RS400, Kempele, Finland). The collection of such data will permit a detailed quantification of the exercise intervention. Patients who do not undergo surgery in week 5 will complete one HIT session per week up until surgery to maintain fitness [35]. All adverse events will be recorded.

Information in relation to *participant's perceived enjoyment of exercise* is important to monitor. This is of relevance in adherence to the programme, whilst providing valuable information for planning a definitive study. We therefore plan to assess:

1. Changes in enjoyment of exercise both within sessions and throughout the programme. Perceived or likely enjoyment can change prior, during and after exercise as a consequence of a variety of factors e.g. anxiety, enjoyment, fatigue. We therefore plan to ask participants to assess enjoyment/perceived enjoyment of exercise prior to commencing, during and 20 minutes after exercise using a simple validated rating scale [36]. This will take <30 seconds to administer on each occasion and will be done during the first (baseline), 3rd, 6th, 9th and 12th sessions to track changes consequent to the programme.
2. Overall enjoyment of the exercise programme will be assessed during the week 5 assessment, using the validated multi-dimensional physical activity enjoyment scale (PACES) [37]. This will be 2-3 days following completion of the overall programme, allowing participants reflection and evaluation time (see week 5 assessment below).

Two experienced exercise scientists will be responsible for ensuring treatment fidelity of the exercise programme (GT, MW).

Safety Considerations

There are two main safety considerations regarding running a programme of HIT in patients with AAA disease:

1. Cardiac risk – as previously outlined 60-70% of individuals with AAA disease suffer from comorbid cardiac disease. The baseline assessment of clinical risk profile and CPET will be instrumental in assessing this risk in detail, under the stress of exercise, at the outset. A recent review by Guiraud *et al*. [23] highlights the safety of HIT in patients with underlying coronary disease, heart failure and patients at risk of cardiovascular disease. We are reassured by their conclusion which states "there is growing scientific evidence that HIT presents little danger for selected stable cardiac patients, provided that the prescribed protocols are respected".

   In the event of an adverse cardiac event we will have the following in place:
   - Staff experienced and Intermediate Life Support-trained
   - Resuscitation equipment and oxygen immediately available
   - Hospital cardiac arrest team fully informed of time and place of training sessions
   - Participants requiring further assessment will be transferred to the Accident and Emergency Unit within the relevant hospital.

   All institutions have Cardiology expertise immediately available on site.

2. Risk of AAA expansion or rupture – an intuitive concern regarding exercise testing and training in patients with aneurysms is of excessive rises in double-product (systolic blood pressure × heart rate) evoking aneurysm expansion and rupture. However, the available evidence suggests that these concerns are unfounded. For example, no aneurysm ruptures or excessive aneurysm growth rates were reported in any of the three studies of moderate-intensity exercise training in patients with early AAA disease (from >4000 exercise sessions; [19, 20, 38]), two of which were conducted at our institutions [19, 20]. Further unpublished data from our institutions indicate no ruptures from >1300 maximal exercise tests in patients with large asymptomatic AAA being considered for elective aneurysm repair. Moreover, through national networked connections, and other relevant publications, we believe this position of safety to be correct for >5000 maximal exercise tests. This position is also supported by the European guidelines for the management of AAA disease, which state that physical activity is not associated with AAA growth [39], as well as the ACC/AHA Practice Guidelines for the Management of Patients with Peripheral Vascular Disease [40], which suggest that AAA patients should not be fearful of vigorous activity. The only reported adverse event we are aware of came from the patient series of Best *et al*. [41] where a rupture occurred 12 hours after maximal exercise testing in a patient with a 6.1 cm AAA, yielding a rupture rate for this study of 0.4%. However, the causal relationship between exercise and rupture is difficult to establish given the 12-hour intervening period.

   It would therefore appear that the risk of AAA growth or rupture is very low in the context of exercise training for individuals with both small and large aneurysmal disease. This risk would appear to be <1:5,000. When balanced against national perioperative mortality/morbidity figures available for surgery in the UK at present, we feel that this represents clear benefit in favour of undertaking the preoperative exercise as set out.

   In the event of a suspected AAA rupture patients would immediately be transferred to the Accident and Emergency department for prompt further evaluation. All clinical institutions have on-site vascular teams able to immediately respond to such a situation.

Despite this we see risk minimisation in this context as our primary concern and will implement the following control measures:

- Thorough pre-participation screening
- Exclusion of high-risk patients
- Hospital-based exercise testing and training
- Exercise sessions supervised by experienced cardiac physiotherapists trained in Intermediate Life Support
- Exercise sessions performed >3 hours after waking given the higher frequency of cardiovascular events during the morning hours [42]
- Prompt evaluation of prodromal symptoms
- Resuscitation equipment and oxygen immediately available
- Exercise termination if a patient has signs/symptoms suggestive of distress, cardiac or AAA adverse event

- Reduction in exercise intensity if a patient has systolic blood pressure rise to >180 mm Hg, or heart rate >95% of their maximum (from baseline CPET)

Safety Governance

In line with Medical Research Council guidance we have developed the following safety governance structure for the study:

- Data Monitoring and Ethics Committee (DMEC) – the DMEC comprises three academics/clinicians with appropriate expertise who are independent from the running of the study. Any serious adverse events will be reported to and fully investigated by the DMEC. The DMEC will make recommendations to the Trial Steering Committee with regards to any ethical or safety concerns they may have.
- Trial Steering Committee (TSC) – this committee is led by the Chief Investigator (CI), with representation from all collaborating clinical and academic institutions. A lay representative will be approached to sit on the committee. The TSC will meet 3 times per year to discuss all elements of study progress and conduct.
- TSC Safety Committee – a formal study safety committee has been established and comprises 3 study investigators, including the CI. This group has the remit of ensuring all appropriate safety standards are in place prior to study commencement, and during the course of the research.

All adverse and serious adverse events will be managed within the strict governance arrangements of the study sponsor and participating clinical institutions.

Week 5 assessments

During week 5 it is anticipated that participants will undergo AAA repair. In the same week, but 1-2 days prior to surgery, assessments will be performed in all participants. The outcomes, which are primarily aimed at investigating the safety and effectiveness of the exercise intervention compared with usual care, will include:

- Cardiopulmonary fitness via CPET (to assess fitness changes from baseline)
- Maximum AAA diameter via trans-abdominal ultrasound (to establish safety of exercise in relation to aneurysm growth)
- HRQOL questionnaires
- PACES assessment for overall exercise programme enjoyment (exercise intervention group only)

Due to logistical reasons it is anticipated that not all participants will undergo surgery in week 5. This will mainly be due to a temporary lack of hospital beds for admission preoperatively, or critical care post-operatively. In this situation, surgery will be rescheduled, where possible, within 4 weeks. A repeat CPET will be undertaken in patients whose surgery is delayed >4 weeks, to ensure we have an accurate assessment of pre-operative fitness in all patients. A CPET assessment of those patients who have performed one high-intensity training session per week from week 5 onwards will provide further valuable information of the dose-response nature of high-intensity training in this population.

An overview of data to be collected for this aspect of the study can be seen on the study Case Report Form (see Additional file 1).

Perioperative period

Participants will undergo open or endovascular aneurysm repair as determined at the multidisciplinary team meeting. All perioperative care will be at the discretion of the vascular teams (as per usual practice) who will be blinded to group allocation. Perioperative data will be collected as seen in Additional file 1.

Post-operatively an investigator blinded to group allocation will determine the following:

- Destination – ward or critical care unit
- Postoperative Morbidity Survey Score (POMS) – a validated tool used to assess organ-specific morbidity in the post-operative period [43, 44]. Scores will be collected daily.
- Mortality
- Length of critical care and hospital stay

Post-discharge follow-up

At hospital discharge patients will be asked to keep a service receipt inventory to record treatment/care requirements for a 12-week period to inform the resource utilisation analysis. Participants will be interviewed via telephone at 6 weeks, with a follow-up appointment at 12 weeks after discharge to assess:

- HRQOL
- Resource utilisation
- Hospital readmissions, with diagnosis, within 12 weeks of initial discharge

Analysis Plan of Quantitative Study

Adherence with the exercise intervention will be analysed as described in the sample size justification, above, via the confidence interval for a single proportion. For the potential primary outcomes for a subsequent definitive trial, the likely effect of the exercise intervention will be estimated via standard intervention minus control comparisons (accounting for the type of variable and its distributional properties). We will examine the disposition of the 90% confidence interval for the observed effect to the minimum clinically important difference for each variable. Inasmuch as this is a feasibility study, these comparisons are exploratory and are intended to inform the subsequent trial. Data management will be performed according to the governance arrangements of the institutions involved in the project.

Analysis of Health Economics and Cost Effectiveness

A prospective economic evaluation will be rehearsed to develop and refine methods for a subsequent definitive trial. The main focus will be on how to accurately identify, quantify and value the additional costs of delivering the intervention and the potential resource implications versus usual care post-operatively and post-discharge. The costing approach will incorporate a broad analytical perspective (National Health Service and Social Services), which will help to detect cost-shifting between sectors. Resources utilised in the exercise group will be identified in terms of capital equipment and staff time. A staff-reported health economics questionnaire has been

developed to facilitate this (available upon request). Post-operative resource use will also be explored for all participants in terms of bed days (including critical care bed days). Post-discharge resource use for all treatment/care related to AAA surgery will be assessed retrospectively for 12 weeks by piloting the use of a self-report Service Receipt Inventory (patient diary). This will facilitate the development of a reliable and valid tool to capture resource use. Appropriate unit costs to be applied to resource use will be identified. These will be sourced from a combination of local costings and national databases [45, 46]. All costs will be combined to rehearse the methods for total health and social care cost estimation in a subsequent definitive trial.

The methods to estimate an incremental cost-effectiveness ratio for exercise versus usual care in terms of Quality Adjusted Life Years will be rehearsed (using EQ-5D 5L administered at baseline and 12 weeks post discharge). In particular, issues relevant for sensitivity analysis will be explored to help understand how best to deal with statistical imprecision and other uncertainties in the full trial. For example, data will be bootstrapped to account for the expected skewness evident in economic cost data. The data collected as part of this feasibility study could be used to inform subsequent pre-trial modelling.

Analysis of Participant Interviews

We aim to explore participants' post-discharge experience. From a critical realism perspective, semi-structured interviews will cover quality of life, function and attitudes to exercise including fear.

Sixteen participants will be recruited using purposive sampling and the following criteria: men and women; a range of ages; both study groups; both forms of aneurysm repair; and a range of experiences post-discharge. The interviews (1 hour with a research nurse; audio-recorded and transcribed) will take place in the hospital at the 12-week post-discharge visit. Transcripts will be analysed thematically using quantitative and diary data for triangulation.

Qualitative data (brief interview) will also be collected from all participants (and from clinical outcome assessors where relevant) to assess the ease of data collection for each potential primary outcome (participant and clinician burden), to evaluate the perceived enjoyment of the exercise intervention, and to examine the strength of patient preferences for either the intervention or control arms. These data will be elicited from all patients assessed as eligible, to help determine the extent to which preferences affect both recruitment and adherence.

Criteria for success

A subsequent definitive RCT will be deemed feasible if:
1. An appropriate primary outcome variable is defined;
2. The lower limit of the 90% confidence interval for the proportion of the exercise intervention group complying with the intervention is ≥67%. A patient is defined as having complied with the intervention if he completes ≥75% of the scheduled sessions;
3. Patient preferences are not so strong that they result in the conclusion that an RCT is not a feasible design.

Dissemination strategy

The dissemination strategy for this research will be to inform a wide range of local, national and international audiences about the results and conclusions. It must however be remembered as part of this strategy that the current proposal is for preliminary work aimed at defining a subsequent definitive clinical trial.
1. Health professionals – we aim to publish our research in journals that cover the relevant medical specialties and with preference for those that deposit publications in open access databases to increase free dissemination. In addition, we aim to present this research at appropriate national and international conferences.
2. Users – from this perspective we aim in the first instance to collaborate with our patient representatives (from advisory and steering groups) and local experts in patient and public involvement to best facilitate user dissemination. We plan to write a specific news piece that will be forwarded to appropriate groups and organisations.
3. Service managers – as an exploratory study it is unlikely that results from this study will directly influence commissioning processes in the short term. More we will engage with appropriate primary and secondary care groups to discuss support for our proposed definitive study leading on from this research.

Trial status

Start date: 1 August 2013

Expected end date: 30 May 2015

Expected publication date: 1 January 2016

Status at time of submission of this article: approvals obtained, but not yet recruiting

Funder: UK National Institute of Health Research - Research for Patient Benefit Programme (PB-PG-1111-26068)

List of abbreviations used (if any)

AAA	abdominal aortic aneurysm
CPET	cardiopulmonary exercise testing
EVAR	endovascular aneurysm repair
HIT	high-intensity interval exercise training
HRQOL	health-related quality of life
PACES	physical activity enjoyment scale
POMS	post-operative morbidity survey
RCT	randomised controlled trial

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

GT drafted the manuscript and contributed to the design of the study. Original study concept was by GD and AB. All co-authors contributed to the design of the study. GD is Chief Investigator for the project. EK is Principal Investigator (PI) at James Cook University Hospital (South Tees), SN is PI at Northern General Hospital (Sheffield) and DY is PI at York Hospital. All authors contributed to the critical revision of the manuscript for important intellectual content and read and approved the final manuscript.

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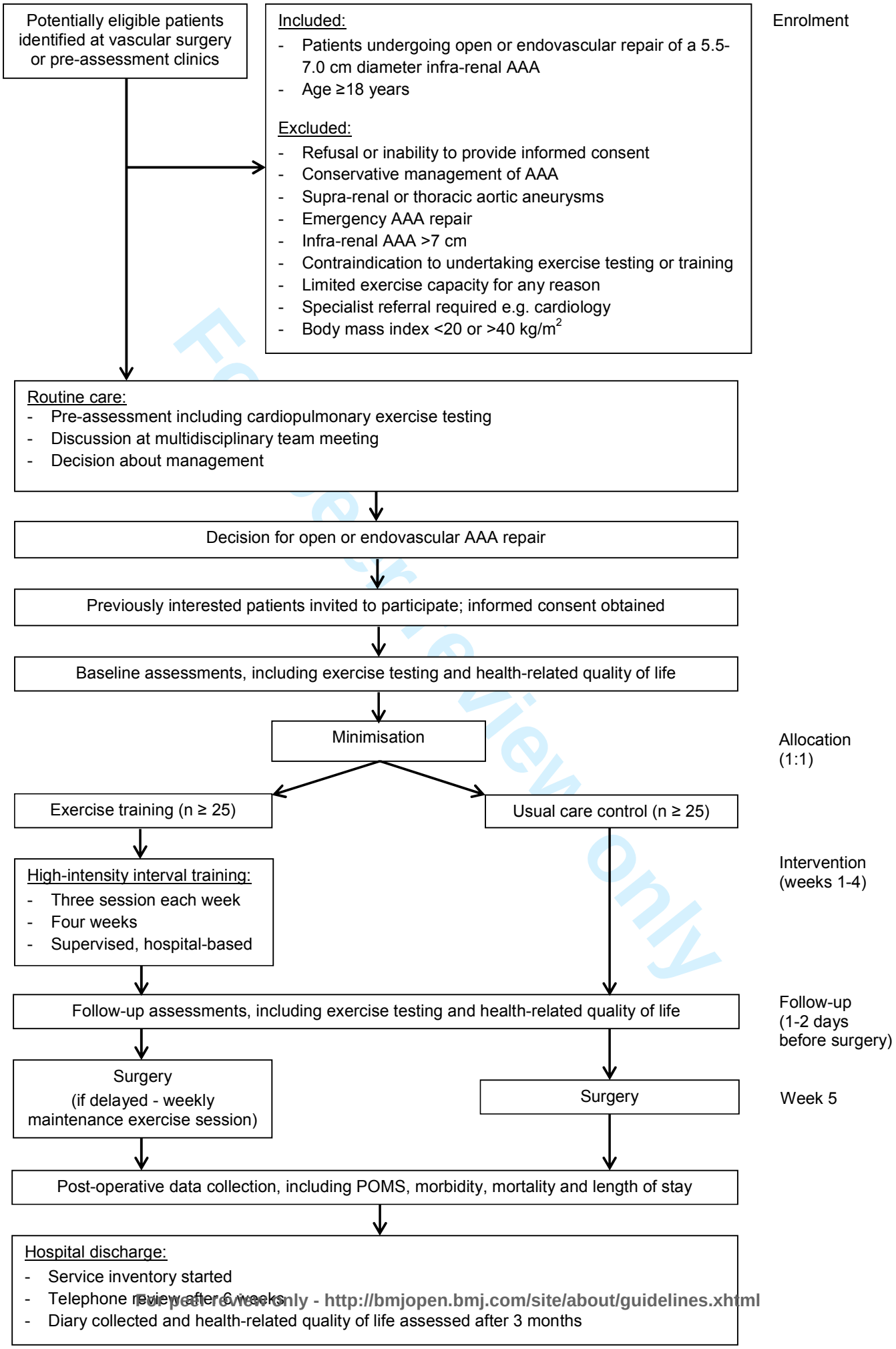
Figure legends

Figure 1 Study flowchart



HIT-AAA: Study Data Collection Form (Case Report Form)

Participant study number: _____ Participant initials: _____

Site: South Tees / York / Sheffield

Paperwork checklist (please tick):

- Written informed consent provided? [ ]
- Patient information sheet and copy of consent to patient [ ]
- Patient information sheet and copy of consent in medical notes [ ]
- Place study sticker in patient's notes [ ]
- Complete GP letters informing of patient's entry into study [ ]

1. Baseline data (week 0) **Date……**

Age	years	**Body mass**	kg
Sex		**Stature**	cm
Body mass index	kg/m^2	**Size of AAA**	cm
Baseline observations	BP:	RHR:	Sats: %
Date of vascular pre-assessment clinic			
METs score			
ASA score			
Modified revised cardiac risk index (answer yes or no)			
	Ischaemic heart disease		
	Congestive cardiac failure		
	Cerebrovascular disease		
	Insulin for diabetes mellitus		
	Creatinine > 177 µmol/l		
	Age >70 years		
	Abnormal electrocardiogram		
	Rhythm (other than sinus)		
Quantify abnormality			
	Uncontrolled blood pressure (systolic >160 mmHg, diastolic >90 mmHg)		
Other co-morbidities	Chronic obstructive pulmonary disease		
	Asthma		
	Other respiratory disease		
	Smoker (also tick if quit within 6 months)		
	Diabetes mellitus		
	Peripheral arterial disease		
	Gastrointestinal disease		
	Other (free text):		
Baseline creatinine (µmol/l)			
Baseline eGFR (ml/min)			
Baseline haemoglobin (mg/dL)			
Medications (please circle)	ACE inhibitor	Statin	Beta-blocker
	Calcium channel blocker	Antiplatelet A C D	Angiotensin II receptor antagonist
	NSAIDs	Diuretic	Insulin
	Warfarin	Oral hypoglycaemics	

A, aspirin; AAA, abdominal aortic aneurysm; ACE, angiotensin converting enzyme; ASA, American Society of Anesthesiologists; BP, blood pressure; C, clopidogrel; D, dypiridamole; eGMR, estimated glomerular filtration rate; MET, metabolic equivalents; NSAID, non-steroidal anti-inflammatory drug; RHR, resting heart rate.

Preference for exercise group (before randomisation) Yes / No

2. Baseline cardiopulmonary exercise test data (week 0)

Date……

Data	**Results or comment**	
Body mass		kg
Resting blood pressure		mmHg
Resting heart rate		beats/min
VO_2 at rest : Indexed		ml/kg/min
Absolute		ml/min
Anaerobic threshold Indexed		ml/kg/min
Absolute		ml/min
Power output at anaerobic threshold		W
Anaerobic threshold achieved (please circle)	Yes	No
VE/VCO_2 at anaerobic threshold		
VO_2 peak Indexed		ml/kg/min
Absolute		ml/min
Power output at VO_2 peak		W
O_2 pulse at the start of exercise		ml/beat
Peak O_2 pulse		ml/beat
Peak heart rate		beats/min
Peak blood pressure		mmHg
VE at rest		l/min
Peak VE		l/min
Inducible ischaemia (please circle)	Yes	No
Heart rate at ischaemia onset		beats/min
Ischaemia before / after anaerobic threshold (please circle)	Before	After
Oscillatory breathing pattern? (please circle)	Yes	No
Lowest exercise O_2 saturation		%
Oxygen Uptake Efficiency Slope (VO_2 ml/min / log VE l/min)		
Peak rating of perceived exertion		
Peak respiratory exchange ratio		
Reason for termination		

VCO_2, carbon dioxide production; VE, volume of expired air; VO_2, oxygen consumption.

3. Multi-disciplinary team data

Date…….

Type of surgery:	Open	EVAR	
Complexity of EVAR:	Complex	Non-complex	
Post-op destination:	Ward	HDU	ITU
Dated for surgery?	Yes	No	

Date if known: _____

4. Week 5 cardiopulmonary exercise test data

Date……

Data	**Results or comment**	
Body mass		kg
Resting blood pressure		mmHg
Resting heart rate		beats/min
VO_2 at rest : Indexed		ml/kg/min
Absolute		ml/min
Anaerobic threshold Indexed		ml/kg/min
Absolute		ml/min
Power output at anaerobic threshold		W
Anaerobic threshold achieved (please circle)	Yes	No
VE/VCO_2 at anaerobic threshold		
VO_2 peak Indexed		ml/kg/min
Absolute		ml/min
Power output at VO_2 peak		W
O_2 pulse at the start of exercise		ml/beat
Peak O_2 pulse		ml/beat
Peak heart rate		beats/min
Peak blood pressure		mmHg
VE at rest		l/min
Peak VE		l/min
Inducible ischaemia (please circle)	Yes	No
Heart rate at ischaemia onset		beats/min
Ischaemia before / after anaerobic threshold (please circle)	Before	After
Oscillatory breathing pattern? (please circle)	Yes	No
Lowest exercise O_2 saturation		%
Oxygen Uptake Efficiency Slope (VO_2 ml/min / log VE l/min)		
Peak rating of perceived exertion		
Peak respiratory exchange ratio		
Reason for termination		

VCO_2, carbon dioxide production; VE, volume of expired air; VO_2, oxygen consumption.

Preference for exercise group (following intervention) Yes / No

Week 5 Size of AAA (exercise group only) cm

If surgery delayed by >4 weeks please complete repeat exercise test sheet (p. 9)

5. Intra-operative data

Date of admission: _____

Date of intervention: _____

Days since last exercise test: _____ Test number: **1** **2** **3**

Intra-operative details

Type of repair (circle)	Open repair	EVAR
Open repair only:		
Surgical data	Aortic cross-clamp time	min
	Use of supra-renal clamp (please circle)	Yes / No min
Incision type (please circle)	Vertical / Transverse	
Other information (please circle)	Hostile abdomen Bi-iliac graft Inflammatory aneurysm	
Anaesthetic data for open repair or EVAR		
Type of anaesthetic Tick or comment as appropriate	General anaesthetic	
	Spinal	
	Spinal catheter	
	Epidural	Lumbar/Thoracic Intraop/ postop
	Combined spinal epidural anaesthesia	
	Local anaesthesia alone	
Estimated blood loss		ml
Urine output		ml
Intra-operative fluids	Crystalloids	ml
	Colloids	ml
	Cell salvaged blood	ml
	Packed cells	Units
	Fresh frozen plasma	Units
	Platelets	pools
	Cryoprecipitate	Units
Any intraoperative CVS support (circle)	Bolus	Infusion
Any intraoperative vasodilators (circle)	Bolus	Infusion
Requirement for CVS support at end of operation	Yes / No	Comment:
Post-operative care facility (circle)	Ward / HDU / ITU	

CVS, cardiovascular system; EVAR, endovascular aneurysm repair; HDU, high-dependency unit; ITU, intensive treatment unit.

Any intraoperative adverse events:
_____
_____
_____

Any adverse events between operation and midnight on day 0:
_____
_____
_____

Any other comments:
_____
_____
_____

Signature of intraoperative data collector: _____

6. Postoperative Morbidity (free text below) – including date

(a) Cardiac event

(b) Respiratory event

(c) Other event

Post-operative Morbidity Survey (POMS) data to be collected from end of surgery until discharge from hospital

7. Discharge Data

Date of discharge: _____

Date of death (write NA if not applicable): _____

Cause of death (write NA if not applicable): _____

Total hospital length of stay (nearest half day): _____

Days on ITU (write NA if not applicable): _____

Days on HDU (write NA if not applicable): _____

Date when POMS = 0: _____

8. Additional cardiopulmonary exercise test data

Date……

Data	Results or comment	
Body mass Resting blood pressure Resting heart rate		kg mmHg beats/min
VO_2 at rest : Indexed Absolute		ml/kg/min ml/min
Anaerobic threshold Indexed Absolute		ml/kg/min ml/min
Power output at anaerobic threshold		W
Anaerobic threshold achieved (please circle)	Yes	No
VE/VCO_2 at anaerobic threshold		
VO_2 peak Indexed Absolute		ml/kg/min ml/min
Power output at VO_2 peak		W
O_2 pulse at the start of exercise		ml/beat
Peak O_2 pulse		ml/beat
Peak heart rate Peak blood pressure		beats/min mmHg
VE at rest		l/min
Peak VE		l/min
Inducible ischaemia (please circle)	Yes	No
Heart rate at ischaemia onset		beats/min
Ischaemia before / after anaerobic threshold (please circle)	Before	After
Oscillatory breathing pattern? (please circle)	Yes	No
Lowest exercise O_2 saturation		%
Oxygen Uptake Efficiency Slope (VO_2 ml/min / log VE l/min)		
Peak rating of perceived exertion		
Peak respiratory exchange ratio		
Reason for termination		

VCO_2, carbon dioxide production; VE, volume of expired air; VO_2, oxygen consumption.

Postop day (0 = day of operation) Days run from 0000 – 2359	1	2	3	4	5	6	7
Put a tick in the box for each system if any criteria are fulfilled. **Level of care (1 / 2 / 3)** *All criteria are changes in comparison with preoperative status.*							
Pulmonary: New requirement for supplemental oxygen or other respiratory support. *(Include even if institutional practise or preventative for initial postoperative period)*							
Infectious: Currently on antibiotics or temperature >38 °C in the last 24 hr. *(Include antibiotic prophylaxis)*							
Renal: Presence of oliguria (500 ml/24 hr), OR increased serum creatinine (>30% from pre-op level) [baseline Cr x 1.3 = _____ µmol/L] OR urinary catheter in place.							
Gastro-intestinal: Unable to tolerate an enteral diet for any reason, including nausea, vomiting, and abdominal distension, or use of antiemetic.							
Cardiovascular system: Diagnostic tests or therapy within the last 24 h for any of the following: New myocardial infarction or ischaemia, Hypotension (requiring pharmacological therapy or fluid therapy >200 ml/hr), Atrial or ventricular arrhythmias, Cardiogenic pulmonary oedema, Thrombotic event (requiring anticoagulation).							
Central nervous system: Presence of new focal deficit, confusion, delirium or coma.							
Wound: Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound.							
Haematological: Requirement for any of the following within the last 24 hr: packed erythrocytes, platelets, fresh-frozen plasma, or cryoprecipitate.							
Pain: New postoperative pain significant enough to require strong opioids or regional analgesia. (*score until epidural is removed, strong opioids are IV morphine or oxycodone/oxycontin)*							
Data collector initials							

Please provide comments overleaf detailing:
- Any significant morbidity not described above.
- Reasons why patient still in hospital if no morbidity described above.

If patient discharged, please complete discharge data on page eight of this form

Day	Post-operative comments (include initials of data collector)
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