Hull University Teaching Hospitals NHS Trust

Title: High INtensity Interval Training In pATiEnts with intermittent claudication (INITIATE)

Short title: INITIATE

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This protocol has regard for the HRA guidance and order of content;

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'This trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements'.

Signature: Date:

Sponsor:
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Signature: Date:

List of abbreviations:

PAD = Peripheral Arterial Disease

PVD = Peripheral Vascular Disease

CAD = Coronary Artery Disease

IC = Intermittent Claudication

SEP = Supervised Exercise Programme

HEP = Home-based Supported Exercise Programme

HIIT = High-Intensity Interval Training

CPET = Cardio-Pulmonary Exercise Testing

PPO = Peak Power Output

PFWD = Pain-Free Walking Distance

MWD – Maximum Walking Distance

ABPI = Ankle Brachial Pressure Index

TBPI = Toe Brachial Pressure Index

BP = Blood Pressure

SBP = Systolic Blood Pressure

DBP = Diastolic Blood Pressure

BMI = Body Mass Index

HR = Heart Rate

VO_{2Peak} = Peak Oxygen Consumption

VO_{2Max} = Maximal Oxygen Consumption

VAT = Ventilatory Anaerobic Threshold

RPE = Rating of Perceived Exertion

RER = Respiratory Exchange Ratio

VO_2 = Oxygen Uptake

RCT = Randomised Control Trial

REC = Research Ethics Committee

ECG = Electrocardiogram

VCO_2 = Carbon Dioxide Production

VE = Minute Ventilation

AE = Adverse Event

SAE = Serious Adverse Event

Background Information:

What is Peripheral Arterial Disease? How does it manifest as intermittent claudication?
Peripheral arterial disease (PAD) is caused by occlusive atherosclerotic lesions of the arteries that supply blood to the legs (1, 2). The National Institute for Health and Care excellence (NICE) clinical guidance 147 notes that the incidence of PAD is approximately 20% in those over the age of sixty (3). The incidence is also high in certain populations such as diabetics, smokers and those with coronary artery disease (CAD) (3). However, some PAD patients may be asymptomatic, meaning that it's true incidence may be underestimated (2). There is an increased 10-year mortality risk associated with PAD, which is 3- and 6-fold for all-cause and CV mortality respectively, when compared to those with no evidence of the disease (4). One common symptomatic manifestation of PAD is a reproducible lower limb muscle pain on ambulation or during exercise known as intermittent claudication (IC). This is caused by reduced blood flow due to the narrowing of the arteries, resulting in an oxygen supply-demand imbalance (5, 6). The risk factors associated with IC are similar to those relating to myocardial infarction and angina pectoris such as smoking, hypercholesterolemia and diabetes (5). It is therefore unsurprising that within a cohort of 381 patients with lower extremity ischaemia, only 10% had normal coronary arteries identified via angiography (7).

What effect does it have on the patient?
IC can have a profoundly negative effect on a patient's life due to a number of factors, including a reduction in walking capacity, altered gait and balance and a likely reduction in muscle strength. In addition, this symptomatic disease affects functional capacity whilst also disrupting daily activities due to its restriction on ambulation (5, 8). A recent qualitative analysis explored patient experiences of IC and found that most patients described their symptoms as being detrimental to daily activities (9). Furthermore, research has demonstrated that IC can also have a negative effect on a patient's quality of life (QoL). In comparisons to members of the general population, IC sufferers have a worse QoL for all health aspects including; general health, vitality, social and physical functioning, physical role and bodily pain all of which are further reduced with increasing disease severity (10).

How is it diagnosed and managed?
IC is diagnosed based on history, clinical assessment and an abnormal ankle-brachial pressure index (ABPI). The classic symptoms of IC are pain in one or both legs on walking, which primarily affects the calves and only subsides with rest (1). An index of between 0.91-1.30 is considered normal, with claudicants usually presenting with an ABPI between 0.41-0.90. Those with values of 0.40 or less are considered to have critical leg ischaemia (1). It is also important to note that values >1.30 may be falsely elevated due to calcified vessels that are non-compressible. In these patients, further tests should be carried out, such as toe brachial pressure index (TBPI) to determine the presence of PAD (1).

NICE (147) notes that the first-line treatment which should be offered to all patients with IC is a supervised exercise programme (SEP) (3). A recent Cochrane review demonstrated that SEP's are efficacious for improvements in both pain-free (PFWD) and maximum walking distance (MWD) whilst also potentially providing improvement in QoL for those who suffer with IC (11). However, the UK guidelines for SEPs are limited and recommend that it should entail two hours of supervised exercise per week for three months whilst encouraging patients to exercise to the point of maximal pain. This is somewhat arbitrary and previous researchers have noted that for IC patients there is a glaring omission of the most appropriate exercise intensity and that within the PAD trial literature, SEP interventions are not sufficiently described, especially with regard to exercise mode and intensity (12, 13). This has implications for the replication of exercise protocols in clinical practice (13), meaning that there is no standard rehabilitation programme.
Furthermore, despite being the recommended first-line treatment for IC, a systematic review demonstrated that only one in three patients were eligible and willing to take part in a SEP (14). In addition, a survey of all UK vascular centres demonstrated that only 42% had exercise programmes for their patients to access (14). Therefore, there is clearly a gap in the literature to develop an exercise programme that is more accessible and / or acceptable to patients (14).

Two possible developments are high-intensity interval training (HIIT) and home-based supported exercise programmes (HEP). One previous study in the USA using a HIIT programme demonstrated that patients in the HIIT group had similar improvements in peak oxygen uptake (VO_{2Peak}), PFWD and MWD compared to those who completed low-intensity exercise (12). However, high-intensity was prescribed using 80% of the maximum workload (i.e. treadmill grade) achieved during the initial baseline maximal effort test (12), which is slightly conservative, given that HIIT is usually prescribed between 85-95% of peak workload or HR (15, 16). Despite this limitation, this study does suggest that HIIT may be at least as effective as current exercise programmes and should be explored as an alternative SEP treatment option.

In comparison to HIIT there has been much more evidence for the use of HEP. One randomised controlled trial (RCT) in the USA demonstrated that HEP significantly improved PFWD and MWD with results equivalent to the SEP (17). With increasing technologies HEPs or "facilitated self-managed exercise programmes" are becoming more prominent. Indeed, a study identifying patient preference in the IC literature demonstrated that over half of patients would prefer to exercise in the home setting (Harwood et al, JVN 2018).

Study Aims:

This study aims to compare the efficacy and acceptability of two novel exercise interventions (HIIT and HEP) versus current practice (SEP) for exercise rehabilitation in IC. As a cycle-based HIIT protocol has not been previously investigated in the IC population an initial observational cohort study of HIIT will be conducted, followed by semi-structured interviews, meaning the research will be split into two work-streams.

Work-stream 1: Considering the safety, tolerability, acceptability and efficacy of high-intensity interval training as a novel intervention for the treatment of intermittent claudication.

Study-design: A Two-centre, mixed methods, prospective, "proof of concept" cohort study.

Objective: To investigate the utility, safety, tolerability, acceptability and efficacy of high-intensity interval training as a novel intervention for the treatment of intermittent claudication.

Primary outcomes measures: Utility, assessed by screening, eligibility, recruitment and adherence rates. Safety, assessed by determining the occurrence of adverse and serious adverse events, and tolerability, assessed by patient ability to achieve and maintain exercise in the appropriate exercise intensity domain.

Secondary outcome measures: Acceptability assessed via semi-structured interview and changes in MWD and PFWD assessed via graded treadmill test, VO_{2Peak}, ventilatory anaerobic threshold (VAT) assessed via CPET, ABPI and QoL.

Primary endpoint

The primary endpoint for this study will be assessing the utility, safety and tolerability of a 6-week HIIT intervention.

Secondary endpoints

Additional endpoints will include acceptability and improvements in MWD, PFWD, VO_{2Peak}, VAT, ABPI and QoL.

Study design

Identification and screening of patients:

Potential participants will be identified by vascular surgeons / nurses / technologists (as appropriate to each site) in vascular outpatient clinics or multidisciplinary team meetings (as appropriate to each site) at two tertiary vascular centres, Hull Royal Infirmary (Hull, United Kingdom) and University Hospital Coventry and Warwickshire (Coventry, United Kingdom)

and referred to research nurses / research fellows or exercise physiologists (appropriate to each site) for screening..

Patient Selection

Patients will have a confirmed diagnosis of intermittent claudication made by their consultant either clinically or by questionnaire. Diagnosis will be made with an ABPI of <0.9, a drop-in ankle pressure of ≥20mmHg after exercise, or documented significant atherosclerosis on radiological imaging.

Patient consent

Patients will be sent a letter and patient information sheet. This will provide details of the study, the 6-week HIIT programme and the interview. Patients will then be contacted via telephone call at least a week later to ask any questions and decide whether they would like to partake in the study intervention. Those who do not wish to partake in the research will be offered the usual care SEP without research as is usual practice for IC. Those who also decline this will be referred back to their consultant for future management.

Those who decide to participate will be asked to attend a baseline visit prior to beginning their exercise programme to determine if they are suitable. The research project will be re-explained and questions encouraged. Following this, informed consent will be obtained if appropriate. A clause outlining the conduction of an interview, voice recording and use of anonymous quotes will be included in the consent form, but this will be optional. Patients will still be able to participate in the study without completing an interview.

Baseline and follow-up visits

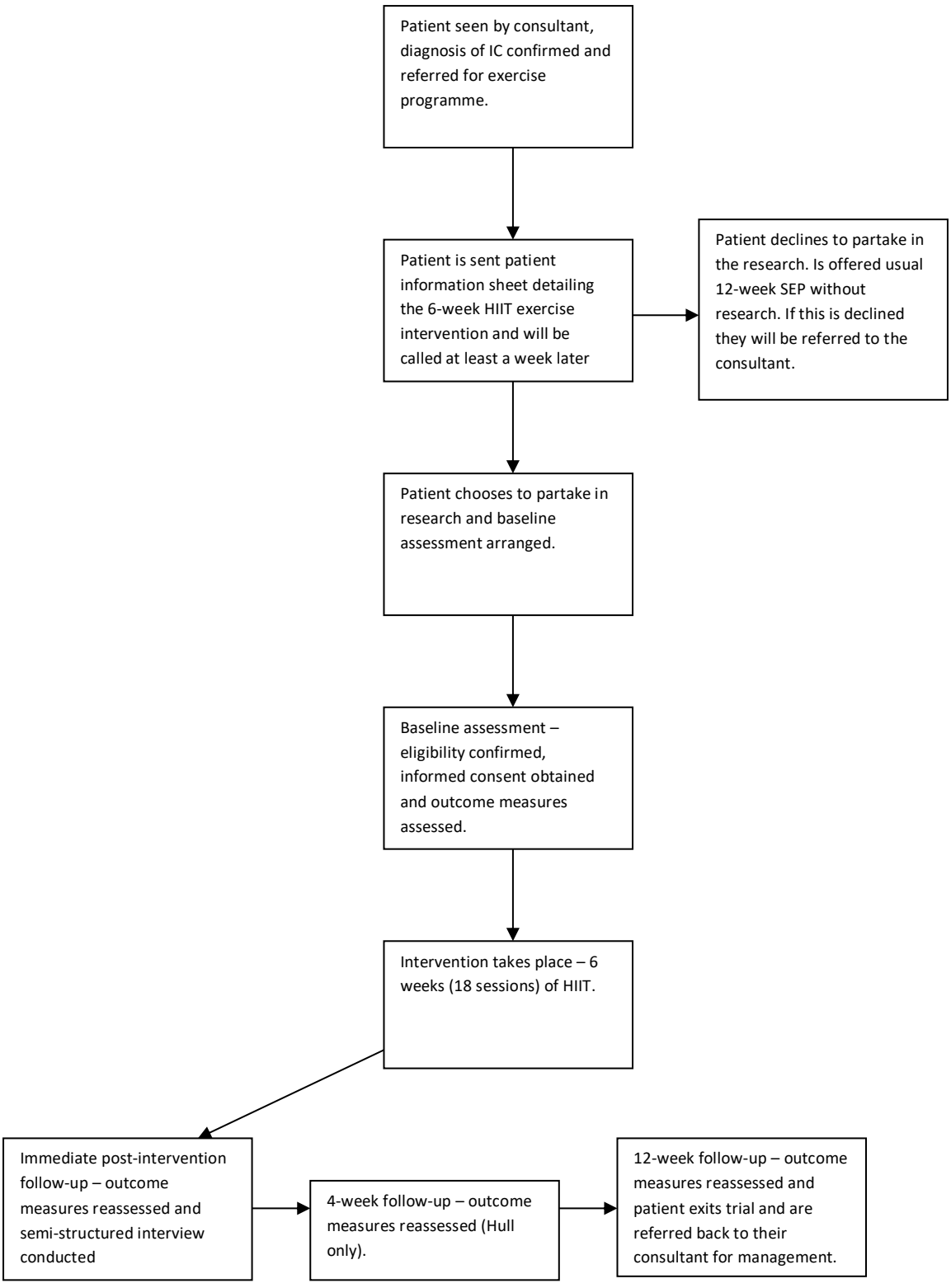
Baseline and follow-up visits will be completed for all research participants who complete the full intervention timeframe (i.e. 6-8 weeks). Those choosing to discontinue the intervention before completing the full intervention timeframe will be withdrawn. Follow-up visits will be completed immediately following completion of the HIIT programme, and then 12-weeks post-intervention. An additional follow-up will also be completed 4-weeks post-intervention at the Hull site only.

Travel expenses for study visits (baseline and follow-ups) will be reimbursed. Patients can be reimbursed a maximum of £75 to cover the costs of transport/parking that may be accrued.

Patients will be asked not to eat a heavy meal or smoke for 3 hours before the visit and testing (18). Patients will also be asked to dress appropriately, especially in terms of footwear and instructed to avoid unusual physical activity efforts in the preceding 12 hours (18). As testing will not be performed for diagnostic purposes, patients will not be asked to withdraw or refrain from taking any medications (18). At each study visit, the patient's medical notes will be reviewed before assessment of current and past medical history. Patients will be asked questions relating to previous medical history including previous

diagnoses, current symptoms, and medications to determine the presence of any contraindications to exercise testing (18, 19).
Resting blood pressure and HR will then be taken followed by height, weight, body mass index (BMI), waist circumference, hip circumference and waist to hip ratio. During the baseline and subsequent visits, a number of objective physiological and subjective patient-level measures will be performed.

Trial Procedures



Measurement of primary and secondary endpoints

Primary endpoint – safety, utility and tolerability

Safety will be determined by the occurrence of any adverse events (AE) or serious adverse events (SAE). In accordance with the GCP decision tree for adverse event reporting all events will be reported to the sponsor and recorded to determine the safety of the intervention.

Utility will include eligibility (n = eligible/screened), recruitment (recruited/eligible), and adherence (number of patients completing the HIIT programme). The number of patients screened, recruited and commencing the HIIT programmes will be monitored at each hospital site. A register (if required, i.e. more than one patient attending), will be taken at each exercise class to record patient adherence and the completeness of each session will be recorded (i.e. how many minutes the patient completed). It is estimated that all patients should complete 18 sessions in total within 6 weeks. However, where any sessions are missed, the intervention period can be extended to 8 weeks to allow these sessions to be added on. Those not completing 18 sessions over the extended 8-week period will be deemed to have satisfactorily completed the intervention as long as they have completed >80% of the intervention (i.e. ≥15 out of 18 sessions). All patients completing the allotted 6-8 weeks for the intervention (regardless of whether they have completed ≥ or <15 sessions) will still be followed up. Those choosing to discontinue the intervention before completing the full intervention timeframe will be withdrawn.
Tolerability will be assessed by identifying if patients are able to reach and maintain the prescribed training range required to perform HIIT, for each full interval. Heart rate (HR) data will be collected throughout each HIIT session and saved on an encrypted USB stick this will then be compared to the 85-100%HRMax training range that has been prescribed – to determine if patients are able to achieve it. This range will be in line with an ongoing HIIT trial in CAD at 85-90% peak power output (PPO), aiming to achieve >85%HRMax, derived from CPET (15). If patients are not able to achieve 85-100%, this will determine the suitability of this HIIT protocol in this population. Reasons for stopping the HIIT exercise sessions (e.g. leg pain), will be recorded.

Secondary endpoints

Acceptability

Acceptability will be assessed by patient feedback using semi-structured interviews.

conducted using a sample of patients in three groups:

Group 1: Patients who are eligible for the study but decide not to participate (non-consenters). The interviews will explore reasons why patients chose not to participate in the

study and whether study material could be amended to be more appealing. Patients in this group will be signposted to the relevant interview section of the patient information sheet that they have already received. Those who agree to participate in an interview will sign an interview specific consent form.

Group 2: Those who agree to participate in, and complete, the exercise programme. The interviews will explore patient's experiences of the HIIT programme, how easy/hard they found it, whether they enjoyed it and whether they would be willing to undertake it again. They will also be asked to provide any additional information related to potential problems/barriers to the programme and any changes they may feel are required.

Group 3: Those who agree to participate but discontinue after at least one session. Patients will be asked the same initial questions as group 1, but they will be asked why they dropped out of the programme and what could have been changed to prevent them doing so.

An interview guide with a pre-determined set of open questions will be used but the interviews will be flexible to allow the interviewer to ask further probing questions based on patient responses. All interviews will be conducted face-to-face in a private room, recorded using a Dictaphone, transcribed verbatim and anonymised. Patients will be informed that they do not have to answer any questions that they feel uncomfortable with and all responses are confidential.

Clinical outcome measures:

Pain-free and maximal walking distance:

The test that will be used starts at 2mph and 0% grade, with grade increasing by 2% every two minutes whilst speed remains constant (20). This test will be used to determine PFWD and MWD at each study visit. A stopwatch will be started when the patient walks, they will indicate to the researcher when they begin to feel IC pain, which will be recorded as PFWD. The patient will continue to walk until the pain is too severe and they need to stop, this will be recorded as MWD.

Quality of life:

Two questionnaires will be used;

Generic: The SF-36 is a generic health measure which does not target specific populations but is recommended as the most appropriate generic QoL tool for those with lower limb ischaemia (21-23). It fulfils strict reliability and validity criteria and is practical, acceptable, brief and easy to use, which is important for researchers who can use it to add a general health measurement tool to a disease specific questionnaire (21). The SF-36 contains 36 questions, yielding an eight-scale scoring profile including; physical function (PF), role-

physical (RP), bodily pain (BP), generic health (GH), vitality (VT), social functioning (SF), role-emotional (RE) and mental health (MH) (22). Each scale is scored from 0-100, based on the responses given, with 0 indicating worst possible health and 100 best possible health. Scales can also be combined to give a summary measure of mental and physical health. PF, RP, BP and GH all contribute to the physical component summary (PCS) and VT, SF, RE and MH contribute to the mental component summary (MCS) (22).

Specific: The VascuQol is a disease-specific questionnaire developed for use in studies involving patients with lower-limb ischaemia (24). It has demonstrated good reliability and is responsive to within patient change (24). It consists of 25 items, which are subdivided into five domains; pain (4 items), symptoms (4 items), activities (8 items), social (2 items) and emotional (7 items) (24). Each item is rated on a seven-point scale, with 1 representing the worst score and 7 the best. A sum score is then calculated by dividing the total score by 25 (the number of items), with a domain sum score also calculated by dividing the total score per domain by the total number of items in that domain (25).

Cardiorespiratory measures

CPET/spirometry:

This study will utilise a cycle CPET with a ramp protocol at each study visit as a non-invasive assessment of cardiovascular function, utilising a safety protocol on the basis of the ACSM guidelines (19). Prior to the start of the test the patient will observe a 3-minute rest period whilst sitting on the cycle ergometer so that resting measurements can be obtained. After this, the patient will begin a 3-minute reference or warm-up period of unloaded cycling followed by progressive graded exercise with adequately increasing workload to induce volitional exhaustion within 8-12 minutes, concluding with a post-maximal effort recovery period (26). During the CPET, patients will be continuously monitored via a 12-lead electrocardiogram (ECG; applied after adequate skin preparation), with measurements of HR, blood pressure and rating of perceived exertion (RPE) taken at regular intervals (19). Patients will also be observed for any signs or symptoms and asked to confirm that they are asymptomatic periodically throughout (19). Upon completion of the CPET, this monitoring will continue for at least 6 minutes or until ECG changes return to baseline and significant signs and symptoms subside (19, 27). HR and blood pressure will also be monitored until they return to near resting values (19). Gas analysis will also be conducted on a breath-by-breath basis to allow determination of important secondary outcome measures such as VO_{2Peak} and VAT. VO_{2Peak} will be determined as the average oxygen uptake value during the last 30-seconds of the test whilst VAT will be estimated using the widely adopted V-slope method and verified using the ventilatory equivalents (28).

Spirometry, which will be performed prior to CPET, is an effective screening tool of general respiratory health that can be used to establish whether exercise intolerance is primarily

caused by or contributed to by ventilatory limitation (29, 30). Therefore, unforced (vital capacity; VC and inspiratory capacity; IC) and forced (forced expiratory volume in 1 second; FEV_1 and forced vital capacity, FVC) spirometry manoeuvres will be conducted, in line with American thoracic society guidelines, to substantiate the extent of any respiratory limitation during CPET (29, 30).

For the unforced manoeuvres, patients will be relaxed in a seated position and asked to breathe regularly until the end-expiratory lung volume is stable. They will then take a deep breath to total lung capacity (to record IC), then exhale to residual volume (to record expiratory VC) and inhale maximally again. For the forced manoeuvres, the patient will be asked to assume the correct posture and inhale completely and rapidly, with a pause of <1s at total lung capacity before starting exhalation with an initial blast. Exhalation is continued until no more air can be expelled, and an upright posture should be maintained at all times (30).

There is however, only limited information available from resting lung function tests, which cannot sufficiently predict the extent to which respiratory disease limits exercise capacity (29). Other measures such as maximum voluntary ventilation (MVV) and breathing reserve derived from CPET can be used in adjunction to determine normal respiratory function (29). MVV, the maximum volume of air ventilated in 60 seconds, can be directly determined by breathing deeply and rapidly for 12 or 15 seconds (31). However, MVV is a difficult manoeuvre that is reliant upon subject co-operation, effort and technique, meaning that it is often estimated from FEV_1, with FEV_1 x 40 providing the optimal estimate in normal subjects and those with obstructive lung disease (31). The breathing reserve is calculated by subtracting the maximal exercise ventilation, recorded during CPET, from the MVV. A normal breathing reserve value is considered to be >20%MVV, as in healthy subjects respiratory capacity usually exceeds the demand of peak exercise (27, 29). Those limited by respiratory disease however, will have a breathing reserve close to zero, as cardiovascular efficiency exceeds respiratory efficiency (29).

ABPI

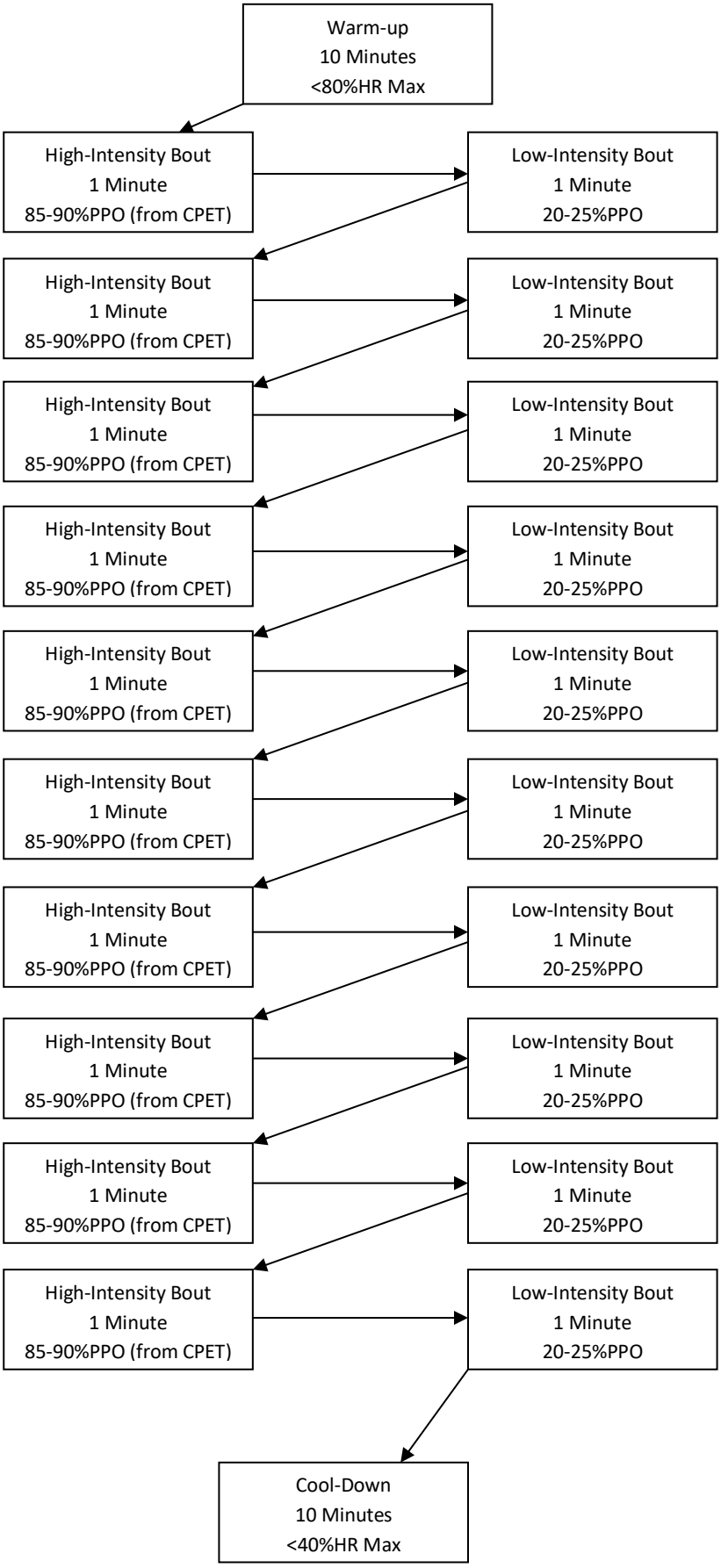
ABPI will be determined both at rest and after the MWD treadmill test by measuring the systolic blood pressure in the brachial, dorsalis pedis and posterial tibial arteries using an appropriately sized sphygmomanometer, placed on the arms and above the ankles (1). A hand-held Doppler probe will be used to determine systolic pressure by initially locating an optimal flow signal before the cuff is inflated. The cuff will then be inflated until the signal is no longer audible and the highest pressure at which the flow signal returns during gradual deflation will be recorded as systolic pressure. The ABPI is then calculated for each leg by dividing the higher ankle pressure of each leg by the highest arm pressure, with a value of <0.9 or a post-exercise drop of $\geq$20mmHg indicating presence of PAD (1).

An ABPI >1.3 is suggestive of non-compressible, calcified arteries due to other co-morbidities such as diabetes (32). In this case, TBPI will be measured by placing a small occlusive cuff on the first or second toe and the return of toe pulsatility (indicative of systolic pressure) is measured via a plethysmographic detection device (32). This index is then calculated by dividing the toe pressure by the brachial pressure with values of <0.7 indicating presence of PAD (32).

Intervention:

High intensity interval training (HIIT) programme

This study will use a pragmatic and flexible HIIT protocol with a higher intensity than that previously used in the IC population (12). The protocol will consist of 3 sessions per week for 6 weeks, with a work to rest ratio of 1:1 (one-minute interval of HIIT interspaced by one-minute interval of low-intensity exercise), completing 10 sets of HIIT with an overall exercise session time of 20 minutes. The intensity will be set at 85-90% PPO (from CPET) during high-intensity, (aiming to achieve 85-100% HRMax), and at 20-25%PPO during low-intensity bouts. The variation from high to low intensity will be achieved by altering the cycle cadence (rpm). This work to rest ratio has been selected as although HIIT is often prescribed in similar clinical populations using 4-minute intervals at 85-95%HRMax (33), a large RCT recently concluded that HIIT at this intensity is hardly feasible, at least not for a full 4-minutes (15). Our personal experience with cardiac patients has demonstrated that patients may exceed their peak heart rate (from CPET) during HIIT sessions. This is also likely to be the case for those with IC, especially those who are unable to achieve a maximal effort CPET. We will adopt a pragmatic approach to this by allowing it to occur but monitoring on a case-by-case basis and will reduce intensity when deemed appropriate. We will also record these occurrences to allow appropriate reporting.
The HIIT sessions will be preceded and followed by a 10-minute warm up and cool down as is standard practice in exercise rehabilitation for older adults with chronic disease. In addition, patients will be monitored for up to 10 minutes following the cool-down to ensure heart rate is returning to near resting values and/or any symptoms have subsided.
The HIIT intervention will be performed by using a cycle ergometer with exercise prescription based on the workload achieved during a cycle CPET. The use of a treadmill may preclude patients from reaching their prescribed HIIT training zones due to the onset of claudication whilst a cycle may reduce the risk of falls in very deconditioned patients (34). It has been demonstrated that the limiting symptoms during treadmill walking were often experienced in the leg, mainly the calf, whereas the limiting symptoms during cycling were much more varied (34). Furthermore, one study, albeit small, noted that cycle testing was better tolerated than treadmill testing, which is important considering that the HIIT training zone requires the patient to exercise to near-maximal levels, similar to during a CPET (35).


Warm-up
10 Minutes
<80%HR Max
High-Intensity Bout
1 Minute
85-90%PPO (from CPET)
Low-Intensity Bout
1 Minute
20-25%PPO
Cool-Down
10 Minutes
<40%HR Max

Inclusion criteria:

- Community dwelling adults aged 18 or over.
- ABPI <0.9 at rest or a drop of more than 20mmHg after exercise testing
- Ability to walk unaided
- English speaking and able to comply with exercise instructions

Exclusion criteria:

- Patients who are unable to provide informed consent
- Critical limb ischaemia/rest pain
- Active cancer treatment
- Significant comorbidities precluding participation in exercise testing and/or training as per the American College of Sports Medicine Guidelines (19).
- Resting/uncontrolled tachycardia (>100bpm) and/or Resting/uncontrolled hypertension (SBP >180mmHg or DBP >100mmHg)
- Symptomatic hypotension

Additional exclusion criteria

Further to analysis of CPET results, patients will be prevented from continuing their involvement in the study if there is indication of:

- Exercise-induced ischaemia or significant haemodynamic compromise.

N.B. – Patients who are able to perform a maximal effort CPET according to previously published guidelines (19) will undergo the intervention which will be prescribed on the basis of their initial CPET. This will be referred to as maximal HIIT.
Patients unable to perform a maximal effort CPET, will still undergo the intervention which will be prescribed on the basis of their initial CPET values, but will be referred to as submaximal HIIT.

Subject recruitment

Patients who are deemed appropriate for referral to SEP as is usual practice will be informed of the research study evaluating HIIT as a novel exercise intervention for IC. Patients will then be sent a patient information sheet, detailing the aims and details of the study and what the intervention entails. Patients will then be contacted via telephone at least a week later to discuss their interest to undertake the intervention. Those who choose to participate in the study will be asked to attend for baseline assessment. Those who do not choose to partake in the research will be offered the usual SEP, without research. Those also declining the usual SEP will be referred back to their consultant.

Withdrawal of subjects

Participants are free to withdraw at any time and do not have to give a reason for doing so. If a participant exhibits any of the exclusion criteria or loses capacity to consent after enrolment on the study, they will be withdrawn. Full details of any withdrawal will be recorded in the case report form and withdrawal can occur at any time, including during the intervention or follow-up.

Trial exit

Patients will exit the trial if:

- They have completed their intervention and all follow-up assessments.
- They request or are unable to continue intervention or follow-up
- They suffer an adverse or serious adverse event meaning they are no longer able to continue
- They lose the capacity to consent
- They die.

General information

Potential patient benefits

SEPs have proven to be effective for improving walking distance in patients with IC but are not always feasible or available (11, 14, 36). Other exercise interventions may provide a similar benefit and allow access for a greater number of patients. HIIT has demonstrated beneficial effects in the cardiac population (33, 37), which may be transferrable to the IC population, due to the similar disease aetiology. Therefore, patients may benefit from having a greater range of exercise options that may provide similar benefits, allowing them

to choose their preferred option, thus increasing availability and potentially uptake and adherence.

Potential risks/barriers to the patient

The study requirements and participant expectations will be clearly explained in the patient information sheet. This will be sent to the patient and they will be given adequate time to read it at their own leisure without any pressure to partake in the study from the researcher. Informed consent will only be obtained once patients have understood all study requirements, asked any questions they may have and have agreed to participate.

Patients will be required to attend their exercise sessions 3 times per week for 6 weeks. This may be problematic for patients and may cause them to decline this intervention or withdraw once recruited. However, this may also provide a patient benefit, as this means the patient only has to attend half the number of sessions than is usually required for SEP. Furthermore, travel and parking costs may prove to be a barrier. Travel expenses for study visits (baseline and follow-ups) will be reimbursed. Patients can be reimbursed a maximum of £75 to cover the costs of transport/parking that may be accrued.
Patients will be required to attend three or four 2-3-hour study visits s. This time, on top of the time required to undertake the intervention may preclude some patients from taking part in the study.
Some study elements (such as CPET or HIIT) may propose a risk to the participants. HIIT is a novel intervention in the IC population, meaning its safety is unknown. However, a large multi-centre RCT in the cardiac population (similar disease aetiology to IC) demonstrated that HIIT was a safe intervention (15). Furthermore, standards for exercise testing from the American heart association, note that the occurrence of death as a result of testing is rare with a frequency estimated at 1 per 10000 tests, maybe less (26). Therefore, although the testing and intervention procedures carry some risk, it is minimal and is outweighed by the potential patient benefits.

Sample size

Due to the pilot nature of this proof of concept study it is not possible to calculate the sample size. The main aim is to assess the conceptual benefit of the proposed interventions. We aim to recruit 20 patients from the additional Coventry site, which in addition to the target of 50 patients at the Hull site, totals 70 patients.

Descriptive statistics and statistical analysis

Data obtained from all participants will be included in the data analysis and no data will be excluded on the basis of intervention and follow-up adherence. Therefore, all collected data at each time point will be analysed.
Baseline characteristics will be summarised descriptively using mean (±SD) for normally

distributed data and using median and range for non-normally distributed data. Categorical variables will be presented as frequency and percentages.
Rates of uptake, completion, dropout, adverse or serious adverse events and missing outcome data will be summarised and participation in the intervention will be described as the mean number of sessions attended and the mean time to completion (in weeks) to allow for comparison between actual and theoretical total intervention time.
In addition, tolerability will be assessed by comparing the mean heart rate achieved during each HIIT session to the 85-100% maximum heart rate range calculated from CPET.
Secondary endpoints such as changes in MWD, PFWD, VO_{2Peak}, VAT, ABPI and QoL at each time-point will be assessed using a repeated-measures general linear model.
All quantitative analyses will be conducted using the SPSS statistics software at the conventional two-sided 5% significance level with results presented as mean difference with 95% confidence intervals, associated *p* values and effect sizes where appropriate. Sub-group analysis will also be conducted comparing those who are able to give maximal effort during baseline CPET (and therefore able to perform maximal HIIT) and those who are not (therefore performing submaximal HIIT). Maximal effort will be based on previously published criteria (19, 38). Further sub-group analysis will also be performed comparing those who satisfactorily completed the intervention (i.e. completed ≥15/18 sessions) and those who did not, presuming they do not withdraw from the intervention.

The qualitative data will also be analysed using an inductive thematic analysis. Thematic analysis involves identifying, analysing and reporting themes that become apparent within the data (39). Themes collate important or patterned responses from within the data that are related to the research question (39). This means that as the researcher reads and re-reads the transcriptions, a pattern of responses will emerge that are related to the research question and can be grouped together under a theme heading. The approach will be inductive, which means that the themes are data-driven, thus emerging from the data, do not fit into a pre-existing coding frame and are not driven by the researcher's theoretical interest in the area (39).

In an attempt to minimise missing data from losses to follow-up patients will be contacted well in advance of their follow-up appointment and the researcher will attempt to rearrange any missed follow-ups. However, any missing data due to loss to follow-up will be recorded and reported adequately. Any missing data that should have been collected during a study visit will be investigated via source data and patient notes to exhaust all options. If data is still missing, it will be coded adequately during analysis and reported in results. Missing data will not be imputed by the researcher to avoid bias.

Safety reporting

Collecting and reporting data on adverse and serious adverse events will be in accordance with GCP and the Research Governance Framework v. 3.3, 2017.

Adverse events (AE)

An adverse event is any untoward occurrence that happens to a subject during the conduct of the study. The event may be as a result of the study conduct or intervention or there could be no relationship between the study and the AE at all.

Serious adverse events (SAE)

An AE is deemed serious if it:

- Results in death
- Is life-threatening (patient is at risk of death at the time of the event)
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect

Hospitalisation that was planned before partaking in the study (i.e. elective surgery) should not be considered a SAE unless it has to be prolonged.

Reporting period:

The AE reporting period for each patient begins as soon as they have given informed consent for the trial and ends 30 days after their final study visit.

The researcher will record any AE's upon knowledge of the event. Most evets will occur outside of study activity and the site team will be informed at a later point. A discussion about the patient's general health will take place at each study visit to identify any AE's as patients may not inform the researcher about an event that they do not believe is related to the study, such as having a cold. Once knowledge of the event has been received, the researcher will gather as much information as possible and if necessary report to the sponsor.

Reporting serious adverse events

If a trial subject experiences a serious adverse event which in the opinion of the chief investigator is both

- **Related -** that is, it resulted from administration of any of the research treatments or procedures; and
- **Unexpected -** that is, the type of event is not listed in the protocol as an expected occurrence.

Then it will be reported to the Research Ethics Committee (REC) that gave a favourable opinion of the study and the Sponsor (Hull University Teaching Hospitals NHS TrustNHS Trust R&D department) **within 15 days** of the Chief Investigator becoming aware of the event using the non-CTIMP safety report form, available from: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

Urgent safety measures

The chief investigator (or sponsor) may take appropriate safety measures to protect subjects from immediate hazard to their health or safety, without prior authorisation from a regulatory body. However, the chief/principal investigator must alert the sponsor (HEY R&D) as soon as possible of the urgent measures by contacting the R&D Office telephone number 461883 or 461903 (Mon - Fri 8am - 6pm) or the Trust Switchboard 875875 (out-of-office hours) and asking for either the R&D Director or the R&D Manager.

The main REC will be notified immediately, at least within three days, by completing a substantial form and giving information about the measures taken and why.

Annual progress report:

An annual progress report will be submitted to the REC that gave the favourable opinion 12 months from the date of the favourable opinion. The relevant form, available from: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/progress-reports/ will be used. It will be completed and signed by the chief investigator and emailed to the REC within 30 days of the anniversary date of the favourable opinion and annually until the trial is completed.

Data collection, handling, management and record keeping

Data will be collected by the local principal investigator at all time points during the study. Collection of data will be via standardised questionnaires (VascuQoL and SF-36) and physical assessment. To ensure completeness of data, questionnaires will be issued and completed during the study visits to allow patients to ask questions or clarify information about the questionnaire. Data will be collected and retained in accordance with the Data Protection

Act 1998. All patients will be given a study code along with the abbreviate hospital title to ensure anonymity, for example the first patient recruited at Hull and Coventry would be 01H and 01C respectively. Data will be stored on computers in the research office at the vascular laboratory in Hull Royal Infirmary and Coventry and Warwickshire University Hospital respectively with the same identification code. These computers are password protected and have both antivirus and firewall software. Only named investigators will have access to the patient data. Transfer of electronic data will be anonymous and only be carried out through encrypted password protected USB devices or via the secure www.nhs.net email account. Data will be stored for five years following trial completion.
IT services department has a backup procedure approved by auditors for disaster recovery. Servers are backed up to disk media each night which run on a 4-week cycle, meaning anything deleted more than 4 weeks previously is lost. Files remain on the server unless deleted either accidently or deliberately. Additional 'archive' backups are taken for archived data, so data should not be lost from this system e.g. FileVision. Disks are stored in a fireproof safe.

Study documents (paper and electronic) will be retained in a secure location during and after the trial has finished. All essential documents including source data will be retained for a minimum period of 5 years after study completion. A sticker stating the date that documents need to be retained until will be placed on the inside front cover of participant case report forms.
Direct access will also be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections – in line with participant consent.

Project Management Group;
The overall management of this study will be the responsibility of the Programme Management Group. This will be chaired by the R&D Director, HEYHT, who is independent of the research team. Membership of the Project Management Group will comprise all coapplicants, patient representatives and Susan Walker (Finance Manager). The Trust will discharge its sponsorship responsibilities through this Group including research governance and financial oversight and will ensure that the research conducted is congruent with that specified in the proposal and of value to the NHS. Additionally this group will o provide specialist advice in areas of data collection, analysis and interpretation, consider the implications of the findings, develop a dissemination strategy, and consider any issues brought to their attention by the research staff. The Project Management Group will meet on a quarterly basis and receive reports from, and oversee, the work of the Project Delivery Group.

Combined Trial Steering / Data Monitoring Committee; will be formed to monitor the progress of the study, provide independent advice, and monitor the data arising from the study to recommend whether there are any ethical or safety reasons why the study should not continue. This committee will comprise independent clinicians and health service

researchers with appropriate expertise, a patient representative and will also be attended by the trial statistician. This committee will meet every 6 months to provide oversight to the study.

Source data

It is important that information from a patient study visit is recorded clearly into the casenotes so that other clinicians and healthcare professionals can be aware of any relevant results or information which may affect ongoing care.

The minimum information recorded in patient notes following each study visit or phone call will be:

- Clearly written date of visit, study short title and visit number.
- The date that the patient information sheet was given
- The date informed consent was obtained
- Medical history (including reasons for referral), concomitant diseases, and medications and any changes between visits. Any changes or newly developed symptoms or are they asymptomatic.
- Anything relevant to the ongoing care of the subject
- Relevant investigations and results of these – i.e. ABPI, CPET (any ECG changes)
- Brief description of any AE's with start and end dates if appropriate, any significant tests/results or a medical summary of events.
- Any other relevant information.

Protocol deviations/serious breaches

Protocol deviations and serious breaches will be acted upon in line with the HRA standard operating procedure version 7.2 available from https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/research-ethics-committee-standard-operating-procedures/.
Protocol deviations involves not complying with the protocol as a result of fraud or misconduct. Accidental protocol deviations must be adequately documented and reported to the CI and sponsor immediately. However, the sponsor does not need to notify the REC unless the deviation constitutes a serious breach. Any deviations will also be documented in the patients notes and with a file note in the site, detailing as much information as possible.

Importantly, frequent and/or recurrent deviations are not acceptable and will require immediate action and could lead to a serious breach.
A serious breach is defined as a breach of the protocol, conditions or principles of GCP which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects or the scientific value of the research. Serious breaches will be reported to the sponsor immediately upon knowledge of the breach. The PI will take a leading role in resolving any serious breach whilst completing any addition activities required by the sponsor to investigate or address the breach.
The sponsor should also notify the REC of a serious breach within 7 days of being informed. A report of the serious breach which should outline when and where it occurred, who was involved, the outcome and any information given to the participant should be provided by the CI or other representative of the sponsor, and copied to the sponsor. The REC should receive an explanation and informed of any further action that the sponsor plans to take.

End of trial

The trial will be complete once the last patient has attended their final follow-up visit, for this study, the last study visit will be 12-weeks post-intervention.

The REC which gave the favourable opinion with be notified of the study conclusion by the CI within 90 days or within 15 days if the trial is terminated early (with reasons). This notification will be in writing (sent via email) using the appropriate form available from: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/

A final research report summary will be emailed by the CI to the REC within 12 months of the end of the trial. The summary will include information about whether the research achieved its objectives, the main findings and arrangements for publication, including any patient feedback.

Quality control and assurance:

Peer review

This study has been peer reviewed by:

Dr Amy Harwood, Postdoctoral research fellow, academic vascular surgical unit, Hull Royal Infirmary.
Mr. George Smith, consultant vascular surgeon, Hull Royal Infirmary.
Professor Ian Chetter, consultant vascular surgeon, Hull Royal Infirmary.
Dr Catriona McDaid, Reader in Trials and member of the Senior Management at the York Trial Unit. Dr McDaid is also the lead for the North and East Yorkshire spoke of the Research Design Service Yorkshire and Humber (RDS-YH). This application has been developed in

collaboration with our PPI members of the “Humberside Peripheral Arterial Research Involvement Group

Monitoring

Research will be monitored in accordance with GCP. The sponsor has the responsibility to ensure that the rights and safety of participants are protected, study data is complete and accurate and that conduct of the study complies with the protocol and GCP. Monitoring will be risk based as required by the sponsor.

Ethical considerations

REC review and reports:

Before trial commencement, approval will be sought from the REC for the trial protocol, informed consent forms and other relevant documents such as GP letters and patient information sheets.
Substantial amendments requiring review from the REC will not be implemented until the REC grants a favourable opinion. All correspondence with the REC will be retained in the trial master file.

Indemnity

This is an NHS-sponsored research study. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff and medical academic staff with honorary contracts only when the trial has been approved by the Trust R&D department. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Where the Chief/Principal investigator is employed by the University of Hull, the University has an insurance policy that includes cover for no-fault compensation in respect of accidental injury to a research subject.

Amendments

Amendments involve changes to a project after initial approval has been granted. It is the responsibility of the sponsor to decide whether an amendment is substantial or non-substantial. If the sponsor deems an amendment to be non-substantial the template available from https://www.hra.nhs.uk/approvals-amendments/amending-approval/ will be emailed to hra.amendments@nhs.net. The amendment will receive two possible outcomes; ‘HRA approval for the amendment confirmed’ or ‘HRA approval for the amendment pending’.
The applicant will communicate this outcome, along with the amendment application, with the site team, R&D office and local CRN. For category A and B amendments, the site team have 35 days to raise any objections, after which if no objections are raised, the amendment

can be implemented. Category C amendments can be immediately implemented. Where HRA approval is required, the amendment will be reviewed and approval issued. The applicant should then notify the site team and provide the approved documentation.

A similar process is followed for substantial amendments. The notice of substantial amendment form in IRAS will be used to generate a PDF form for the amendment that will be emailed to the REC that gave the favourable opinion of the original study. The REC staff will validate the amendment and if necessary, categorise it. The applicant will then receive a validation letter which will also outline the categorisation – which should be passed onto site staff. The REC will then review the amendment, with three possible outcomes; an unfavourable opinion, which will require restarting the process and resubmitting, or a favourable opinion either with or without further review from the HRA. If either of the favourable opinion outcomes is given, the same outcome communication and implementation process as described above for a non-substantial amendment will be followed.
An amendment history table will also be used to identify the most recent protocol version (appendix 1).

Reporting and dissemination

The final trial dataset will be developed by the principal investigators but will be owned by the Academic Vascular Surgical Unit and as such can be accessed by site investigators. Upon completion of the trial, data will be analysed and tabulated with a final trial report prepared and submitted to the REC. The study will also be reported in peer-reviewed scientific journals, an internal report and conference presentation. Patients will be offered individual information regarding post-intervention improvements and access to publications should they request it.

Finance and conflicts of interest

Patients will not be paid for participating in the trial, but will be offered a discounted parking permit of £20 per month if required for the intervention period.

There are no ownership or commercial ties related to any of the interventions. The principal investigator in Hull is funded by a University of Hull scholarship.

Study equipment

Height measure – Leicester height scale, Seca LTD. UK

Weight scales – Marsden, Charder M-420, UK

Resting Blood Pressure monitor – Welch Allyn, Sure Temp. technology, UK

Ambulatory blood pressure monitor –

12-lead ECG – Mortara Instruments, T2, USA

ECG electrodes – 3M Red dot, Canada

Cycle ergometer – Lode Corival, Neterlands

CPET system and metabolic cart – MedGraphics Ultima series with BreezeSuite software

Doppler – Ultrasonic Doppler flow detector, LifeDop, Summit Doppler, Wallach, USA.

Wattbike – Wattbike Ltd. Nottingham, UK.

Heart rate monitor – Polar F2, Polar Electro, OY. Kempele, Finland.

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Appendix 1: Amendment history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made