Study Title: An investigation into the feasibility of incorporating an exercise rehabilitation programme for people with intermittent claudication into an already established Cardiac Rehabilitation service

Protocol

Overview

This study will look at the feasibility of combining patients with peripheral artery disease (PAD) and coronary artery disease (CAD) into one supervised exercise programme (SEP). The study will assess the effects of the intervention quantitatively, and also investigate the patient experience qualitatively by applying a mixed methods design (figure 1). The initial phase of the research will quantitatively analyse pre and post-intervention outcomes, followed by qualitative investigation into the thoughts and concerns about the intervention. The rationale for this mixed methods approach is that it provides strengths that offset the weaknesses of both qualitative and quantitative methods when used in isolation (Creswell & Plano Clarke, 2007). Also in clinical settings such as in the NHS, exploring the views and experiences of the service users to gain greater understanding has been shown to improve service provision and subsequently patient uptake (Risom et al., 2013).

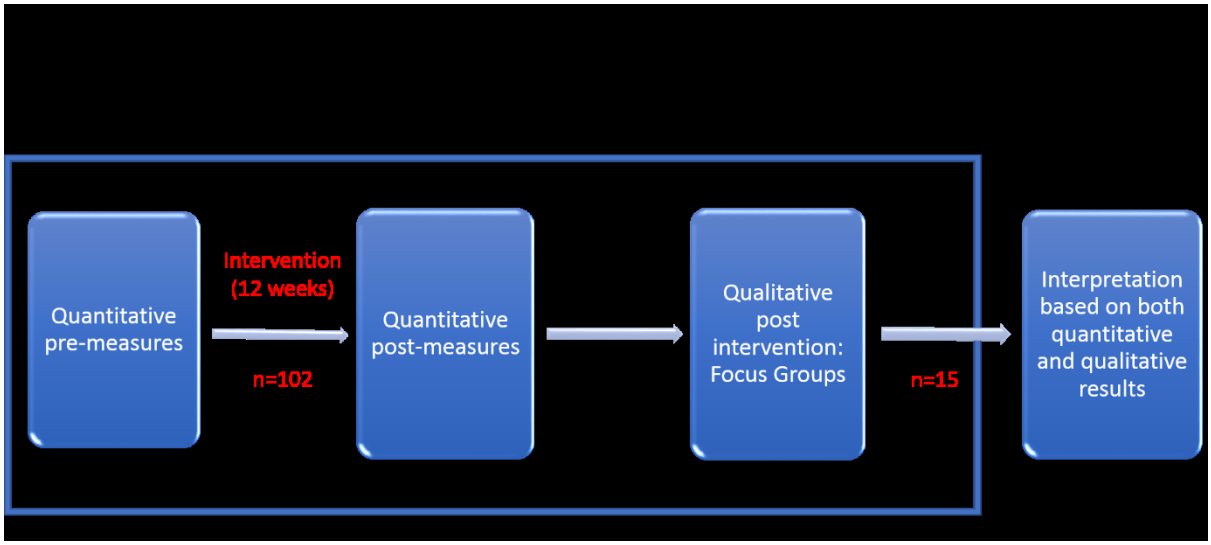

Figure 1: This diagram shows the mixed methods approach of the research study, with the qualitative element following on from the quantitative measurement of the intervention outcomes. The results of each arm will be merged to show the overall effectiveness of the intervention.

Recruitment Strategy:

Intervention group:

Participants for the combined SEP will be recruited from a local NHS Vascular Service at Salford Royal NHS Foundation Trust (SRFT). They will be identified by the vascular specialist teams (surgeons, nurses and podiatrists) and asked if they wish to take part in the study. The participants will be asked during the face-to-face consultation with their specialist, or a telephone consultation. This will give participants 1-2 week period to consider enrolling in the research programme. Participation will be on a voluntary basis. Simultaneously, an age-matched group of coronary artery disease (CAD) patients will be recruited to the combined programme to assess the impact of combined SEP on CAD patients. These participants will be identified by the Cardiac Rehabilitation Specialist Nurses at SRFT upon referral to the CR SEP and will have a similar 1-2 week period to decide about enrolling.

Control group or "standard care" group:

A control group will also be recruited. This group will be made of PAD patients only and will take place at an established SEP at Central Manchester University Hospitals. The use of a SEP has been chosen as the control group or "standard care" group, even though most patients are unable to receive the standard care in the UK. Other research in this area has had an "exercise advice only" group as control (Cheetham et al., 2004) however, it has been established that SEPs are better than "exercise advice only" as a treatment option (Bendermacher, Willigendal, Teijink and Prins, 2009). Therefore it would be unethical for some participants to be missing out on the recommended SEP treatment.

The CAD patient's outcomes will be compared to the National Audit of Cardiac Rehabilitation (NACR) as it is outside of the scope of this investigation to have a CAD only control group. The NACR data is compiled annually and records all of the outcome measures that are included in this study. The recent year's audit results will be used for comparison.

Informed Consent

In order to gain informed consent from prospective participants, the content and layout will verbally be given to prospective participants, along with an easy-to-read leaflet/letter with full description of the study (see Patient Information Sheet in supporting documents). To avoid any risk of coercion, it will be explicitly stated that they have the right to withdraw from the study at any point, and that no present or future treatment will be affected by enrolling or not enrolling on the study. All documents will be available in large print if required.

Sample size:

The sample size of this investigation has been guided by a study by Evans et al., (2010) which investigated the suitability of combining two different patient groups (heart failure and chronic obstructive pulmonary disorder) into one rehabilitation programme. The authors of this study established that 17 participants were required in each group to reach significance level.

There will be 3 participant groups in this study: The stand-alone PAD group; the combined PAD group, and the combined CR group (see figure 2). In order to generate sufficient data 34

patients will be recruited to each group with an aim to achieve 17 completers from each group**.** This is due to an expectation of high dropout rate for both PAD and CAD programmes seen at a national level (NACR, 2016; Shalhoub et al., 2009). The total recruited will therefore be 102 subjects, to gain 51 completers totally (17 per group).

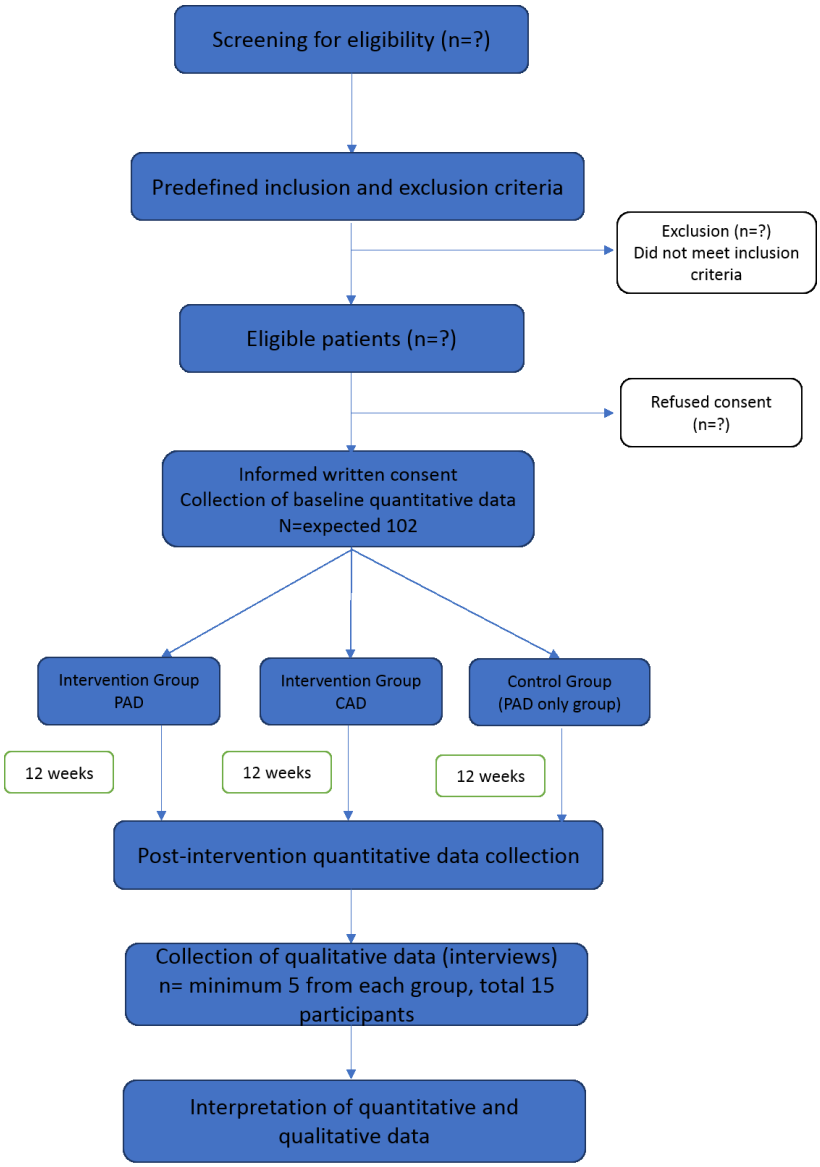

Figure 2 - Flowchart of study. This shows the outline of the 12 week study with the 3 groups involved

Inclusion and Exclusion Criteria

General criteria

As part of this study participants will be required to wear an accelerometer on the first week and last week of the 12 week study. The accelerometer will be kept in place by a medical dressing (e.g. Tegederm). People with an existing skin condition such as psoriasis or eczema

that would be affected by the application of a medical dressing will be excluded from the study.

All participants must be able to start the incremental shuttle walk test (walking speed of 1.8kph, 1.1 mph). If they are unable to walk at this pace they will be excluded from the study.

All participants must be able to engage in the exercises prescribed in the programme (see Supervised Exercise Programme outline below).

No participant will be excluded due to age or gender.

Inclusion Criteria – PAD patients:

All patients recruited will have had a recent diagnosis (0 – 12 months) of PAD made by either a vascular surgeon, vascular specialist nurse or specialist podiatrist.

Exclusion criteria – PAD patients:

Any patient who has had previous intervention for PAD e.g. balloon angioplasty, stent, bypass or medication, or who have previously completed an SEP will be excluded from the study. This is due to the possibility of previous interventions having an impact on patient perceptions.

Participants who are on medication for PAD (e.g. naftidrofuryl oxalate) will also be excluded from the study as this can increase symptom management and improve functional capacity.

Any PAD patient who also has a diagnosis of other cardiovascular conditions such as CAD or stroke, or chronic heart failure will be excluded from this study, as the investigation is looking at the specific improvements in PAD, not CAD gains.

Inclusion Criteria – CAD patients:

All patients recruited to the CR group will have had a recent diagnosis (0-12 months) of CAD (angina, myocardial infarction (MI), or coronary artery bypass graft (CABG) or valve surgery).

Exclusion criteria – CAD patients:

Any patient who has had previous diagnosis of PAD will be excluded from the study, as this may mask any gains in improvement due to CAD-specific rehabilitation in the CAD group (Tam et al., 2016).

Any participant who has unstable CAD (e.g. unstable angina) will be excluded from the study as this is a contraindication partaking in structured exercise programme (BACPR, 2012).

Study Design

Initial Assessment

All participants will be fully assessed prior to starting their 12 week SEP. This assessment is a standard part of the SEP process where a range of standard clinical measures are recorded (e.g. resting BP, BMI, and waist circumference). This will be conducted by one of the rehabilitation team members. All outcome measures will be taken prior to the patients starting their SEP and repeated upon completion of the programme. A summary of all outcome measures is shown in table 1. Completion will be categorised as attending 8 or more of their 12 sessions.

Quantities subjected to post hoc analysis

Quantity	Time of measure (weeks)
Demographic	
Sex (M/F)	BL
Age (years)	BL
Clinical	
Blood Pressure (mmHg)	BL, 12 weeks
Resting Heart rate (bpm)	BL, 12 weeks
Height (m), weight (kg), BMI ($kg.m^2$)	BL, 12 weeks
Waist circumference (cm)	BL, 12 weeks
Medication	BL, 12 weeks
Physical Functioning	
Incremental Shuttle Walk Test (ISWT)	BL, 12 weeks
7-day activity monitoring	BL, 12 weeks
Questionnaires	
VascuQol (PAD only group)	BL, 12 weeks
Hospital Anxiety and Depression Scale (HADS)	BL, 12 weeks
Walking Impairment Questionnaire (WIQ)	BL, 12 weeks

BL, Baseline; PAD, peripheral artery disease

Table 1 – This table provides a summary of quantitative outcome measures and the time-point at which they will be recorded

Outcome measures:

The following items are the outcome measures that will be recorded. The PAD-specific tests have been recommended by the TransAtlantic Inter-Society Consensus (TASC) Working Group for the Management of PAD (2007). The others are standard outcomes measures recommended by the British Association of Cardiovascular Prevention and Rehabilitation (BACPR).

- Incremental shuttle walk test (ISWT): This will assess walking distance, peak walking speed and functional capacity. For PAD patients it will also establish the pain-free and maximal walking distances. The ISWT is a functional exercise test (FET) that is commonly used throughout exercise rehabilitation programmes and research (Zwierska et al., 2005; Evans et al., 2010; ACPICR, 2015)
- Walking behaviour and physical activity will be recorded by an Activpal® accelerometer (as used in Clarke et al. 2012) to quantify free-living walking. It will be attached to the front of the thigh using a medical grade waterproof dressing. It weighs 15g so will not be a physical burden to the participants. It will remain in place on the leg for a seven-day period, prior to starting the SEP. This will show baseline activity, and during the last week prior to them completing their SEP.
- Quality of Life Measures
    - Hospital Anxiety and Depression Scale (HADS) questionnaire
        - This is a 14-item questionnaire with 7 questions measuring anxiety and 7 questions measuring depression levels. This is a commonly used in clinical settings and is a standard questionnaire used in Cardiac Rehab departments (Coats et al, 1995; BACPR, 2012; ACPICR, 2015). It takes on average 5 minutes to complete this questionnaire.

- King's College Vascular Quality of Life (Vascu-QoL) Questionnaire (PAD-specific)
  - This is a 25-item questionnaire with 5 domains looking at disease-specific quality of life that has been widely used in PAD research (Morgan et al. 2001; Vries et al. 2005). Disease-specific quality of life measures are recommended by TASC (2007) in combination with generic questionnaires (such as HADs) as they are more sensitive to change in specific symptoms that are related to the condition. This questionnaire takes on average 10 minutes to complete.

- Walking Impairment Questionnaire (WIQ): This is a PAD disease-specific questionnaire assessing the perceived impact of claudication symptoms on the individual being measured. This is a commonly used questionnaire in PAD research since its development by Regesteiner et al. (1995), and is recommended by TASC (2007) to assess patient perceived symptoms. It takes on average 5 minutes to complete.

Supervised Exercise Programme Outline:

The Programme

Patients from all groups will attend a 2 hour supervised exercise session once a week, for 12-weeksEach session will start with a pre-screening interview to confirm suitability to exercise that day. The exercise will start with a 10-15 minute warm up, followed by a 20-25 minute conditioning phase, and a 10 minute cool-down. Successful completion of the programme will be achieved when 8 or more sessions are attended.

PAD specific exercise

The conditioning phase for the IC patients will involve completion of a range of exercises designed to bring on claudication within 3-4 minutes. Participants are encouraged to exercise to near-maximal claudication pain, and then rest until the pain has subsided before starting the next exercise. This is accordance with the AACVPR (2013) and NICE (2012) recommendations and will ensure safe and effective exercise. Monitoring and guidance will

be given throughout the exercise session by the rehabilitation team. The exercises will include:

- Treadmill walking
- Heel raises
- Trampette walking/jogging
- Sit to stands
- Corridor walking

CAD specific exercise

The conditioning phase for CAD patients will consist of a range of cardiovascular exercises designed to improve cardiovascular fitness. This will follow the standard cardiac rehabilitation programme guidelines set by the BACPR (2012) and Association of Chartered Physiotherapist working in Cardiac Rehabilitation (ACPICR) (2015).

Physical Activity and exercise advice:

As the programme of exercise is only once a week, the rehabilitation team will provide guidance and encouragement for patients to keep active outside of the sessions. Patients will be given pedometers to use and weekly activity goals will be set and reviewed each week by a member of the rehabilitation team to assess progression.

Patient education:

Following each exercise session all patients will be invited to attend education sessions. The sessions are based on the clinical guidance from NICE (2012) recommending patients are educated on the importance of lifestyle interventions including:

- aggressive lipid modification and statin therapy
- smoking cessation
- diet, weight management and exercise
- the prevention, diagnosis and management of diabetes
- the prevention, diagnosis and management of high blood pressure

- antiplatelet therapy

Qualitative post-intervention study

Upon completion of the 12-week supervised exercise programme, participants will be invited to attend focus groups to explore their thoughts and concerns about the intervention (Figure 2). Themes will be constructed from the data to give insight into the experiences of the different participant groups. As participation is important for rehabilitation departments, it is essential to include the participants' perspective in the evaluation of the treatment programme.

Data Analysis:

Quantitative data:

The outcome data will be tested to see if it is normally distributed or not. SPSS software will then be used to assess for any statistically significant differences between the groups. Within groups and between group differences in exercise capacity will be analysed using a factorial ANOVA to compare the difference in the levels of improvement between groups. Wilcoxon tests will be used to analyse the questionnaire data.
The CAD group will also be compared to the National Audit of Cardiac Rehabilitation (NACR) data to assess the impact on the CAD group performance against expected national levels. The effect sizes will be calculated using the Cohen's *d* so that the results can be compared to other studies.

Qualitative Data:

The analysis will be influenced by Braun & Clarke's (2006) six phases of thematic analysis as described in Table 2.

Phase	Description of the process

1. Familiarizing yourself with your data:	Transcribing data (if necessary), reading and re-reading the data, noting down initial ideas.
2. Generating initial codes:	Coding interesting features of the data in a systematic fashion across the entire data set, collating data relevant to each code.
3. Searching for themes:	Collating codes into potential themes, gathering all data relevant to each potential theme.
4. Reviewing themes:	Checking if the themes work in relation to the coded extracts (Level 1) and the entire data set (Level 2), generating a thematic 'map' of the analysis.
5. Defining and naming themes:	Ongoing analysis to refine the specifics of each theme, and the overall story the analysis tells, generating clear definitions and names for each theme.
6. Producing the report:	The final opportunity for analysis. Selection of vivid, compelling extract examples, final analysis of selected extracts, relating back of the analysis to the research question and literature, producing a scholarly report of the analysis.

Table 2 This table outlines the steps taken in the thematic analysis of the focus group data. ***Taken from: Braun & Clarke, (2006) Using thematic analysis in psychology. Qualitative Research in Psychology. 3: pp77-101***

The results of both the quantitative data analysis and the thematic analysis from the focus groups will then be used to draw conclusions about the effectiveness of the treatment options.

References:

American Association of Cardiovascular and Pulmonary Rehabilitation (2013) *Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs (4th ed.)*. Human Kinetics Publishers

Association of Chartered Physiotherapist in Cardiac Rehabilitation (2015) *ACPICR Standards for Physical Activity and Exercise in the Cardiovascular Population*. ACPICR.

BACPR (2012) Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation (2nd ed.). Available at: http://www.bacpr.com/resources/46C_BACPR_Standards_and_Core_Components_2012.pdf

Bendermacher, B., Willigendael, E., Teijink, J. and Prins, M. (2009) 'Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication'. *Cochrane Database of Systematic Reviews*, (2). doi: 10.1002/14651858.

Braun, V., and Clarke, V. (2006) Using thematic analysis in psychology. *Qualitative Research in Psychology, 3*: 77-101 doi: 10.1191/1478088706qp063oa

Burns, P., Gough, S., & Bradbury, A. W. (2003). Management of peripheral arterial disease in primary care. *British Medical Journal, 326* (7389), 584-588. doi:10.1136/bmj.326.7389.584)

Cheetham, D. ., Burgess, L., Ellis, M., Williams, A., Greenhalgh, R. and Davies, A. (2004) 'Does Supervised Exercise Offer Adjuvant Benefit Over Exercise Advice Alone for the Treatment of Intermittent Claudication? A Randomised Trial'. *European Journal of Vascular and Endovascular Surgery*, *27*(1), pp. 17–23. doi: 10.1016/j.ejvs.2003.09.012.

Clarke, CL., Holdsworth, RL., Ryan, CG., and Granat, MH. (2012) Free-living Physical Activity as a Novel Outcome Measure in Patients with Intermittent Claudication. *European Journal of Vascular and Endovascular Surgery*. http://dx.doi.org/10.1016/j.ejvs.2012.11.027

Creswell, JW., and Plano-Clarke, VL. (2007*) Designing and Conducting Mixed Methods Research*. London: SAGE

de Vries, M,. Ouwendijik, R., Kessels. AG., de Haan. MW., Flobbe, K., Hunink, MGM., van Engelshoven, JMA, and Nelemans, PJ. (2004) Comparison of generic and disease-specific

questionnaires for the assessment of quality of life in patients with peripheral arterial disease. *Journal of Vascular Surgery;* 41(2): 261-8

Evans, RA., Singh, SJ., Collier, R., Loke, I., Stiner, MC., and Morgan, MDL. (2010) Generic, symptom based, exercise rehabilitation; integrating patients with COPD and heart failure. *Respiratory Medicine, 104*: 1473-1481 doi: 10.1016/j.rmed.2010.04.024

Morgan, MBF., Crayford, T., Murrin, B., and Fraser, SCA. (2001) Developing the Vascular Quality of Life Questionnaire: A new disease-specific quality of life measure for use in lower limb ischaemia. *Journal of Vascular Surgery;* 33:679-87 doi: 10.1067/mva.2001.112326

NACR (2016) *The national audit of cardiac rehabilitation annual statistical report 2016*. British Heart Foundation: London

Found at: http://www.cardiacrehabilitation.org.uk/docs/BHF_NACR_Report_2015.pdf (accessed online January 2017).

National Institute for Health and Clinical Excellence (2012). Lower Limb peripheral artery disease: diagnosis and management. NICE Guidance (147)

Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Journal of Vascular Surgery, 45* (Suppl S):5-67.

Regensteiner, JG., Steiner, JF., Panzer, RJ., and Hiatt, WR. (1995) Evaluation of Walking Impairment by Questionnaire in Patients with peripheral Artery Disease. *Journal of Vascular Medicine and Biology*. *2* (3):142-152

Risom, SS., Zwilser, AO., Rasmussen, TB., Sibilitz, KL. Svendsen, JH., Gluud, C.,…Berg, SK. (2013) The effect of integrated cardiac rehabilitation versus treatment as usual for atrial fibrillation patients treated with ablation: the randomised CopenHeart RFA trial protocol. BMJ Open; *3*:1-12 doi: 10.1136/bmjopen-2012-002377

Shalhoub, J., Hamish, M. and Davies, A. H. (2009) 'Supervised exercise for intermittent claudication – an under-utilised tool'. *Annals of The Royal College of Surgeons of England*, *91*(6), pp. 473–476. doi: 10.1308/003588409x432149

Tam, MC., Longenecker, CT., Chow, C., Vest, MV., Sukeena, R., Mohan, SKM., Carman, T., Parikh, SA, and Josephson, RA. (2016) Occult peripheral artery disease is common and limits the benefit achieved in cardiac rehabilitation, *Vascular Medicine, 21*(“): 130-136

doi: 10.1177/1358863X15625370

Zwierska, I., Walker, RD., Wood, RFM., Choksy, SA,. Male, JS., Pockley, AG., and Saxton, JM. (2005) Upper- vs lower-limb aerobic exercise rehabilitation in patients with symptomatic peripheral arterial disease: A randomized controlled trial. *Journal of Vascular Surgery, 42*: 1122-30. doi: 10.1016/j.jvs.2005.08.021