Considering the feasibility, tolerability and safety of high-intensity interval training as a novel treatment for patients with intermittent claudication

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INTRODUCTION

Peripheral arterial disease (PAD) is characterised by atherosclerosis of the arteries supplying the lower limbs, resulting in a reduced blood supply[1] and is estimated to affect 237 million people globally[2]. The most common symptom of PAD is intermittent claudication (IC), characterised by reproducible ischaemic muscle pain in the leg, precipitated by exertion and relieved by rest[3-6]. IC has deleterious effects on walking ability, functional capacity and quality of life (QoL), whilst also carrying a markedly increased mortality risk[3,4,7-9]. First line management of IC includes a supervised exercise programme (SEP)[10,11]. Interval walking is the recommended exercise component of SEP, though improvements are also obtainable with other modalities, including stationary cycling[12,13]. Cycle testing is also better tolerated than treadmill testing in IC patients, whilst inducing greater cardiometabolic responses, likely because patients may prematurely terminate treadmill testing due to claudication pain, precluding them from reaching higher intensities[14].

The evidence for the clinical efficacy of SEP, irrespective of exercise modality, is irrefutable[12]. Despite this, less than half of vascular units in the UK have access to them[15], and recruitment rates are often as low as 25%[16]. Patients cite time and SEP duration as reasons for inability to attend[17].

In addition, SEP exercise prescription usually adopts ‘a one size fits all’ approach based on a subjective measure of claudication pain, potentially limiting its benefit. High-intensity interval training (HIIT) is a more time-efficient, personally prescribed exercise intervention based on

objectively measured cardiorespiratory fitness via cardiopulmonary exercise testing (CPX). It therefore has the potential to maximise individual benefit and overcome the aforementioned patient cited barriers. HIIT has demonstrated similar or superior physiological benefits compared to lower intensity programmes across both healthy and clinical populations[18-24], and may be the preferred intensity option for IC patients[17]. A recent systematic review has provided initial, limited evidence that HIIT may be beneficial for IC patients whilst recommending further studies of low-volume, short-term HIIT[25]. However, such HIIT interventions remain largely untested in those with IC. Therefore, in line with the Medical Research Council guidance, a feasibility study is required to develop and test the intervention to identify problems with acceptability, compliance, delivery, recruitment and retention that can be addressed prior to larger-scale evaluation[26]. Therefore, the aim of this study was to assess a novel HIIT programme for patients with IC in terms of feasibility, tolerability, safety and indicators of efficacy.

METHODS

DESIGN

This prospective, interventional, before-after cohort study was conducted at a tertiary vascular centre in the United Kingdom and registered on clinicaltrials.gov (NCT04042311). Approval was obtained via a local NHS research ethics committee and all patients provided informed consent.

PARTICIPANTS

Patients with IC referred for our conventional SEP were screened for study participation. Patients were eligible if they were aged >18 yr, English speaking and able to follow exercise

instructions and provide informed consent, walk unaided and had a resting ankle-brachial pressure index (ABPI) <0.90 or a reduction of ≥20mmHg in systolic pressure, measured at the ankle following treadmill testing. Those who had critical limb-threatening ischaemia (rest pain/tissue loss), were undergoing active cancer treatment, had inadequately controlled cardiometabolic diseases, or elicited any contraindications to exercise testing or training were excluded[27]. Patients meeting these criteria who were willing to participate were invited to attend a baseline assessment which included a CPX. Following this, patients were also excluded if they elicited significant exercise-induced myocardial ischaemia or were unable to achieve maximal effort test criteria (supplementary table),[28,29] as this is required for accurate and effective 'traditional' HIIT exercise prescription. However, following a review of the inclusion/exclusion criteria due to a completion rate that was lower than anticipated for the first 20 patients, this maximal effort criterion was removed and no longer applied to the final 10 patients that make up the 30 patients in this cohort.

OUTCOMES

The primary aims of this study were to assess the, feasibility, tolerability and safety of short-term, low-volume HIIT for IC. Potential efficacy was also considered.

Feasibility assessment included; eligibility, recruitment and completion rates.

Tolerability assessment included; reasons for withdrawal (i.e. whether they were related to the intervention) and the ability of patients to achieve and maintain exercise in the appropriate exercise intensity domain.

Safety assessment included; adverse event (AE) reporting related to the intervention/outcome measures.

Indicators of clinical efficacy assessment included; initial claudication (ICD) and maximal walking distance (MWD), ABPI, QoL and cardiorespiratory fitness measurements. These measures were assessed at baseline and immediately following the HIIT programme.

PROCEDURES

ABPI was recorded at rest using standardised methods[11], followed by a graded treadmill walking test, with a constant speed of 3.2km/h and incremental gradient starting at 0% and increasing by 2% every two min, for a maximum of 15 min[30]. Those unable to walk at 3.2km/h were permitted to walk at a slower speed, selected by the assessor, which was kept consistent at follow-up to ensure standardisation.
ICD and MWD was recorded as the distance which patients first reported claudication pain and the distance at which pain became too severe and they needed to stop. Post-exercise ABPI was then recorded.

Quality of Life

QoL was measured using the Medical Outcomes Study Short-Form 36 v.2 (SF-36) and the King's College Hospitals Vascular QoL (VascuQoL) questionnaires[31,32]. Both questionnaires have several domains with the SF-36 also producing component summary scores and the VascuQoL producing a total score.

Cardiorespiratory fitness

All patients performed a symptom-limited ramp incremental cycle ergometer (Lode Corival Serial) CPX. Breath-by-breath gas exchange data were collected using a metabolic cart

(Ultima2, Medgraphics), calibrated to manufacturers' instructions prior to each test. Heart rate and rhythm was monitored continuously via 12-lead ECG (Mortara X-scribe, Mortara). Oxygen saturation and blood pressure (Tango M2 system, SunTech Medical) were assessed periodically throughout the test.

Each CPX was preceded by a 3-minute rest period and a 3-minute unloaded phase prior to a patient-specific ramp protocol of 10, 15, or 20 Watts per minute, designed to induce volitional exhaustion within 8-12 min[33]. Patients were instructed to maintain 60-70 revolutions per minute and in the absence of clinical indications for stopping[27], were encouraged to exercise until volitional exhaustion. The Borg 6 to 20 rating of perceived exertion (RPE) scale was used to quantify subjective effort. The requirement to give a maximal effort was explained thoroughly and strong verbal encouragement was given throughout. Expired ventilatory gases were continuously collected during the rest and exercise periods and for at least 6 min into recovery[34].

Peak oxygen uptake was defined as the highest value achieved during the last 30s of exercise or early in recovery. The ventilatory anaerobic threshold was determined using the V-slope and ventilatory equivalents methods[35,36].

Intervention

The HIIT intervention was based on an ongoing randomised controlled trial in patients with coronary artery disease[28], and consisted of 6 wk of supervised, intermittent cycling 3 d per wk, prescribed on the basis of the baseline CPX. Patients completed 10 x 1-minute high-intensity intervals (set at 85-90% peak power output, to achieve ≥85% peak heart rate by the second interval) interspersed with 1-minute recovery intervals on a Wattbike Trainer, to achieve a total of 20 min exercise time. Patients were permitted to complete less than 10 intervals, progressing

up to 10 bouts on an individual basis. The variation in intensity was achieved by altering cycling cadence and patients were continuously monitored via a Polar heart rate monitor (FT2, Polar electro) and RPE[37], with both recorded at the end of each high-intensity interval. Each session was preceded and followed by a 10-minute warm-up and cool-down as is recommended for patients with cardiovascular disease[38].

Data analysis

The primary aims of this study were to consider the, feasibility, tolerability and safety of a novel HIIT programme. Therefore, descriptive rather than statistical analysis was performed. Data is presented as mean/mean difference ± SD. Due to the nature of this study and analysis, no formal sample size calculation was required.

RESULTS

Baseline characteristics of all recruited patients (n = 30) are shown in table 1. Mean age was 69±9 yr, body mass index was 29±4 kg/m^2, and 77% were male. The mean ABPI was 0.75±0.21. Exercise programme completers and non-completers were similar in baseline characteristics.

Feasibility and Tolerability

Between April 2018 and July 2019, 144 patients with IC were referred for SEP of whom 95 were eligible (66%) and 30 consented to participate in supervised HIIT (32%).

Of the initial 20 patients recruited, seven were excluded from further participation; two had abnormal ECG changes and five could not meet the criteria for a maximal effort CPX. The

peak respiratory-exchange-ratio and percentage of age-predicted maximum heart rate (%) in the patient's excluded and those meeting maximal exercise test criteria were 0.9 and 1.1 and 72% and 83% respectively (table 2). Of the remaining thirteen patients eligible and able to commence the HIIT programme, one withdrew due to an inability to tolerate the intervention, two withdrew due to developing a concurrent illness and one moved out of the area. One participant withdrew due to an AE probably related to the exercise intervention.

Thereafter, eight of these twenty (40%) patients completed the HIIT programme.

Following a review of the inclusion/exclusion criteria and to improve pragmatism it was decided that patients would no longer be excluded on the basis of an inability to achieve a maximal effort CPX. Once this exercise testing entry criterion was removed, a further ten patients were recruited of which seven (70%) completed the programme. One patient was excluded due to ischaemic ECG changes, and another withdrew due to reported time constraints. One further withdrawal was due to a serious adverse event (SAE) that was possibly related to the intervention.

Of this second cohort of ten patients, two (20%) were unable to achieve a maximal effort CPX, comparable to the 25% in the initial cohort. Of these, one completed the programme and is included in the analysis. The full study processes are outlined in Figure 1.

Overall, fifteen (50%) of the thirty patients recruited in the total cohort completed the programme and attended eighteen sessions, for a 100% adherence rate, over an average of 6.5±0.8 wk. ≥85% peak heart rate was achieved by the second interval in 79% of sessions. All ten intervals were completed in 87% of sessions, with 14 of the 15 patients able to complete ten intervals by wk two. Just one patient was unable to complete ten intervals by the end of the programme.

Safety

There was one AE and one SAE possibly related to the intervention. The AE was a first, isolated episode of a 'dull chest ache' that occurred in the period between two exercise sessions. Following referral to cardiology a diagnosis of probable angina was made but not confirmed as diagnostic angiogram was refused.

The SAE was a thrombosed popliteal aneurysm that occurred in the period between two exercise sessions. The patient was admitted for surgery and underwent a lower limb bypass procedure. Whilst it is possible that this was related to the intervention, the first symptomatic manifestation (acute limb ischemia) occurred two d after the last exercise session, meaning that it was not definitively attributable to the exercise intervention.

No AEs occurred during or immediately following any HIIT exercise sessions or study visits.

Efficacy

Improvements were noted in a number of efficacy measures including ICD, MWD, PPO and physical functioning (tables 3 and 4).

DISCUSSION

The eligibility (66%) and recruitment (32%) rates for this HIIT programme were similar to those previously reported for standard SEP[16]. Completion rates, although lower than reported within the literature[16], were comparable to the rates for the usual-care SEP provided in our centre and likely reflective of "real-world" exercise programmes[39]. However, for the first 20 patients, given the post-recruitment CPX exclusion criterion, it is likely that the inclusion/exclusion criteria were not comparable to SEPs. For the final 10 patients, for whom the inclusion/exclusion criteria were likely comparable to those applied within SEPs, the

completion rate was similar to that reported in the literature and higher than the usual-care SEP in our centre[16,39]. This suggests that HIIT may be a feasible alternative to traditional SEP for claudication and implementation of it was relatively straightforward. The patient withdrawal rate (20%) in this study was somewhat higher than HIIT programmes in other clinical populations[40,41]. However, this may be due to the small sample in this cohort, the close attention given to recording patient referrals, recruitment/withdrawals which may not be comparable within other reports and some older age and comorbidity profile characteristics of PAD cohorts. Further, the present withdrawal rate was similar to SEP[16], and the majority of sessions were completed in full and at the required intensity, suggesting that HIIT is no less tolerable than current practice.

There was one SAE possibly related to the intervention, though it did not require any changes to the study procedures. The AE rate was higher in this HIIT group (2/30) than has been noted in our SEP (1/109), though a larger group of HIIT patients is required for direct comparison[39].No AEs occurred during or immediately following any HIIT sessions or study visits. Accordingly, this study provides an early indication that HIIT may be safe in IC patients, though further evidence is required, including direct comparison to a SEP group. However, these early safety findings may be confounded by the use of a baseline CPX, which may help to screen out those at higher risk of a cardiac event during HIIT. Current evidence suggests that CPX prior to SEP is not necessary[42], as the number of patients screened out is low (3.5%). Furthermore, the AE rate is approximated to be one in every 10,340 patient-hr[42]. It would be reasonable to assume that the relative intensity of SEP is lower than that for HIIT and therefore may be less likely to elicit an adverse cardiac response. Furthermore, a large proportion of PAD patients have co-existing coronary artery disease[43], and a number of these will be undiagnosed. Indeed, 10% of patients were excluded following a positive baseline CPX in this study. One later had confirmed triple vessel disease and underwent quadruple coronary artery bypass

grafting, whilst another required permanent pacemaker insertion. The potential cardiac risks presented by HIIT in IC patients remains largely undefined and further evidence is needed from a larger cohort of patients. Certainly, any exercise programme adopting HIIT should undertake a baseline CPX (with exercise ECG screening) to ensure accurate exercise prescription and patient safety.

One salient finding of this study is that several patients were excluded as they were unable to achieve a maximal effort CPX, precluding prescription of a 'traditional' HIIT programme. This inability to achieve a maximal test is likely to be due to severe deconditioning of patients with IC due a cycle of pain and physical activity avoidance[5]. The mean baseline peak oxygen uptake for the patients in this study was higher than previously reported in those with IC at approximately 15 $mL \cdot kg^{-1} \cdot min^{-1}$[39,44], but lower than reported in recent HIIT studies in those with coronary artery disease (23 $mL \cdot kg^{-1} \cdot min^{-1}$) and heart failure (17 $mL \cdot kg^{-1} \cdot min^{-1}$)[40,41]. This suggests that IC patients terminate exercise prematurely due to a perception of fatigue and/or are markedly more deconditioned than those with chronic and advanced heart disease. This may explain why a number of patients were unable to achieve a maximal effort CPX, despite subjectively feeling they have performed to their limit. Indeed, the patients unable to achieve a maximal effort test in this cohort reported a mean RPE score of >18/20.

However, those who are most deconditioned, have the potential to accrue the most benefit from participating in supervised, structured exercise following a personalised HIIT prescription. Indeed, the ventilatory anaerobic threshold, a submaximal marker of cardiorespiratory fitness has been demonstrated to be a significant predictor of improvement in walking distance following SEP, with the least fit having the greatest improvement in walking distance[39].

Based on the proportion of patients who were excluded due to an inability to achieve a maximal CPX, we altered the inclusion/exclusion criteria and conducted further feasibility work. This

'submaximal' version of the short-term HIIT programme did not exclude patients on the basis of an inability to achieve a maximal CPX. Instead patients received the same personalised, time-efficient programme prescribed on the basis of their baseline submaximal CPX. The rationale for this alteration was two-fold. Firstly, the patients excluded on this criterion, may have the potential to achieve the largest clinical benefits. Secondly, despite a similar withdrawal rate, the completion rate for the first 20 patients was just 40%. Once the maximal exercise test criterion was removed in the secondary cohort, the completion rate improved to 70%.

Those who completed HIIT, had improvements in walking distance and QoL. Our small sample and study design, however, precludes statistical comparison and substantive evidence of clinical benefits. Despite this, the results show promise given the improvements in MWD in this sample, were comparable to SEP (122m vs. 117m) and represent a large minimally clinically important change, provided in half the usual programme duration[39,45].

Therefore, HIIT programmes for IC patients appear to have the potential to provide clinical and symptomatic improvements. As the intervention period is reduced from twelve to six wk, with potentially comparable outcomes, it can reduce patient burden and may be easier to deliver. This may therefore provide a cost reduction at both patient and provision level. Finally, this exercise prescription moves away from a 'one size fits all' approach and adopts a personalised exercise prescription based on a CPX, with the ability to maximise patient benefit, which has also been recommended for cardiovascular rehabilitation programmes, both in the UK and internationally[46,47].

LIMITATIONS

One key limitation of this study is that participants were recruited from patients referred to a usual-care SEP. It is therefore not possible to identify if patients who chose to take part in this study are simply those who would have also chosen to take part in SEP. Also, patients who chose to take part in HIIT rather than SEP, may have been more motivated to do so, meaning the results may not be reflective of the overall population.The small sample size precluding statistical analysis, the single-centre design and the lack of a comparison group are also limitations of this study. However, this feasibility work is vital to ensure the intervention and inclusion criteria are appropriate, or whether they need to be altered, as in this case, to inform the design of future studies to assess the efficacy of this exercise intervention.

CONCLUSIONS

This study has provided preliminary findings to suggest that patients with IC can perform HIIT, with uptake and completion rates similar to standard SEP. It has also provided an early indication that with relevant pre-screening HIIT may be safe for patients with IC. It is also well tolerated and potentially efficacious. Following a small change, the intervention and inclusion/exclusion criteria now appear appropriate for this population. A larger, proof-of-concept study appears warranted prior to randomised controlled trials of HIIT versus usual SEP in patients with IC.

References:

1. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med.* 2001;344(21):1608-1621.
2. Song P, Rudan D, Zhu Y, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *The Lancet Global Health.* 2019;7(8):e1020-e1030.
3. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circulation research.* 2015;116(9):1509-1526.
4. Meru AV, Mittra S, Thyagarajan B, Chugh A. Intermittent claudication: an overview. *Atherosclerosis.* 2006;187(2):221-237.
5. Beebe HG. Intermittent claudication: effective medical management of a common circulatory problem. *The American journal of cardiology.* 2001;87(12):14-18.
6. Peach G, Griffin M, Jones KG, Thompson MM, Hinchliffe RJ. Diagnosis and management of peripheral arterial disease. *BMJ.* 2012;345:e5208.
7. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *New Engl J Med.* 1992;326(6):381-386.
8. Pell J. Impact of intermittent claudication on quality of life. *European Journal of Vascular and Endovascular Surgery.* 1995;9(4):469-472.
9. Golomb BA, Dang TT, Criqui MH. Peripheral Arterial Disease: Morbidity and Mortality Implications. *Circulation.* 2006;114(7):688-699.
10. NICE. *Peripheral arterial disease: diagnosis and management. Clinical guidance 147.* 2012.
11. Aboyans V, Ricco J-B, Bartelink M-LE, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS) Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries Endorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *European heart journal.* 2017;39(9):763-816.
12. Lane R, Harwood A, Watson L, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev.* 2017;12:CD000990.
13. Lauret GJ, Fakhry F, Fokkenrood HJ, Hunink MG, Teijink JA, Spronk S. Modes of exercise training for intermittent claudication. *Cochrane Database Syst Rev.* 2014(7):CD009638.
14. Tuner SL, Easton C, Wilson J, et al. Cardiopulmonary responses to treadmill and cycle ergometry exercise in patients with peripheral vascular disease. *J Vasc Surg.* 2008;47(1):123-130.
15. Harwood A, Smith G, Broadbent E, Cayton T, Carradice D, Chetter I. Access to supervised exercise services for peripheral vascular disease patients. *The Bulletin of the Royal College of Surgeons of England.* 2017;99(6):207-211.
16. Harwood A-E, Smith GE, Cayton T, Broadbent E, Chetter IC. A systematic review of the uptake and adherence rates to supervised exercise programs in patients with intermittent claudication. *Annals of vascular surgery.* 2016;34:280-289.
17. Harwood AE, Hitchman LH, Ingle L, Doherty P, Chetter IC. Preferred exercise modalities in patients with intermittent claudication. *Journal of Vascular Nursing.* 2018.

18. Hannan AL, Hing W, Simas V, et al. High-intensity interval training versus moderate-intensity continuous training within cardiac rehabilitation: a systematic review and meta-analysis. *Open access journal of sports medicine.* 2018;9:1.
19. Liou K, Ho S, Fildes J, Ooi SY. High Intensity Interval versus Moderate Intensity Continuous Training in Patients with Coronary Artery Disease: A Meta-analysis of Physiological and Clinical Parameters. *Heart Lung Circ.* 2016;25(2):166-174.
20. Elliott AD, Rajopadhyaya K, Bentley DJ, Beltrame JF, Aromataris EC. Interval training versus continuous exercise in patients with coronary artery disease: a meta-analysis. *Heart Lung Circ.* 2015;24(2):149-157.
21. Weston KS, Wisløff U, Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br J Sports Med.* 2014;48(16):1227-1234.
22. Batacan RB, Duncan MJ, Dalbo VJ, Tucker PS, Fenning AS. Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. *Br J Sports Med.* 2016:bjsports-2015-095841.
23. Reljic D, Wittmann F, Fischer JE. Effects of low-volume high-intensity interval training in a community setting: a pilot study. *European journal of applied physiology.* 2018:1-15.
24. Jayo-Montoya JA, Maldonado-Martín S, Aispuru GR, et al. Low-volume high-intensity aerobic interval training is an efficient method to improve cardiorespiratory fitness after myocardial infarction: pilot study from the INTERFARCT Project. *Journal of Cardiopulmonary Rehabilitation and Prevention.* 2020;40(1):48-54.
25. Pymer S, Palmer J, Harwood AE, Ingle L, Smith GE, Chetter IC. A systematic review of high-intensity interval training as an exercise intervention for intermittent claudication. *Journal of Vascular Surgery.* 2019.
26. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions; 2018. *Medical Research Council, London.* 2019.
27. ACSM. *ACSM's Guidelines for Exercise Testing and Prescription.* 9th ed. Baltimore: Lippincott, Williams, & Wilkins.; 2014.
28. McGregor G, Nichols S, Hamborg T, et al. High-intensity interval training versus moderate-intensity steady-state training in UK cardiac rehabilitation programmes (HIIT or MISS UK): study protocol for a multicentre randomised controlled trial and economic evaluation. *BMJ Open.* 2016;6(11):e012843.
29. Nichols S, Taylor C, Ingle L. A clinician's guide to cardiopulmonary exercise testing 2: test interpretation. *Br J Hosp Med (Lond).* 2015;76(5):281-289.
30. Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc.* 1991;23(4):402-408.
31. Morgan MB, Crayford T, Murrin B, Fraser SC. Developing the Vascular Quality of Life Questionnaire: a new disease-specific quality of life measure for use in lower limb ischemia. *J Vasc Surg.* 2001;33(4):679-687.
32. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ.* 1992;305(6846):160-164.
33. Balady GJ, Arena R, Sietsema K, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation.* 2010;122(2):191-225.
34. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation.* 2013;128(8):873-934.

35. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *Journal of applied physiology.* 1986;60(6):2020-2027.
36. Mezzani A, Agostoni P, Cohen-Solal A, et al. Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association for Cardiovascular Prevention and Rehabilitation. *European Journal of Cardiovascular Prevention & Rehabilitation.* 2009;16(3):249-267.
37. Borg GA. *Borg's Rating of Perceived Exertion and Pain Scales.* Champaign, IL: Human Kinetics; 1998.
38. ACPICR. Standards for Physical Activity and Exercise in the Cardiovascular Population. 2015. Accessed 28/11/16.
39. Harwood AE, Totty JP, Pymer S, et al. Cardiovascular and musculoskeletal response to supervised exercise in patients with intermittent claudication. *Journal of vascular surgery.* 2019;69(6):1899-1908. e1891.
40. Ellingsen Ø, Halle M, Conraads V, et al. High-intensity interval training in patients with heart failure with reduced ejection fraction. *Circulation.* 2017;135(9):839-849.
41. Conraads VM, Pattyn N, De Maeyer C, et al. Aerobic interval training and continuous training equally improve aerobic exercise capacity in patients with coronary artery disease: the SAINTEX-CAD study. *Int J Cardiol.* 2015;179:203-210.
42. Gommans LN, Fokkenrood HJ, van Dalen HC, Scheltinga MR, Teijink JA, Peters RJ. Safety of supervised exercise therapy in patients with intermittent claudication. *Journal of vascular surgery.* 2015;61(2):512-518. e512.
43. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *Jama.* 2006;295(2):180-189.
44. Gardner AW, Parker DE, Montgomery PS, Scott KJ, Blevins SM. Efficacy of quantified home-based exercise and supervised exercise in patients with intermittent claudication: a randomized controlled trial. *Circulation.* 2011;123(5):491-498.
45. Gardner AW, Montgomery PS, Wang M. Minimal clinically important differences in treadmill, 6-minute walk, and patient-based outcomes following supervised and home-based exercise in peripheral artery disease. *Vascular Medicine.* 2018;23(4):349-357.
46. Pymer S, Nichols S, Prosser J, Birkett S, Carroll S, Ingle L. Does exercise prescription based on estimated heart rate training zones exceed the ventilatory anaerobic threshold in patients with coronary heart disease undergoing usual-care cardiovascular rehabilitation? A United Kingdom perspective. *European journal of preventive cardiology.* 2019:2047487319852711.
47. Mezzani A, Hamm LF, Jones AM, et al. Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation, and the Canadian Association of Cardiac Rehabilitation. *J Cardiopulm Rehabil Prev.* 2012;32(6):327-350.

Figure Legend: Figure 1: Participant flow chart