SECTION 1: ADMINISTRATIVE INFORMATION

Study title: **Pain Management and Patient Education for Physical Activity in Intermittent Claudication: Feasibility Randomised Controlled Trial (PrEPAID Feasibility Trial)**

Trial Registration: NCT03204825

SAP Version 1.0

Date: 27/11/2017

Reference Trial Protocol: 2.0

SAP Revisions:

Roles and Responsibilities:

Dr Chris Seenan, Glasgow Caledonian University is the study chief investigator. He provided the guidance to the development of the plan based on the trial specific objectives.
Prof Julie Britttenden, NHS GGC is the study co-chief investigator. She contributed guidance on the development based on the trial objectives
Mr Ukachukwu Abaraogu, Glasgow Caledonian University, is the co-investigator who is blinded to the group allocator. He wrote the initial draft of the SAP using inputs from team members, and guided by the study statistician.
Prof Jon Godwin, Glasgow Caledonian University, is the study statistician. He provided the background guidance, critically evaluated the development, and gave final vetting to the plan.
Dr Philippa Dall, Glasgow Caledonian University is a co-investigator. She contributed to the development of the SAP, particularly regarding the analysis of the activPAL data.
Dr Garry Tew is a co-investigator. He contributed to the development of the SAP, particularly regarding the analysis of feasibility outcomes data.

Signatures

Prof. Jon Godwin (Statistician Responsible)	Dr Chris Seenan (Co-chief Investigator)
Prof Julie Brittenden (Co-chief Investigator)	Dr Philippa Dall (Co-investigator)
Dr Garry Tew (Co-instigator)	Ukachukwu Abaraogu (Co-instigator)

SECTION 2: INTRODUCTION

Background and Rationale

Patients with symptomatic PAD should receive the same secondary prevention management as patients with symptomatic coronary artery disease. Improving daily physical activity (PA) is particularly important in individuals with IC as lower PA levels have been recognised as a strong predictor of increased morbidity and mortality in this population.[3] Current NICE guidelines recommend the use of supervised exercise programmes (SEPs), encouraging patients "to exercise to the point of maximal pain", as first line treatment.[4] However, while systematic reviews (e.g.[5]) show that SEPs lead to a significant improvement in the absolute walking distances of patients with IC on a treadmill, it is unclear if this is sustained or leads to improvement in daily PA.[5] Furthermore, due to the considerable resources required to deliver the recommended 3 months exercise programme (30-45 minutes 3x weekly), SEPs are not always routinely available to NHS patients, and time and travel costs tend to lead to low patient uptake and high attrition rates.[6] Therefore, investigating the feasibility of using low-cost, patient-centred interventions that can support increased PA is warranted.

Lack of self-efficacy, attributed to poor understanding of the disease and uncertainty regarding the importance of exercise, has been shown to be a major barrier to exercise uptake in patients with PAD and IC.[7] Educating patients with IC about their disease pathology and the benefits of walking is key to enhancing success of secondary prevention strategies for people with IC.[7,8] We recently piloted a structured, patient-centred education intervention (SEDRIC)[9] with the specific aim of educating patients with IC about their condition, improving patient ownership, and promoting self-managed walking. In addition to improved treadmill walking distances, we found out that there was a trend for patients to increase their daily PA.

For patients with IC to gain benefits of secondary prevention, exercising beyond the point when pain occurs is recommended, representing another barrier to engagement in PA.[10] Despite this, our systematic review[11] found that pain management as a route to facilitate exercise and PA has rarely been explored. Recent interest has focused on the use of TENS (a low-cost, non-invasive pain management device) to improve angiogenesis, muscle function,[12] pain and walking distances in patients with IC.[13,14] TENS has a strong placebo effect in pain conditions,[15] and testing effectiveness against placebo is advocated. In a proof-of-concept pilot study, we demonstrated that TENS could significantly improve pain and increase treadmill walking distances above placebo levels.[14]Our exploratory study also established that home use of TENS was both acceptable and provided self-reported improvement in PA in individuals with IC.[16]

Although patient-centred education (SEDRIC) and TENS have both demonstrated potential to improve daily PA in people with IC, the use of these components in combination has not previously been evaluated. We therefore propose a 2 x 2 (TENS versus placebo TENS x SEDRIC versus no additional education) feasibility RCT[17] that will compare use of TENS against placebo TENS with and without a patient-centred education programme.

Aims: To determine the feasibility of Transcutaneous Electrical Nerve Stimulation device used within or without a patient centred education programme to improve walking distances in patients with PAD.

General Research Questions:

What is the feasibility (i.e. recruitment and retention rates, adherence, safety, sample size for a definitive trial, potential for effectiveness) of conducting a definitive RCT comparing TENS with and without patient-centred education?

How acceptable are TENS and patient-centred education as interventions on their own or in combination in patients with IC?

Specific Objectives:

To estimate rates of recruitment, retention, intervention uptake and adherence, and outcome completion for a definitive RCT.

To monitor, record, manage and follow-up specified adverse events in all groups.

To collect and synthesise data, including walking outcomes, physical activity and patient reported outcomes, PROMs, from which the sample size of a definitive RCT could be estimated.

To explore participants' experiences and perceptions of the interventions and trial procedures via focus groups.

SECTION 3: STUDY METHODS

Trial design:

We will conduct a 2 x 2 parallel group (TENS versus placebo TENS x SEDRIC versus no additional education) feasibility RCT to compare use of TENS against placebo TENS with and without a patient-centred education programme. Permuted block randomisation will be implemented to allocate patients to trial arms. The intervention will last for 6 weeks, and patients recruited within the first eight months will be further followed up for 3 months. Outcomes assessments will be implemented at baseline, after six weeks treatment and at 3 months follow up. We will collect information regarding the recruitment rate, intervention uptake, outcome measure completion rate, attrition rate, blinding fidelity, efficacy related to the primary, secondary and other PROMs, and patients experience of intervention including acceptability and ease of intervention.

Randomisation:

A central randomisation facility (interactive voice response system, IVRS) will allocate the randomised therapy per patient. The IVRS, based at the Data Centre, will be available by telephone. Stratified permuted block randomization procedures will be utilised to allocate patients to groups (Patients allocation will be stratified by gender and age, ABPI values). Permuted block design (PBD) will be used to allocated patients to the PE+TENS, PE+Placebo TENS, TENS, Placebo TENS using 4-way randomisation throughout the whole time until the recruitment of a minimum of 20 subjects in the each of the larger comparison groups are achieved.

Sample size:

Details regarding sample size calculation can be found in section 8. 7 of the full study protocol (version 2.0). Summarily, 16 participants per group will allow detection of an effect size of 1.0sd of ACD in active TENS group compared to placebo control. Allowing for 20% attrition, we will recruit 20 participants in each group, and therefore aim to recruit 80 patients.

Framework

The superiority comparison will be implemented to compare change in physical activity and PROMS between treatment groups (PE+TENS, PE+Placebo TENS, TENS) versus Placebo TENS. Also superiority comparison will be implemented for within treatment groups from baseline. A non-superiority comparison shall be made between the PE+TENS group versus each of the PE+Placebo TENS, TENS groups. The feasibility, acceptability (the recruitment, retention, outcome completion, intervention uptake and attrition rates, and patient tens feedback) and adverse events data will be summarised by randomised group and overall using descriptive statistics. No formal statistical tests comparing the randomised groups will be pre-specified. Framework analysis will be implemented for the qualitative focus group data.

Statistical analysis and stopping guidance

Interim analysis will not be conducted, and the study will stop at last patient last study visit. All outcomes will be analysed collectively at the end of the study. P-value will be set at $p<0.05$.

Timing of outcome assessments

Physical activity and PROMs outcomes will be assessed at baseline, end of six weeks intervention (up to 2 weeks window), and 3 months post-randomisation (up to 2 weeks window). The recruitment, retention, outcome completion, intervention uptake and attrition rates will be assessed at the end of the study. Blinding and patients acceptability of TENS and

ease of use will be assessed at the point of patient exit from the study. Further assessment regarding patients' qualitative experience of intervention will be done at 3 months post-randomisation (up to 2 weeks window).

SECTION 4: STATISTICAL PRINCIPLES

Level of confidence interval and p-values

Analysis will be conducted at 95% CI, and 0.05 level of significance.

Adherence and Protocol Deviations:

Patient adherence to the intervention will be defined, as applicable, by patients attendance at the education session, and answering to at least one of the 2-weekly phone calls, and/or using TENS at least 30 mins per day 3x/wkly for at least 50% of the 6 weeks of intervention. Specifically, the TENS log (questionnaire) as well as inbuilt record of TENS device usage will both be used to analyse patients utilisation of TENS. Researcher adherence to intervention protocol will be defined as implementation of intervention and outcome assessment according to the approved study protocol.

Protocol deviation will be defined as accidental or unintentional changes to, or non-compliance with the research protocol that does not increase risk or decrease benefit or; does not have a significant effect on the subject's rights, safety or welfare; and/or on the integrity of the data. We will document deviations due to rescheduled study (If they fall outside the specified window), failure to complete a physical activity outcome assessment or self-report questionnaire, patients' refusal to complete scheduled research activities. Details regarding level (major or minor) number and type of protocol deviations per group will be summarised in addition to potential impact on analysis populations.

Analysis populations

Comparisons will be undertaken to investigate the feasibility of studying the proposed outcomes for definitive trial and to calculate estimates for the likely effect sizes and 95% confidence intervals, even though determining differences in clinical outcomes is not the primary purpose of this feasibility trial. Inferential analysis will be implemented using the principles of intention-to-treat.

SECTION 5: STUDY POPULATION

Screening, Eligibility and Recruitment Data:

The number of potential participants screened, eligible and the number recruited will be analysed and presented in a CONSORT flow diagram. Data regarding level of withdrawal from intervention and/or follow up as well as timing of withdrawal/lost to follow up will be analysed. In addition, data descriptive of reasons and details patterns of withdrawal/lost to follow up will be presented.

Baseline patient characteristics

The following patient baseline characteristics will be summarised: Age, gender, ABPI score, Diagnosis of APD, Diagnosis of IC, Past medical history, Cardiac risk factors, Present drug history. Also selected outcome measures including, ICD, ACD, McGill and VAS pain scores, SF-36 and ICQ OoL scores, Geriatric depression questionnaire, Pain self-efficacy questionnaire, and Brief illness perception questionnaire scores will be presented as baseline characteristics. Categorical data will be presented using counts and percentages. Continuous data will be presented using number of patients, mean (SD), median (min-max), and IQR.

SECTION 6: ANALYSIS

Outcome definitions

Feasibility and acceptability outcomes:

Measure recruitment rates -reasons for non-eligibility and non-recruitment of eligible patients will be recorded via the study screening log
Measure participant's retention throughout the trial and reasons for withdrawal
Monitor, record, manage and follow-up defined adverse events in all groups
Measure uptake of intervention (log of TENS use and attendance at education) and acceptability of these interventions via a questionnaire
Measure blinding fidelity via TENS feedback questionnaire
Outcome completion rate – number of day activPAL is worn at each outcome time point.

Efficacy outcomes

Measurement will be obtained at baseline, following six weeks intervention and at 3 months follow up

Primary efficacy outcomes

Treadmill assessed Absolute Claudication Distance (ACD) (cm).

Secondary efficacy outcomes will include:

Physical activity capacity secondary outcomes
Treadmill assessed Initial Claudication Distance (ICD), assessed by a treadmill exercise using the Gardner treadmill protocol.[19] Measurement will be obtained at baseline, following six weeks intervention and at 3 months follow.
Daily physical activity. We shall specify 3 days activPAL data at each measure as minimum for including patient activPAL data in the efficacy analysis. However, activPAL were time (number of day worn) will be also be reported as part of the feasibility analysis. For secondary efficacy analysis, activPAL data outcomes: total number o**f i)** steps; **ii)** upright events**; iii)** walking events**; iv)** Event-based claudication index (ratio of walking events to upright events) participants undertake in a day. [20]
PROM secondary outcomes
Disease specific quality of life will be as assessed using the Intermittent Claudication Questionnaire (ICQ).
Generic quality of life via the SF-36;
Pain quality will be recorded using the McGill Pain Questionnaire (MPQ) 5 minutes after every treadmill test.
Average Pain intensity in the past 7 days will be recorded using a Visual Analogue Scale
Illness beliefs and psychosocial determinants of health and behaviour will be recorded using the Illness Perception Questionnaire (IPQ), Geriatric Depression Scale (Short Form) (GDS-SF) and the Pain Self-Efficacy Questionnaire (PSEQ).

Qualitative Experience outcome

Analysis Methods

Feasibility and qualitative data analysis

Descriptive statistics will be used to characterize the groups at baseline and to present the feasibility outcomes.

Outcomes related to experience and perception via focus groups will be analysed by framework analysis.

To determine the feasibility of conducting a definitive trial, descriptive statistics will be used to report the number and proportion of participants who meet the inclusion criteria, who consented to participating, and who dropped out during the trial. Also descriptive analysis will report compliance with intervention by recording participants' attendance to education session, follow up calls, attendance to TENS training session, (rate of use of TENS) rate of outcome measure completion, and total accelerometer wear time. Specifically, the TENS log (questionnaire) as well as inbuilt record of TENS device usage will both be used to analyse patients utilisation of TENS. Acceptability of TENS will be obtained by TENS feedback questionnaire

Further exploration will be carried out to determine factors that impact on propensity to participate looking at the difference in characteristics between participants and non-participants. If less than 10% of the individuals with PAD/IC in the clinic are eligible to participate, or if less than 10% of eligible patients agreed to participate, then the eligibility criteria and recruitment strategy will be adjusted prior to conducting a definitive trial. Adjustment of the recruitment strategy in a definitive trial will be made comparing the difference in the baseline characteristics between participants and non-participants. Similarly, association between participants' baseline characteristics and trial outcome will also inform decision on adjustment of recruitment strategy and stratification factors in the definitive trial. Data collection for the definitive trial will be adjusted based on the information related to type, quantity of missing data, and the mechanisms by which these data are missing.

The transcripts from the focus group discussions will be analysed using framework analysis. The data gathered from the exit interview will form part of acceptability analysis and be used to adapt the intervention to enhance it acceptability in a definitive trial.

Primary efficacy analysis

Differences in the change in ACD will be analysed and effect scores calculated using Chi-squared tests, Mann-Whitney U or Wilcoxon signed-rank tests as applicable for between and within-group comparisons and log-rank method for pooled samples or sub-strata. Baseline participants' variability will be controlled for using the analysis of co-variance.

Secondary efficacy analysis

Differences in the changes in activPAL outcomes, ICD, SF-36 and ICQ scores, MPQ score, IPQ, GDS-SF, PSEQ, ABI, and Biomarkers will also be analysed and effect scores calculated using Chi-squared tests, Mann-Whitney U or Wilcoxon signed-rank tests as applicable for between and within-group comparisons and log-rank method for pooled samples.

Safety analysis

The safety data (adverse events)- both numbers of subjects and events – will be summarised by randomised group and overall using descriptive statistics. No formal statistical tests comparing the randomised groups will be pre-specified.

Software for statistical analysis

The statistical software to be used is either SAS 9.2 for Windows, Cary, NC, USA or SPSS Version 22.

Table 1: Participant characteristics at baseline

	PE+TENS	PE+ Placebo TENS	TENS	Placebo TENS
Age				
Sex (%male)				
Ankle-brachial index				
Diagnosis of PAD				
Date of diagnosis: ≥3months <6months ≥6months<12moths ≥12moths				
Type of PAD Iliac Femoral Popliteal Other				
Diagnosis of IC				
Date of diagnosis: ≥3months <6months ≥6months<12moths ≥12moths				
Limb affected Left				

Right Both				
Fontaine Classification I II III IV				
Past Medical History				
IHD: Y/N MI: Y/N LVH: Y/N				
Cardiac risk factors				
DM : Y/N Family History of IHD/CVA/ BP: Y/N Hypercholesterolemia: Y/N Hypertension: Y/N				
Alcohol excess: Current Previous				

Never				
Smoking: Current Previous Non-smoker				
Present drug history: Statin Y/N Antiplatelet Y/N Anticoagulant Y/N				
Outcome measures				
Treadmill maximal walking distance				
Treadmill pain free walking distance				
Daily steps				
Pain intensity(VAS)				
McGill pain score				
QoL SF-36 score				
ICQ score				
Geriatric depression questionnaire score				
Pain self-efficacy questionnaire score				
Brief illness perception questionnaire				

Table 2: Feasibility related outcome tables

Participants recruitment					
Total number of participants screened(n)					
Total number of eligible participants (n/%)					
Reasons for non-eligibility X (n/%) Y (n/%) Z (n/%)					
	Whole study sample	PE+TENS	PE+ Placebo TENS	TENS	Placebo TENS
Recruitment target/Number recruited.					
Recruitment rate (n/centre/month)					
Outcome completion rate					
Reasons for withdrawal from intervention					
Retention rate (proportion of participants with valid primary outcome data at 3-months follow-up)					
Retention rate (proportion of participants with valid ActivPAL outcome data at 3-months follow-up)					
Reason for withdrawal from follow up					
Timing of withdrawal					
Intervention uptake and Adherence rate					
Attendance to PE					
Summary from phone calls					
TENS log summary					
Objective record of TENS use					
Acceptability of intervention					
Acceptability questionnaire					
Adverse events rate					
List them					
TENS blinding					

Table 3: Changes in groups' outcomes at 6-wweks compared to placebo (usual care alone)

	TENS	PE+TENS	PE
ACD	x±sd vs x±sd; p=xxx(95%cl)		
ICD			
Daily steps			
Upright events			
Walking events			
EBCD			
ICQ			
SF-36			
7-day Average pain intensity			
Pain quality			
IPQ			
GDS-SF			
PSEQ			

*Also compare between PE+TENS and each of TENSs and PE alone (May not present in a table)

Table 4: Changes in groups' outcomes at 3 months compared to placebo (usual care alone)

	TENS	PE+TENS	PE
ACD	x±sd vs x±sd; p=xxx(95%cl)		
ICD			
Daily steps			
Upright events			
Walking events			
EBCD			
ICQ			
SF-36			
7-day Average pain intensity			
Pain quality			
IPQ			
GDS-SF			
PSEQ			

*Also compare between PE+TENS and each of TENSs and PE alone ((May not present in a table)

Table 5: Within group comparisons between baseline and after 6 weeks intervention and 3 months follow up

	TENS	PE+TENS	PE	Usual care alone
ACD *Post 6 wks* *Post 3 months follow up*	x±sd vs x±sd; p=xxx(95%cl)			
ICD *Post 6 wks* *Post 3 months follow up*				
Daily steps *Post 6 wks* *Post 3 months follow up*				
Upright events *Post 6 wks* *Post 3 months follow up*				
Walking events *Post 6 wks* *Post 3 months follow up*				
EBCD *Post 6 wks* *Post 3 months follow up*				
ICQ *Post 6 wks* *Post 3 months follow up*				
SF-36 *Post 6 wks* *Post 3 months follow up*				
7-day mean pain intensity *Post 6 wks* *Post 3 months follow up*				
Pain quality				

Post 6 wks *Post 3 months follow up*				
IPQ *Post 6 wks* *Post 3 months follow up*				
GDS-SF *Post 6 wks* *Post 3 months follow up*				
PSEQ *Post 6 wks* *Post 3 months follow up*				