PrEPAID
Pain Management and Patient Education for Physical Activity in Intermittent Claudication

Study full title: Pain Management and Patient Education for Physical Activity in Intermittent Claudication: Feasibility Randomised Controlled Trial

Study acronym: PrEPAID

Running title: Pain management and patient education in intermittent claudication

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Amendment number	Date	Details	Protocol version
2	09/01/2019	**1) Amendment to table of content (p6) and section 3.4 (p20), and patient information sheet to clarify that follow up timing (visit 5) is at 3 months post intervention.** **2) Amendment to study synopsis (p10) and section 3.3 (p19) to specify that participants < 40 years of age will be excluded.** **3) Changes to consent form to specify that patients will be audio recorded at focus group.** 4) **Updating the patient information sheet to specify that patients will be audio-recorded during focus group.**	3.0

Amendment number	Date	Details	Protocol version
1	12/9/2017	1) Amendments to sections 8 (p26) for accuracy related to who will conduct the statistical analysis. 2) Optional blood sample in laboratory tests- corrected information to accurately reflect study schedule (4.3 Laboratory Tests p24) 3) TENS Feedback Questionnaire - to reflect that participants will be exiting the study at different points, the timing of the TENS questionnaire has been amended to be the final data collection for all participants. (Study Schedule p13-14 and section 4.1	2.0

		p22-23) 4) Assessment of ABPI has been removed from visits 4 and 5 (Study Schedule p13-14). We do not intend to analyse ABPI data but only need to control for baseline variations in the final analysis. 5) Amendment made to consent form to correct the name of Robertson Centre for Biostatistics. 6) Participants information sheet amended to correctly reflect intervention protocol i. Visit 3: 1 hour or 4 hour maximum instead of 1 hour max in version 1.0 ii) Visit 5: will be a repeat of the first and fourth visits where you will complete the questionnaires, treadmill test and blood sample (optional). 7) Participants information sheet amended to specify that activPAL physical activity data will be stored at Glasgow Caledonian University. 8) Study schedule Visit 4: Specific queries regarding adverse events added	

This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

CONTACTS

Chief Investigator
Dr Chris Seenan
Designation: Lecturer in Physiotherapy
Mailing address: Department of Psychology, Social Work and Allied Health Sciences
Glasgow Caledonian University Cowcaddens Road Glasgow G4 0BA
Tel: (0)141 331 8151
E-mail: Chris.Seenan@gcu.ac.uk

Co-chief investigator
Professor Julie Brittenden
Director of Research and Development/Director of CRF/Professor of Vascular Surgery West Glasgow Ambulatory Care Hospital
Dalnair Street
Glasgow
G3 8SW
Tel: 0141 2019328
E-mail: Julie.Brittenden@ggc.scot.nhs.uk

Co-Investigators
Mr Ukachukwu Abaraogu
PhD Student
School oh Health and Life Sciences
Glasgow Caledonian University Cowcaddens Road Glasgow G4 0BA
Tel: 0141 331 3343
Email: Ukachukwu.Abaraogu@gcu.ac.uk

Dr Philippa Dall
Senior Research Fellow
School of health and Life Sciences
Glasgow Caledonian University Cowcaddens Road Glasgow G4 0BA
Tel: 01413318003
Email: Philippa.Dall@gcu.ac.uk

Professor Jon Godwin
Institute of Applied Health Research
Glasgow Caledonian University Cowcaddens Road Glasgow G4 0BA
Tel: 01413313482
Fax: 01413318211
Email: Jon.Godwin@gcu.ac.uk

Mr Wesley Stuart
Vascular Surgeon and Clinical Director/ Horary Senior Lecturer
Glasgow and Clyde, Glasgow/ Department of Vascular Surgery University of Glasgow
1345 Govan Road, Govan, G514TF
Telephone: 0141 452 5944
Email: Wesley.Stuart@ggc.scot.nhs.uk

Dr Garry Tew
Associate Professor
Department of Sport, Exercise and Rehabilitation
Northumbria University Newcasctle
Tel: 0191 2437556
Email: garry.tew@northumbria.ac.uk

Study Statistician
Professor Jon Godwin
Professor Institute of Applied Health
Glasgow Caledonian University
Glasgow G4 0BA
Tel: 01413313482
Fax: 01413318211
Email: Jon.Godwin@gcu.ac.uk

Data Centre
Robertson Centre for Biostatistics/Glasgow Clinical Trials Unit
University of Glasgow
Level 11, Boyd Orr Building
University Avenue, Glasgow
G12 8QQTel: 0141 330 4744
Fax: 0141 330 5094
Email: contactus@glasgowctu.org

Professor Jon Godwin
Professor of Applied Statistics Institute of Applied Health
Glasgow Caledonian University
Glasgow G4 0BA
Tel: 01413313482
Fax: 01413318211
Email: Jon.Godwin@gcu.ac.uk

Chair of the Trial Steering Committee
Dr Stephen McSwiggan
Designation: Head of Commercial Services at the University of Dundee/NHS Tayside
Mailing address: School of Medicine
University of Dundee, Nethergate, Dundee, DD1 4HN,
Tel: 01382 383233
Email: s.j.mcswiggan@dundee.ac.uk

Sponsor
Glasgow Caledonian University

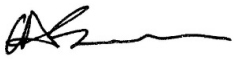
Funding Body
Chief Scientist Office
Ground Rear
St Andrews House
Regent Road
Edinburgh
EH1 3DG

PROTOCOL APPROVAL

Study full title: Pain Management and Patient Education for Physical Activity in Intermittent Claudication: Feasibility Randomised Controlled Trial

Study Acronym: PrEPAID

Chief Investigator Dr Chris Seenan
Designation: Lecturer in Physiotherapy
Mailing address: Department of Psychology, Social Work and Allied Health Sciences, School of Health and Life Sciences, Glasgow Caledonian University, Glasgow G4 0BA
Tel: (0)141 331 8151
E-mail: Chris.Seenan@gcu.ac.uk

Signature: 

Date: 5/4/2017

Sponsor's representative

Signature:

Date:

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ABBREVIATIONS

ABPI	Ankle Brachial Pressure Index
ACD	Absolute claudication distance
ACSM	The American College of Sports Medicine
AE	Adverse event
CI	Chief Investigator
CRF	Clinical Research Facility
CSO	Chief Science Office
DESMOND	Diabetes Education and Self-Management for Ongoing and Newly Diagnosed
FCD	Functional claudication distance
GCP	Good clinical practice
GGC	Greater Glasgow and Clyde
GP	General Practitioner
HF-TENS	High Frequency
IC	Intermittent Claudication
ICD	Initial Claudication distance
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICQ	Intermittent Claudication Questionnaire
ICQ	Intermittent claudication questionnaire
LF-TENS	Low Frequency
MPQ	McGill Pain Questionnaire
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
PA	Physical Activity
PAD	Peripheral Arterial Disease
PE	Patient education
PrEPAID	Pain management and Patient Education for Physical Activity in Intermittent clauDication
PROMS	Patient reported outcome measures
P-TENS	Placebo TENS
OEUH	Queen Elizabeth University Hospital
R&D	Research and Development
RCB	Robertson Centre for Biostatistics
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SEDRIC	Structured EDucation for Rehabilitation in Intermittent Claudication
SEP	Structured Exercise Programme
SF-36	General Quality of Life Questionnaire (Short version)
SOP	Standard Operating Procedure
TENS	Transcutaneous electric nerve stimulation
TIA	Transient Ischaemic Attack
TSC	Trial Steering Committee
UK CRN	United Kingdom Clinical Research Network
VAS	Visual Analogue Scale
WIQ	Walking impairment questionnaire

STUDY SYNOPSIS

Title of Study:	Pain Management and Patient Education for Physical Activity in Intermittent Claudication (PrEPAID): Feasibility Randomised Controlled Trial
Study Centre:	Clinical Research Facility at Queen Elizabeth University Hospital/ Glasgow Caledonian University/ Robertson Centre for Biostatistics
Duration of Study:	26 months
Research aims:	1. To determine the feasibility of conducting a definitive trial that would assess the effects of a TENS intervention with/or without patient-centred education on physical activity in people with intermittent claudication. 2. To collect preliminary data on the acceptability of TENS and patient education, both as separate and combined interventions in people with Intermittent Claudication (IC).
Research objectives:	1. To estimate rates of recruitment, retention, intervention uptake and adherence, and outcome completion for a definitive RCT which would investigate the effects of TENS and/or patient-centred education in people with IC. 2. To determine the potential effect of the interventions on patient outcomes including walking, physical activity and PROMs 3. To explore participants' experiences and perceptions of the interventions and trial procedures via focus groups
Primary Endpoints:	1. Proportion of eligible patients, after full screening, who agreed to be randomized; and proportion of randomised participants who successfully completed each of the trial arm (intervention and outcome measure assessment). 2. The Absolute Claudication Distance, assessed by a treadmill exercise using the Gardner treadmill protocol shall be assessed as the primary outcome for this feasibility trial.
Rationale:	This is a feasibility trial that primarily aim to assess the feasibility of conducting a definitive trial that would assess the effects of a TENS intervention with and without patient-centred education on physical activity in people with intermittent claudication. Therefore, successful delivery and uptake of interventions by patients and evidence of improvement in patient outcomes are the most important and compelling consideration to make decision regarding feasibility of a definitive trial.
Methodology:	This a randomised controlled feasibility trial using a 2x2 factorial design of TENS versus placebo TENS with or without patient-centred education. Participants will be blinded to the type of TENS they receive. Outcome assessment of the primary outcome will be done by a blinded assessor.
Sample Size:	80
Screening:	Participants will be screened for eligibility by Research Nurse
Registration/Randomisation:	Randomisation by Robertson Centre for Biostatistics
Main Inclusion Criteria:	• Clinical diagnosis of symptomatic Peripheral Arterial Disease (PAD) including resting ABPI <0.9 in at least one leg

	• Stable IC for ≥3 months • Walking limited primarily by claudication • Able to exercise on a treadmill • Able to read and speak English to a level allowing satisfactory completion of the study procedures • Able to provide written informed consent for participation
Main Exclusion Criteria:	• Planned surgical or endovascular intervention for PAD within the next 3 months • Critical limb ischaemia • The presence of any absolute contraindications to exercise testing/training as defined by the American College of Sports Medicine (ACSM) • Previous experience of using TENS/ structured patient education for PAD • Contraindications to TENS (including epilepsy, dermatological conditions, indwelling electrical pumps/pacemakers) and inability to apply TENS independently. • Patients who require walking aids including artificial limbs • Major surgery, myocardial infarction or stroke/ TIA in the previous 6 months • Co-morbidities that cause pain or limit walking to a greater extent than IC (e.g. severe arthritis) • >20% variation in baseline ACD on treadmill • Severe peripheral neuropathies above the ankle. • Participation in another research protocol • Participants < 40 years of age
Product, Dose, Modes of Administration:	One-off 3 hours structured patient education + twice weekly phone call follow up to six weeks; High frequency TENS for daily use up to six weeks; placebo TENS for daily use for six weeks
Duration of Treatment:	Six weeks
Statistical Analysis:	Descriptive statistics for participants' characteristics, recruitment and intervention completion rates will be used to analyse results related to the feasibility and acceptability outcomes. In addition, the transcripts from the focus group discussions will be analysed using framework analysis. *Patient outcomes* - 95% CI will be analysed using Chi-squared tests, Mann-Whitney U or Wilcoxon signed-rank tests as applicable; and log-rank method for pooled samples or sub-strata.

GLOSSARY OF TERMS

I. **Transcutaneous electric nerve stimulation**: the use of electric current produced by a device to stimulate the nerves for therapeutic purposes.

II. **Initial Claudication Distance (ICD):** the distance in metres and centimetres walked by a patient on a treadmill under standardized conditions before the onset of claudication symptoms, regardless of whether this is manifested or characterized as muscle pain, ache, cramp, numbness or fatigue. This does not include joint pain or other pain not associated with claudication.

III. **Functional Claudication Distance**: the distance, **during a treadmill test,** a patient with peripheral arterial would prefer to stop walking because of claudication pain.

IV. **Absolute Claudication Distance (ACD):** the maximum distance in metres and centimetres walked by a patient on a treadmill under standardized conditions. The patient should continue the test until walking can no longer be tolerated because of claudication symptoms. It is critical that the patient not stop walking when they normally would do so. The patient should be asked to continue to walk until they feel they must stop due to claudication symptoms.

V. **Patient-centred structured education**: a planned and graded programme that is comprehensive in scope, flexible in content, responsive to an individual's clinical and psychological needs, and adaptable to his or her educational and cultural background. Key criteria of a structured education programme include:

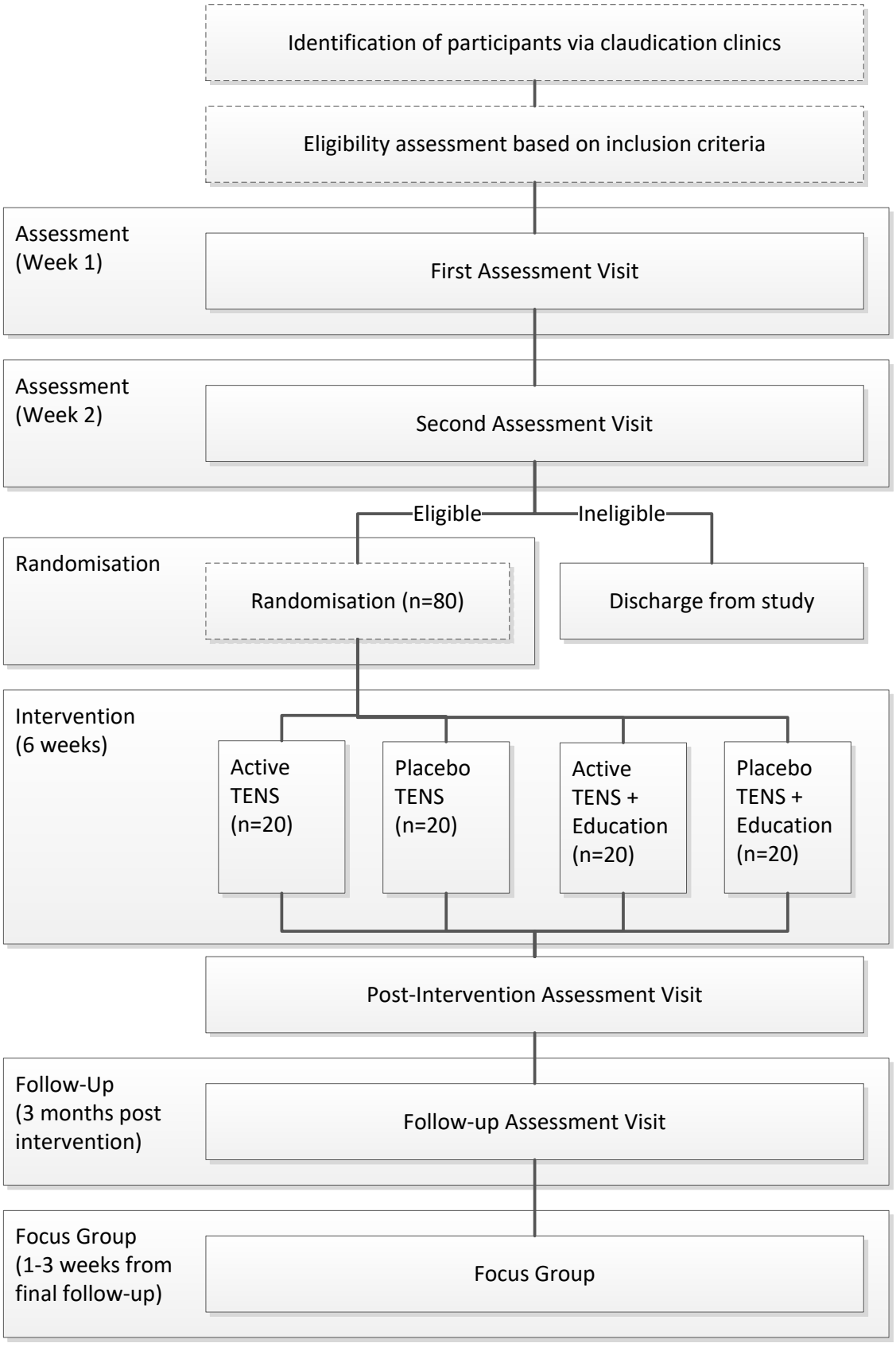
- A clear underlying philosophy on which the programme is based
- A structured written curriculum
- Trained educators familiar with the programme and its delivery
- A quality assurance system applied to the structure, process, content, and delivery of the programme.
- A process of audit of programme outcomes including biomedical, psychological, and patient experience

VI. **Free living physical activity:** Accumulation of physical activity in a daily community living situation as opposed to laboratory or clinics assessed measures**.**

VII. **Structured exercise programme:** Structured exercise includes activities specifically geared toward a purpose, usually to improve cardiovascular fitness, strength, flexibility, or balance and agility. In the context of this research protocol, Structured exercise programme refers to 2 hours of supervised exercise a week (usually 40minutes x3 day/week) for a 3-month period encouraging people to exercise to the point of maximal pain.

VIII. **ActivPAL:** A small physical activity monitor worn on the front of the thigh, which allows researchers to objectively measure time spent sitting/lying, standing and walking, sit-to-stand transitions and step counts.

STUDY FLOW CHART



STUDY SCHEDULE

Visit	Study Procedure	Time (mins)	Responsible
First Assessment (90 mins)	Review of Inclusion/Exclusion Criteria Obtain Informed Consent	20	RN/UA
	Participant demographics • Gender / Date of birth / Height / Weight / Heart rate / Blood pressure Patient history • Diagnosis of PAD (Date of diagnosis/Type of disease) • Present drug history (Statin/Antiplatelet/Anticoagulants) • Past Medical History (IHD/MI/LVH) • Cardiac risk factors (DM/Family History of IHD,CVA/Smoking: Current, Previous, Non-smoker/Alcohol excess: Current, Previous, Never/Hypercholesterolemia/Hypertension)	20	
	Complete questionnaires: 1. Generic quality of life questionnaire (SF-36) 2. Intermittent Claudication Questionnaire (ICQ) 3. Visual Analogue Scale (VAS) 4. Geriatric Depression Scale (Short Form) (GDS-SF) 5. Pain Self-Efficacy Questionnaire (PSEQ) 6. Illness Perception Questionnaire (IPQ)	20	
	Taking of blood sample	10	
	Treadmill protocol • ABPI assessment • McGill Pain Questionnaire (MPQ) (5 minutes post-treadmill protocol)	20	
	Fitting of ActivPAL to participants and instruction for use	20	
Second Assessment (30 mins)	Return of ActivPAL by participants	5	RN/UA
	Treadmill protocol McGill Pain Questionnaire (5 minutes after completion of the treadmill protocol)	20	
Intervention as per randomisation	1. Education session + Placebo TENS & instructions for the use at home	240	CS + RN
	2. Education session + Active TENS & instructions for the use at home	240	

(Duration depends on group; 4 hours max)	3. Active TENS and instructions for use at home	60	
	4. Placebo TENS and instructions for use at home	60	
Post-Intervention (70 mins)	a.Complete questionnaires: 1. Generic quality of life questionnaire (SF-36) 2. Intermittent Claudication Questionnaire (ICQ) 3. Visual Analogue Scale (VAS) 4. Geriatric Depression Scale (Short Form) (GDS-SF) 5. Pain Self-Efficacy Questionnaire (PSEQ) 6. Illness Perception Questionnaire (IPQ) **b.If participant is exiting the study at this point:** 7. TENS feedback questionnaire c.Questionnaire on adverse events of interest	20	UA/JB
	Treadmill protocol • MPQ (5 minutes post-treadmill protocol)	20	
	Fitting of ActivPAL to participants and instruction for use	20	
	Taking of blood sample	10	
Follow-up (70 mins)	Complete questionnaires: 1. Generic quality of life questionnaire (SF-36) 2. Intermittent Claudication Questionnaire (ICQ) 3. Visual Analogue Scale (VAS) 4. Geriatric Depression Scale (Short Form) (GDS-SF) 5. Pain Self-Efficacy Questionnaire (PSEQ) 6. Illness Perception Questionnaire (IPQ) **If participant is exiting the study at this point:** 7. TENS feedback questionnaire	20	UA/JB
	Treadmill protocol • MPQ (5 minutes post-treadmill protocol)	20	
	Fitting of ActivPAL to participants and instruction for use	20	
	Taking of blood sample	10	
Focus Group (90 mins)	Introduction	15	RN + Independent
	Focus group interview	60	

	Debrief and discharge **If participant is exiting the study at this point:** 1. TENS feedback questionnaire	15	researcher

INTRODUCTION

1.1 Background

Peripheral Arterial disease (PAD) affects 2.7 million people in the UK.[1] The most common symptom that patients experience is Intermittent Claudication (IC), which is pain in the buttock, calf or thigh precipitated by exercise and relieved by rest.[1] The underlying cause of PAD is atherosclerosis, which leads to arterial stenosis, inadequate blood flow and build-up of lactic acid during exercise. Patients with IC have impaired quality of life due to reduced physical capacity. Furthermore, due to the diffuse nature of atherosclerosis and the involvement of other arterial beds, they have 3-4 times increased mortality compared to age and sex matched controls.[2]

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.

1.2 Rationale

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.

1.3 Prior experience of intervention in *disease area*

We have conducted a series of pilot studies underpinning both aspects of the intervention. In an experimental lower limb ischaemic pain model in healthy volunteers (n=28) we have shown that TENS (High frequency TENS, HF-TENS 200 ms biphasic pulsed currents at 120 Hz in a "continuous" pulse pattern) significantly reduced onset of pain (by 29 seconds; 23%), tolerance of pain (by 203 seconds; 53%) and the pain endurance (by 173 seconds; 67%), compared to placebo TENS, P-TENS.[18] (See figure 1 below)

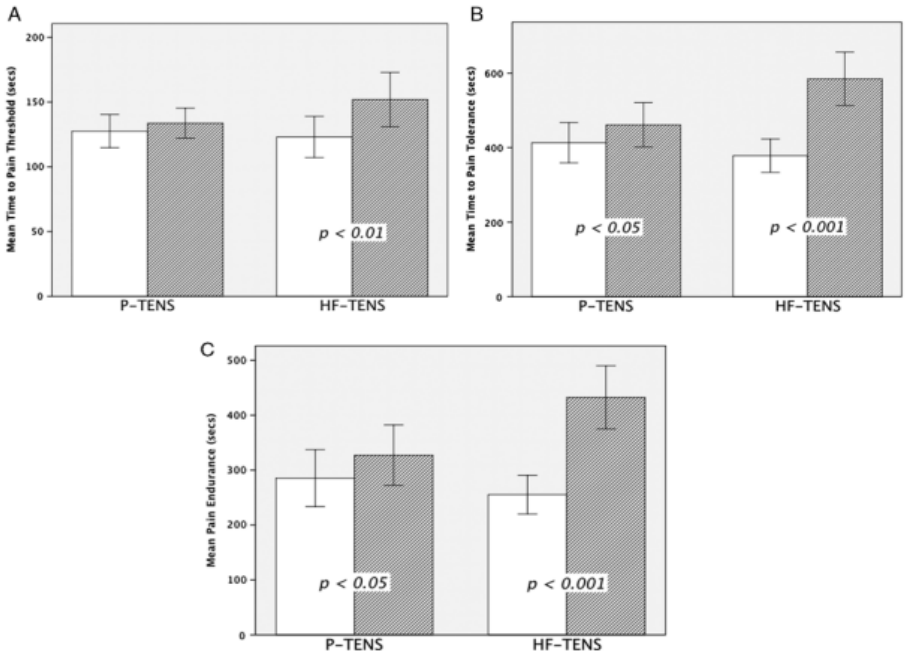


Figure 1: Graph of mean time taken (seconds) to report (A) pain threshold, (B) pain tolerance, and (C) pain endurance for placebo TENS, P-TENS and (high frequency transcutaneous electrical nerve stimulation, HF-TENS. Open bars indicate baseline; shaded bars, intervention. Error bars = 95% confidence interval [From Seenan et al Clin J P 2012 28(8): 693-699].

Following this, in a proof-of-concept pilot study, we demonstrated that TENS when applied to patient with IC exercising on a treadmill (n=40) significantly improved absolute claudication distance (ACD) above placebo levels (approx. mean individual increase in ACD of 40%, p=.025, r= .53)[14](See figure 2 below). Our phase 2 study also established that home use of TENS was both acceptable and provided self-reported improvement in PA in individuals with IC.[16] We have not assessed the ability of TENS to improve ACD when used during daily life.

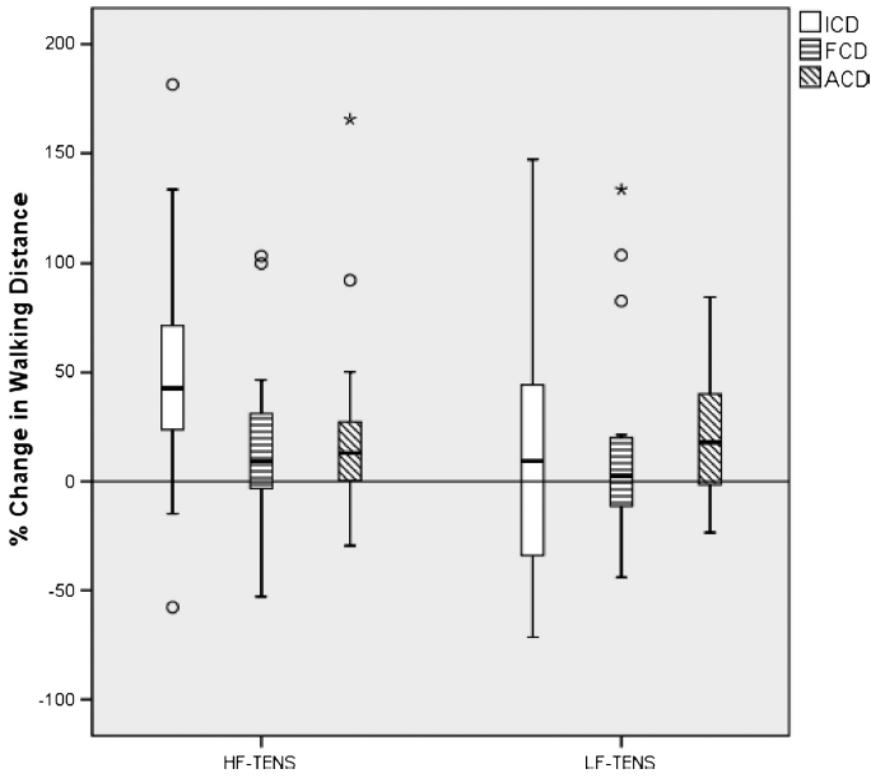


Figure 2: Boxplots representing changes in walking measures (meters) with TENS intervention. Positive values represent a positive change with TENS (From Seenan et al J Cardiovasc Nurs 2016 31(4): 323-30)

Similarly, our group developed and piloted SEDRIC,[9] a structured, patient-centred education intervention with the specific aim of educating patients about their condition, improving patient ownership, and promoting self-managed walking. We found that in patients with PAD (n=14), treadmill walking distances (30%) and quality of life (32%) improved from baseline after 6 weeks of structured education, and there was a trend for patients to increase their daily PA (approx. 8% change from baseline).

2. STUDY AIM, OBJECTIVES, AND RESEARCH QUESTIONS

2.1 Aims

1. The aim is to determine the feasibility of electrical stimulation via a low-cost CE-marked device used within a patient centred education programme to improve walking distances in patients with PAD.

2.2 Research Objectives

1. To estimate rates of recruitment, retention, intervention uptake and adherence, and outcome completion for a definitive RCT
2. To monitor, record, manage and follow-up specified adverse events in all groups
3. To collect and synthesise data, including walking outcomes, physical activity and PROMs, from which the sample size of a definitive RCT could be estimated
4. To explore participants' experiences and perceptions of the interventions and trial procedures via focus groups

2.3 Research Questions:

1. 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?
2. How acceptable are TENS and patient-centred education as interventions on their own or in combination in patients with IC?

3. STUDY DESIGN

Feasibility Randomised Controlled Trial, blinded for primary outcome

3.1 Study Population

80 patients with a history of stable IC and an ABPI≤0.9 attending the NHS Greater Glasgow & Clyde vascular out-patient clinics will be invited to take part in this study.

3.2 Inclusion criteria

- Clinical diagnosis of symptomatic Peripheral Arterial Disease (PAD) including resting ABPI <0.9 in at least one leg
- Stable IC for ≥3 months
- Walking limited primarily by claudication
- Able to exercise on a treadmill
- Able to read and speak English to a level allowing satisfactory completion of the study procedures
- Able to provide written informed consent for participation

3.3 Exclusion criteria

- Planned surgical or endovascular intervention for PAD within the next 3 months
- Critical limb ischaemia
- The presence of any absolute contraindications to exercise testing/training as defined by the American College of Sports Medicine (ACSM)
- Previous experience of using TENS/ structured patient education for PAD
- Contraindications to TENS (including epilepsy, dermatological conditions, indwelling electrical pumps/pacemakers) and inability to apply TENS independently.
- Patients who require walking aids including artificial limbs
- Major surgery, myocardial infarction or stroke/ TIA in the previous 6 months
- Co-morbidities that cause pain or limit walking to a greater extent than IC (e.g. severe arthritis)
- >20% variation in baseline ACD on treadmill
- Severe peripheral neuropathies above the ankle.
- Participation in another research protocol
- Participant aged <40 years

3.4 Identification of participants and consent

Potential participants will be identified by members of the vascular surgery and/or direct study team when the potential participants attend the vascular out-patient clinics held at various hospital sites within NHS GGC. Potential participants will be identified in advance by the study nurse from Trakcare clinic lists. They will be provided with a participant information leaflet and contact details will be recorded on a study log. The nurse or other members of the study team will contact the patient, address any questions, and arrange to meet. At this meeting, assuming the participants fulfils the trial eligibility criteria informed consent may be taken by the

nurse, or if the patient wishes, the patient given more time to consider participating in the trial. Potential participants who have recently attended the claudication clinic will also be contacted by post and sent a brief outline of the study and the patient information leaflet. They will be asked to return a pre-paid response slip stating whether they wish to be contacted further regarding the study.

If problems arise with recruitment, then the option of using the Safe Haven or primary care records to help identify patients diagnosed with PAD/IC will be explored and appropriate approval obtained. Participants recruited within the first eight months of recruitment will be followed-up for assessment 3 months post intervention.

3.5 Retention Rates

The study is an intention to treat analysis and therefore if a patient does not apply the TENS or attend the education class (if randomised to this arm) they will continue to be followed up. However, all participants will have the right to withdraw from the study at any stage. If willing the reasons for withdrawal will be documented and any data already collected from that participant will be analysed.

4 Trial procedures

Study design: This is a double-blind, feasibility RCT.[17] TENS/placebo and patient education interventions will be 6 weeks in duration and all participants will receive secondary prevention therapy as recommended by NICE including advice to exercise (usual care). A sub-group of participants (those recruited within the first 8 months of recruitment) will be followed up for 3 months post-intervention. A qualitative, focus group study will also be conducted after final follow up.

Interventions:
TENS: Participants will be given TENS at intervention visit. They will be instructed to use the device daily at home or elsewhere. They will be specifically advised to use the device prior to, or during, a challenging walk each day. Challenging walk could be for activities of daily living (ADL) or planned exercise. For those with bilateral claudication they are advised to wear the device on the worst limb and could alternate it as symptoms fluctuates. The active group will receive High Frequency-TENS (120 Hz, 200μs and a patient-determined intensity of "strong but comfortable").[14]
Placebo TENS: Participants will receive the same model and instructions for use as those in the active group except that the stimulation dose is be safely altered to produce non-therapeutic, ineffective stimulation. For the purposes of blinding, participants will be told that different dosages of TENS are being tested some of which they might not feel anything even though the device is working. This method of effecting placebo has been successfully used in previous TENS trials.[23,24]
Both the statistician conducting the randomization and the outcome assessor would be blinded to active TENS and placebo TENS. Importantly, participants will receive the same set of instructions as those in active TENS with the addition of a statement that two TENS are being tested. Blinding will be assessed at the end of the intervention period. Participants will be asked if they believed their TENS unit was functioning properly.
Patient-Centred Education: Intervention in these groups will be adopted from the successfully piloted SEDRIC study:[9] A one-off three-hour workshop of structured group education (4-5 persons in each group) and three 2-weekly phone calls. Two educators will implement the session. Training for educators will involve completion of the DESMOND core training, reading and demonstrating understanding of the SEDRIC curriculum, and completion of at least two practice workshops that are

quality assessed prior to delivering any sessions to patients. The aim of the patient education will be to modify patients' illness beliefs and perceptions about IC/PAD by educating them on disease pathology and self-management philosophy. After the workshop, each patient will be supported to set goals for walking using the pedometer (Yamax SW-200 Digi-Walker pedometers), develop an action plan regarding how these goals will be met and encouraged to repeat this process for each new walking goal. See SEDRIC curriculum for details.

4.1 Study schedule

Participants will be asked to attend the CRF on 6 occasions.

Visit 1- First Assessment Visit:

At the first visit, participants will be assessed for eligibility and those eligible will be requested to consent for further screening. Baseline outcome measurements will be conducted including weight/height/HR/blood pressure, ABPI, Treadmill assessments, questionnaires and taking of blood sample (Ukachukwu and/or Research Nurse). Participants will be fitted with the activPAL™ monitor and advised to wear this continuously for seven days. They will be given an instruction on how to use the activPAL, and provided with a sleep diary to complete during the duration of wearing the activPAL.

First Assessment Visit (90 mins)	Time (mins)	Responsible
Review of Inclusion/Exclusion Criteria Obtain Informed Consent	20	RN/UA
Participant demographics • Gender / Date of birth / Height / Weight / Heart rate / Blood pressure Patient history • Diagnosis of PAD (Date of diagnosis/Type of disease) • Present drug history (Statin/Antiplatelet/Anticoagulants) • Past Medical History (IHD/MI/LVH) • Cardiac risk factors (DM/Family History of IHD,CVA/Smoking: Current, Previous, Non-smoker/Alcohol excess: Current, Previous, Never/Hypercholesterolemia/Hypertension	20	
Complete questionnaires: 1. Generic quality of life questionnaire (SF-36) 2. Intermittent Claudication Questionnaire (ICQ) 3. Visual Analogue Scale (VAS) 4. Geriatric Depression Scale (Short Form) (GDS-SF) 5. Pain Self-Efficacy Questionnaire (PSEQ) 6. Illness Perception Questionnaire (IPQ)	20	
Taking of blood sample	10	
Treadmill protocol • ABPI assessment • McGill Pain Questionnaire (MPQ) (5 minutes post-treadmill protocol)	20	
Fitting of ActivPAL to participants and instruction for use	20	

Visit 2- Second Assessment Visit (usually within 2 weeks after visit 1):

Participants will then attend for a second visit to undergo a second Treadmill test, and to return the activPAL and sleep diary. Only participants with ≤20% variation in ACD will continue in the trial. After this visit eligible participants will be randomized, and given a date for them to return for intervention (TENS/Placebo ± Education) as applicable. Recruitment and randomisation will be done in waves to allow groups to be formed for the education session.

Second Assessment Visit (30 mins)	Time (mins)	Responsible
Return of ActivPAL by participants	5	RN/UA
Treadmill protocol • McGill Pain Questionnaire (5 minutes after completion of the treadmill protocol)	20	

Visit 3- Intervention Visit (within 3 weeks after randomisation):

Participants attend the clinic to receive the TENS and training instructions for its daily use as required, plus or minus the patient education per randomization group. Participants allocated to receive education will undergo a group structured education session (4-6 persons per group). This intervention is adopted from the successfully piloted SEDRIC study:[9] a one-off three-hour workshop of structured group education followed by three 2-weekly phone calls (see SEDRIC curriculum).

The aim of the structured education is to modify patients' illness beliefs and perceptions about IC/PAD by educating them on disease pathology and management philosophy. After the workshop, each patient will be supported to set goals for walking based around a pedometer and daily steps, develop an action plan regarding how these goals will be met and encouraged to repeat this process for each new walking goal through a 2-weekly phone calls from the educators (research team- Chris and Research Nurse) during which the progress, barrier and challenges are further discussed, and new walking goal will be set.

Before the education session, participants allocated to receive TENS will be provided with the device and instruction to use of the device. Also, the use of the device will be demonstrated, and patients shown how to put on and remove the device. Participants will try it out so on that to be sure they understand the procedure.

Intervention Visit (as per randomisation) (approx. 4 hours)	Time (mins)	Responsible
1. Education session + Placebo TENS & instructions for the use at home	240	CS + RN
2. Education session + Active TENS & instructions for the use at home	240	
3. Active TENS and instructions for use at home	60	
4. Placebo TENS and instructions for use at home	60	

Visit 4- Post Intervention Assessment Visit (end of the 6-week intervention):

Outcome assessments and procedure followed in Visit 1 will be repeated including questionnaires, treadmill protocol, blood sample collection and fitting of activPAL. The treadmill test will be by the investigators who are blinded to the participants group allocation. Participants will be given a prepaid envelope to return activPAL.

Post-Intervention Visit (70 mins)	Time (mins)	Responsible
a.Complete questionnaires: 1. Generic quality of life questionnaire (SF-36) 2. Intermittent Claudication Questionnaire (ICQ) 3. Visual Analogue Scale (VAS) 4. Geriatric Depression Scale (Short Form) (GDS-SF) 5. Pain Self-Efficacy Questionnaire (PSEQ) 6. Illness Perception Questionnaire (IPQ) **b.If participant is exiting the study at this point**: 7. TENS feedback questionnaire c.Questionnaire on adverse events of interest	20	UA/JB
Treadmill protocol • MPQ (5 minutes post-treadmill protocol)	20	
Fitting of ActivPAL to participants and instruction for use	20	
Taking of blood sample	10	

Visit 5- Follow-up Assessment Visit (3-months post-intervention):

All participants recruited within first eight months of recruitment will be invited to return for a 3-month follow-up visit. Outcome assessments and procedure followed in Visits 1 and 4 will be repeated including questionnaires, treadmill protocol, blood sample collection and fitting of activPAL. The treadmill test will be by the investigators who are blinded to the participants group allocation. Participants will be given a prepaid envelope to return activPAL. We shall allow assessment visit window of ± 2 weeks.

Follow-up Assessment Visit (70 mins)	Time (mins)	Responsible
Complete questionnaires: 1. Generic quality of life questionnaire (SF-36) 2. Intermittent Claudication Questionnaire (ICQ) 3. Visual Analogue Scale (VAS) 4. Geriatric Depression Scale (Short Form) (GDS-SF) 5. Pain Self-Efficacy Questionnaire (PSEQ) 6. Illness Perception Questionnaire (IPQ) **If participant is exiting the study at this point:** 7. TENS feedback questionnaire	20	UA/JB
Treadmill protocol • MPQ (5 minutes post-treadmill protocol)	20	
Fitting of ActivPAL to participants and instruction for use	20	
Taking of blood sample	10	

Visit 6- Focus Group Visit (usually 1-3 weeks after the final follow-up):

All participants be invited to participate in a focus group discussion. The discussion sessions, lasting 1 hour, will explore the acceptability of and satisfaction with the PrEPAID programme, components that were useful or not (in terms of helping them with physical activity), and participants' suggestions for changes. Each focus group, will consist of 4-6 participants, and will be facilitated by an independent investigator.

The number of focus groups to be conducted will be determined by data saturation and the sessions will be audio-recorded and will be transcribed verbatim.

Focus Group Visit (90 mins)	Time (mins)	Responsible
Introduction	15	RN + Independent researcher
Focus group interview	60	
Debrief and discharge **If participant is exiting the study at this point:** 1. **TENS feedback questionnaire**	15	

4.2 Study Outcome Measures

4.2.1 Outcomes of feasibility study:

1. Measure recruitment rates -reasons for non-eligibility and non-recruitment of eligible patients will be recorded via the study screening log
2. Measure participant's retention throughout the trial and reasons for withdrawal
3. Measure patient reported outcomes proposed for a definitive RCT
4. Monitor, record, manage and follow-up defined adverse events in all groups
5. Measure uptake of intervention (log of TENS use and attendance at education) and acceptability of these interventions via a questionnaire

4.2.2 Outcomes to synthesize data from which the sample size of a definitive RCT could be estimated.

For sample size calculation, the **Absolute Claudication Distance (ACD)**, assessed by a treadmill exercise using the Gardner treadmill protocol[19] shall be assessed as **the primary outcome**.

Secondary outcomes will include other patient outcomes including physical activity, PROMs and blood biomarkers.

A. Physical activity capacity secondary outcomes
   i. **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.
B. **Daily physical activity (ActivPAL data outcomes)**, **total number of 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]
C. **PROM secondary outcomes**
   i. **Disease specific quality of life** will be as assessed using the Intermittent Claudication Questionnaire (ICQ).
   ii. Generic quality of life via the SF-36;
   iii. **Pain quality** will be recorded using the McGill Pain Questionnaire (MPQ) 5 minutes after every treadmill test.
   iv. **Average Pain intensity** in the past 7 days will be recorded using a Visual Analogue Scale
   v. **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).
D. **Blood biomarkers:** to assess angiogenesis/inflammatory response.

4.3 Laboratory Tests

20mls of blood will be taken from rested subjects at visit**s 1, 4 and 5**, spun and stored as per the SOP at CRF at QEUH for future analysis of markers of angiogenesis and inflammatory response.

5. ASSESSMENT OF SAFETY

This is a low risk study which involves a widely-used CE-marked device. The patients will continue to see their GP, continue to receive the usual care and normal medication throughout the period of the intervention.

There is a low risk of skin itching in small percentage of participants who may be allergic to the pads of the TENS, and their skin may become red and irritated. Therefore, hypoallergenic electrode pads will be used for all participants. Participant will be withdrawn from the study in the unlikely event that they experience a SAR related to the medical device. All interventions and assessments including standard treadmill protocol and safety precaution will be adhered to and provided by trained and qualified individuals. A designated phone number of the CRF will be given to the patients to dial in case of any complaint during the office hours.

There is a very low risk that participants will develop a skin reaction to the adhesive in the strip used to attach the activPAL3 device to the thigh. The attachments used are all hypoallergenic and medical grade to minimize this possibility. The participants will be given a contact number of the research team to call if they have any concerns and are told to remove the device if they encounter any skin irritation. Some of the older participants may have fragile skin, with a very low risk of skin degradation when wearing or removing the monitor. The participants will be trained in appropriate removal of the waterproof dressing and monitor. The PrEPAID team has considerable expertise in the use of activPAL monitors, including extended use in a frail older adult population.

6. DEVICE INFORMATION

Patients who are eligible for the study will be randomised to receive either active TENS or Placebo TENS.

6.1 Active TENS:

A MTR+ Dolito TENS machine (EME Service Ltd., Manchester, United Kingdom) calibrated to 120Hz, 200μs, and patient-determined intensity of “strong but comfortable.”

6.1.1 Treatment schedule:

Participants will be asked to wear active TENS everyday as often as they can when they are awake and switch it on when they are standing/ walking or about to engage in activity which they anticipate would trigger their IC pain. They will be instructed to switch it off after a maximum period of 1hr, for a rest period of at least 10-20 minutes, and to repeat this as often as warranted during daily activity.

6.1.2 Rationale for chosen TENS frequency:

In a proof of concept study, HF-TENS was found to increase the distance IC patients walked before reaching pain tolerance, and that HF-TENS (compared to low frequency TENS) was more effective at prolonging the time to reach pain threshold.

6.1.3 Attachment:

Patients will fit a TENS unit during wake periods and daily activity using 2 self-adhesive carbon rubber electrodes measuring 5 x 5 cm (StiMus® Hydrogel Premium

Self-Adhesive Electrodes, EME Service Ltd., Manchester, United Kingdom) attached to the TENS unit via the manufacturers leads. The area of pain reported by the participant would determine the electrode placement sites with the 2 electrodes to be placed at least 2cm apart. Before it is handed out to the patients for daily use, the TENS machine will be calibrated with a digital oscilloscope and tested manually by the research team.

6.2 Placebo TENS:

Placebo effect has been reported while using TENS in other conditions therefore, testing active TENS against placebo is advocated. The same model as used in active TENS will be used in the placebo TENS group but an infective setting (current intensity of about 6mA) will be used. Patients will be told that different doses of TENS are being tested. This will allow the unit to be switched on with the appearance of a working unit. All TENS units will be calibrated, checked and confirmed prior to being issued to participants. This method of achieving placebo has been successfully used in previous TENS trials.[23,24]

6.2.1 Treatment schedule:

Participants will be asked to wear placebo TENS everyday as often as they could when they are awake and switch it on when they are standing/ walking or about to engage in activity which they anticipate would trigger their IC pain. They will be instructed to switch it off after a maximum period of 1hr, for a rest period of at least 10-20 minutes, and to repeat this as often as warranted during daily activity.

6.2.2 Attachment:

The same material will be used and similar instruction related to device attachment will be similar as active TENS.

7.0 ADVERSE EVENTS

7.1 Definitions of adverse events

Adverse Event (AE) – Any untoward medical occurrence in a subject to whom a medicinal device has been administered, including occurrences which are not necessarily caused by or related to that product.

7.2 Serious Adverse Event (SAE)

Any adverse event or adverse reaction that:

a. results in death
b. is life threatening
c. requires hospitalisation or prolongation of existing hospitalisation
d. results in persistent or significant disability or incapacity
e. consists of a congenital anomaly or birth defect
f. is otherwise considered medically significant by the investigator
g. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

7.3 Recording and reporting of Adverse Events

We do not anticipate that the use of the CE-marked TENS device will result in any serious adverse events. Participants will be given prior information regarding the reporting of adverse events and measure to take including instructions to contact the research team via a dedicated phone line.

Participants will be specifically queried regarding the following adverse events of special interest: any case of itching, skin breakdown, mild electrical burn, other skin allergies, or mild autonomic responses at each study visit, and reported related adverse events will be documented in an applicable adverse event form.

8. STATISTICS AND DATA ANALYSIS

8.1 Statistical analysis plan

The Robertson Centre for Biostatistics, part of the Glasgow Clinical Trials Unit, a fully registered UK CRN Clinical Trials Unit, will manage trial data.

Statistical analysis will be conducted by the Study Statistician from the Institute for Applied Health Research, Glasgow Caledonian University who is blinded to group allocation. The activPAL data will be downloaded and data input quality inspected visually and with diary information prior to statistical analysis. A detailed analysis plan will be prepared by the statistician and agreed with the Project Management Group and Trial Steering Committee.

Descriptive statistics will be used to characterize the groups at baseline and to present the feasibility outcomes. Outcomes related to experience and perception via focused group will be analysis by framework analysis. 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. The flow of participants through each stage of the trial will be presented in a CONSORT diagram.

8.2 Feasibility and acceptability 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.

8.3 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.

8.4 Secondary efficacy analysis

Differences in the changes in activPAL outcomes, ICD, SF-36 and ICQ scores, MPQ score, IPQ, GDS-SF, PSEQ, 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.

8.5 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.

8.6 Software for statistical analysis

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

8.7 Sample size

For the primary outcome measure, at 80% power and a two-tailed 5% significance level, 16 participants per group will allow detection of an effect size of 1.0 standard deviations of ACD in active TENS group compared to placebo control. Attrition rates in our previous pilot studies ranged from 7.1%[9] to 10% [14]. We will recruit 20 participants in each group, allowing for 20% attrition, and therefore aim to recruit 80 patients. If this effect size were applied to our separate pilot studies, this would provide the ability to detect a change of 169m (TENS) or 322m (SEDRIC) in our primary outcome measure of ACD. Indeed, in these studies, a sample size of 20 per group (TENS) and 14 per intervention group (SEDRIC) was sufficient to detect a significant difference in this outcome measure.

8.8 Management and delivery

Data analysis will be implemented by the trial statistician blinded to the group allocations. All statistical analyses will be conducted according to a pre-specified Statistical Analysis Plan.

9.0 STUDY CLOSURE / DEFINITION OF END OF TRIAL

The study will end when the steering committee agrees that one or more of the following situations applies:

- Last patient last study visit

10. DATA HANDLING

10.1 Randomisation

A central randomisation facility (interactive web response system, IWRS) will allocate the randomised therapy per patient. The IWRS, based at the Data Centre, will be available by email.

10.2 Case Report Forms / Electronic Data Record

An electronic case report form (e-CRF) will be used to collect study data. The e-CRF will be developed by the study Data Centre at the Robertson Centre for Biostatistics, University of Glasgow and access to the e-CRF will be restricted, with only authorised site-specific personnel able to make entries or amendments to the patients' data. It is the responsibility of the research team to ensure completion and to review and approve all data captured in the e-CRF.

All data handling procedures will be detailed in a Study Specific Data Management Plan. Data will be validated at the point of entry into the e-CRF and at regular intervals during the study. Data discrepancies will be flagged to the study site and any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change).

10.3 Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigators agree to keep records, including the identity of all participating subjects (sufficient information to link records), all original signed informed consent forms, serious adverse event forms, source documents, and detailed records of treatment disposition in accordance with ICH GCP, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. Data will be retained at the Data Centre for a minimum of 5 years.

11.0 TRIAL MANAGEMENT

This research will fall under the auspices of the clinical governance structure of Glasgow Caledonian University (GCU) and NHS GGC Clinical research facility. The project is sponsored by GCU and the GCU Research and Development Office will have responsibility for oversight, including audit of adherence to protocol and research governance Standard Operating Procedures

11.1 Routine management of trial: Trial Management Group

The trial will be coordinated from Glasgow Caledonian University by the Trial Management Group. This will consist of the co-applicants, CRF research nurse, Robertson Centre for Biostatistics, and Glasgow Clinical Trial Unit. The trial Management Group will be responsible for the overall management and completion of the project to timescales. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The group will meet bimonthly mainly via telephone conferences.

11.2 Trial steering committee (TSC)

The Steering committee will utilise the strengths of diverse experts, including NHS services users. This will help ensure that the research is relevant and accessible to a diverse audience. The committee will have an independent chair (Dr Stephen McSwiggan). Specifically, the committee will advise on the suitability of the interventions for the population group and design and participate in dissemination activities. The group members will consist of: the chief investigators; Co-investigator

(Ukachukwu); 2 patient representatives; an expert in patient education interventions and physical activity behaviour change; and an NHS management representative. The steering group will meet four times spread throughout the study and aims to provide advice from a broad perspective.

13. PROTOCOL AMENDMENTS

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CIs following discussion with the TSC and any required amendment forms will be submitted to the ethics committee, funder, sponsor and NHS GGC R&D for approval as appropriate to their role. The CIs and the TSC will liaise with study sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor representative.

14. ETHICAL CONSIDERATIONS

14.1 Ethical conduct of the study

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996] and Edinburgh [2000]). Favourable ethical opinion will be sought from an appropriate REC before patients are entered into this clinical trial. Patients will only be allowed to enter the study once they have provided written informed consent. The CI will be responsible for updating the Ethics committee of any new information related to the study.

14.2 Informed consent

Written informed consent shall be obtained from each trial participant. The Research Nurse will explain the exact nature of the study in writing, provision of patient information sheet, and verbally and will be responsible for consenting the participants. Trial participants will be informed that they are free to withdraw their consent from the study or study treatment at any time.

15. INSURANCE AND INDEMNITY

NHS indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS), and the Glasgow Caledonian University Indemnity insurance

16. FUNDING

The trial is funded by CSO, grant award number TCS/16/55 (10 January 2017).

17. ANNUAL REPORTS

An annual progress report will be submitted to the funder (CSO), the first being submitted 6 months from the date that all trial related approvals are in place. Annual reports will be submitted to the ethics committee and sponsor with the first submitted one year after the date that all trial related approvals are in place.

Recruitment data will, on a monthly basis, be uploaded to the UKCRN Portfolio database (and agreed successor to the database) through the mechanisms provided for the purpose, as part of CSO requirement. Also, updated information on the outputs from the project shall be uploaded through the e-VAL system, which is now accessed through the ResearchFish website - https://www.researchfish.com/. A final project report and other information and actions as required by CSO as part of the project completion will be available and completed to the satisfaction of CSO by the

end of the funding period. Copies of all publications originating from this trial shall be provided to CSO.

The Chief Investigators and Project Management Group will produce all reports. All statistical reports will be produced by the Study Statistician from the Institute for Applied Health Research, Glasgow Caledonian University.

18. DISSEMINATION OF FINDINGS

Findings of this feasibility study will be disseminated to a range of stakeholders, including researchers, clinicians, individuals with IC, and students. At least 1 paper will be submitted to international peer-reviewed journals (i.e. Circulation and European Heart Journal). Also at least 1 abstract will be submitted to international conferences. We will hold a stakeholder event at the end of the project as a method for guiding best practice for researchers. Glasgow Caledonian University is rated No. 1 in Scotland for physiotherapy education, and this research will be used to inform undergraduate and postgraduate modules on clinical research. The project will also form part of a PhD thesis at the Glasgow Caledonian University.

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