Guy's and St Thomas' NHS
NHS Foundation Trust

PROTOCOL TITLE:

A brief physiotherapist-led behaviour-change intervention to facilitate walking in older people with peripheral arterial disease: A randomised controlled trial

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Study Synopsis

Title	A brief physiotherapist-led behaviour-change intervention to facilitate walking in older people with peripheral arterial disease: A randomised controlled trial
Protocol Short Title/Acronym	Motivating Structured walking Activity in Intermittent Claudication (MOSAIC)
Protocol Version number and Date	Version 6, 28/8/2018
Study Phase if not mentioned in title	Phase II
Is the study a Pilot?	No
Study Duration	3 years
Methodology	Multi-centre, two-arm randomised controlled trial with nested qualitative exploration of participant and physiotherapist views
Sponsor name	King's College London/Guy's & St Thomas Foundation NHS Hospital
Chief Investigator	Dr Lindsay Bearne
REC number	17/LO/0568
Medical condition or disease under investigation	Peripheral Arterial Disease (PAD)
Purpose of clinical trial	*Phase II efficacy trial*
Primary objective	To answer the question "Does MOSAIC improve walking ability (measured by the 6 Minute Walking Distance [6MWD]) at 3 months compared to usual NHS care in older people with intermittent claudication (IC)?"
Secondary objective (s)	To answer the questions 1) "Does MOSAIC improve a) activities of daily living and quality of life [QoL] at 3 months; and b) walking ability, activities of daily living and QoL at 6 months compared to usual NHS care in people with IC?" 2) "Is it feasible to collect the measures required to estimate cost utility in future phase 3 trials in people with IC?" 3) What are the Minimal Clinically Important Difference (MCID) values for the clinical assessments used for people with IC?
Number of Subjects/Patients	192
Trial Design	Phase II, multi-centre, parallel group, two-arm, randomised, controlled superiority trial

Endpoints	Primary endpoint: 3 month post-intervention, secondary endpoint: 6 months post randomisation.
Main Inclusion Criteria	Inclusion criteria: a) ≥50 years of age; b) established PAD (Ankle Brachial Pressure Index ≤0.90 and/or radiographic evidence or clinician reported diagnosis) and IC (presence of symptoms reported on the San Diego Claudication Questionnaire (SDCQ)); c) able to participate in MOSAIC and d) able and willing to provide informed consent. Exclusion criteria: a) Unstable IC (self-reported change in symptoms during previous 3 months); b) walking >90 minutes/week (reported on Brief International Physical Activity Questionnaire (IPAQ)); c) contraindications to walking exercise (e.g., unstable angina) confirmed by their vascular specialist; or d) have completed any prescribed supervised exercise sessions in the previous 6 months or been offered prescribed exercise sessions in the next 6 months.
Statistical Methodology and Analysis	The analysis will be conducted according to the intention to treat. The primary outcome will be analysed using multiple regression with the baseline 6MWD value and the stratification factor, centre, included as covariates. Results will be reported as the difference in mean 6MWD between the intervention and control groups with a 95% confidence interval (CI). Other continuous outcomes will be similarly analysed. Logistic regression will be used to analyse binary outcomes, with the models including the stratification factor, centre, as a covariate. The sensitivity and consistency of the EQ-5D-5L will be analysed using correlations with VascuQoL-6 and other clinical measures. Feasibility of collecting service use data using an adapted version of the CSRI will be assessed. A small number of participants (N=20) will be invited to complete the scale with a researcher and describe their thoughts whilst completing it to ensure it is clear and appropriate. A short rating scale will be added to scales at follow up to allow the calculation of Minimal Clinically Important Differences (MCID).

Glossary of Terms and Abbreviations

6MWD	6 minute walking distance
6MWT	6 minute walking test
AE	Adverse Event
ANOVA	Analysis of Variance
AR	Adverse Reaction
ASR	Annual Safety Report
Brief IPQ	Brief Illness Perception Questionnaire
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRN	Comprehensive Research Networks
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EARS	Exercise Adherence Rating Scale
EC	European Commission
EQ-5D-5L	EuroQoL- 5 Dimension -5 Level
GAfREC	Governance Arrangements for NHS Research Ethics Committees
IC	Intermittent Claudication
ICF	Informed Consent Form
IPAQ	Brief International Physical Activity Questionnaire
ISRCTN	International Standard Randomised Controlled Trial Number
MA	Marketing Authorisation
MCID	Minimal Clinically Important Difference
MRC	Medical Research Council
MS	Member State
Main REC	Main Research Ethics Committee
NEADL	Nottingham Extended Activities of Daily Living
NICE	National Institute for Health and Care Excellence
NHS R&D	National Health Service Research & Development
PAD	Peripheral Arterial Disease
Participant	An individual who takes part in a clinical trial
PI	Principal Investigator
QA	Quality Assurance
QALYs	Quality Adjusted Life Years
QC	Quality Control
QoL	Quality of Life
RA	Research Associate
ROC curve	Receiver Operating Characteristic Curve
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event

SDCQ	San Diego Claudication Questionnaire
SDV	Source Document Verification
SEM	Standard error of the mean
SOP	Standard Operating Procedure
SR-MWD	Self-Reported Maximum Walking Distance
SSA	Site Specific Assessment
TASC	Trans-Atlantic Inter-Society Consensus
TMG	Trial Management Group
TPBQ	Theory of Planned Behaviour Questionnaire
TSC	Trial Steering Committee
VascuQol-6	Vascular Quality of Life Questionnaire
WELCH	Walking Estimated-Limitation Calculated by History

1. Introduction

Intermittent claudication (IC) is a severe ischaemic leg pain which occurs during walking in ~30% of people with Peripheral Arterial Disease (PAD), an age-related atherosclerotic condition [Wang et al., 2005]. It results in reduced mobility, participation in daily activities [Treat-Jacobson et al, 2002], quality of life (QoL) [Pell, 1995; Regensteiner et al, 2008] and feelings of powerlessness, inadequacy and isolation [Treat-Jacobson et al, 2002, Gibson et al, 1998]. Walking is an effective treatment for IC [Vemulapalli et al, 2015], improving walking distances and duration compared to usual NHS treatment [Lane et al, 2014] or pharmaceutical therapy [Ahimastos et al, 2011] and with comparable outcomes to revascularisation [Murphy et al, 2012; 2015]. The Trans-Atlantic Inter-Society Consensus (TASC)-II Group recommends supervised walking at an intensity that induces pain within 3–5 minutes, for 30–60 minutes/session conducted 3 times/week for 3 months [Norgren et al, 2007]. Similarly, the National Institute for Health and Care Excellence (NICE) recommends 2 hours supervised exercise/week for 3 months [NICE 2012]. However, guideline implementation is poor [NICE 2014] and only 24% of UK vascular surgeons have access to supervised walking programmes [Stewart & Lamont, 2007], so usual care for most individuals with IC is simple advice to “go home and walk”[Stewart & Lamont, 2007; Makris et al, 2012]. Despite advice, self-directed walking is frequently overlooked as a management strategy [Galea Holmes et al 2015] and participation is low [Garg et al, 2006, Galea et al, 2008], leading to reduced mobility and a need for higher-risk invasive treatments.

There are unique barriers to walking among people with IC [Galea et al, 2008], as walking is both a stimulus for pain and a therapy, which makes walking counterintuitive without appropriate guidance and support. Our previous work identified modifiable psychosocial factors, such as people’s understanding of IC, perceptions of and confidence in their ability to manage IC [Galea Holmes et al, 2015a; 2015b], and unrealistic expectations of treatment as key factors influencing walking [Galea Holmes et al, 2015]. Evidence from our recent systematic review, including 6 randomised controlled trials (RCT), suggests that targeting these psychological barriers using behaviour-change techniques (e.g., using motivational interviewing

to elicit patient values and desire for change) in addition to exercise or advice may increase walking in people with IC [Galea et al, 2013].

Two psychological models which we applied to change health behaviour are the Theory of Planned Behaviour [Ajzen 1985; 1991] and Common Sense Model of Illness Representations [Leventhal et al, 1980; Leventhal et al, 1984]. The Theory of Planned Behaviour proposes that behaviour (e.g., walking) is goal-directed and driven by beliefs about social (e.g., approval from a healthcare professional), personal (e.g. confidence to engage in walking), and environmental factors (e.g., perceived access to a safe walking route) [Ajzen 1985; 1991]. The Common Sense Model proposes that individuals form personal, lay explanations of their illness, which reinforce maladaptive coping behaviours (e.g., avoid painful walking) or drive change (e.g., increase walking to improve symptoms), and that inaccurate or limited understanding of their illness and treatment may prevent healthy behaviour change [Leventhal et al, 1980; Leventhal et al, 1984]. Our work was the first to combine processes from these two theories to target walking behaviour change among people with IC.

Consistent with MRC guidelines for developing complex healthcare interventions, we worked with people with IC and clinicians to co-design and test the feasibility of a novel physiotherapist-led behaviour-change intervention (2 face to face sessions and 2 follow-up telephone sessions over 3 months) to increase walking in people with IC. The feasibility study (n=24) was successful: We enrolled 39% of identified patients, study retention was good (92%), compliance with the intervention was high (100% meetings and 87% phone calls), 86% of participants completed all outcome measures and a subsample of participants and the physiotherapist reported the study was a positive and acceptable experience during qualitative interviews [Galea Holmes et al, 2015]. The feasibility study was not designed to estimate the effect of our intervention on walking ability but did show that walking increased by mean (SD) 837 (626) steps/day. We refined the intervention in response to participant feedback (e.g. provision of a pedometer).

This study will build on our previous work to investigate the efficacy of our brief physiotherapist-led behaviour change intervention (**Mo**tivating **S**tructured walking **A**ctivity in people with **I**ntermittent **C**laudication – MOSAIC) on walking ability compared to usual care in older people with IC in a RCT.

2 Trial Objectives, Design and Statistics

2.1. Trial Objectives

- **Primary objective:** To answer the question “Does MOSAIC improve walking ability (measured by the 6 Minute Walking Distance [6MWD]) at 3 months compared to usual NHS care in older people with IC?”
- **Secondary objectives:** To answer the questions 1) “Does MOSAIC improve a) activities of daily living and QoL at 3 months; and b) walking ability, activities of daily living and QoL at 6

months compared to usual NHS care in people with IC?" 2) "Is it feasible to collect the measures required to estimate cost utility in future phase 3 trials in people with IC?" 3) What are the Minimal Clinically Important Difference (MCID) thresholds for the assessment measures in this population?

- ***Primary End Point:*** *3 months post-randomisation*
- ***Secondary End point:*** *6 months post-randomisation*

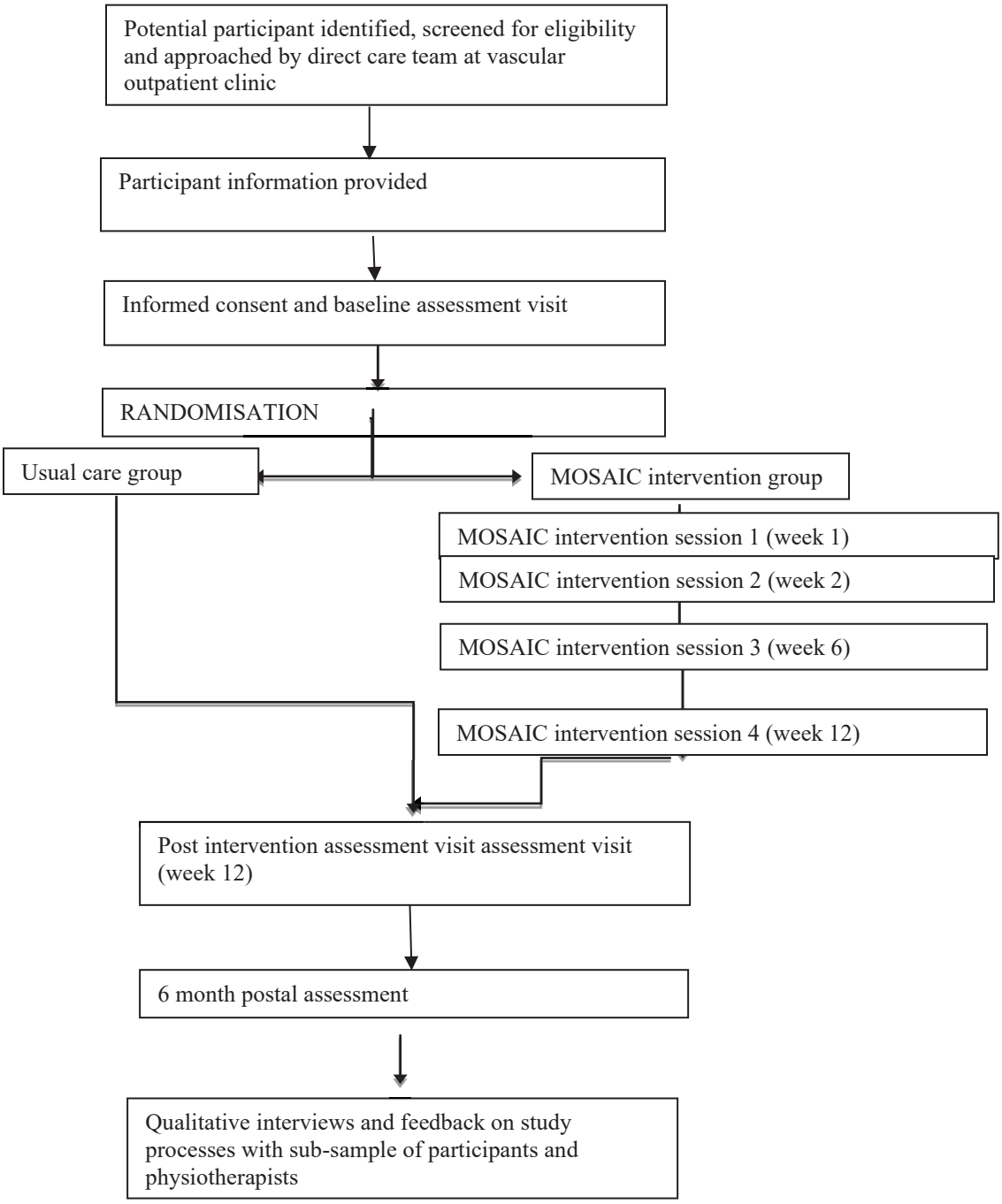
2.2 Trial Design & Flowchart

Trial Design: MOSAIC is a phase II, multi-centre, parallel group, two-arm, randomized, controlled superiority trial with 1:1 allocation ratio, stratified by recruitment site. Participants will be randomized to receive either usual NHS care or MOSAIC in addition to usual NHS care.

MOSAIC comprises 2 x 60-minute individual face-to-face consultations (weeks 1 & 2) and 2 x 20-minute follow-up telephone calls (weeks 6 & 12) delivered at a convenient time and location of participant's choice (local NHS Trust or participant's home). All sessions are delivered by a trained Band 6/7 physiotherapist. A checklist outlining the components for each session will be provided to each physiotherapist. All participants randomized to receive MOSAIC will be provided with a pedometer and a patient manual which will include information on IC, risk factors, walking guidelines, goal setting, problem solving and action planning worksheets and a walking diary.

Usual Care comparison: Participants randomized to the comparison group will continue to receive usual NHS care for IC which typically consists of an initial assessment, drug therapy and simple advice to walk provided by a vascular specialist and delivered in the vascular outpatient clinic. The type and duration of usual care treatment received by both groups will be recorded. The opportunity for between group contamination is low as usual NHS care is not delivered by physiotherapists.

2.3 Trial Flowchart



2.4 Trial Statistics

The analysis will be conducted according to the intention to treat. The primary outcome will be analysed using multiple regression with the baseline 6MWD value and the stratification factor, centre, included as covariates. Results will be reported as the difference in mean 6MWD between the intervention and control groups with a 95% confidence interval (CI). Other continuous outcomes will be similarly analysed. Logistic regression will be used to analyse binary outcomes, with the models including the stratification factor, centre, as a covariate. The sensitivity and consistency of the EQ-5D-5L will be analysed using correlations with VascuQoL-6 and other clinical measures.

Two analytical methods will be applied to calculate the MCID:
1. Anchor-based calculation of MCID: Change scores for clinical outcomes will be determined by subtracting the initial result from the post-programme result for each participant. Correlations will be determined for participant self-assessment of performance scores and change in clinical outcomes and the RA assessment of the participant's performance and change in clinical outcomes. The mean change in scores for patients scoring no change, small improvement and substantial improvement will be compared by ANOVA. The sensitivity and specificity for change in score to distinguish patients classified as changed (≥2) from those whose performance was unchanged (-1–1) will be calculated and a ROC curve obtained (Deyo et al., 1991). The data point corresponding to the upper left corner of the curve will represent the MCID.
2. Distribution-based calculation of MCID: The standard error of the mean (SEM) for all patients scoring will be used to estimate the MCID based on the following equation: $SEM=\sigma 1\times\sqrt{(1-r)}$, where $\sigma 1$ is the baseline standard deviation and r is test-retest reliability of the scale. The intraclass correlation coefficient for test-retest reliability will be calculated using the baseline and post-treatment scores for each participant at post-programme evaluation. Using this method, one SEM represents the estimated MCID (Wyrwich et al., 1999).

3. Sample Size, Selection and Withdrawal of Participants

Participants and recruitment: Potentially eligible adults will be identified by one of two methods which can proceed in parallel and are described below:

(a) Patients aged ≥50 years with peripheral arterial disease will be identified from existing clinical lists/databases (depending on availability of these at participating sites) at both recruiting sites and Participant Identification Centres and will be invited to participate in the trial using a mailshot approach. Invitation packs will include an information letter including an expression of interest letter and preferred method of contact form, a participant information sheet and a prepaid return envelope. Patients will also be provided with study recruitment personnel contact details for seeking further information. Non-responders will be contacted by telephone by a member of the direct care team approximately 4 weeks later

(b) Eligible patients will be identified and approached by the direct care team during routine appointments.

Written informed consent will be obtained prior to baseline assessment and the participant's Vascular Surgeon, where available and General Practitioner will be informed of their enrolment into the trial.
Sample size: Based on our previous work, 192 participants will be required to detect a mean 6MWD difference of 58 metres (SD=111; α=0.05, 1-β=0.90), accounting for 20% attrition at 3 month follow up.
Justification for recruitment: Participants will be recruited from tertiary centres for vascular surgery (e.g. Guys and St Thomas' NHS Foundation Trust) and District General Hospitals (e.g. Ashford & St Peter's NHS Trust). During our feasibility study, we enrolled 39% of eligible patients approached from two tertiary centres (GSTT and KCH) and estimate that we will recruit ~2 patients/month/site to achieve our target sample in 24 months.

3.1 Inclusion Criteria

a) ≥50 years of age;
b) established PAD (determined by either (i) Ankle Brachial Pressure Index≤0.90; (ii) radiographic evidence; or (iii) clinician reported diagnosis) and IC (symptoms reported on the San Diego Claudication Questionnaire SDCQ);
c) able and willing to participate in MOSAIC and
d) able and willing to provide informed consent.

3.2 Exclusion Criteria

a) Unstable IC (self-reported change in symptoms during previous 3 months);
b) walking >90 minutes/week (reported on Brief International Physical Activity Questionnaire IPAQ); or
c) contraindications to walking exercise (e.g., unstable angina) confirmed by the direct care team.
d) have completed any prescribed supervised exercise sessions in the previous 6 months or been offered prescribed supervised exercise sessions in the next 6 months.

3.3 Criteria for Premature Withdrawal

Participants will be free to withdraw their participation in the trial at any time. We do not anticipate that there will be any requirement for a premature withdrawal.
All adverse events will be reported to the Chief Investigator who will be responsible for reporting to the Trial Steering Committee/ Data Monitoring and Ethics Committee, study sponsors, Research and Development departments and Research Ethics Committee. (Please see section 6, Appendix 1)

4. Study procedures

Informed Consent Procedures

Informed consent will be sought from all participants.

It is the responsibility of the Investigator to obtain written informed consent for each participant prior to performing any trial related procedures. However, this task may be delegated to suitably trained individuals e.g. Research Nurses, Research Associate (RA) if local practice allows and this responsibility has been delegated by the Principal Investigator as captured on the MOSAIC Trial site signature and delegation log.

Once a potential participant has decided they want to take part in the study, they will be asked to sign a consent form. Given the low risk nature of the trial and the limited mobility of some of the potential participants, patients can consent on the day they are informed of the trial, or if they prefer, they can take the participant information sheet and invitation letter home and decide to join the trial at a later date. If the patient would like to be contacted by the RA, they will be asked to provide permission to be contacted to speak on the telephone about the study and/or arrange an appointment to attend King's College London (or their local hospital, if available). At this appointment the RA, who has completed training in Good Clinical Practice and the collection of informed consent, will review the information sheet, answer any further questions and the patient can sign an informed consent form.
The investigator or delegates (as per the MOSAIC Trial site signature and delegation log) will then sign and date the form. A copy of the informed consent form will be given to the participant, a copy will be filed in the medical notes, and the original placed in the Investigator Site File.
Whilst the initial trial procedures may vary across recruitment sites, it is likely that research nurses from the Comprehensive Research Networks (CRN) will assist in the screening and consent processes.

4.1 Participant identification and Screening Procedures

Potentially eligible adults will be identified by one of two methods which can proceed in parallel and are described below:

4.1a Patients with intermittent claudication will be identified from existing clinical lists/databases (depending on availability of these at participating sites) at both recruiting sites and Participant Identification Centres and will be invited to participate in the study using a mailshot approach. Invitation packs will include an information letter including an expression of interest letter and preferred method of contact form, a participant information sheet and a prepaid return envelope. Patients will also be provided with study recruitment personnel contact details for seeking further information. Non-responders will be contacted by telephone by a member of the direct care team approximately 4 weeks later.
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4.1b Eligible participants will be identified, via screening of medical records, and approached by the local care team.

It is usually the responsibility of the Investigator to confirm eligibility of potential participants, using the inclusion and exclusion criteria, however, given the low risk nature of this trial, this may be delegated to suitably trained individuals if local practice allows and this responsibility has been delegated by the Principal Investigator as captured on the MOSAIC Trial site signature and delegation log. To assess eligibility relating to inclusion criteria 2 (presence of IC) and exclusion criteria 2 (currently walking >90 mins per week), potential participants will also be asked to complete the International Physical Activity Questionnaire (IPAQ) and the San Diego Claudication Questionnaire (SDCQ). These data will be used for screening purposes only.

Potential participants will be provided with a full explanation of the trial, an invitation letter and participant information sheet. They will be invited to ask any questions about the study, be reassured that their participation is entirely voluntary and that their decision to take part or not will in no way affect the care that they receive. They will also be told that they may withdraw their participation from the study at any time without giving a reason and without consequence. With participant agreement, the participant's GP and Consultant Vascular Surgeon, where available, will be informed of their participation

To assess whether the patient sample is representative of those attending the sites with PAD, the Investigator or delegate will ask individuals who do not wish to take part if their age and gender may be recorded, and if they wish to provide a reason for opting not to participate.

4.2 Randomization Procedures

Following informed consent and completion of the baseline assessment, the participant can be randomised into the trial. Participants will be randomised at the level of the individual, stratified within recruitment site, to receive either MOSAIC plus usual NHS care or usual NHS care alone in a ratio of 1:1. The King's College London Clinical Trials Unit will provide randomisation. The system is online and can be accessed 24 hours a day. The RA will log in, enter key information about the participant, and the randomisation allocation occurs instantly. Confirmation emails will be generated automatically and sent to the CI (and delegated members of the research team) and trial physiotherapists delivering MOSAIC. The RA, who is the outcome assessor, will be blind to group allocation. Once the participant is randomised they will be given a unique trial identifying number.

4.4 Schedule of Treatment for each visit

MOSAIC intervention: Participants randomized to receive MOSAIC will take part in two 60-minute face-to-face consultations (weeks 1 & 2) and two 20-minute follow-up telephone calls (weeks 6 & 12). This will comprise:

Session One (60-minute face-to-face):
Introduction: Intervention aims and format
Elicit psychosocial factors: a) Patient understanding of IC and symptom response; b) Treatment experiences, including walking, and appraisal of treatment efficacy.
Education: Pathophysiology of IC, risk factors, treatment options, benefits of walking exercise; address inaccurate or inappropriate illness or treatment beliefs.
Walking advice: Elicit current walking activity and past experiences; provide walking recommendations.
Preparing for change: Discuss the impact of IC on daily life; elicit motivation and value-basis for change (i.e., hobbies, work, or family).
Prompt practice: provide and explain pedometer and walking diary/manual.

Session Two (60-minute face-to-face):
Introduction: Review understanding of IC and treatment options, assess pedometer use.
Goal setting: Discuss role of walking in achieving valued activities (e.g., hobbies); agree a goal to progressively increase walking.
Walking prescription: Agree and record (in manual) a tailored exercise prescription and walking Action Plan. Encourage progress toward achieving >2,500 steps as purposeful walking on ≥3 days/week (~30 minutes walking assuming 90 steps/minute cadence).
Problem solving: Identify potential barriers to goals and measures for overcoming anticipated or unexpected obstacles.
Self-monitoring: Identify milestones for goal achievement (e.g., pedometer step count, diarised walks).

Session Three (20-minute telephone call):
Review and feedback: Review goals and Action Plan. Elicit attempts at behaviour change (using pedometer, walking diary); provide feedback, reinforcing successes.
Problem solving: Discuss any new barriers and measures to overcome these.
Revision: Discuss and revise goals and action plan if necessary.

Session Four (20-minute telephone call):
Review and feedback: Discuss progress toward goals, and attempts at behaviour maintenance (using pedometer, walking diary).
Problem solving: Discuss new barriers and measures to overcome these.
Prepare for self-management: Integration of walking to daily life, relapse management, and signpost to community resources.

All sessions will be delivered by a trained clinical physiotherapist and will take place at a time and location convenient to the participant.

4.3 Therapist training and supervision

Clinical physiotherapists will be trained to deliver the MOSAIC intervention by the trial team. Therapists will receive up to two days training which will introduce the trial objectives and provide training on research processes, underpinning psychological theories, and intervention content and materials. All physiotherapists will be trained in Motivational Interviewing and competency of intervention delivery will be assessed. Additional training will be provided until competency is achieved if necessary. Once the trial has commenced, ongoing supervision of the physiotherapists will be provided to ensure consistent and accurate delivery of MOSAIC. Individualised feedback on audio-recorded sessions and group supervision sessions will be provided by members of the research team.

Usual Care comparison:

Participants randomized to the comparison group will continue to receive usual NHS care for IC which typically consists of an initial assessment, drug therapy and advice to walk provided by a vascular specialist and delivered in the vascular outpatient clinic. The type and duration of usual care treatment received by both groups will be recorded.

4.4 Follow up Procedures

None of the assessments listed below are part of usual care for this population.

A: Clinical assessments

Baseline and post-intervention (3-month) follow-up measures will be collected at either King's College London or the local hospital (subject to availability and patient preference). Participants who are unable or refuse to attend, and therefore cannot complete the primary outcome, will be invited to complete secondary outcomes at home either electronically using a computer or phone or via a standard postal pack with pre-stamped return envelope. At 6-months all self-reported measures will be collected from participants either electronically or via a standard postal pack with pre-stamped return envelope. Attrition will be minimised via standardised telephone, text and email reminders to participants.

- First reminder: (+7 days) email reminder (if email provided) or text reminder (if mobile provided) with the option to request a link to online questionnaire or a new or additional paper copy.
- Second reminder: (+14 days) email reminder (if provided and not already contacted via email), or second text-reminder (if mobile provided)
- Third reminder: (+21 days) telephone call to request completion of minimum data set by telephone (< 10 minutes duration).

Baseline visit:
Sociodemographic & clinical characteristics including age, gender, smoking history and co-morbidities will be collected at baseline by self-report and standard measures of body mass index and Ankle-Brachial Pressure Index obtained. The SDCQ will also be repeated to describe current IC symptoms.

Primary outcome: 6 Minute Walking Distance (6MWD in metres) is measured during a self-paced, standardised 6 Minute Walk Test (6MWT) conducted around a level, 100-foot circuit (Montgomery et al., 1998; American Thoracic Society, 2002). During the 6MWT, maximal walking ability (time (seconds) walked before resting) and pain free walking ability (time (seconds) walked before reported pain onset) will be measured. Pain intensity will also be measured before and after the walking test using the Claudication Pain Scale. The walk test is completed twice, with the results from the best test used for analysis.

Secondary outcomes:
Self-reported Maximum Walking Distance (SR-MWD) is measured by one global item: "What is the maximum distance (in metres) you can walk at your usual pace on a flat surface before leg pain forces you to stop?"

Walking Estimated-Limitation Calculated by History (WELCH) is a 4 item measure of walking limitation in patients with IC (Ouedraogo et al, 2013; Tew et al., 2014). Scores range from 0-100, with 0 indicating ability to walk for 30 seconds slowly and usually slower than others of the same age and 100 indicating ability to walk ≥3 hours quickly and usually faster than others of the same age.

Nottingham Extended Activities of Daily Living (NEADL) (Nouri & Lincoln, 1987; Lincoln & Gladman, 1992) scale is a 22 item measure with 4 subscales (mobility, kitchen tasks, domestic tasks, leisure activities). Each item is scored 0-3 with a total score ranging from 0-66.

Vascular Quality of Life Questionnaire-6 (VascuQol-6) is a disease specific measure comprising 6 items (each scored 1-4; total score, 6-24) (Nordanstig et al, 2014).

Brief International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003) is a valid and reliable 7-item measure of daily physical activity. The self-administered short form asks participants to recall the frequency (days) and duration (minutes) of moderate and vigorous activities, walking for ≥10 minute bouts, and sitting over the last 7 days.

Post intervention (3 month) visit:
6 Minute Walking Distance (6MWD),
Self-reported maximum walking distance (SR-MWD),
Walking estimated-limitation calculated by history (WELCH),
Nottingham extended activities of daily living (NEADL)
Vascular quality of life questionnaire (VascuQol-6)

Brief International Physical Activity Questionnaire (IPAQ)
Adverse events - the response to a single open ended item "Have you had any problems since your last assessment?" will be recorded (please see section 6)

6 month postal pack:
Self-reported maximum walking distance (SR-MWD),
Walking estimated-limitation calculated by history (WELCH),
Nottingham extended activities of daily living (NEADL)
Vascular quality of life questionnaire (VascuQol-6)
Brief International Physical Activity Questionnaire (IPAQ)
Adverse events- the response to a single open ended item "Have you had any problems since your last assessment?" will be recorded

If the participant does not return the postal questionnaires despite two reminders the researcher will telephone the participant to collect the minimum data set (Adverse events, SR-MWD, IPAQ, VascuQoL-6)

B: Cost effectiveness assessment
The feasibility of collecting measures to estimate the economic impact (cost effectiveness analysis) of our intervention in future definitive Phase 3 trials will be assessed. The EQ-5D-5L, which provides utility weights to generate Quality Adjusted Life Years (QALYs), will be administered at all time points and compared against the VascuQoL-6 and other clinical outcomes. EQ-5D-5L evaluates five dimensions (self-care, mobility, usual activities, pain/discomfort and anxiety/depression; score, 0-5).
A resource use questionnaire will be developed based on previous work (e.g. Client Service Receipt Inventory) to identify key cost drivers (both NHS and non NHS) and evaluated at all time points to determine completion rates, redundant questions and additional resource use items.
To qualitatively evaluate understanding, recall and scale completion, a sub sample of participants (up to n~20) will be invited to complete the questionnaire whilst describing their thoughts. If needed, the researcher will ask probe questions (e.g. what do you think this question is asking you? Is the question confusing? If so, what would make it easier to answer? How did you arrive at your answer? What does the word/phrase ___ mean to you?) The sessions will be audio-recorded and transcribed verbatim, following which recordings will be destroyed. The transcripts from separate questions will be coded thematically (informed by content analysis) to identify the type and degree of difficulty the participants expressed with answering it (French 2007). Identified patterns will be reviewed by the research team and the final scale amended to maximise understanding and usability.

C: Process evaluation
Informed by guidelines, the implementation of MOSAIC (e.g., adoption at sites, characteristics of trial physiotherapists, intervention attendance and adherence, context of treatment delivery), maintenance (at 6 months), unexpected pathways and consequences (referral to and

uptake of other treatment and AEs) and mechanisms of impact (e.g., mediation analysis of psychological processes) will be evaluated. The Brief Illness Perception Questionnaire (Brief IPQ), a measure of individuals' representation of their illness as defined by the Common Sense Model and Theory of Planned Behaviour Questionnaire (TPBQ) which assesses goals and beliefs about walking as treatment for IC will be assessed at each time point. A validated Self-Regulation questionnaire will assess action planning and action control scale (Luszczynska and Schwarzer, 2003; Sniehotta et al., 2005a). To assess adherence to walking goals participants will complete the Exercise Adherence Rating Scale (EARS) at 3 and 6 month follow up assessments

D: Qualitative interviews with participants and physiotherapists

Semi structured interviews lasting 30-60 minutes will be conducted with a purposive sample of up to ~30 participants. Sampling will ensure engagement of trial participants with different age and disease severity. Participants invited to be interviewed will be able to withdraw their consent to being interviewed without withdrawing from the MOSAIC trial or affecting their care. Interviews will last 30-60 minutes, can be conducted via the telephone or face to face either at King's College London, the local hospital or participant's home, based on the participant's preference, and will be arranged at a mutually convenient time. Interviews will be transcribed verbatim, anonymised and analysed thematically. Cross referencing of emerging codes with a second researcher, presenting themes to participants and reporting of deviant findings will be employed to ensure validity of the findings. A sample of ~10 trial Physiotherapists will also be interviewed to explore the experience and implementation of MOSAIC and be given a unique identifier, corresponding personal details will be kept in hard copy only, securely at King's College London.

E: Fidelity assessment

All face-to-face and telephone sessions will be audio recorded with the participants' permission to allow an assessment of fidelity to the protocol. At the end of the study, a random sample of 10% of the recorded sessions per physiotherapist will be reviewed by 2 raters from the research team using standardised checklists to assess treatment fidelity. Any disagreements between raters will be resolved through discussion.

G: MCID assessment

After completing the clinical assessments at the 3-month and 6-month follow up points participants will be asked to provide a global rating of change in their score for each scale by answering the following question: "Has there been any change in your walking ability/walking distance/daily activities etc since the last test?" Participants will be asked to respond on a transitional 3-point scale as follows: 1, worse; 2, about the same; 3, better. If they indicate no change, the patient will be given a score of 0. If they indicate there has been an improvement or deterioration, they will be asked to score their change on the following 15-point Likert scale (Jaeschke et al., 1989, Juniper et al., 1994):

-7, a very great deal worse; -6, a great deal worse; -5 a good deal worse; -4, moderately worse; -3, somewhat worse; -2 a little worse; -1, almost the same,

hardly any worse at all; 0, no change; 1, almost the same, hardly any better at all; 2, a little better; 3, somewhat better; 4, moderately better; 5, a good deal better; 6 a great deal better; and 7 a very great deal better.

Scores of -1, 0 and 1 will be considered no change, scores of 2–3 small improvement and scores of 4–7 substantial improvement (Juniper et al., 1994). (For analysis please see section 2.4).

The RA will also complete the same question at 3-month follow for the 6MWD to give their own rating of improvement in the participant's walking since the previous assessment.

H: Physiotherapist training evaluation

Physiotherapists will be invited to complete a brief questionnaire before MOSAIC group training commences, immediately following training, and then at 6 month follow-up to evaluate the effects of the 2-day group training as well as the ongoing supervision. A self-report questionnaire will assess the following outcomes: a) demographics; b) Therapeutic Empathy (validated Helpful Responses Questionnaire – 6 items); c) Motivation (Readiness to Change Questionnaire); d) knowledge and confidence (adapted 4-item measure); e) Learning outcomes (3 open items); f) learning needs (3 open items); g) Changes to training (1 open item).

4.5 Radiology Assessments *(if applicable)*

Not applicable

4.6 End of Study Definition

The end of the study is defined as 3 months after the completion of the final data capture (i.e. final data collection with final participant). The CI will notify the REC that the trial has ended and a summary of the trial report will be provided within 12 months of the end of trial.

5. Laboratories *(if Applicable)*

Not applicable

6. Assessment of Safety

The collection and reporting of adverse events (AEs) and Serious Adverse Events (SAEs) will be in accordance with Good Clinical Practice and the Research Governance Framework 2005. Definitions will be as defined in the Guys and St Thomas Foundation NHS Trust Standard Operating Procedures for the Identifying, Recording and Reporting Adverse Events.

Safety will be assessed continuously throughout the trial. There are no Investigational Medicinal Products being used as part of the MOSAIC study.

There may be a small increased risk of a temporary increase in pain on walking during the assessment and completion of MOSAIC as it is a requirement of the walking exercise that pain is

induced within 3-5 minutes of commencing walking. Physiotherapists are trained to identify and address any untoward increases in pain. No other risks are expected to arise from taking part in the trial. It is therefore, reasonable to collect only targeted treatment-related AEs.

Adverse events (AEs)) will be recorded from date of consent to the 6 month outcome assessment.
All AEs will reported to the CI.
Physiotherapists treating participants randomized to MOSAIC will be trained to identify and report AEs in a standard format.
All participants will report AEs to the RA at follow up assessments (in response to one open ended question "Have you had any problems since your last assessment /questionnaires?"). These will be reported by the RA in a standard format.

Serious Adverse Events
Investigators (or their delegates) should contact the CI within 24 hours of becoming aware of a suspected SAE.
Participants will be contacted by the PI and the PI will decide whether a SAE has occurred and act in accordance to Safety Reporting in Non-CTIMP Research Stand operating procedures (Appendix 1). The PI will be also asked to provide a categorisation of seriousness and causality. The form should be sent to the CI and a copy kept in the site file.
Investigators should also report SAEs to their own Trust in accordance with local practice.

The Trial Steering Committee/Data and Ethics Monitoring Committee will monitor all AEs.

6.1 Ethics Reporting
Annual progress reports will be submitted to the Research Ethics Committee.

7. Trial Steering Committee (if applicable)
The Trial Management Group (TMG) comprising Chief Investigator, RA, trial statistician and other research team members, as required, will meet weekly to monitor the day to day running of the trial. The independently chaired combined Trial Steering Committee /Data Monitoring and Ethics Committee will meet every 6 months and oversee the trial procedures including monitoring recruitment, data completeness and patient safety (i.e., AEs). The TSC/DMEC will include the research team, a statistician, an independent chair and other independent members including at least one Patient Advisor.

8. Ethics & Regulatory Approvals
The study will be submitted to an NHS REC and the governance review (following REC approval) will be undertaken by local Research and Development departments.

9. Data Handling
Confidentiality

Personal data, including address and telephone number, will be held for all participants for the duration of the study in a secured database maintained confidentially and separately from patient-reported research outcomes.
Participants will be allocated a unique participation number which will be used to anonymously label all data from questionnaires and assessments.
Audio recording may be used during the qualitative interviews and questionnaire feedback sessions. Recordings will be transcribed for analysis and audio files will be destroyed once transcription is complete. Any transcription service will sign a privacy agreement.
Direct quotations may be used from the transcriptions but all identifiable information will be removed (e.g, names of people or hospitals etc) prior to publication.
For participants assigned to the intervention group, all treatment sessions will be audio recorded and a proportion analysed by the research team against standardised checklists to assess therapists' fidelity to the protocol (see Section 4.5E).
All data will be password protected and encrypted and stored on secure servers at King's College London. Data stored on external devices such as laptops and external hard drives will be encrypted and password protected. Only anonymised data will be stored on external devices.
Personal identifiable information such as names and address will be stored as hard copy in a locked filing cabinet or in a password protected, encrypted file on the King's College London secure server.
In line with the Data Protection Act (1998), the minimum identifiable data will be sought and the identification list of participant details will be stored in a locked cabinet and on the desktop university password protected computer inside the locked office of the CI. Paper copies (for example signed consent forms and any questionnaires completed on paper) will be stored in a locked filing cabinet at King's College London and available only to members of the research team. Electronic files will be encrypted and password protected and stored on a secure server within King's College London and again, will only be accessible by members of the research team.

Case Report Form

A case report form (CRF) will be completed for each participant. The following details will be included in the case report form for each participant: eligibility/exclusion criteria checklist, date of consent, baseline assessments, date of intervention commencement, AEs, withdrawal from study, follow up of outcomes, SAE form. The form will be completed by the Principal Investigator (or delegates, as recorded on the MOSAIC trial delegation log) i.e. research nurse, the trial physiotherapist and the RA.

Record Retention and Archiving

All records will be anonymised and kept for 5 years after the end of the trial.

Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements

including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

10. Finance and Publication Policy

Name and address of funder
Name: Dunhill Medical Trust
Address: 5th Floor, 6 New Bridge Street, London EC4V 6AB;
Telephone: 020 7403 3299
Fax: 020 7403 3277
Email: admin@dunhillmedical.org.uk

Amount of funding awarded: £299,495

The trial will be registered on the ISRCTN trial registry as well as the UKCRN Research Portfolio.

Dissemination plan;

Service users, participants and funding body will be provided with a summary of our findings. Patient Advisors will present the findings and share their own related experiences, supporting the impact of this research to practitioners, researchers and patients. The study protocol will be published in an open access journal (e.g. Trials/BMJ Open) and results will be published in relevant clinical and academic journals (e.g., European Journal of Vascular and Endovascular Surgery, Physiotherapy, British Journal of Health Psychology). Abstracts will be presented at academic (e.g. The Vascular Society of Great Britain and Ireland, Physiotherapy UK, UK Society of Behavioural Medicine) and clinical forums (e.g. King's Health Partners). We will publish study updates and results via social media (e.g. twitter) and the King's Health Partners and Division of Health and Social Care Research websites.

Appendix 1 – Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone	Main REC and Sponsor

			Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	Main REC with a copy to be sent to the sponsor

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