MOSAIC
MOtivating Structured walking Activity in Intermittent Claudication

Guy's and St Thomas' NHS
NHS Foundation Trust

KING'S College LONDON

MOSAIC TRIAL

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

Statistical Analysis Plan

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Contents

1 Abbreviations

6MWD - 6 Minute Walking Distance
6MWT - 6 Minute Walking Test
ABPI - Ankle Brachial Pressure Index
AEs - Adverse Events
ANOVA - Analysis of Variance
BMI - Body Mass Index
Brief IPQ - Brief Illness Perception Questionnaire
CI - Chief Investigator
CTIMP - Clinical Trial of an Investigational Medicinal Product
CTU - Clinical Trials Unit
EARS - Exercise Adherence Rating Scale
IC - Intermittent Claudication
ICC - Intraclass Correlation Coefficient
IPAQ - International Physical Activity Questionnaire
IQR – Interquartile Range
ITT - Intention to Treat
MCID - Minimal Clinically Important Difference
MOSAIC - MOtivating Structured walking Activity in Intermittent Claudication
NHS - National Health Service
NEADL - Nottingham Extended Activities of Daily Living
PAD - Peripheral Arterial Disease
PI - Principal Investigator
PP - Per Protocol

QoL - Quality of Life
RA - Research Associate
REC - Research Ethics Committee
ROC - Receiver Operating Characteristic
SAEs - Serious Adverse Events
SD - Standard Deviation
SDCQ - San Diego Claudication Questionnaire
SEM - Standard Error of Measurement
SR-MWD - Self Reported-Maximum Walking Distance
TPBQ - Theory of Planned Behaviour Questionnaire
TSC/DMEC - Trial Steering Committee/Data Monitoring and Ethics Committee
VasculQoL-6 - Vascular Quality of Life Questionnaire-6
WELCH - Walking Estimated Limitation Calculated by History

2 Preface

This document is to provide a more technical and detailed description of the principal features of the analysis stated in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

The following document was written based on the MOSAIC protocol version 5.

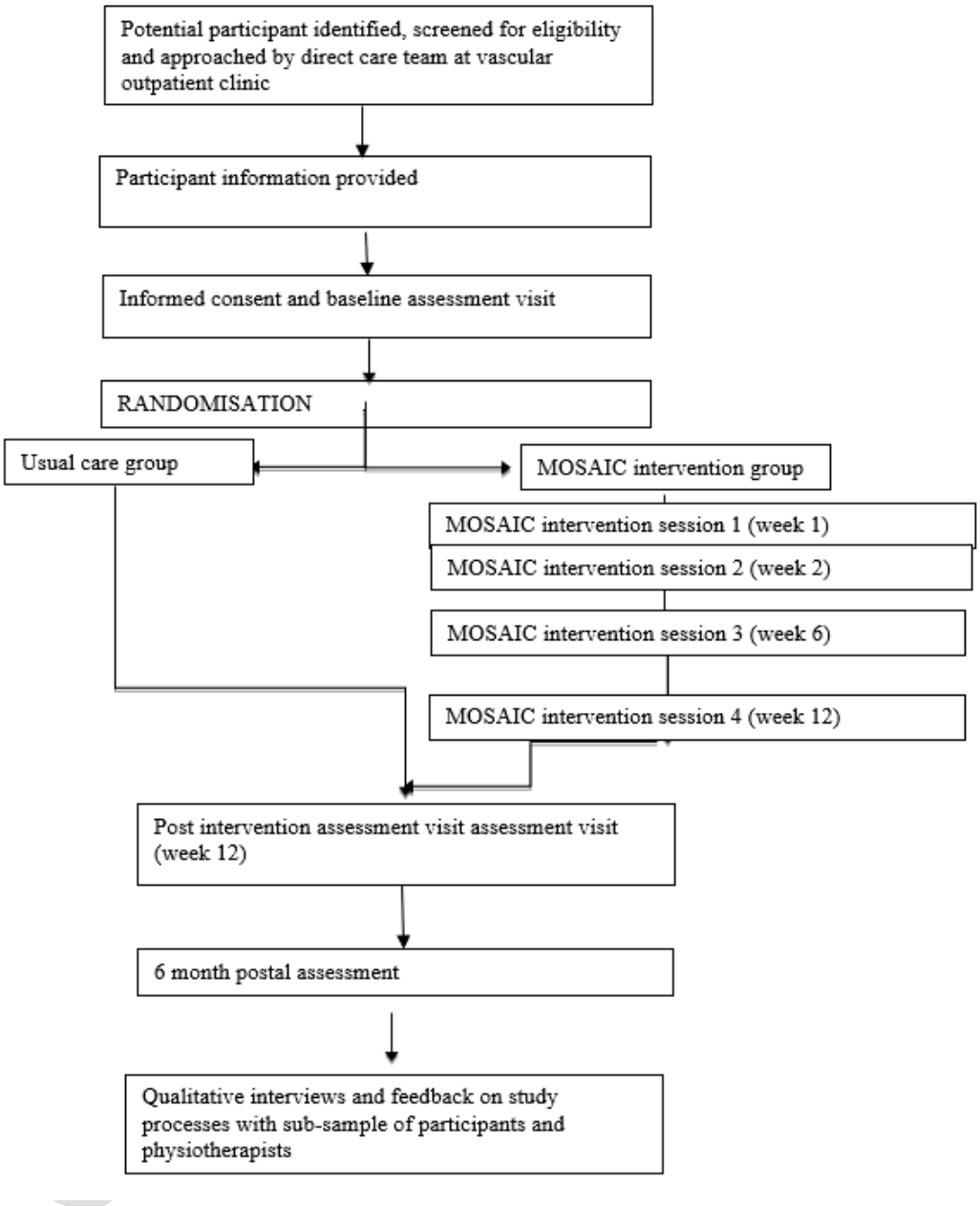
3 Study Design

Motivating Structured walking Activity in Intermittent Claudication (MOSAIC) is a phase II, multi-centre, parallel group, two-arm, randomised, controlled superiority trial with a 1:1 allocation ratio, stratified by recruitment site. Participants will be randomised to receive either usual National Health Service (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 randomised to receive MOSAIC will be provided with a pedometer and a patient manual which will include information on intermittent claudication (IC), risk factors, walking guidelines, goal setting, problem solving and action planning worksheets and a walking diary.

Usual care comparison: Participants randomised 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 NHS 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.

3.1 Trial Flowchart



4 Method of allocation to groups

Once baseline assessments are complete, the individuals will be randomised to one of the treatment arms. Randomisation will be done in a 1:1 ratio. Randomisation is at the participant level and is performed using an online randomisation system set up by the King's College London Clinical Trials Unit (CTU). Randomisation is stratified by recruitment site with

variable block sizes to ensure that equal numbers of patients are allocated to the two arms within each site. The procedure is as follows: On receipt of the baseline questionnaire, the Trial Co-ordinator electronically submits details of each participant to the CTU. This includes: participant ID number, site, initials and date of birth. The system immediately notifies the chief investigator (CI) and assigned members of the research and clinical teams, as well as recording the randomisation outcome. The Trial Co-ordinator does not receive the randomisation outcome.

4.1 Duration of the treatment period

The treatment period is 12 weeks (3 months).

4.2 Frequency and duration of follow-up

Participants will complete follow up measures at 3 months for the primary outcome. Participants will complete follow up measures at 3 and 6 months for the secondary outcomes.

4.3 Visit windows

The MOSAIC intervention visit windows are weeks: 1, 2, 6 and 12.

Both groups are assessed at week 0 (baseline), week 12 (3 months) and week 24 (6 months) follow up.

5 Data collection

5.1 Inclusion criteria

Participants will be eligible for the trial if they meet the following inclusion criteria:

- ≥50 years of age;
- Established peripheral arterial disease (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)).
- Able and willing to participate in MOSAIC.
- Able and willing to provide informed consent.

5.2 Exclusion Criteria

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

5.3 Measures

5.3.1 Baseline

Measures collected by self-report include:

- Age
- Gender
- Ethnicity
- Marital status
- Smoking history
- Co-morbidities
- Duration of PAD diagnosis and IC symptoms
- Prescribed medication for IC
- History of revascularisation
- Walking advice

The following measures will be obtained by the outcome assessor:

- Standard measures of body mass index (BMI)
- Ankle Brachial Pressure Index (ABPI)
- Current symptoms described by the SDCQ

5.3.2 Primary

6 Minute Walking Distance (6MWD in metres) is measured during a self-paced, standardised 6 Minute Walking Test (6MWT) conducted around a level, 100-foot circuit [1, 2]. 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 (i.e. the highest 6MWD) used for analysis; using the highest 6MWD is based on the American Thoracic Society guidelines for the 6MWT [2].

5.3.3 Secondary

The following secondary measures will be collected at baseline, 3 months and 6 months:

- Self-reported Maximum Walking Distance (SR-MWD)
- Walking Estimated-Limitation Calculated by History (WELCH) questionnaire
- Nottingham Extended Activities of Daily Living (NEADL) questionnaire
- Vascular Quality of Life Questionnaire-6 (VasculQoL-6)
- The Brief Illness Perception Questionnaire (Brief IPQ)
- The Theory of Planned Behaviour Questionnaire (TPBQ)
- The action planning and action control scale
- Brief International Physical Activity Questionnaire (IPAQ)

5.3.4 Additional post randomisation measures

These measures will be assessed at 3 months and 6 months:

- Exercise Adherence Rating Scale (EARS)

5.4 Adverse events

Safety will be assessed continuously throughout the trial. There are no investigational medicinal products being used as part of the MOSAIC trial.

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 to 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 (AEs).

The collection and reporting of 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.

AEs will be recorded from date of consent to the 6-month outcome assessment. All AEs will be reported to the CI. Physiotherapists treating participants randomised to MOSAIC will be trained to identify and report AEs in a standard format.

All participants will report AEs to the Research Associate (RA) at 3 and 6 month 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.

The number of AEs will be reported with proportions and 95% confidence intervals for differences between the groups, where appropriate.

5.4.1 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 principal investigator (PI) and the PI will decide whether a SAE has occurred and act in accordance to Safety Reporting in Non-CTIMP Research Standard 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 (TSC/DMEC) will monitor all AEs.

The number of SAEs will be reported with proportions and 95% confidence intervals for differences between the groups, where appropriate.

6 Study Objectives

6.1 Primary Objective

To answer the question “Does MOSAIC improve walking ability (measured by the 6MWD) at 3 months compared to usual NHS care in older people with IC?”.

6.2 Secondary Objectives

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?

7 Endpoints

7.1 Primary Endpoint

The difference in mean 6MWD at 3 months between the intervention and comparison groups, adjusted for baseline 6MWD and site

7.2 Secondary Endpoints

The difference in mean walking ability at 6 months between the intervention and comparison groups, adjusted for baseline walking ability and site.

The difference in QoL at 6 months between the intervention and comparison groups, adjusted for baseline QoL and site.

The difference in activities of daily living at 6 months between the intervention and comparison groups, adjusted for baseline activities of daily living and site.

The MCIDs for the following measures will be calculated: 6MWD, SR-MWD, WELCH, NEADL, VascuQol-6.

8 Sample Size Considerations

Based on previous work, 192 participants will be required to detect a mean 6MWD difference of 58 metres (standard deviation (SD) =111; α=0.05; 1-β=0.90) accounting for 20% attrition at 3 months follow up.

9 Analysis Sets

The definitions of different analysis populations are shown below:

9.1 ITT Population

The intention to treat population (ITT) comprises all randomised participants, regardless of their compliance with the trial protocol (e.g. eligibility error, post-randomisation withdrawal, and whether the correct trial treatments were received).

9.2 Per-protocol population

A per-protocol population (PP) will also be employed to mirror the ITT population but exclude any patients defined as having a *major protocol deviation*. The planned PP analysis will be applied to the primary outcome only.

Note: A *major protocol deviation* is considered "relevant" if it can be expected that the deviation had a distorting influence on the assessment of the treatment effect on the primary endpoint of the trial or could affect the patient's safety/rights. The items that should be checked are mainly from the inclusion/exclusion criteria as well as other important protocol violations but the final decision regarding important protocol violations and exclusion from the ITT population will be identified by the TSC/DMEC prior to database lock.

9.3 Safety set population

All participants.

10 General Consideration for Data Analyses

10.1 General Methodology

All analyses will not be carried out unless the trial database has been authorised as complete and final, and all protocol deviations have been identified.

The analyses will be performed by the trial statistician and the primary analysis will be reviewed by a second statistician. ITT will be the main strategy of analysis adopted for the primary outcome and the secondary outcomes 1a; 1b and 3. Also, all regression analysis will include the stratification factor, centre, as a covariate.

Continuous data will be summarised in tables using descriptive statistics, including the number of participants, mean, standard deviation, median and range as appropriate. Summaries of continuous characteristics will be based on non-missing observations. For categorical variables, counts and percentage per treatment group will be presented. Percentage for categorical variables will be calculated based on number of patients with non-missing values for the variable. Range checks of the data will be performed to identify anomalous values.

All statistical hypothesis testing will be done using two-sided tests with type I error of 0.05, unless otherwise stated.

10.2 Loss to follow up and Missing Data

At 3 and 6 month follow up 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).

10.3 Interim Analysis and Data Monitoring

No interim analysis for data monitoring purposes is planned. No adjustment for interim analyses is necessary for data monitoring.

10.4 Multiple Comparison/multiplicity adjustments

Adjustments for multiple comparisons will not be made in this trial since there is a single primary outcome which will be used as the main determinant of effectiveness of the intervention.

10.5 Sociodemographic and Clinical Descriptive Characteristics

Summary statistics of the sociodemographic and clinical characteristics collected by self-report or by the outcome assessor at baseline will be reported.

10.5.1 Exploratory analyses

Exploratory analyses will be performed to provide an overview of the data and the distributions of each of the continuous variables will be produced. For categorical variables contingency tables will be produced and bar charts, where appropriate.

10.6 Primary Analysis

The analysis will be conducted using the ITT population. 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 mean difference in 6MWD between the intervention and control group with a 95% confidence interval.

11 Secondary analysis

The secondary endpoints QoL and activities of daily living, will at both 3 and 6 months be analysed respectively using multiple regression with the baseline value and the stratification factor, centre, included as covariates. Results will be reported as the mean difference in the relevant secondary endpoint between the intervention and control groups with a 95% confidence interval. Other continuous outcomes will be similarly analysed.

11.1.1 Calculation of MCID

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.

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 [3, 4]:

-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 to 3 small improvement and scores of 4 to 7 substantial improvement [4].

Correlations will be determined for participant self-assessment of performance scores and change in clinical outcomes. Correlations will be determined for 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 to +1) will be calculated and a receiver operating characteristic (ROC) curve obtained [5]. The data point corresponding to the upper left corner of the curve will represent the MCID.

11.1.2 Sensitivity analysis

As a sensitivity analysis the MCID will be calculated using a distribution based approach.

Distribution-based calculation of MCID: The standard error of measurement (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 σ_1 is the baseline standard deviation and r represents the intraclass correlation coefficient (ICC), which is a measure of the test-retest reliability of the scale. The ICC 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 [6].

11.1.3 Model assumption checks

For the primary analysis, the model assumes that the difference in walking distances between the group receiving MOSAIC and the group receiving usual NHS care are normally distributed. If this is found to be skewed, transformations will be considered. Residuals will be plotted to check for normality and inspected for outliers. Non-parametric tests may be used if the parametric methods do not appear to be appropriate e.g. the assumptions do not appear to hold.

11.1.4 Mediation analysis

If appropriate, a regression based analysis will be performed to explore this.

11.1.5 Subgroup analyses

There are no planned subgroup analyses.

12 Baseline data analysis

Histograms will be produced for continuous variables and summarised using mean, standard deviation, number with median and range if the data are very skewed.

Categorical data will be summarised by frequencies and percentages.

The number of AEs and SAEs will be reported with proportions and 95% confidence intervals for differences between the groups where appropriate.

13 Software

Statistical analysis: Stata 15 or (later if there is an update before analysis), will be used for data analysis.

14 Bibliography

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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 Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor 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