UNIVERSITY OF LEICESTER
Clinical Trials Unit

Statistical Analysis Plan

Developing and evaluating an education programme aimed at increasing physical activity in individuals with diagnosed coronary heart disease: a randomised controlled trial

(The PACES Study – Physical Activity after Cardiac EventS)

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Revision History

Version	Date	Author(s) and Role	Summary of Changes/Comments
0.1	23-12-2018	Trial statistician	Information from protocol included
0.2	14-02-2019	Trial statistician	Completing SAP
0.3	26-02-2019	Trial statistician	Changes made for collaborators' and senior statistician's comments on draft
0.4	14-03-2019	Trial statistician	Changes made for primary and secondary outcome measures

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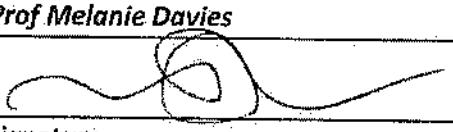
SAP approval for finalised versions:

Chief Investigator	***Prof Melanie Davies***	
		24.3.2019
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	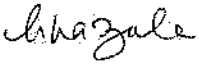	26-03-2019
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LIST OF ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
BMI	Body Mass Index
BP	Blood pressure
CHD	Coronary heart disease
CV	Cardiovascular
CVD	Cardiovascular disease
EQ-5D	EuroQol five dimensions
HADS	Hospital Anxiety and Depression Scale
ILS	Immediate Life Support
ISWT	Incremental Shuttle Walk Test
MI	Myocardial Infarction
MVPA	Moderate to Vigorous Physical Activity
PA	Physical Activity
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RPAQ	Recent Physical Activity Questionnaire
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
UHL	University Hospitals of Leicester

Contents

1 Introduction

This Statistical Analysis Plan (SAP) outlines the proposed statistical analyses for the PACES study, where a detailed and comprehensive description of the statistical methods is provided. The PACES Study is a randomised controlled trial that is being conducted to assess the effectiveness of a low-cost pragmatic intervention to increase daily physical activity in participants 12-36 months post diagnosis of a cardiac event in order to reduce subsequent cardiovascular events.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials [1]. All work planned and reported for this SAP will follow nationally and internationally accepted guidelines, published by the American Statistical Association and the Royal Statistical Society for statistical practice [2,3].

The purpose of this SAP is to outline the planned analyses that are to be performed on the data to support the completion of the study publication for protocol V6 13_03_18. The SAP will be amended if substantial changes are made to the planned analyses, and in any case, will be finalized before the database lock for this study. Exploratory post-hoc or unplanned analyses not necessarily identified in this SAP may be performed on these data as required. These analyses will be clearly identified in the study publication.

The reader of this SAP is encouraged also to read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for the process of completing a patient in this study.

The outlined boxes in this SAP represent information from the protocol. The analyses will be carried out by the Trial Statistician (Ghazala Waheed) and supervised by the Senior Statistician (Prof Laura Gray) to ensure the integrity of the data processing at all stages.

1.1 Study Objectives

1.1.1 Primary objective

To assess the effectiveness of a low-cost pragmatic intervention to increase daily physical activity in participants at least 12-36 months post diagnosis of a cardiac event in order to reduce subsequent cardiovascular events.

1.1.2 Secondary objectives

1- To assess the effectiveness of a structured education intervention to improve CV risk factors such as smoking status, blood pressure, lipid profile, obesity, self-reported physical activity and objectively measured physical activity intensity.

2- To assess the acceptability, uptake and feasibility of implementing the programme in a population at high future risk of another CVD event in primary care.

1.2 Study design

1.2.1 Summary

The PACES study has been designed to facilitate service development; three main phases have been undertaken:

1. Development of the intervention for patients after a cardiac event.
2. Recruitment and training of the facilitators for programme delivery.
3. Delivery of a single centre, 2-arm parallel 12 month RCT to determine whether an education programme with text message support has an impact on the primary (average daily physical activity) and secondary outcomes (see section 2.2) compared with usual care.

1.2.2 Randomisation

Participants will be randomised 1:1; stratified by gender (male; female) and ethnicity (White European; other) to either intervention or control groups.

If two people are taking part from the same household they will be randomised to the same arm to prevent contamination taking place.

Control participants will be sent a standard information booklet and letter informing them of their results and the outcome of randomisation. Intervention participants will also be sent a letter informing them of their results and the outcome of randomisation and subsequently contacted to book them onto an education programme.

1.2.3 Study treatment interventions

This will be a randomised control trial with an intervention group and a control group.

1) Intervention group: Participants randomised to the intervention group will receive the standard information leaflet and will be invited to attend two group-based structured education sessions. These education sessions will be delivered by trained facilitators approximately two weeks apart. The participants will receive 82 physical activity related text messages at different weekly frequencies following the second education session up until the 12 month follow-up assessment.
These structured education sessions have been developed and refined in conjunction with PPI work and through the use of existing infrastructure consisting of Diabetes Education and Self-Management in on-going and Newly Diagnosed (DESMOND) groups and a network of trained facilitators.

2) Control group: Participants randomised to control group will not receive the intervention. Participants will be provided with general health advice in the form of a standard information leaflet and will continue with their 'usual' GP care.

1.2.4 Inclusion Criteria

- Aged 18 years or older
- 12-36 months post confirmed diagnosis of a cardiac event (myocardial infarction, angina or acute coronary syndrome)
- Able to speak and read English to participate effectively in a group education programme
- Willing and able to attend the education sessions and clinic visits
- Willing and able to give informed consent
- Access to a mobile phone in order to receive text messages
- Willingness to allow GP notification of their participation in study and access to patient records for purpose of study
- Able to take part in moderate physical activity as assessed using Incremental Shuttle Walk Test (ISWT) (Level three or above)[4]

1.2.5 Exclusion Criteria

- Individuals with a diagnosis of heart failure where the underlying primary cause is not myocardial disease as a result of atherosclerosis will be excluded from this study
- Musculoskeletal limitations that would limit physical activity (e.g. musculoskeletal injury)
- Participation in another clinical intervention study in the past 12 weeks
- Lacks capacity to give informed consent
- Severe life-threatening co-morbidity (e.g. malignancy)
- Poor exercise capacity, (< level three on the ISWT [120 metres]), these individuals will be directed back into cardiac rehabilitation (good practice)[4]
- Housebound or immobile
- Unstable symptoms (chest pain or breathlessness at rest; unstable stage II hypertension [160/100mmHg], not on necessary medications)
- Individuals with no or limited understanding of written or verbal English

1.2.6 Sample size calculations

The primary outcome is change from baseline to 12 months average daily physical activity, as quantified by the Euclidean norm minus one (ENMO) method measured in milligravity units (mg). This is the main measure of activity derived from the activity monitor that will be used in this study (PACES). In order to detect a minimum clinically significant difference of 2.1 mg, which is equivalent to an overall increase in physical activity volume of approximately 30 minutes of light walking at 4km/h, assuming a standard deviation of 5.3 mg [1], a power of 80% and significance level of 5%, the sample size requires 202 participants. To allow for 20% loss to follow-up and 10% non-compliance of the activity monitor, we will therefore need to recruit 290 participants (145 in each group).

2 Outcome Measures

2.1 Primary outcome measures

The primary outcome measure is change in overall volume of physical activity measured using accelerometer between baseline and 12 months.

A complete case population will be used for the primary analysis. This will be followed by sensitivity analyses which will include an intention to treat (ITT) population by imputing missing data to assess the robustness of the findings to missing data.

2.2 Secondary outcome measures

Below is a list of all of the secondary outcomes collected at baseline and 12 months.

Aerobic fitness:

Incremental Shuttle walk test (metres) - as part of the ISWT blood pressure, heart rate, oxygen saturation, rating of perceived exertion and breathlessness will be obtained.

Ambulatory activity:

Patients will be asked to wear an accelerometer for up to eight days to record total physical activity, which includes light, moderate, vigorous and moderate to vigorous physical activities (MVPA). The measures will be

- Time spent above a threshold/ equivalent intensity to walking
- MVPA (1 min bouts)
- Sedentary time
- Sleep duration
- Intensity gradient metric
- Average acceleration for the most active 30 minutes per day

Anthropometric measures:

- Body mass (kg)
- Body mass index (kg/m^2)
- Waist circumference (cm)
- Hip circumference (cm)
- Waist to hip ratio

Cardiovascular measures:

- Blood pressure (mmHg)
- Resting heart rate (bpm)

Biomedical measures:

- Total cholesterol (mmol/l)
- HDL cholesterol (mmol/l)
- LDL cholesterol (mmol/l)
- Triglycerides (mmol/l)
- HbA1c (mmol/mol, %)

TC:HDL ratio

- Health historyMedical history and medication
- Family history of CHD

Smoking status, alcohol intake & employment status

Questionnaire Measures

A number of different questionnaire measures will be completed by participants at baseline, 6 months and 12 months. Details of these questionnaire measures are as follows:

- Jenkins self-efficacy for exercise expectations scale[5]
- Hospital Anxiety and Depression scale (HADS)[6]
- MacNew Heart Disease [7,8]
- Recent Physical Activity Questionnaire RPAQ[9]
- EuroQoL EQ-5D-5L Health-related quality of life instrument [10,11]
- Morningness- Eveningness Questionnaire [12,13] (Baseline only)

Use of health care services (12 months only)No attempt will be made to impute the missing values for the secondary endpoints measured.

3 Analysis Sets/Populations

3.1 Missing values and outliers

Missing values represent a potential source of bias in clinical trials. Therefore, every effort will be made to ensure the data is fully explored for potential problems and have been correctly entered into the database. Participants who did not attend the baseline assessment after consent will be excluded from all analyses, but will be noted on the CONSORT flow chart. For the primary and secondary analyses, participants who do not have an outcome measurement will be excluded; as discussed in section 3.2. Sensitivity analyses will be performed to assess the robustness of the findings to missing data.
Outliers will be identified by examining graphical plots such as normality plots, box plots and histograms. Values that visually appear outside of the main distribution (i.e. outliers) will be further investigated and if this is the correct observation it will remain in the analysis, however further assumptions will be made to assess possible influences on the results using a sensitivity analysis; by removing the outlier or outliers to compare results. Where results from the two analyses are discrepant, this fact will be reported and discussed in the study publication.

3.2 Complete Case Population

The level of missing data for each outcome will be assessed. If missing outcome data is present the initial analysis will be based on the complete cases. All tests of the effect of treatment on outcomes will be conducted on a complete case (CC) population. That is, all

the recruited participants will be included in the analysis, with the exception of those with missing outcome data. This will be done on a 'by analysis' basis, i.e. only those participants with missing data for variables required for a specific analysis will be removed.

3.3 Intention-to-treat Population/Full analysis set

The intention-to-treat (ITT) analysis population will consist of all participants randomised. Participants will be analysed in the group to which they were randomly allocated and regardless of any protocol deviations or violations. Multiple imputation methods will be used to impute missing outcome data. This will be a sensitivity analysis.

3.4 Per-protocol Population

The per protocol (PP) population are those who were compliant with the protocol and have complete data for the analysis concerned on 'by analysis' basis. In the control arm, the PP population will include all participants randomised to that arm with complete outcome data. In the intervention arm, the PP population will be defined as participants who have attended at least one group session of the programme and have outcome complete data. This will be a sensitivity analysis.

4 General Issues for Statistical Analysis

4.1 Multiplicity, Multiple Comparisons and Interim Analyses

All tests and reported p-values will be two-sided, where a p-value of < 0.05 will be considered to be statistically significant. Estimates will be presented with 95% confidence intervals. There will be no formal adjustment for multiple significance testing. The outcomes however, are clearly categorised by the degree of importance (primary and secondary). No formal interim analyses were planned.

4.2 Analysis Software

All data manipulations, tables, figures and analyses will be performed using Stata version 15.0 [14]. The validated program code (do file) and any other outputs created shall be documented and archived together.

5 Statistical Methodology

5.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics for individual participants will be summarised by randomisation group. Numbers (with percentages) for binary and categorical variables and means (and standard deviations), or medians (with lower and upper quartiles) for

continuous variables will be presented. The number of missing values will be reported in the footnote of the summary table. There will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any of the baseline variables.

5.2 Primary Endpoint Analysis

5.2.1 Primary Analysis of Primary Endpoints

The primary outcome is change in overall volume of physical activity (average acceleration, ENMO) from baseline to 12 months. For the primary outcome treatment arm will be compared using linear regression modelling with

1. a binary indicator for randomisation group as the explanatory variable

2. terms for stratification factors (gender and ethnicity) as confounders

3. adjustment for the change from baseline in accelerometer wear time and baseline average daily physical activity.

The primary analysis at 12 months will be based on complete data.

5.2.2 Sensitivity Analyses

5.2.2.1 Per Protocol Population

For the PP analysis, participants who have engaged with at least one group session of the programme will be included. The PP will adhere to the same steps as the primary analysis.

5.2.2.2 Intention-to-treat Population

To allow for full analysis set, missing data will be imputed using a multiple imputation procedure which substitutes predicted values from a regression equation. The imputation will be carried out by the MI command in Stata [15]. MI replaces missing values with multiple sets of simulated values to complete the data, performs standard analysis on each completed dataset, and adjusts the obtained parameter estimates for missing-data uncertainty using Rubin's rules to combine estimates [16].

The following procedure will be followed:

- The MI will be set as wide
- The MI will register imputation of the average daily physical activity at 12 months and at baseline

- A regression method will be used , where the registered variables will be individually adjusted for the randomisation and stratification factors (sex and ethnicity), with 100 imputations to avoid biased estimates, rseed (2259) and the force options
- MI estimate will provide the final results using the same regression model as the primary analysis and covariate adjustments.

5.2.2.3 Stratified analyses

Interaction effects will be fitted between intervention arm and gender (male vs. female) and ethnicity (White European vs. other). If the interaction term is statistically significant at the 10% level then stratified analyses will be performed for that factor using the same model as the primary analyses.

5.3 Secondary Endpoint Analyses

The analyses of the secondary outcomes will be conducted in a similar manner as the main analysis using the appropriate model type, logistic regression for binary outcomes, linear for continuous and ordinal for ordinal outcome.

The assumptions of each analysis will be assessed and alternate parameterisations will be considered where appropriate.

5.4 Subgroup Analyses

We will conduct the following subgroup analyses to assess if the intervention effect is statistically different between these groups.

- Ethnicity
- Gender
- Age < 60 & ≥ 60 years
- ISWT: High risk < 420 & Low risk ≥ 420
- Cardiac condition – (MI, Angina or ACS)

The main analysis for each subgroup will involve using the same analytic principles as the primary analysis, but stratifying by the subgroup to estimate the mean difference in average daily physical activity when compared to the control group. Further subgroup analyses will investigate the interaction effects between the treatment and subgroup, this will include an

additional interaction term to the model; 'subgroup × treatment'. Subgroup results will be graphically presented as forest plots, with the estimated difference of average daily physical activity between treatment groups with 95% confidence interval for the interaction.

6 Safety Reporting

6.1 Adverse Events (AEs)/ Serious Adverse Events (SAEs)

All AEs/SAEs occurring during the study observed by the investigator or reported by the participant, attributed to the study, will be recorded on the CRF. The relationship of AEs/SAEs to the study will be assessed by a medically qualified investigator.

AEs will be recorded on the AE Record Sheet and periodically discussed by the study steering group committee as required. Any safety concerns arising from the team will be reported to the Sponsor as soon as possible.

All SAE information must be recorded on an SAE form and sent to the Sponsor using the appropriate reporting form and the contact details on there within 24 hours of the study team being made aware of the SAE.

Any adverse event/serious adverse event occurring whilst a participant is continuing in the study, whether or not attributed to the study, will be documented in the study publication.

7 References

1. ICH Topic E9: Statistical Principles for Clinical Trials. CPMP/ICH/363/96. September 1998. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928.pdf Accessed on 28-September-2016

2. ASA. Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics. 1999.

3. RSS. The Royal Statistical Society: Code of Conduct. 1993

4. Singh SJ, Jones PW, Evans R, Morgan MD. Minimum clinically important improvement for the incremental shuttle walking test. Thorax 2008; 63(9): 775-7.

5. Resnick B, Jenkins LS. Testing the reliability and validity of the Self-Efficacy for Exercise scale. *Nursing research* 2000; **49**(3): 154-9.

6. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta psychiatrica Scandinavica* 1983; **67**(6): 361-70.

7. Dempster M, Donnelly M, O'Loughlin C. The validity of the MacNew Quality of Life in heart disease questionnaire. *Health and Quality of Life Outcomes* 2004; **2**: 6-.

8. Hillers TK, Guyatt GH, Oldridge N, et al. Quality of life after myocardial infarction. *J Clin Epidemiol* 1994; **47**(11): 1287-96.

9. Besson H, Brage S, Jakes RW, Ekelund U, Wareham NJ. Estimating physical activity energy expenditure, sedentary time, and physical activity intensity by self-report in adults. *Am J Clin Nutr* 2010; **91**(1): 106-14.

10. EuroQol Research Foundation. How to use EQ-5D. 2016. http://www.euroqol.org/about-eq-5d/how-to-use-eq-5d.html (accessed 01.05 2016).

11. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2011; **20**(10): 1727-36.

12. Terman M, Terman JS. Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety, and side effects. *CNS Spectr* 2005; **10**(8): 647-63; quiz 72.

13. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International journal of chronobiology* 1976; **4**(2): 97-110.

14. StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

15. StataCorp. STATA Multiple Imputation Reference Manual: Release 13. 2013 [cited 2016 July 8]; 13:[Available from: https://www.stata.com/manuals13/mi.pdf]

16. Rubin DB. Inference and missing data. Biometrika. 1976 Dec 1;63(3):581-92.