Statistical Analysis Plan

PRomotion Of Physical activity through structured Education with different Levels of ongoing Support for people at high risk of type 2 diabetes (PROPELS): a randomised controlled trial

Trial registration number: ISRCTN83465245

SAP revision history

Date	Version	Justification for SAP version
2 May 2019	1	First draft for review
17 May 2019	2	Incorporating comments from Thomas Yates and Laura Gray
23 May 2019	2.1	Incorporating further clarifications from Thomas Yates
17 June 2019	3	Incorporating comments from TC on 14 June 2019, in particular from Simon Griffin
1 July 2019	4	Adding information from Thomas Yates to resolve disparities with the protocol paper and describe any deviations from this paper.
16 September 2019	5 - FINAL	Incorporating comments from Richard Morris (DMC).

SAP responsibilities

Role in SAP development	Name, affiliation	Role in trial
SAP author	Stephen Sharp, University of Cambridge	Study statistician
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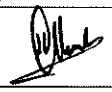
SAP reviewer 4	Kamlesh Khunti, University of Leicester	Study Principal Investigator
SAP reviewer 5	Richard Morris	DMC Chair

SAP signatures

Role	Name, affiliation	Date	Signature
Trial PI	Kamlesh Khunti, University of Leicester		
SAP author	Stephen Sharp, University of Cambridge	16 Sep 2019	

1 Introduction

1.1 Trial background and rationale

The prevention of type 2 diabetes is recognised as a health care priority. Lifestyle change has proven effective at reducing the risk of type 2 diabetes, but limitations in the current evidence have been identified in: the promotion of physical activity; availability of interventions that are suitable for commissioning and implementation; availability of evidence-based interventions using new technologies; and physical activity promotion among ethnic minorities. The aim of the trial was to investigate whether a structured education programme with differing levels of ongoing support, including text-messaging, can increase physical activity over a 4 year period in a multi-ethnic population at high risk of diabetes.

1.2 Trial objectives/hypotheses

- To investigate whether an intervention to support physical activity change and maintenance, offered to an ethnically diverse population with prediabetes, can lead to sustained increases in physical activity over four years.
- To investigate the effectiveness of the intervention when delivered at two levels of intensity, with and without follow-on support that enhances self-monitoring with pedometers through tailored text-messaging and telephone calls.
- To investigate the effect of the intervention within White Europeans and South Asians sub-groups.

2 Methods

2.1 Trial design

The trial is a 2-centre parallel group randomised controlled trial, in which participants are randomised (1:1:1) to either a control group, a Walking Away (WA) Group, or a Walking Away Plus (WA+) group. Participants are followed up for 48 months, with an intermediate assessment after 12 months.

2.2 Randomisation

Randomisation is stratified by centre (Leicester/Cambridge), sex (men/women) and ethnicity (White European/South Asian/Other). Individuals recruited in the same household were randomised to the same group.

2.3 Sample size

The aim was to recruit 436 individuals per group (total 1308). Details of the sample size calculation are provided in Yates 2015.

2.4 Framework

This is a superiority trial. Each of the 2 intervention groups (Walking Away and Walking Away Plus) will separately be compared to the control group.

2.5 Interim analyses and stopping guidance

A planned interim analysis was performed for an independent Data Monitoring and Ethics Committee (DMEC); results were not disseminated more widely.

2.6 Timing of final analysis

Analyses described in this SAP will be performed following completion of the trial and database lock.

2.7 Timing of outcome assessments

Outcomes are assessed at 48 months, with an intermediate assessment at 12 months.

3 Statistical principles

3.1 Confidence intervals and p-values

Since there are 2 primary comparisons (each intervention group vs control), the estimates of effect will be reported with 97.5% confidence intervals, for both primary and secondary outcomes.

3.2 Adherence and protocol deviations

Adherence to the intervention will be summarised as follows:

Walking Away (WA) group – number (%) attending initial education AND at least 1 follow-up annual support session.

Walking Away Plus (WA+) group – number (%) attending initial education AND at least 1 follow-up annual support session AND registered with the text service AND received the initial telephone calls AND received at least 1 telephone call during the trial.

The number (%) of individuals fulfilling each of the separate criteria defined above will also be reported, along with the number of step count text messages sent and the number asking for the test messaging service to be stopped.

3.3 Analysis populations

The primary analyses will use a modified Intention-to-Treat (ITT) population, in which individuals are included in the group to which they were randomised, although individuals with missing outcome data at follow-up will be excluded.

A secondary analysis of the primary outcome will be performed using two approaches: (1) an ITT approach, but where missing outcome data are replaced using multiple imputation (see section 5.2.2 for further details), (2) a Per-Protocol (PP) population, comprising the following:

Control – all individuals.

WA – attended initial education AND at least 1 follow-up annual support session.

WA+ – attended initial education AND at least 1 follow-up annual support session AND registered with the text service AND received the initial telephone calls AND received at least 1 telephone call during the trial.

4 Trial population

4.1 Screening data

No screening data were collected.

4.2 Eligibility criteria

Eligibility criteria are described in Yates 2015.

4.3 Recruitment

The numbers of individuals invited and recruited from primary care and from existing databases will be reported in the CONSORT diagram.

4.4 Withdrawal/loss to follow-up

The number (%) of individuals with missing data for the primary outcome (ambulatory activity) and all specified secondary outcomes at baseline, 12 and 48 months will be reported by randomised group.

4.5 Baseline characteristics

The following baseline characteristics will be summarised by randomised group, using mean and standard deviation (SD) for continuous variables with reasonably symmetric distributions, median and interquartile range (IQR) for continuous variables with skewed distributions, and number and percentage for binary or categorical variables.

- Age (yrs).
- Sex (men/women)
- Ethnicity (White European/South Asian/Other).
- Family history of diabetes in first degree relatives (yes/no).
- CVD (MI, heart failure, angina, stroke).
- Medication type (antihypertensive, lipid lowering, steroid, metformin).
- Social deprivation (IMD score).
- Smoking status (current, past, never).
- Employment type (FT employment, PT employment, unemployed, retired, other).
- Education (highest qualification: none; GCSE or equivalent; A-level or equivalent; degree, higher degree or equivalent).
- Marital status (married/civil partner, other).
- Access to the internet (yes/no).
- Height (m).

Baseline values of outcome variables will be summarised alongside the results at 12 and 48 months, as described in section 5.2.2.

5 Analysis

5.1 Outcomes

5.1.1 Primary outcome

The primary outcome is change in ambulatory activity (steps/day) between baseline and 48 months, assessed by accelerometer (Actigraph GT3X+). Acceleration data are captured and stored at 100 Hz. Data processing will be undertaken on a commercially available analysis tool (KineSoft). Data will be integrated into 60 second epochs. At least 3 valid days of wear will be required, with a valid day defined as at least 10 hours of wear. Non-wear time will be determined by 1 hour or more of consecutive zero counts.

5.1.2 Secondary outcomes

Deviation from the published protocol

Secondary outcomes are consistent with those reported in the protocol paper (Yates et al. Trials 2015), with the exception of:

- The Neighbourhood Environment Walkability Survey (NEWS) questionnaire is not considered an outcome, as the intervention will not change the environment, and will not be reported as such.
- Health resources will not be reported in the main outcomes paper, but will be used in a separate health economics paper.
- Bio-impedance derived measures of body composition have been added to the anthropometric outcomes.
- The number reporting development of musculoskeletal injury that prevents physical activity from baseline to follow-up has been classified as a safety outcome (detailed below).

Reported secondary outcomes

Change in ambulatory activity (steps/day) between baseline and 12 months will be a secondary outcome.

Change in the following continuous variables between baseline and 12 months, and between baseline and 48 months, will be secondary outcomes:

Assessed by accelerometer:

- Number of censored steps/day (i.e. steps taken above an intensity used to distinguish between purposeful and incidental ambulation).
- Time spent sedentary (mins).
- Time spent in light physical activity (mins).
- Time spent in moderate-to-vigorous physical activity (mins).
- Compliance with recommendation to undertake at least 21.4 minutes/day (150 mins /week) of moderate-to-vigorous intensity physical activity in bouts of at least 10 minutes.
- Compliance with recommendation to undertake at least 21.4 minutes/day (150 mins/week) of moderate-to-vigorous intensity physical activity without bout restriction.

Assessed by activPAL3:

- Time spent sitting or lying down (mins).
- Time spent standing (mins).
- Time spent walking (mins).

Assessed by Recent Physical Activity Questionnaire (RPAQ):

- Overall physical activity expenditure (kJ/day).
- Time sedentary (mins), in light (mins), moderate-to-vigorous (mins) intensity physical activity.

Main biochemistry outcomes:

- HbA_{1c} (mmol/mol).
- HbA_{1c} (%).
- Total cholesterol (mmol/l).
- HDL cholesterol (mmol/l).
- LDL cholesterol (mmol/l).
- Triglycerides (mmol/l).
- Vitamin D (nmol/l).

Other biochemistry outcomes:

- Sodium (mmol/l).
- Potassium (mmol/l).
- Urea (mmol/l).
- Estimated glomerular filtration rate (eGFR; ml/min/1.73m^2).

- Total bilirubin (umol/l).
- Alkaline phosphatase (IU/l).
- Alanine transaminase (IU/l).
- GGT (IU/l).
- Urine albumin creatinine ratio (mg/mmol).

Cardiovascular risk:

- Modelled cardiovascular risk based on the Framingham risk equation (D'Agostino 2008) (%).

Anthropometry:

- Weight (kg).
- BMI (kg/m^2).
- Waist circumference (cm).
- Body fat percentage (%).
- Fat mass (kg).
- Fat free mass (kg).

Depression and anxiety:

- Depression score.
- Anxiety score.

Diet:

- Frequency (portions/week) of fresh fruit, green leafy vegetables, other vegetables, oily fish, other fish, chicken, meat, eggs, cheese, wholemeal/brown bread.
- Alcohol: Frequency (drinks/day).
- Number of days/week on which individual reported limiting total fat intake.
- Number of days/week on which individual reported limiting saturated fat intake.
- Number of days/week on which individual reported limiting sugar intake.
- Number of days/week on which individual reported limiting salt intake.

Sleep:

- Time spent asleep last night (hrs).
- Average sleep duration (hrs/night).

Health related quality of life:

- Summary mental and physical component scores from SF-8.
- Summary index from EQ-5D-5L.
- Self-related health based on the Visual Analogue Scale questionnaire.

Diabetes (yes/no) at 12 months and 48 months will be secondary outcomes.

5.1.3 Intermediate outcomes

Change in theoretical behavioural constructs hypothesised to be determinants of behaviour change will be considered "intermediate outcomes" and assessed between baseline and 12 months, and between baseline and 48 months. Intermediate outcomes are defined below.

Walking self-efficacy

- Confidence (0-100%) to walk for a short (10 minutes), moderate (30 minutes) and long (60 minutes) duration each day.

Illness perception

- Scores (0-10) for each item of the illness perception questionnaire:
  1. How much does your risk of diabetes affect your life?
  2. How long do you think your risk of diabetes will continue?

3. How much control do you feel you have over your risk of diabetes?
4. How much do you think treatment can help your risk of diabetes?
5. How much do you experience symptoms from your risk of diabetes?
6. How concerned are you about your risk of diabetes?
7. How well do you feel you understand your risk of diabetes?
8. How much does your risk of diabetes affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)

Self-regulation

- Categorical responses (most of the time, some of the time, rarely, never) for self-regulation items (assessed at 12 and 48 month follow-up only):
  1. Set yourself regular goals detailing the amount of exercise you would do each day.
  2. Regularly set yourself a plan detailing where, when and how you would exercise.
  3. Worn a pedometer.
  4. Kept an exercise log recording your activity levels.
  5. Been aware of your activity levels.
  6. Tried to exercise regularly.

5.2 Analysis methods

5.2.1 Deviations from the published protocol

A brief analysis plan was reported in the published protocol (Yates et al. Trials 2015). The analysis plan described below is intended to supersede the published protocol. In particular, a more comprehensive definition of those included in the per-protocol analysis has been provided, along with greater detail on the sub-group analysis, missing data and the reporting of diabetes incidence.

5.2.2 Analysis of continuous outcomes (primary and secondary)

The mean and SD of ambulatory activity will be calculated at baseline, 12 months and 48 months, by randomised group.

For the primary outcome, estimates, 97.5% confidence intervals and p-values for the comparison of each intervention group with the control group will be derived from a linear regression model with ambulatory activity at 48 months as the outcome, and including 2 indicator variables for randomised group (WA vs Control, WA+ vs Control), wear time at baseline, wear time at 48 months, number of valid days at baseline, number of valid days at 48 months, the 3 randomisation stratification variables (centre, ethnicity, sex), and ambulatory activity at baseline as covariates. By adjusting for baseline, this is an analysis of covariance (ANCOVA) model. Individuals with missing ambulatory activity data at baseline will be included in the analysis using the missing indicator method (White 2005). To account for potential clustering between individuals within the same household, robust standard errors will be calculated using the "cluster" option in Stata.

Secondary outcomes that are changes in continuous variables between baseline and either 12 or 48 months will be analysed using the same method, but without adjustment for wear time and number of valid days, except for outcomes based on accelerometer data. Distributions of each outcome variable (i.e. the change from baseline to either 12 or 48 months) will be inspected, and any outcomes whose distribution is skewed will either be log transformed prior to analysis, or an alternative generalised linear model (e.g. using a gamma distribution) may be considered.

5.2.3 Analysis of binary outcomes (secondary)

The odds of compliance with MVPA recommendations at 12 and 48 months will be analysed using logistic regression, including 2 indicator variables for randomised group (WA vs Control, WA+ vs Control), the 3 randomisation stratification variables (centre, ethnicity, sex), and compliance with MVPA recommendations at baseline as covariates, with robust standard errors calculated as described above.

The odds of diabetes at 12 and 48 months (HbA1c ≥ 6.5% [48 mmol/mol] or doctor diagnosed) will be analysed using logistic regression, including 2 indicator variables for randomised group (WA vs Control, WA+ vs Control) and the 3 randomisation stratification variables (centre, ethnicity, sex) as covariates, with robust standard errors calculated as described above. Those diagnosed with diabetes, but with an HbA1c value subsequently recorded in the non-diabetes range will still be classified as having diabetes.

A cross-tabulation of diabetes status at baseline (normal glycemia, prediabetes, diabetes) and at 12 and 48 months will be presented separately by randomised group.

5.2.4 Analysis of intermediate outcomes

For the walking self-efficacy and illness perception outcomes, the mean and SD will be calculated at baseline, 12 months and 48 months, by randomised group.

For the self-regulation outcomes, the number (%) of individuals within each category (most of the time, some of the time, rarely, never) will be presented at 12 months and 48 months, by randomised group.

No statistical comparisons between randomised groups will be performed for these outcomes.

5.2.5 Missing data

All continuous outcomes: missing baseline values

For continuous outcomes, participants with a missing baseline value of the variable, but with a value at the relevant follow-up time (12 or 48 months), will be included in the analysis using the missing indicator method, which is a valid method for pre-randomisation measures in trials (White 2005), ensuring that no further participants are excluded while maintaining the advantage of improved precision. In the analysis of accelerometer outcomes, the method will also be used for wear time and number of valid days, which are part of the outcome definition.

All continuous outcomes: missing follow-up data

For all outcomes, participants with missing data at the relevant follow-up time (12 or 48 months) will be excluded from the analysis. This "complete-case analysis" is valid under the assumption that the outcome is missing at random (MAR), conditional on randomised group, baseline value and other covariates in the model.

Key characteristics of participants at baseline (age, sex, ethnicity, family history of diabetes, HbA1c, BMI, smoking status, IMD score) will be summarised in those with and without data for ambulatory activity at 48 months.

Primary outcome: further analyses

A secondary analysis of the primary outcome, also assuming that the data are MAR, will be performed using multiple imputation by chained equations, with 10 imputed datasets. The imputation model will include all the covariates and outcome from the analysis model, as well as age, family history of diabetes, HbA1c, BMI, smoking status and IMD score.

If ambulatory activity data at 48 months are missing for more than 5% of participants, a further sensitivity analysis on the primary outcome will be performed to investigate the potential impact of plausible departures from MAR on the estimated intervention effect. The approach described in White 2012 will be used, which is based on jointly modelling the data and the missingness using a pattern mixture model. A parameter δ is defined which represents the difference between the mean of the observed outcome and the mean of the unobserved values. Under the MAR assumption, $\delta=0$. The impact on the intervention effect of varying δ in one or both of the treatment groups will be displayed graphically.

5.2.6 Subgroup analyses for primary outcome

For the primary outcome only, interactions between randomised group and (1) sex (men/women), (2) age (<60 years/≥60 years), (3) ethnicity (White European/South Asian/Other), (4) family history of T2D (yes/no), (5) prediabetes at baseline (yes/no), (6) baseline obesity status (<30kg/m^2 [27.5 kg/m^2 for South Asians], ≥30kg/m^2 [27.5 kg/m^2 for South Asians]), and (7) baseline deprivation (split at median IMD score into high vs low) will be tested by including the relevant interaction parameters in the analysis model and performing an F-test of the null hypothesis that these parameters are 0 (i.e. no interaction).

If the p-value for any of the interactions tested above is <0.05, then estimates and 97.5% confidence intervals of the 2 intervention effects (WA vs Control, WA+ vs Control) on the primary outcome will be reported within the relevant subgroups, based on fitting the linear regression model described in section 5.2.1 within each subgroup. For example, if the p-value for the randomised group x sex interaction is <0.05, then the primary outcome results will be presented separately within men and women.

If the p-value for the randomised group x ethnicity interaction is <0.05, then the secondary outcomes described in section 5.1 will also be analysed separately within each ethnic group.

5.2.7 Other analyses

For the primary outcome only, if the p-value for either of the 2 intervention effects is <0.025, the effect of WA+ vs WA and 97.5% confidence interval will also be estimated using the same linear regression model described in section 5.2.2.

5.2.8 Multiplicity

Since there are 2 primary comparisons, 97.5% (rather than 95%) confidence intervals will be reported.

No formal corrections will be made to account for the large number of secondary outcomes and comparisons that will be presented. However, p-values for secondary outcomes will not be reported, and interpretation of the effects and confidence intervals will be made with caution, recognising the potential for chance findings among the multiplicity of outcomes and comparisons.

5.3 Safety data

The number (%) of individuals experiencing either an adverse event or a serious adverse event will be summarised by randomised group.

The number (%) of individuals reporting development of musculoskeletal injury that prevents physical activity between baseline and 48 months will be summarised by randomised group.

5.4 Statistical software

Analyses will be performed using Stata version 15.1 (StataCorp 2017).

6 References

Yates T et al. PRomotion Of Physical activity through structured Education with differing Levels of ongoing Support for people at high risk of type 2 diabetes (PROPELS): study protocol for a randomized controlled trial. Trials. 2015;16:289.

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