e-coachER - A multicentre randomised controlled trial of an augmented exercise referral scheme using web-based behavioural support in individuals with metabolic, musculo-skeletal and mental health conditions

Statistical Analysis Plan v2.3 27 September 2018

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1. Introduction

This statistical plan sets out the methods to be used to analyse the primary and secondary outcome and economic data from the e-coachER trial. This plan is based on the updated study protocol (v6.1 20.11.2017).

Analyses are in accord with ICH-9 statistical guidelines for clinical trials, updated CONSORT reporting guidelines for non-drug trials (Boutron et al., 2008; Schulz et al., 2010; ICH, 1998).

Research questions & hypotheses

The overarching research question is whether, for individuals with obesity, hypertension, type 2 diabetes, osteoarthritis or history of depression, the addition of web-based support (e-coachER) to a usual Exercise Referral Scheme (ERS) ('intervention') can increase physical activity at twelve months, compared with ERS alone ('control'), and whether such an intervention is cost-effective?

It is hypothesised that the additional support provided by e-coachER will improve the level of access to initial ERS support, improve the level of motivational support, and improve adherence to the ERS over a longer period of time than usual ERS, and thereby result in improved levels of sustained physical activity (PA).

Economic and process evaluations will be undertaken to investigate costs/cost-effectiveness and mediation (mechanisms/intervention fidelity etc). These analyses will be specified elsewhere.

2. Description of variables

2.1 Outcomes

Primary outcome:

Total weekly minutes of MVPA in ≥10 minute bouts, recorded objectively by accelerometer, over one week at twelve months. To be included participants need to provide activity recorded on at least 4 days, including a weekend day, for at least 16 hours per day.

Secondary outcomes:

- Average minutes of MVPA, measured by accelerometer, over one week at 4 and 12 months post-randomisation.
- Achievement of at least 150 minutes of MVPA, measured objectively by accelerometer, over one week at 12 and four months.
- Self-reported achievement of at least 150 mins of MVPA over one week using the Seven Day Physical Activity Recall Questionnaire at four and twelve months.
- Self-reported health-related quality of life, assessed by the EuroQol-5 dimension–5 level (EQ-5D-5L) at four and twelve months.
- Self-reported symptoms of anxiety and depression, assessed by the Hospital Anxiety and Depression Scale (HADS) at four and twelve months.
- Average daily hours/minutes of sedentary behaviour (objectively measured by accelerometer) at baseline, four and twelve months.
- Average daily hours/minutes of sleep (objectively measured by accelerometer) at baseline, four and twelve months.
- Uptake of the ERS according to the attendance records held by the ERS service provider, with imputed patient-reported attendance at 4 weeks and/or 4 months where the ERS service data are missing
- Adherence to the ERS using a composite measure to describe the proportion in each arm of the trial who achieved the primary outcome at four months and were still doing so at twelve months.

2.2 Baseline characteristics

The following participant demographic data will be collected at baseline: geographical location, age, gender, clinical condition (type 2 diabetes; lower limb osteoarthritis; obesity; recent history of depression; hypertension), BMI, blood pressure, ethnic group, relationship status, domestic residents status, smoking

status, employment status, education status, GP Physical Activity Questionnaire score, internet use capability, and requirement for translator for trial purposes.

3. Follow up & participant flow

All outcomes will be assessed at 4 and 12-months post randomisation. Patient numbers and progression through the key stages of the trial i.e. screened, recruited, randomised, attrition and completed outcomes will be summarised in detail according to CONSORT flow diagram (Boutron et al., 2008).

4. Statistical analysis

Following data lock by PenCTU, the analyses following will be undertaken by the statistician blinded to group (randomised groups will be coded 'A' or 'B'). Following the blinded presentation of the trial results to the TMG and agreed interpretation of the results, the groups will be unblinded.

4.1 Descriptive analyses

A summary of baseline characteristics and baseline outcome values in intervention and control groups will be undertaken and between group equivalence assessed descriptively. Since differences between randomised groups at baseline could have occurred by chance, no formal significance testing will be conducted. Any notable baseline differences between groups will be discussed with the TMG and consideration as to whether these factors are likely to be predictive of outcomes and whether this factor(s) should be included in the inferential analysis models.

4.2 Interim analysis

No interim inferential analysis is planned and an inferential analysis of 4-month outcome data will not be undertaken in advance of 12-month analyses.

4.3 Inferential analyses

Inferential analyses will focus on the between group comparison of intervention vs. control.

Definition of comparison groups

Intention to treat (ITT) complete case: groups according to original randomised allocation in participants with complete data at follow up.

Intention to treat (ITT) imputed: groups according to original randomised allocation in all participants.

Per protocol (CACE): include all ITT complete case participants with a coded variable indicating whether participants have completed Step 5 'Making your activity plans' or not. In Step 5, users make their SMART activity plan, and then review their step goal and SMART activity goal.

Primary analysis

The primary analysis using linear model (continuous outcomes – using STATA 'regress') or logistic model (binary outcomes – using STATA 'logistic' command) will compare primary and secondary outcomes between groups in according to the principle of intention to treat (i.e. according to original randomised

allocation) in participants with complete outcomes at twelve months adjusting for baseline outcome values and stratification (site: (1=South West; 2=Birmingham; 3=Glasgow) and minimisation variables (patient's perception of main medical referral reason: 1=control diabetes; 2=weight loss; 3=lower blood pressure; 4=manage lower limb osteoarthritis symptoms; 5=manage mood/depression; and IT literacy level: 1=lower confidence; 2=higher confidence). Given age and gender are known to be predictive of physical activity, these baseline characteristic will also added to the adjusted model.

Secondary analysis

Secondary analyses will be undertaken to compare groups at follow up across all follow up points (i.e. four and twelve months) using a mixed model repeated measures approach (using STATA 'xtmixed' command). In addition we will seek to undertake secondary per protocol (as defined above) analysis using a complier average casual effect (CACE) approach (using STATA 'ivregress' command) to examine the impact of adherence to the e-coacher intervention on primary and secondary outcomes at 12-months.

4.4 Subgroup analyses

The primary analysis model will be extended to fit interaction terms to explore possible subgroup differences in intervention effect in stratification and minimisation variables for the primary outcome at 12-months. Given the relatively low power for testing interactions, these results should be considered exploratory only.

4.5 Handling of missing data

Data entry and cleaning will be conducted by PenCTU staff according to the e-coachER Data Management Work Instruction. For the purposes of this analysis plan, missingness is defined as those patients with the absence of data at follow up for one or more outcomes. Reasons for missingness (e.g., drop out, loss to follow up) will be recoded and a comparison made of baseline characteristics of completers and those to lost follow up. Missing data at 12-months follow-up for primary and secondary outcomes will be imputed regardless of the reason(s) they was missing. For participants with missing outcomes, we used the baseline outcomes and other explanatory covariates (e.g. treatment group, sex, age, ethnicity, region, and disease duration) to impute the missing data, assuming unobserved measurements were missing at random (using STATA 'ice' and 'mim' commands). Using the same primary analysis model as described above, between group outcomes will be compared in ITT complete case and imputed data sets for primary and secondary outcomes at 12-months.

4.5 Adverse events

Safety data and adverse events will be listed descriptively by group and include details of the event, and the likely relatedness to either treatment.

5. Data presentation

Results will be reported as between group mean differences with 95% confidence intervals; global P-values will also be provided with regard to categorical explanatory variables. . The threshold for determining significant effects will be $P<0.05$. No adjustment of P-values will be made to account for multiple testing, although the implications of multiple testing will be considered when evaluating the results of the analyses. Analysis of the primary outcome will be performed prior to all other analyses.

6. Model checking and validation

All analyses will be undertaken using STATA v14.2.

Checks will be undertaken to assess the robustness of models, including assessment of model residual normality and heteroscedasticity.

Rod Taylor, University of Exeter Medical School

7. References

Boutron I, Moher D, Altman D, Schulz K, Ravaud P, CONSORT Group. Extending the CONSORT statement to randomized trials of non-pharmacologic treatment: explanation and elaboration. *Ann Intern Med*. 2008;148;295-309.

ICH 1998, ICH Topic E 9: Statistical Principles for Clinical Trials, European Agency of Medicines, London, CPMP/ICH/363/96.

Schulz K, Altman D, Moher, D. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. *Annals Inter Med.* 2010;152:1-15.

8. Proposed results table templates

Table 1. Baseline demographic and health related characteristics for groups

	Group A	Group B
Gender - n male (%)		
Age - mean (SD) [range]		
BMI – mean (SD) [range]		
General Practice Physical Activity Questionnaire (GP PAQ) score – n (%)		
Clinical condition: Patient's perception of main medical referral reason (reason for referral ERS) - n (% of total)		
Patient's perception of main medical referral reason – prevalence (regardless of rank) – n (%)		
Ethnic group – n (%) -		
Relationship status – n (%) -		
Domestic residence status – n (%) -		
Education status – n (%) -		
Smoking status - n (%)		
IT literacy level – n (%) - Lower capability - Higher capability		
Requirement for translator for trial purposes – n (%)		

Table 2. Primary analysis for primary and secondary outcomes at 12-months – ITT complete case

	Baseline		**12-months follow-up**		**Between group Difference***
	Group A N Mean (SD) or n/N (%)	**Group B** N Mean (SD) or n/N (%)	**Group A** N Mean (SD) or n/N (%)	**Group B** N Mean (SD) or n/N (%)	Mean or Odds ratio (95% CI), P-value
Primary outcome					
Total weekly minutes of MVPA in >10 minute bouts					
Secondary outcomes					
Average minutes of MVPA					
Achievement of at least 150 minutes of MVPA					
Etc.(see section 2.1)					

*All analyses adjusted for stratification and minimisation variables (and any other baseline characteristics as appropriate).

Table 2. Secondary analysis for primary and secondary outcomes at 12-months – ITT imputed

	Baseline		**12-months follow-up**		**Between group difference**
	Group A N Mean (SD) or n/N (%)	**Group B** N Mean (SD) or n/N (%)	**Group A** N Mean (SD) or n/N (%)	**Group B** N Mean (SD) or n/N (%)	Mean or Odds ratio (95% CI), P-value
Primary outcome					
Total weekly minutes of MVPA in >10 minute bouts					
Secondary outcomes					
Average minutes of MVPA					
Achievement of at least 150 minutes of MVPA					
Etc.(see section 2.1)					

*All analyses adjusted for stratification and minimisation variables (and any other baseline characteristics as appropriate).

Table 3. Repeated measures analysis of primary and secondary outcomes at 4 and 12-months – ITT complete case

	Baseline		**4-months follow up**		**12-months follow up**		**Between group difference**
	Group A N Mean (SD) or n/N (%)	**Group B** N Mean (SD) or n/N (%)	**Group A** N Mean (SD) or n/N (%)	**Group B** N Mean (SD) or n/N (%)	**Group A** N Mean (SD) or n/N (%)	**Group B** N Mean (SD) or n/N (%)	Global P-value**
Primary outcome							
Total weekly minutes of MVPA in >10 minute bouts							
Secondary outcomes							
Average minutes of MVPA							
Achievement of at least 150 minutes of MVPA							
Etc. (see section 2.1)							

*Global P-value for between comparison group comparison across both 4 and 12-month follow up adjusted for stratification and minimisation variables (and any other baseline characteristics as appropriate).

Table 4. Secondary analysis - CACE analysis of primary and secondary outcomes at 12-months – ITT complete case

	Between group Difference*
	Mean or Odds ratio (95% CI), P-value
Total weekly minutes of MVPA in >10 minute bouts	
Average minutes of MVPA	
Achievement of at least 150 minutes of MVPA	
Etc. (see section 2.1)	

*CACE analyses adjusted for stratification and minimisation variables (and any other baseline characteristics as appropriate).

Table 5. Secondary analysis - subgroup analyses on primary outcome at 12-months – ITT complete case

	Mean difference (95% CI)*	**Interaction P-value**
Trial site South West Birmingham Glasgow		
Patient's perception of main medical referral reason Control diabetes Weight loss Lower blood pressure Manage lower limb osteoarthritis symptoms Manage mood/depression;		
IT literacy level Lower confidence Higher confidence		

*From primary analysis model adjusted for stratification and minimisation variables (and any other baseline characteristics as appropriate).

Amendment History

SAP version	Date	Revisions
Draft version 0.1	13 SEP 2015	N/A
1	16 JAN 2017	Per protocol population defined.
2	09 APR 2017	Text added to Statistical Analysis section (introductory paragraph): 'Following data lock by PenCTU, the analyses following will be undertaken by the statistician blinded to group (randomised groups will be coded 'A' or 'B'). Following the blinded presentation of the trial results to the TMG and agreed interpretation of the results, the groups will be unblinded.' Text added to Descriptive Analysis section: 'Any notable baseline differences between groups will be discussed with the TMG and consideration as to whether these factors are likely to predictive of outcomes and whether this factor(s) should be included in the inferential analysis models.' Intention to treat (ITT) imputed defined as: 'groups according to original randomised allocation in all participants.' In the Primary Analysis section, text added to clarify that stratification will be conducted by site, and minimisation by clinical condition & IT literacy level. Handling of missing outcomes further defined: ..use of baseline outcomes and other explanatory covariates (e.g. treatment group, sex, age, ethnicity, region, and disease duration) to impute the missing data. Data Presentation developed to: 'Results will be reported as between group mean differences with 95% confidence intervals; global P-values will also be provided with regard to categorical explanatory variables. . The threshold for determining significant effects will be $P<0.05$. No adjustment of P-values will be made to account for multiple testing, although the implications of multiple testing will be considered when evaluating the results of the analyses. Analysis of the primary outcome will be performed prior to all other analyses.'

		STATA v14.2 to be used (was v13 in previuos version). Illustrative tables included.
2.1	10 MAR 2018	Definition of primary outcome revised: 'Total weekly minutes of MVPA in ≥10 minute bouts, recorded objectively by accelerometer, over one week at twelve months. To be included participants need to provide activity recorded on at least 4 days, including a weekend day, for at least 16 hours per day.' *Was:* Total weekly minutes of MVPA in >10 minute bouts, recorded objectively by accelerometer, over one week at twelve months. Illustrative tables refined.
2.2	21 MAY 2018	Reference made to updated study protocol version number and date. The secondary outcome, 'average daily hours/mins of sleep' separated out from 'average daily minutes of sedentary behaviour' (both variables were expressed within one bullet point in the previous version).
2.3	27 SEP 2018	Convention for assessing ERS uptake fully described, i.e. 'Uptake of the ERS according to the attendance records held by the ERS service provider, with imputed patient-reported attendance at 4 weeks and/or 4 months where the ERS service data are missing.' SF12v2 removed; it transpired that the data collection form used in the trial was produced and distributed with errors in the response options for 2 SF12 items, rendering the data un-useable in the current format.