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

STUDY PROTOCOL

Version 3.0_20th November 2015

Chief Investigator:	Prof Adrian Taylor Professor of Health Services Research, University of Plymouth
Study Sponsor:	University of Plymouth
IRAS reference**:**	170179
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Funder's number:	13/25/20 (NIHR HTA)

This protocol has regard for the HRA guidance

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: ..... Date: ...../……../.....

Name (please print): .....

Position: .....

Chief Investigator:

Signature: ..... Date: ……/……./.....

Name: (please print): .....

Statistician:

Signature: ..... Date: ……/……/.....

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KEY STUDY CONTACTS

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STUDY SUMMARY

Study title	A multicentre RCT of an augmented exercise referral scheme (ERS) using web-based behavioural support in individuals with metabolic, musculo-skeletal and mental health conditions.
Short title	e-coachER – adding web-based support to an exercise referral scheme.
Trial design	Multi-centre, individually randomised, two arm trial with internal pilot.
Trial participants	Inactive individuals aged 16-74 years with obesity, hypertension, type 2 diabetes, osteoarthritis, or a history of depression, for whom NICE recommends exercise.
Planned sample size	Internal pilot trial – 180 participants. Full trial – 1400 participants inclusive of 180 from pilot (700 per trial arm).
Planned study period	37 months (set-up 6 months, pilot recruitment 3 months, main recruitment 12 months, follow-up twelve months, data cleaning, analysis & reporting 4 months).
Grant start date	01 January 2015
Study aim	To determine whether the addition of a web-based support package (e-coachER) to usual ERS (intervention arm) increases the proportion of people achieving 150 minutes of MVPA physical activity at twelve months, compared with ERS alone (control arm), and whether such an intervention is cost-effective?
Primary outcome measure	Achievement of at least 150 minutes of moderate to vigorous intensity physical activity (MVPA), measured objectively by accelerometer, over one week at twelve months.
Secondary outcome measures	• Average minutes of moderate to vigorous physical activity, 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 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) and 12-Item Short Form Health Survey version 2 (SF12v2) 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 sleep and sedentary behaviour (objectively measured by accelerometer) at baseline, four and twelve months. • Uptake of the ERS by participant self-report at approximately four weeks and four months. • 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. • Monetary costs of intervention development including the 'welcome pack', with a view to costing the (potential) roll-out of the intervention to a wider population. • Self-reported monetary costs of the use of the ERS, and (for the treatment arm) the use of the web-based support package, at four and twelve months. • Mediation measures analysis (i.e. self-reported perceptions of physical activity confidence, importance, autonomy and relatedness, and use of self-monitoring and goal setting). • Moderation analysis, i.e. subgroup analyses for participant characteristics and ERS. • Incremental cost per quality-adjusted life year (QALY) at twelve months. • Measures of engagement with e-coachER, and its content, and use of self-monitoring and goal setting functions, captured on the software platform (LifeGuide). • Qualitative interviews with intervention arm participants focusing on their experiences with ERS and the additional e-coachER intervention.

STUDY SPONSOR AND FUNDER

The study sponsor is University of Plymouth. Selected sponsorship tasks will be delegated to the Plymouth University Peninsula Schools of Medicine and Dentistry (PUPSMD) under the terms of an appropriate service level agreement.

The study is funded by a grant of £1,372,155.80 from the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme. The grant reference number is 13/25/20. The grant will be held by the University of Plymouth.

ROLES AND RESPONSIBILITIES OF TRIAL OVERSIGHT COMMITTEES

Trial Management Group

A Trial Management Group (TMG) including the Chief Investigator, study statistician, trial manager, health economist, lead for process evaluation, lead for intervention development, and other relevant personnel as required (e.g. data manager, patient representatives, Principal Investigators) will meet regularly. The TMG (and other small working groups such as outcomes group, process evaluation group, recruitment group, intervention development and review group, PPI group) will meet approximately every four weeks in person or by teleconference throughout the set-up and internal pilot of the study to review progress, resolve day-to-day problems and monitor participant recruitment ahead of progression to the full trial. Thereafter the TMG will continue to meet regularly to review and respond to emerging issues, as well as to monitor follow-up, oversee budgetary issues, prepare draft reports, discuss analysis and results, and ultimately the final report. The TMG will report to the Project Management Group.

Project Management Group

A Project Management Group including the Chief Investigator, Principal Investigators, co-applicants, Clinical Trials Unit (CTU) trial manager, ERS managers and PPI representative will meet quarterly, usually by teleconference, to provide wider multi-disciplinary input and oversight for the study. Interim communication/discussions will be by telephone or email, as required.

Trial Steering Committee

A Trial Steering Committee (TSC) including an independent chair, independent clinicians and/or academics with relevant expertise, independent statistician/methodologist with relevant expertise and a representative contributing a patient/public perspective will oversee the conduct of the trial. The TSC will meet in person or by teleconference before the start of the internal pilot study, before the start of the main trial and at least annually thereafter (shortly after a Data Monitoring Committee Meeting), to review study progress and protocol adherence, ensure that milestones are achieved and that general scientific probity is maintained. There is the option of the TSC meeting more regularly should either the TSC or research study team think it is necessary. The TSC will function in accordance with agreed terms of reference set out in a TSC Charter.

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will monitor the safety and ethics of the trial by overseeing recruitment, primary outcome data completeness and adverse event (hospitalisation) data. In addition, the DMC will review data from the internal pilot study to help inform a decision about progression to the main trial. Operating procedures for the DMC will be agreed before the start of the study and incorporated into a DMC charter, updated from time to time as required. The committee will meet once before the start of the internal pilot trial and approximately annually thereafter, by teleconference or face-to-face.

Trial Steering Committee nominations

Nominated Members			
Name	**Affiliation**	**Expertise/role**	**Email**
Dr Sharon Simpson (Chair)	Glasgow University	Senior Research Fellow (MRC/CSO Social and Public Health Sciences Unit)	Sharon.Simpson@glasgow.ac.uk
Dr Mark Kelson	Cardiff University	Research Fellow in Statistics, South East Wales Trials Unit	KelsonMJ@cardiff.ac.uk
Prof John Powell	Oxford University	Academic public health physician & health services researcher (interest in e-health) expertise	john.powell@phc.ox.ac.uk
Dr Charlie Foster	Oxford University	Nuffield Dept of Population Health; DH policy advisor on physical activity & sport	charlie.foster@dph.ox.ac.uk
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Member			
Prof Adrian Taylor (CI)	University of Plymouth	Professor of Health Services Research	Adrian.Taylor@plymouth.ac.uk

Observers			
Name	**Affiliation**	**Expertise/role**	**Email**
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Mrs Pam Baxter	University of Plymouth	Sponsor representative	pam.baxter@plymouth.ac.uk

Data Monitoring Committee Nominations

Name	Affiliation	Expertise/role	Email
Prof Paul Aveyard	University of Oxford	Professor of Behavioural Medicine, Department of Primary Care Health Services	paul.aveyard@phc.ox.ac.uk
Dr Anne Haase	University of Bristol	Senior Lecturer in Exercise, Nutrition, and Health, School of Policy Studies	Anne.Haase@bristol.ac.uk
Prof Richard Morris	University of Bristol	Professor in Medical Statistics, School of Social and Community Medicine	Richard.morris@bristol.ac.uk

LIST of CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
ERS	Exercise referral scheme
EQ-5D-5L	EuroQol -5 dimension – 5 level
GCP	Good Clinical Practice
GPPAQ	GP Physical Activity Questionnnaire
HADS	Hospital Anxiety and Depression Scale
ICF	Informed Consent Form
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MVPA	Moderate to vigorous physical activity
NHS R&D	National Health Service Research & Development
OA	Osteoarthritis
PA	Physical Activity
PI	Principal Investigator
PCRN	Primary Care Research Network
PIS	Participant Information Sheet
PMG	Project Management Group
PPI	Patient and Public Involvement
QALY	Quality Adjusted Life Year
RA	Research Assistant
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SF12v2	12-Item Short Form Health Survey version 2
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File

PARTICIPANT PATHWAY

KEY

White boxes: activity at all sites

Orange boxes: activity at South West and Birmingham sites

Green boxes: activity at Glasgow site.

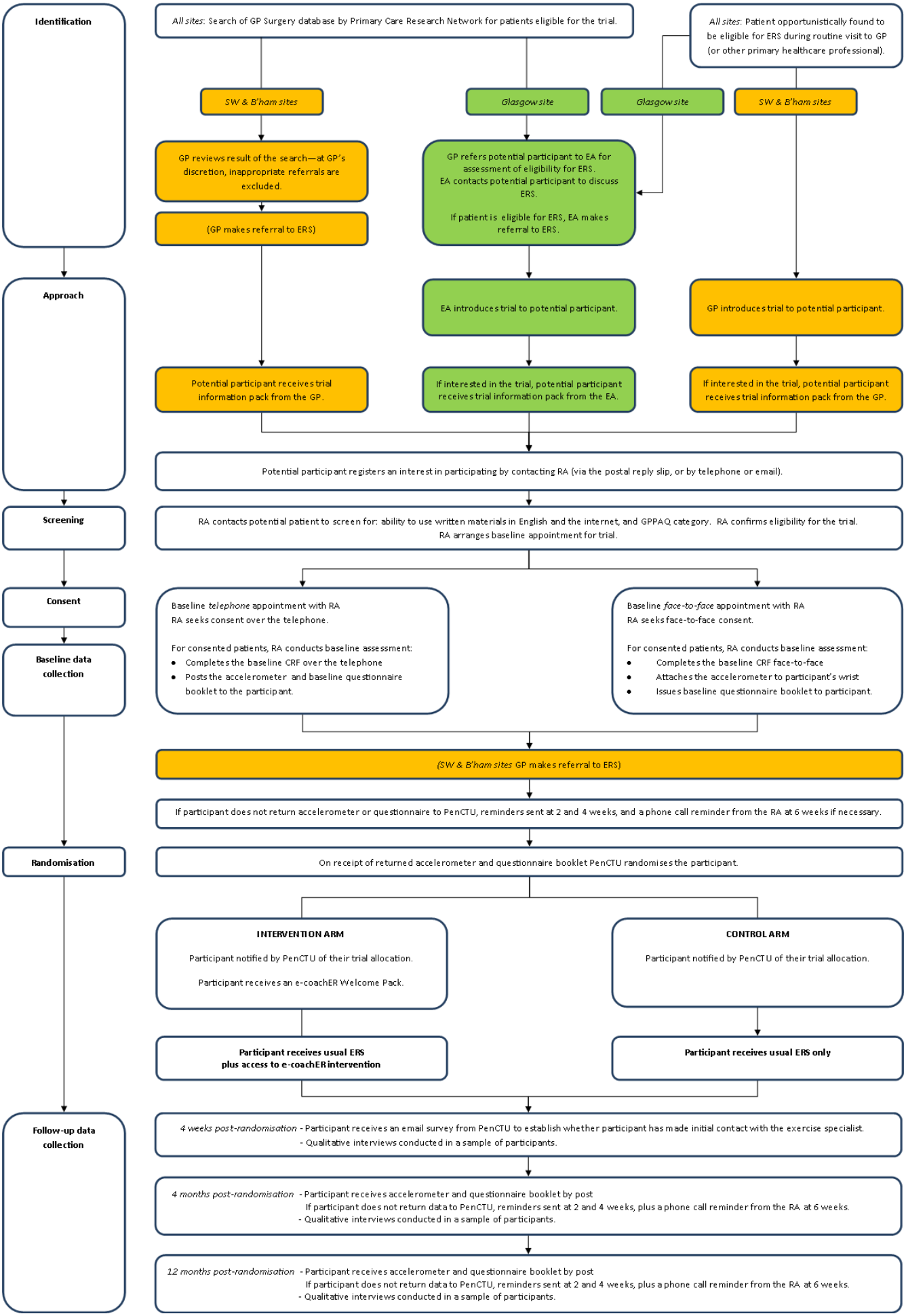
ERS: exercise referral scheme.

EA: Exercise advisor

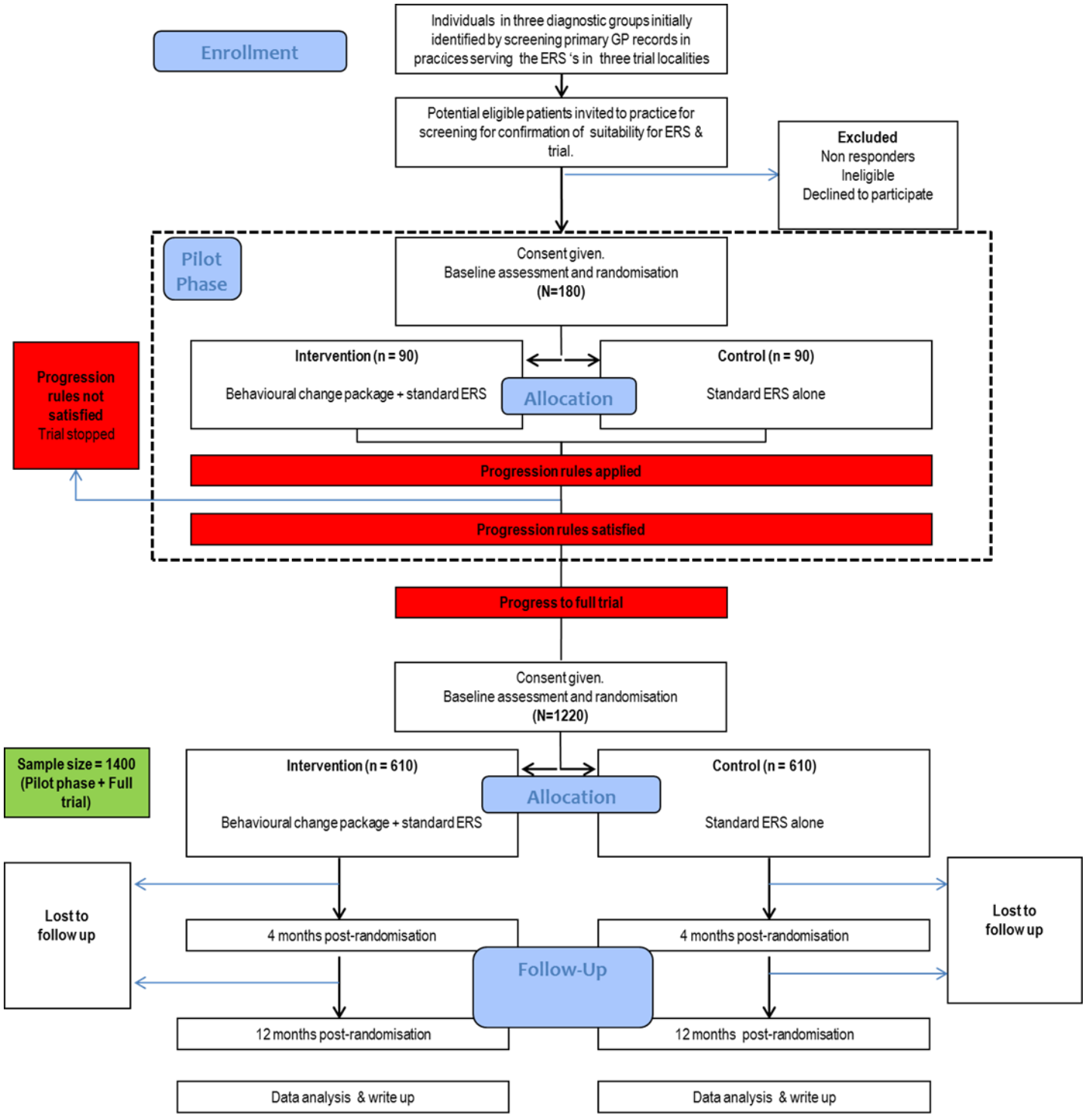
RA: Research Assistant

PenCTU: Peninsula Clinical Trials Unit.

Referral to the ERS may occur at different points, and this is indicated by parentheses.


Identification
Approach
Screening
Consent
Baseline data collection
Randomisation
Follow-up data collection
All sites: Search of GP Surgery database by Primary Care Research Network for patients eligible for the trial.
All sites: Patient opportunistically found to be eligible for ERS during routine visit to GP (or other primary healthcare professional).
SW & B'ham sites
Glasgow site
Glasgow site
SW & B'ham sites
GP reviews result of the search—at GP's discretion, inappropriate referrals are excluded.
(GP makes referral to ERS)
GP refers potential participant to EA for assessment of eligibility for ERS.
EA contacts potential participant to discuss ERS.
If patient is eligible for ERS, EA makes referral to ERS.
EA introduces trial to potential participant.
GP introduces trial to potential participant.
Potential participant receives trial information pack from the GP.
If interested in the trial, potential participant receives trial information pack from the EA.
If interested in the trial, potential participant receives trial information pack from the GP.
Potential participant registers an interest in participating by contacting RA (via the postal reply slip, or by telephone or email).
RA contacts potential patient to screen for: ability to use written materials in English and the internet, and GPPAQ category. RA confirms eligibility for the trial.
RA arranges baseline appointment for trial.
Baseline telephone appointment with RA
RA seeks consent over the telephone.
For consented patients, RA conducts baseline assessment:
Completes the baseline CRF over the telephone
Posts the accelerometer and baseline questionnaire booklet to the participant.
Baseline face-to-face appointment with RA
RA seeks face-to-face consent.
For consented patients, RA conducts baseline assessment:
Completes the baseline CRF face-to-face
Attaches the accelerometer to participant's wrist
Issues baseline questionnaire booklet to participant.
(SW & B'ham sites GP makes referral to ERS)
If participant does not return accelerometer or questionnaire to PenCTU, reminders sent at 2 and 4 weeks, and a phone call reminder from the RA at 6 weeks if necessary.
On receipt of returned accelerometer and questionnaire booklet PenCTU randomises the participant.
INTERVENTION ARM
Participant notified by PenCTU of their trial allocation.
Participant receives an e-coachER Welcome Pack.
CONTROL ARM
Participant notified by PenCTU of their trial allocation.
Participant receives usual ERS plus access to e-coachER intervention
Participant receives usual ERS only
4 weeks post-randomisation - Participant receives an email survey from PenCTU to establish whether participant has made initial contact with the exercise specialist.
- Qualitative interviews conducted in a sample of participants.
4 months post-randomisation - Participant receives accelerometer and questionnaire booklet by post
If participant does not return data to PenCTU, reminders sent at 2 and 4 weeks, plus a phone call reminder from the RA at 6 weeks.
- Qualitative interviews conducted in a sample of participants.
12 months post-randomisation - Participant receives accelerometer and questionnaire booklet by post
If participant does not return data to PenCTU, reminders sent at 2 and 4 weeks, plus a phone call reminder from the RA at 6 weeks.
- Qualitative interviews conducted in a sample of participants.

STUDY FLOW CHART



STUDY PROTOCOL

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

KEY WORDS

Randomised controlled trial; exercise referral scheme, web-based behavioural support.

1 BACKGROUND & RATIONALE

Metabolic, musculo-skeletal and mental health conditions place a major and increasing burden on health care resources, workplace sickness and absenteeism, as well as on individuals. Health problems associated with being overweight or obese, for example, cost the NHS more than £5 billion every year. There may be an increase from 2.6 million to > 4 million people with diabetes in the UK by 2025 as a result of more routine health checks. Hypertension and diabetes significantly contribute to premature mortality and morbidity related to cardiovascular disease, stroke and other serious illness.

Over one million adults each year consult their general practitioner with osteoarthritis and related conditions and this is expected to rise with increasing obesity. Depression is one of the most common reasons for consulting a general practitioner within the UK, and the associated economic burden is considerable and expected to worsen. Low mood and depression are common co-morbidities with metabolic and musculo-skeletal conditions.

The role of exercise

Across the UK the associated costs of inactivity are estimated at £1billion - £1.8billion (DH, 2011). Evidence-based guidelines (e.g. DH, 2011) recommend both aerobic and resistance exercise training for improving health markers and quality of life among those with common chronic metabolic conditions (i.e. obesity – NICE, 2010; hypertension – NICE, 2011; type 2 diabetes - NICE, 2008a) and musculo-skeletal conditions (e.g. osteoarthritis– NICE, 2008b), and mostly aerobic exercise for preventing and reducing depression (NICE, 2009). Significant health benefits and reduced health care costs could be gained with even a 10% increase in the proportion of the population, especially those with medical conditions, achieving the public health guidelines of at least 150 minutes of moderate to vigorous physical activity (MVPA) per week (DH, 2011).

The challenge of increasing physical activity

Patients with obesity, hypertension, type 2 diabetes, osteoarthritis and depression are less physically active than the general population (DH, 2011), and need greater support to overcome real and perceived barriers to increase physical activity (PA). Increases in PA amongst the least active have the potential to provide the largest impact on health but any benefits dissipate without maintained exercise (Dunstan, 2005). Since lower adherence, and lower exercise training volume and intensity, reduces health benefits, the challenge is to find appropriate ways to support sustained increases in aerobic and resistance exercise for those with or at risk of a medical condition.

A variety of initiatives have been explored to promote PA within primary care, including referring patients to ‘exercise on prescription’, i.e. exercise referral scheme (ERS). In the UK, ERS has been one of the most widespread approaches to promoting PA, with an estimated 600 schemes (involving up to 100,000 patients per year) linked to over 90% of primary care organisations (BHF, 2010).

Effectiveness of ERS

Evidence from a meta-analysis of robust trials on the effectiveness and cost-effectiveness of ERS (Pavey et al, 2011a) indicates a small increase in the proportion of participants who achieved 90-150 minutes of PA of at least moderate intensity per week, compared to control at 6-twelve month follow-

up among at risk individuals. But uncertainty remains in the effects for patients with specific medical conditions since no study assessed long-term PA objectively.

Factors influencing effectiveness

In a systematic review (Pavey et al, 2012) pooled ERS uptake (attendance at the first exercise referral session) ranged from 66% in observational studies to 81% in randomised controlled trials, and adherence from 49% in observational studies to 43% in randomised controlled trials.

Predictors of uptake and adherence have rarely been explored but Pavey and colleagues (2012) reported that whilst women were more likely to begin an ERS, they were less likely to adhere to it than men, and also older people were more likely to begin and adhere to an ERS. ERS may help patients become familiar with concepts such as exercise type, intensity, frequency and duration of exercise, matched to their medical condition, and target key processes of behaviour change. However, the following features of an ERS may reduce uptake and adherence (BHF, 2010): inconvenience, cost, limited sustainable PA support (e.g. for 10 weeks), and low appeal for structured exercise and/or the medical model, i.e. 'exercise on prescription', which does little to provide autonomous support nor empower patients to develop self-determined behaviour to manage chronic medical conditions (Rouse et al, 2011).

<u>Development of the trial intervention (e-coachER)</u>

The LifeGuide platform has been extensively used to develop and evaluate acceptability and impact of behaviour change and self-management interventions with a variety of clinical groups, including in primary care (Lloyd et al, 2013; Williams, 2013; Yardley, 2010; 2011). It provides a researcher-led tool to develop interventions drawn from theory and evidence of effective techniques (Greaves 2011; Michie et al, 2009).

The proposed research therefore seeks to examine if web-based support using the LifeGuide platform (www.lifeguideonline.org/), to be referred to in this study as e-coachER, can be coherently combined with usual ERS to provide an effective and cost-effective approach to producing a sustained increase in PA. Both technologies involve relatively low cost (Anokye et al, 2011; Benaissa, 2012), and the proposed intervention has the potential to be rolled out across the UK. The UK prevalence of patients with obesity, hypertension, type 2 diabetes, OA and risk of depression is high and patients with these conditions are routinely referred to ERS (BHF, 2010). Should the approach prove to be effective there is considerable potential for patients with other chronic medical conditions (e.g. low back pain, heart disease), to be referred for exercise in more specialist services with e-coachER support.

A review of web-based public health interventions concluded that adding some human contact results in better long-term outcomes in mood (Newman et al, 2011). LifeGuide-based interventions combined with some human support have provided effective support for patients to self-manage various health behaviours over an extended period, including weight management, and will be used for the first time in this trial to support patients concurrently attending an ERS.

E-coachER was developed between July 2014 and January 2015, predominantly by researchers at the University of Southampton and Plymouth, and with input from PPI for beta testing and pre-piloting the intervention. A Welcome Pack is initially given to participants in the intervention arm, to include a User Guide, pedometer and fridge magnet with recording strips for monitoring daily physical activity steps and minutes of moderate intensity physical activity. Contact details are provided for support from a facilitator to assist with IT issues if required.

Once users have registered and logged on, e-coachER comprises seven short 'steps to health' which aim to increase uptake of the ERS support and the cognitive and behavioural skills to remain physically active. It is interactive in allowing users to record the amount of physical activity achieved, set and review weekly goals, and receive feedback. Throughout, there are short stories about how

others have used the support and overcome barriers. There are also links to carefully vetted websites (e.g. NHS, charities) on exercise and health, other local physical activity opportunities, and ways to use tracking software to monitor a range of health outcomes and behaviours.

Summary

For patients with chronic medical conditions, additional support from an exercise practitioner may be necessary to help them overcome initial and on-going barriers to maintaining a more physically active lifestyle, but it is unclear if current ERS schemes alone can provide this support. Traditional ERS may also create barriers for some patients but have the potential to provide valuable personal support and the opportunity to overcome barriers. We hypothesise 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 PA.

2 OBJECTIVES AND OUTCOME MEASURES

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 ERS (intervention) can increase the proportion of people achieving 150 minutes of MVPA physical activity at twelve months, compared with exercise referral scheme alone (control), and whether such an intervention is cost-effective?

2.1 Objectives

The objectives are as follows:

- To determine whether in the intervention participants compared to the controls, there is an increase in the in the proportion of participants who:
    - Take up the opportunity to attend an initial consultation with an exercise practitioner
    - Maintain objectively assessed physical activity at four and twelve months post-randomisation
    - Maintain self-reported physical activity at four and twelve months post-randomisation
    - Have improved health-related quality of life at four and twelve months post-randomisation
- To quantify the additional costs of delivering the intervention and determine the differences in health utilisation and costs between the intervention and control arms at twelve months post-randomisation.
- To assess the cost-effectiveness of the intervention compared with control at twelve months post randomisation (incremental cost per QALY) and over the lifetime perspective (incremental cost per QALY) using a previously developed decision model to estimate future costs and benefits.
- To quantitatively and qualitatively explore whether the impact of the intervention is moderated by medical condition, age, gender and socioeconomic status, or ERS characteristics, IT literacy.
- To quantitatively and qualitatively explore the mechanisms through which the intervention may impact on the outcomes, through rigorous process evaluation and mediation analyses.

All primary and secondary outcomes will be collected on both intervention and control arm participants unless otherwise indicated below.

2.2 Primary outcome

The primary outcome is the achievement of at least 150 minutes of MVPA, measured objectively by accelerometer, over one week at twelve months post-randomisation.

2.3 Secondary outcomes

Secondary outcomes are:

- Achievement of at least 150 minutes of MVPA, measured objectively by accelerometer, over one week at four months post-randomisation.
- Self-reported achievement of at least 150 minutes of MVPA over one week using the Seven Day Physical Activity Recall Questionnaire at four and twelve months post randomisation.
- Self-reported health-related quality of life, assessed by the EQ-5D-5L and SF12v2 at four and twelve months post randomisation.
- Self-reported symptoms of anxiety and depression, assessed by the Hospital Anxiety and Depression Scale (HADS) at four and twelve months post randomisation.
- Average daily hours/minutes of sleep and sedentary behaviour (objectively measured by accelerometer) over one week at four and twelve months post randomisation.
- Uptake of the ERS by participant self-report at approximately four weeks and four months post randomisation.
- Adherence to the ERS, using a composite measure to describe the proportion in each arm of the trial that achieved the primary outcome at four months and were still doing so at twelve months.
- Process measures, to be described and included in mediation analysis including 1-4 self-reported survey items for each of the following: self-efficacy/confidence to be physically active; importance of being physically active; relatedness (perceived frequency and availability of support); perceived autonomy/control over physically active choices; involvement in self-monitoring and planning PA.
- In the intervention group, measures of engagement with e-coachER, and its content, and use of self-monitoring and goal-setting functions, captured by the software platform (LifeGuide).
- Qualitative interviews with participants in the intervention arm, focusing on their experiences with ERS and the intervention. Also, interviews with eligible participants who decline to enter the study to assess acceptability of trial methods.

2.3.1 Economic outcomes

The costs associated with the following will be determined:

- Development of the intervention to include the 'Welcome Pack', with a view to costing the (potential) roll-out of the intervention to a wider population.
- Self-reported monetary costs of health service use, use of the ERS and use of the web-based support package, at four and twelve months.
- Costs of support (including training) provided by the e-coachER facilitator (RA) and LifeGuide technician.
- Health and personal social care use (self-reported at four and twelve months).
- Personal costs for participation in PA (including use of ERS) at four and twelve months.

The main outcome of the economic analysis will be the incremental cost per Quality-Adjusted Life-Year (QALY) at twelve months, based on EQ-5D-5L.

3 TRIAL DESIGN

The design is a multicentre, parallel group, randomised controlled trial. Patients will be individually randomised to receive usual ERS alone (control) or usual ERS plus access to a web-based support package (e-coachER), and motivational and technical support (intervention). The trial will have parallel economic and process evaluations and will be undertaken in three phases.

Phase 1 (set-up)

In the set-up phase the research team, and ERS associates will adapt and test e-coachER. The Welcome Pack and platform will be tested with ERS patients and final adaptations made in response to users' feedback.

Phase 2 (internal pilot)

180 patients will be recruited to the internal pilot to provide sufficient information to justify progression to a full trial.

Phase 3 (main trial)

A further 1220 patients will be recruited to the main trial to determine the effectiveness and cost-effectiveness of the addition of the intervention to ERS, relative to usual ERS alone.

4 STUDY SETTING

The study is a multicentre study with three participating sites – South West (Devon and Cornwall), Birmingham, and Glasgow, where exercise referral schemes currently exist. All participants will be referred by a GP or health professional working in primary care to a local exercise referral scheme in the community. Those participants randomised to receive the intervention will be given access to the e-coachER support package.

5 ELIGIBILITY CRITERIA

5.1 Inclusion criteria

Patients must satisfy the following criteria to be enrolled on the study:

- Aged 16-74 years
- Have one or more of the following:
  - Obesity (BMI30-40)
  - Diagnosis of hypertension
  - Type 2 diabetes
  - Prediabetes ('borderline diabetes')
  - Lower limb osteoarthritis
  - Recent history of treatment for depression (i.e. last two years) but may not be currently receiving treatment
- Categorised as 'Moderately Inactive' or 'Inactive' according to the physical activity index calculated from the GP Physical Activity Questionnaire.
- Be contactable by e-mail and have at least some experience of using the internet.

5.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from study participation:

- Unstable, severe and enduring mental health problem that may limit involvement in the trial.
- Being treated for an alcohol problem or drug addiction that may limit involvement in the trial.
- Inability to use written materials in English, unless they have access to a readily available designated friend or family member to translate.
- Does not meet the inclusion criteia for a referral to the ERS, e.g. has a medical condition that is contra-indicated for the ERS.

6 RECRUITMENT

Eligible participants will be patients with the chronic conditions of diabetes, prediabetes, obesity, hypertension, osteoarthritis or a history of depression who are suitable for referral to a local exercise referral scheme from a health professional working in primary care.

6.1 Patient identification and approach

Patients will be recruited in more than one way since the usual care pathway varies between sites and participating GP practices (Figure 1). At participating GP practices, patients being actively referred to an ERS or opportunistically found to be eligible for an ERS (e.g. during a routine NHS health check or visit to a surgery) may be identified by the GP/ practice research nurse / PCRN research associate / other health professional as being potentially eligible for the study. In addition, the GP database will be searched by practice staff or PCRN research associate, for patients who are potentially eligible for an ERS, and such patients invited for an appointment with the GP / practice research nurse / PCRN research associate/ Research Assistant to establish eligibility for ERS. Referral to the ERS will be made by a member of the primary care team.

At some sites, potential participants will also be identified by exercise advisors from patients referred by the GP for assessment of suitability for the ERS.

6.2 Approach/invitation to participate

Depending on the identification route and local care pathway, a member of the GP practice team or the exercise advisor will provide potential participants with a trial Information Pack (by post or by hand). Alternatively, potential participants may be given a summary study information sheet containing contact details for the local RA who will send an Information Pack directly to the patient once contact has been made by the patient.

The Information Pack comprises an outer envelope displaying brief information about the trial containing an invitation letter, Participant Information Sheet and reply slip. Patients will be asked to indicate on the reply slip if they are interested in participating in the trial, and to return the reply slip to the local RA in the Freepost envelope provided. Patients may also contact the relevant site research team via a dedicated answer phone at each site or by e-mail.

In addition, interested patients will be asked by the exercise advisor if they are willing for their contact details to be passed on by the ERS service to the local RA, and if so, the local RA will make contact with the patient as described in Section 6.3.

6.3 Screening and consent

On receipt of a completed reply slip (or equivalent expression of interest), a member of the local research team will contact the potential participant to outline the study, answer any queries and establish eligibility for the trial.

If the patient is interested in taking part in the trial and appears eligible, the research team member will offer to arrange a face-to face meeting with the patient to complete the consent process, provide the wrist-worn GENEActiv accelerometer and baseline questionnaire. Alternatively, the consent process can be completed during this same telephone call and the researcher can post the accelerometer and baseline questionnaire to the patient.

6.3.1 Face to face consent process

The face-to-face screening/consent appointment will usually take place at the location of a primary healthcare provider (which will usually be the GP practice), or at the location of the ERS provider

(which is usually a leisure centre). Other locations may also be used to maximise convenience for participants and availability of quiet and secure office space, such as in pharmacies, and academic centres and at peoples' homes.

At this session, the research team member will describe the study, answer any questions the patient may have and check final eligibility for the ERS and trial, including the General Practice Physical Activity Questionnaire (GPPAQ). Patients who are willing and eligible to take part will be asked to complete, sign and date the study consent form, which will also be signed and dated by the person obtaining consent. A copy of the signed consent form will be given to the participant and the original signed form will be retained in the Investigator Site File.

6.3.2 Telephone consent process

If the patient is unable or unwilling to meet with the researcher in person, consent can be obtained via the telephone. Patients will be provided with the same information as in the face to face process (above) and given the opportunity to have any questions answered. Inclusion/exclusion criteria, including the GPPAQ, will be checked. If patients are willing and eligible to take part, the researcher will read out the separate elements of the consent form and get the patient's verbal assent for each one. The researcher should initial each box on the consent form to indicate that each clause has been read to and agreed by the patient. The researcher should sign and date the consent form. A copy of the researcher-only signed consent form will be sent to the participant and the original researcher-only signed form will be retained in the Investigator Site File. Given the nature of the study, there is no requirement for participants to sign the consent form themselves in the case of telephone consent.

6.4 Planned recruitment rate

The recruitment target for the three month internal pilot* is 180 participants and for the main trial will be 1,220 participants, yielding a total of 1,400 participants in the full trial. The recruitment rate for the internal pilot is less than the main trial to account for a potential lag in recruitment at the outset as research teams at sites establish trial processes

* pilot phase extended to encompass 3 months' recruitment activity at eat least two sites (protocol substantial amendment number 02 dated 20.11.2015).

The following strategies to maximise recruitment will be used as necessary:

- Encourage practices to maintain or increase routine identification and referral of patients into local ERS's.
- Engage with GP practices and/or exercise advisors to identify eligible patients.
- Raise patient awareness of the study at GP practices (e.g. presentations, posters, website) to foster opportunistic interest.
- Site PI's and RAs to work closely with the local Research Network, to identify practices for recruitment in a timely manner.
- Utilise the site research assistant (RA) to maintain a proactive approach to recruitment and monitor ERS waiting times (referral throughput) to ensure the recruitment rate approximately matches the ERS capacity.

6.4.1 Addressing trial and intervention 'reach'

There is a risk of recruiting a higher proportion of patients who tend to be more physically active (and hence with less to gain from the intervention), and only those familiar with web-based and mobile technologies. In order to recruit less active patients and those with only limited familiarity with internet and mobile technologies the following approaches have been and will continue to be used:

- Conduct focus groups and individual interviews with patients and practitioners with relevant experience to determine how best to describe the study and intervention in recruitment and intervention (e.g. Welcome Pack) materials.
- Work with local authority and third sector organisations to identify local opportunities to ensure that appropriate IT support can be described in trial materials and provided to participants receiving e-coachER.
- Identify specific roles for the e-coachER RA to support patients' use of the technology.
- Continue to monitor local and academic reports on optimising the use of e-coachER for those with low IT use (e.g. older people, disadvantaged populations).

7 BASELINE DATA COLLECTION

Baseline data collection includes demographic data, a simple IT literacy question the baseline questionnaire booklet and baseline accelerometry data. Demographic data will be collected by direct questioning at the time of consent and recorded in the case report form (CRF).

Participants attending a face to face screening/consent visit will complete the baseline questionnaire booklet at this visit, following consent. Each participant will also be provided with a GENEActiv accelerometer. The researcher conducting the face-to-face screening appointment will attach the accelerometer to the participant's non-dominant wrist. The participant will be asked to wear the accelerometer for the next seven days and to return it to the Peninsula CTU after that time, in the pre-paid envelope supplied. The researcher will send the complete baseline questionnaire booklet to the CTU.

For participants consenting to the study by telephone, the local researcher will post a copy of the researcher-signed consent form, baseline questionnaire booklet, accelerometer, instructions for use and a pre-paid return envelope to the participant following verbal consent. The completed questionnaire booklet and used accelerometer will be returned directly to the CTU by the participant.

The CTU will send a standard letter to participants three days after the accelerometer has been administered by post, as a prompt to the participant to begin wearing the accelerometer, if not already doing so.

The CTU will send up to two reminder letters (at 2 and 4 weeks) and/or make two telephone calls) to participants to prompt the return of both accelerometers and baseline questionnaire booklets. If the participant has not returned the accelerometer after 6 weeks the local Research Assistant will remind the participant via the telephone. Participants who return the accelerometer to the CTU will receive a high street/online store voucher of £20 as a 'thank you' payment.

8 RANDOMISATION

Following receipt of the baseline survey and accelerometer, randomisation will be carried out by the PenCTU. Randomisation will be conducted by means of a secure, password protected web-based system created and managed by the CTU in conjunction with the trial statistician. Participants will be randomised to usual ERS or usual ERS plus access to e-coachER in a 1:1 ratio, stratified by site (1=SW; 2=Birmingham; 3=Glasgow) with minimisation by 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), IT literacy level (1=lower confidence; 2=higher confidence). To maintain concealment, the minimisation algorithm will retain a stochastic element.

CTU will inform the participant of the treatment allocation by standard letter. Participants allocated to the intervention arm will also be sent an e-coachER Welcome Pack (see section 7).

Blinding of trial participants is not possible, given the nature of the intervention. Given that the primary outcome is an objective measure of physical activity recorded by the wrist-worn accelerometer and the secondary outcomes will be assessed by participant questionnaire self-completion, the risk of assessor bias is likely to be negligible in this study. However, to minimise any potential bias, the statistical analysis will be kept blinded and the code for group allocation not broken until the primary and secondary analyses have been completed.

9 TRIAL INTERVENTION

The e-coachER intervention is an engaging support package to help people on an ERS to become and remain more physically active. The intervention consists of an interactive website plus a pedometer and a fridge magnet with paper strips for recording the number of daily activity steps and minutes of moderate intensity physical activity. Without engagement, the intervention can have no additional benefit. The first point of contact with the intervention is therefore a user-friendly Welcome Pack. Figure 2 shows the version to be given out at face-to-face opportunities; a non-boxed version will be used for mailing to participants.

The Welcome Pack contains a User Guide with a unique User ID to enable participants to register and log into the e-coachER website easily. It also includes a good quality pedometer and the fridge magnet with attached record sheets. Contact details for further IT support are also provided. The User Guide shows screenshots of pages in the e-coachER website, including the seven 'Steps to Health'.

Figure 2: The Welcome Pack

E-coachER aims to increase uptake of support offered by exercise practitioners at the ERS, but also provides a stand-alone interactive website to facilitate skill development to remain physically active.

The support provided by the e-coachER website is autonomous in that participants set their own (hopefully progressive) targets and choose their preferred types of activities. Appendix 1 shows each element of the e-coachER support package, the objective of each element, the behaviour change technique used to achieve each objective, and the strategy for implementing each behaviour change technique. The Research Assistant at each site will provide general and local motivational IT support and the LifeGuide technician will support minor operational issues across all sites.

10 TRIAL ACTIVITIES AND FOLLOW-UP

The study schedule is given in Table 1.

10.1 Exercise Referral Scheme

Participants will attend the ERS according to local standard care, typically after completion of baseline assessments and randomisation to trial arm. Protocols for ERS's have been agreed at each site. These

vary from the more traditional approach with patients receiving supervised exercise sessions by a qualified exercise practitioner 1-2 times per week to more office-based support and signposting to exercise in a variety of community settings.

10.2 Follow-up assessments

At four weeks post-randomisation, the CTU will email all participants a survey about ERS attendance. At four and twelve months post-randomisation, the CTU will post all participants an explanatory cover letter, an accelerometer (with an instruction sheet), self-completion questionnaire booklet, and a pre-paid envelope for return of the accelerometer and questionnaire booklet.

The CTU will send a standard letter to participants three days after the accelerometer has been administered, as a prompt to the participant to begin wearing the accelerometer, if not already doing so.

The CTU will send up to two reminder letters to participants (supported by a telephone call or email as required) to prompt the return of both the accelerometer and questionnaire booklet. Participants who return the accelerometer to the CTU will receive a high street/online store voucher (£20 at four months and £20 at twelve months) as a 'thank you' for participating.

Table 1: Study schedule

Measure	Baseline	4 weeks	4 months	12 months
(IT needs assessment at screening)				
Demographics	X			
Medical condition for referral	X			
Accelerometer (worn for 1 week) - minutes of MVPA, sleep, and light activity per week	X		X	X
Sessions held with exercise practitioner (retrospective self-report) as an indicator of ERS engagement			X	X
Self-reported physical activity (7 day PA questionnaire)	X		X	X
Health & social care resource use	X		X	X
EQ-5D-5L, SF12v2	X		X	X
HADS	X		X	X
Process outcomes e.g. confidence, importance	X		X	X
Qualitative interview (sample of participants)		X	X	X
Retrospective check of ERS attendance (by e-mail and questionnaire)		X	X	X

10.3 Qualitative assessments

Qualitative interviews will be conducted by a single e-coachER research assistant, as part of the process evaluation, based in Exeter. The main consent form for the study includes a statement that participants may be contacted for interview but that this part of the study is optional and participants do not have to agree to be interviewed. Upon contacting the participant by phone, the RA will explain the broad interview content, that the interview will be recorded, and processes to ensure the data remains confidential and anonymous during data analysis. Further verbal consent will be obtained, and a consent formed signed by the RA. Interviews will be conducted either face-to-face or over the

telephone. All interviews will be transcribed with any personal data or ways of identifying participants being removed. Transcriptions will be coded, thematic analysis performed to identify key findings. The focus of the interviews will be linked to the phase of the research.

10.3.1 Interviews in the pilot phase

During the internal pilot phase (months 1-3 of recruitment) the focus will be on feasibility and acceptability of the intervention and trial methods as follows:

(1) To inform our understanding of recruitment feasibility and acceptability, participants who are eligible but who decline to join the study will be asked to indicate by return of the reply slip if they are willing to be contacted to determine what influenced their decision not to join the study. Questions will broadly focus on the following: (a) understanding of what the study/intervention is about based on the Information Pack materials; (b) confidence (or lack of) in using the internet; (c) perceptions of available support to overcome IT issues; (d) beliefs about the value of a website in the context of ERS. We will seek to interview as many participants as possible at this stage.

(2) To inform our understanding of perceptions about engaging with the intervention, we will interview those who, within three weeks of being allocated to the on-line intervention group, (a) do not register on-line for e-coachER or (b) register but then never log in again; or (c) register and log in once, but don't get beyond Step 1 and/or 2 (i.e. do not get involved in any of the core behaviour change techniques, including self-monitoring and goal setting). Questions will broadly focus on perceptions of the Welcome Pack, the process of registering on-line and accessing e-coachER, and the initial content and support provided. We will seek to interview as many participants as possible at this stage.

10.3.2 Interviews in the full trial phase

During the full trial phase (months 4-15 of recruitment) the focus will be on interviewing participants who: (a) used e-coachER a few times then stopped, or never get beyond say Step 3 or 4; (b) got through all seven steps. We will select a random sample of about 40 participants but the precise number of interviews will be determined by data saturation and resources available.

The interview schedule will include questions about the value of the Welcome Pack and contents in helping to access e-coachER, the overall web-based support and each of the Steps to Health, in terms of functionality and utility to support behaviour change. Participants will be asked to identify if and how they thought e-coachER provided support in accessing an exercise practitioner within the ERS, and maintaining physical activity. Ideas for additions or revisions to e-coachER will be requested. Questions about support for behaviour change will also attempt to provide qualitative information about some of the processes within our logic model and to be assessed quantitatively within the four and twelve month assessments. For example, questions will focus on changes in perceived importance of physical activity, support used and received to increase physical activity, perceived changes in competence, and autonomy of decisions concerning physical activity.

10.3.3 Interviews with e-coachER facilitators

E-coachER facilitators at each site will record the type and amount of support requested at an individual level, and provided in field notes. Interviews with e-coachER facilitators during and at the end of the trial will be conducted to identify strengths and weaknesses of their supporting role.

10.4 Withdrawal criteria

A participant may, at any time, withdraw from the study without giving a reason and without it affecting his/her clinical care. Participants will be asked to give a reason for withdrawal from the study but do not have to provide one. Participants who wish to withdraw will be given the option to continue with partial follow-up, e.g. provide primary outcome data only, to minimise data loss. Participants who

withdraw from the study will not be replaced. The CTU data management team will ensure that participants who formally withdraw from the study are not contacted for any subsequent follow-up data collection (aside from any partial follow-up arrangements made with individual participants).Data collected prior to withdrawal will be included in the study analysis unless a participant specifically requests that their data are removed from the database.

10.5 End of trial

Participants will normally complete the study after returning the completed twelve month questionnaire booklet and used accelerometer. The trial itself will end on the date that the last participant completes the twelve month follow-up assessments.

11 SAFETY REPORTING

11.1 Definitions

Adverse event (AE)
Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs in study participants whether or not related to any research procedures or to the intervention.

Serious Adverse Event (SAE)
A serious adverse event in the context of this study is any untoward medical occurrence that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalisation
- Results in persistent or significant disability/incapacity

11.2 Reporting requirements for this study

The recording and reporting of non-serious AEs in this study is **not** required. Information about SAEs may be captured in a variety of ways (see below). SAE report forms will be returned to the CTU and entered into the study database. The CTU will prepare quarterly summaries of SAEs, listed by organ system where possible, for review by the DMC and Sponsor.

11.2.2 In-patient data from questionnaires at 4 and 12 months

The resource use questions in the self-completion study questionnaire booklets ask participants to record the number of in-patient episodes within a set recall period. At the four and twelve month time points, participants are asked to record if they have been hospitalised, the reason for any hospital admission during the past four and eight months respectively and whether they think that the hospitalisation was related to participation in this study. On receipt of a questionnaire indicating a past hospital admission, the CTU will liaise with the relevant local RA who will be responsible for ascertaining further details about the SAE from the participant and/or GP records as appropriate.

11.2.3 Notification of SAEs via GP

Once a patient is recruited to the study, the participant's GP will be notified by letter. The notification letter includes a request for the GP to contact the CTU in the event of the GP becoming aware of any SAE. On being informed of an SAE, the CTU will liaise with the relevant local RA who will be responsible for ascertaining further details about the SAE from the participant and/or GP records as appropriate.

11.2.4 Notification of SAEs from other sources

It is possible that the local research team or CTU may become aware of an SAE via patient or relative self-report or some other channel. In such cases, the local RA will be informed of the SAE in order to ascertain further details for reporting to the CTU.

12 STATISTICS AND DATA ANALYSIS

12.1 Sample size calculation

To detect a 10% difference between control and intervention (43% v. > 53%) of participants achieving the primary outcome at twelve months (Pavey et al, 2011a), assuming a loss to follow up of 10% (Murphy et al. 2012; Pavey et al, 2011a) and allowing for clustering by e-coach facilitator (ICC 0.006 estimated from Jolly et al, 2010), and an average cluster size of 25, we require 691 per group for 90% power at an alpha of 5%. For simplicity we round up to 700 per arm. This sample size would allow detection of continuous outcome effect size of 0.20 based on the same assumptions.

Our exploratory modelling indicates that a change of least 10% is required for the intervention to achieve an incremental cost effectiveness ratio of <£20,000/QALY. We would prefer to recruit an approximately equal proportion from each of the five medical conditions though there will be some patients with co-morbidities.

12.2 Statistical analysis

All analyses will be carried out using a detailed *a priori* statistical analysis plan that will be completed and agreed with the TMG and DMC prior to closure of the trial database and the commencement of any data analysis.

Analyses will be reported in full and in accord with CONSORT reporting guidelines (Schultz et al, 2010). Recruitment, intervention and control uptake, outcome completion rates and drop out will be reported (with 95% CIs) as a flow diagram and we will describe baseline participant characteristics in the two trial arms.

The primary analysis will compare the primary and secondary outcomes between intervention and control arms groups according to the principle of intention to treat (i.e. according to original randomised allocation) at twelve months adjusting for baseline outcome values and stratification and minimisation variables (recruitment site, postcode, age gender, and disease indication using logistic regression.

Secondary analyses will be undertaken to compare groups at follow up across all follow up points (i.e. four and twelve months) using a repeated measures approach. In addition we will seek to undertake secondary per protocol analyses to examine the impact of different levels of the adherence to the e-coachER intervention. Pre-defined definitions of per-protocol will be agreed by the TMG and included in the statistical analysis plan.

The primary analysis model will be extended to fit interaction terms to explore possible subgroup differences in intervention effect in stratification and minimisation variables and the pre-defined baseline characteristics. As not formally powered, these subgroup analyses will be regarded as exploratory and hypothesis-generating. Sensitivity analysis, making different assumptions about the imputation model used will be conducted for both primary and secondary analyses to assess the likely impact of missing data.

Contemporary mediational analysis methods (Emsley et al, 2010) will be used to explore the impact of process outcomes identified in the planned intervention components, including e-coachER engagement, use of behaviour change techniques, and motivation and processes of change (e. g., self-efficacy, autonomy, relatedness).

No interim analysis of primary or secondary outcomes is planned.

Models will be fitted using mixed effects regression models and undertaken in STATA v12.

12.3 Interim analysis and criteria for the premature termination of the trial

Progression from the internal pilot to the main trial will be dependent on recruitment rate and engagement with the intervention according to the following scenarios:

Criteria	**Scenario 3**	**Scenario 2**	**Scenario 1**
% of internal pilot sample size target (180 patients) recruited.	< 65%	65- 79%	≥ 80%
Intervention engagement (% who access e-coachER at least once)	< 65%	65-79%	≥ 80%
Proposed Action	No progression	Discuss with TSC and funder about progression and resources needed to achieve target.	Proceed to full trial.

Qualitative interviews with eligible non-participants, and participants not initially engaging with the intervention will be examined to inform the discussion about progression and ways to improve recruitment and engagement. See the section 8.3.

There is no set progression target for recruiting a fixed proportion of patients with each of the five conditions (e.g. 20% of each) since numbers will be small across the three sites after only three months. Progress towards achieving an approximately equal proportion of participants across the conditions will be reviewed regularly. Decisions about any action necessary to achieve these targets will be made in conjunction with the DMC, TSC and funder. No additional pre-specified interim analyses are planned, but will be conducted should this be requested by the DMC.

12.4 Economic evaluation

The economic analysis will include NHS, personal social services and patient perspective (NICE, 2012), with two approaches:

12.4.1 Within-trial-based analysis

Resource use data will be used to determine an incremental cost per Quality-Adjusted Life-Year (QALY: based on EQ-5D-5L). Resource use data will be collected via follow-up surveys at four and twelve months, and by e-mail to capture ERS uptake and engagement. Unit costs will be taken from the NHS reference costs (e.g. DH, 2012), standard unit costs (e.g. PSSRU, 2011), and published literature. QALYs will be estimated over the trial period for individual patients using an 'area under the curve' approach. It will also be possible to present the results in the form of a cost-consequence analysis (disaggregated costs next to the important outcomes). Descriptive analyses will show mean total costs and mean utilities by trial arm and differences between trial arms. Non-parametric bootstrapping will be used to estimate differences in mean costs, with 95% confidence intervals, and incremental cost-effectiveness ratios. Uncertainty will be represented in cost-effectiveness acceptability curves (CEACs) and incremental net benefits for the intervention arm versus control.

12.4.2 Beyond trial modelling

A Markov decision model will be used to examine the impact of PA on lifetime risk of developing a series of conditions which are known to be associated with being physically inactive and for which more robust quantifiable evidence is available (CHD, stroke and type II diabetes, potentially depression- with DH work underway) following extensive previous work (Anokye et al, 2011, Anokye et al, 2014). Costs and QALYs will be discounted at the NICE recommended rates of 1.5% p.a.

13 DATA HANDLING

13.1 Subject numbering

Each participant will be allocated a unique study number following receipt of the reply slip (or telephone call or email equivalent) indicating interest in the study, and completion of baseline assessments (including accelerometer), and will be identified in all study-related documentation by their study number and initials. A record of names, addresses, telephone numbers and email addresses linked to participants' study numbers will be stored securely on the study database for administrative purposes.

13.2 Data collection

Data will be recorded on study specific data collection forms (CRFs), usually by the Research Assistant. Participants will complete participant-reported outcome measures. Data will be collected on paper for both study arms, with additional data collected from the e-coachER intervention (via the LifeGuide software platform) for intervention participants. An e-mail will be sent to participants at 4 weeks with a request for information on the number of sessions held with an exercise professional as part of the ERS, will request a response to indicate ERS uptake. All persons authorised to collect and record study data at each site will be listed on the study site delegation logs, signed by the relevant PI.

13.3 Data handling and record keeping

Completed CRFs will be checked and signed at the research sites by the research assistant or another member of the research team before being sent to the Pen CTU. Original CRF pages and questionnaires will be posted to the CTU at agreed timepoints with copies of the CRF retained at the relevant study site. Forms will be tracked using a web-based study management system. All data will be double-entered by the CTU on to a password-protected database. Double-entered data will be compared for discrepancies using a stored procedure and discrepant data will be verified using the original paper data sheets. Incomplete, incoherent, unreadable or other problem data in the CRF pages will be queried by the CTU with study site staff during data entry to ensure a complete and valid dataset. Questionnaire data will not be queried with participants. The CTU may complete further validation of data items, perform logical data checks and raise further data queries after data collection has been completed. The final export of anonymous data will be transferred to statisticians for analysis after all data cleaning duties have been performed by the CTU, this will usually be via email or a removable storage device. Identifiable information will not be exported from the study database as part of the final export.

Accelerometers will be received by the PenCTU and data will be downloaded via GENEActiv software, and linked to participant ID numbers. Files will be checked before the accelerometers are recirculated. Files will be then further analysed with bespoke software to classify data into levels of physical activity intensity using accepted cut-points. Standard operating procedures will be applied to make adecision about dealing with missing data. Selected primary and secondary accelerometer derived outcomes will be merged into an individual participant data set, and securely stored as below.

13.4 Data confidentiality and security

The research team will ensure that participants' anonymity is maintained on all documents. Data will be collected and stored in accordance with the Data Protection Act, 1998.

Electronic study records will be stored in a SQL server database, stored on a restricted access, secure server maintained by Plymouth University. Data will be entered into the database via a bespoke web-based data entry system encrypted using SSL. Access to electronic data will be permission based, with access to identifiable information limited to those processing questionnaires and performing initial screening activities. Data entered onto the database will be backed up according to PenCTU SOPs.

Within the CTU, anonymised paper-based study data will be stored in locked filing cabinets within a locked office. Any paper-based participant related identifiable data will be stored separately from the study data. Copies of study data retained at study sites will be securely stored for the duration of the study prior to archiving.

13.5 Access to data

The CTU data team will have access to the full dataset, including identifiable data. Site based researchers will have access to the dataset for participants from their site, including identifiable information, to perform screening activities. Other members of the study team and the CTU will have restricted access to anonymised study data. Access will be granted to the Sponsor and host institution on request, to permit study-related monitoring, audits and inspections. Access to the database will be overseen by the CTU data manager and trial manager.

13.6 Archiving

Following completion of data analysis and submission of the end of study report, the Sponsor will be responsible for archiving the study data and essential documentation in a secure location for a period of five years after the end of the trial. No trial-related records should be destroyed unless or until the Sponsor gives authorisation to do so.

14 MONITORING, AUDIT & INSPECTION

A trial monitoring plan will be developed and agreed by the TMG based on a risk assessment. This will involve central data monitoring but may also include on-site monitoring by the CTU trial manager. The Principal Investigators will be required to permit the CTU trial manager or deputy to undertake such monitoring as required to ensure compliance with the approved trial protocol and applicable SOPs, providing direct access to source data and documents as requested.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Research Ethics Committee (REC) review & reports

The study will be undertaken subject to appropriate Research Ethics Committee (REC) approval and local NHS Research & Development approvals. The trial will be conducted in accordance with the protocol, the principles of the Declaration of Helsinki and ICH GCP. Any amendments of the protocol will be submitted to the Sponsor and REC for approval.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion and the amendment has been reviewed by relevant NHS R&D departments as required. All correspondence with the REC will be retained in the Trial Master File and Investigator Site Files. An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the original favourable opinion was given, and annually until the trial is declared ended. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

15.2 Protocol compliance

Protocol deviations will be monitored by the CTU and reported to the Chief Investigator and Sponsor as appropriate. Significant deviations from the protocol which frequently recur are not acceptable and may potentially be classified as a “serious breach”.

15.3 Notification of serious breaches of GCP and/or the protocol

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The Sponsor will be notified immediately of any case where the above definition applies during the trial period. The Sponsor is responsible for notifying the REC of a serious breach in any study within seven days of the matter coming to their attention.

15.4 Indemnity and insurance

The University of Plymouth (as research sponsor) and its research collaborators will be required under the terms of their collaboration agreement to maintain public liability, professional indemnity and employer's liability insurance (together with such other insurance as the sponsor may require from time to time) to cover liabilities arising from the study.

In addition, each party is required under their collaboration agreement to indemnify the other parties and their staff against all claims, proceedings, liabilities, losses and costs incurred by them as a result of or in connection with the indemnifying party’s negligent acts or omissions, negligent delivery of its work under the study, negligent performance or breach of its obligations under the agreement, wilful misconduct or breach of statutory duty (including liability for damage to property, injury or death caused by any such negligent act, omission or wilful misconduct).

All participants taking part in the exercise referral scheme will be covered in case of harm by the relevant exercise provider’s public liability, professional indemnity and premises insurance.

16 DISSEMINATION POLICY

We will use newsletters to maintain contact with participants throughout the trial. At the end of the trial, the study team will prepare a plain English summary of the main study results (comparing the two trial arms) which will be sent by e-mail or post to study participants. The research team will work with stakeholders at each site, and nationally, to help to interpret the results and the implications for policy and practice. Dissemination may involve presentation at meetings of relevant support groups or other lay audiences, as well as NHS strategy forum at local and national level.

There will be a standing item on the agenda for each Project Management Group meeting (quarterly) on the publication plan and establishing authorship rules. We shall aim to submit the trial Protocol for publication no later than the end of the 3 month internal pilot phase of the study. Reports will comply with current CONSORT guidelines for publishing randomised trials (http://www.consort-statement.org/) and TIDieR guidelines for intervention reporting (http://www.equator-network.org/reporting-guidelines/tidier/). The study results will be submitted for publication in relevant international, high impact, peer reviewed journals. Names of key collaborators and groups who have contributed to the trial will be clearly stated in all publications. The study findings will be presented at regional, national and international meetings as appropriate.

17 REFERENCES

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18. APPENDICES

18.1 Appendix 1: e-coachER indicative intervention framework

Sequential process	Performance objectives	Behaviour Change Techniques (Michie et al., 2013)	Implementation Strategy
Welcome Pack and pedometer (print) & User Guide. Introduction to web-based support for self-directed PA	To introduce the user to the philosophy of the website to become personal coach Build on personal support provided by ERS using web-based platform Support those who don't want to /can't engage with ERS personnel Support achievement of personal goals for PA to enhance health	*N/A*	Explain philosophy of using website to become own personal coach. Links provided to local services and other self-help resources to highlight patient autonomy and choice. Offers e-coachER facilitator to help with using technology. Provide link to IT support in Southampton.
Step 1 - Thinking about the benefits of physical activity	Elevate importance of physical activity	*82. Information about health consequences* *83. Information about emotional consequences*	Quiz to engage participants using positive framing. Provide evidence of multiple benefits of PA especially for relevant health condition(s). Elicit and address concerns about PA, describing support given as part of ERS and by website.
Step 2: Support to get active	To encourage user to access and create social support networks To encourage user to take advantage of exercise referral scheme	*1.Social support (practical)* *2.Social support (emotional)* *3.Social support (unspecified)*	Explain how to make the most out of the ERS support to learn how to become own personal trainer in future. Explain how user can create a personal 'PA challenge' and share it with family, friends, peers, and exercise and health professionals. The patient may be encouraged to tell others about how e-coach has been used to support behaviour change. Suggest ways of involving family or friends in longer-term support for continued PA. Link to online sources of local support (e.g., local walking or jogging group, or British Trust for Conservation Volunteers). How to use website to send personalised email/text reminders,

			motivational messages. Draw on positive normative beliefs; identify benefits of social interaction (companionship). Sharing personal PA challenge with others, involve friends and family, online local support links. Identify benefits of informational support (from ERS scheme) in addition to emotional support from family and friends)
Step 3: Counting your steps	To educate and support the user to monitor step counts using a pedometer over a week. Emphasise personal experimentation	*10. Self-monitoring of behaviour*	Provide guidance on how to count steps/use pedometer. Provide guidance on how steps can be implemented into lifestyle. Encourage self-monitoring using diary.
Step 4: Making your step plans	To set explicit step count goals for the following week	*66. Goal setting (behaviour)*	Give rationale and evidence for goal-setting for graded increase in PA. User sets specific, achievable goals for next week (e.g. sessions completed, step count using the supplied pedometers). Links provided to local services and other resources.
Step 5: Making your activity plans	To educate and support the user to identify behavioural goals (types of activities).	*68. Action planning*	User selects walking or 'other physical activities' (which includes options for facility-based activity with practitioner support within ERS). Present options for facility and lifestyle-based activity. Sets specific, achievable goals for next week with a particular focus on avoiding days with less activity by planning walking or other activities. Keeping a PA diary.
Weekly goal and PA review	To promote adherence and graded increase in PA by providing tailored feedback and advice based on self-reported goal progress.	*66. Goal setting behaviour* *68. Action planning,* *69. Review behaviour goals.*	User records extent to which goals achieved in previous week, gets progress graph and personalised feedback: Praise for any goal achievement, encouragement to set more challenging goal if not yet meeting

			target PA criteria. Encouragement where goals not attained, with links to webpages to assist with increasing motivation or confidence, selecting different activities or goals, making better plans, accessing support, overcoming setbacks (with links to relevant sessions below). Each session completed ends with new links to reputable information and resources (e.g. NHS Choices, condition-specific PA advice websites). Help user plan gradual increases in PA.
Step 6 – Finding ways to achieve your plans	To help the user harness their environment to provide support for PA Identifying personal motivations, building confidence.	*30. Restructuring the physical environment* *31. Restructuring the social environment* *32. Avoidance / reducing exposure to cues for behaviour*	Make plan to use environment to automatically support PA (with examples e.g. fitness equipment in living room, route to work/shops that involves more PA, committing self to specific routine). Advise user on how to use website to send personalised email/text reminders, motivational messages. Overcoming barriers in work, leisure, home and travel. Building self-efficacy. Using smart phone apps for mobile support (e.g. PowerTracker, MyFitnessPal) Invite user to identify personal motivations for becoming more active.
Motivational Messages (text or/and emails)	To provide reminders of users personal reasons (not necessarily health reasons) for becoming more active	*15. prompts/cues*	Invite user to write motivational message to be sent weekly or monthly detailing their own motivations for becoming more active
Step 7 – Dealing with setbacks	To provide strategies for overcoming relapse in levels of PA.	*5. Reduce negative emotions*	Identify possible causes of relapse (e.g., illness, holidays, change in work hours, new caring responsibilities) and plan ways to overcome barriers. Challenging catastrophic negative thoughts about lapses from intended PA. How to learn from a lapse and plan to avoid or overcome in future.

			Provide salient role models of people overcoming barriers to successfully engage with PA.