Feasibility study to assess the delivery of a novel isometric exercise intervention for people with Grade 1 hypertension in the NHS.

Statistical Analysis Plan

Including Health Economics Analysis

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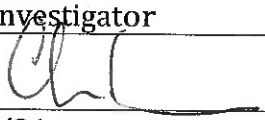
Signature	
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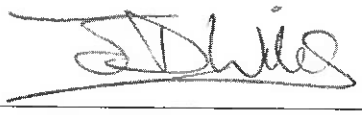
Signature	
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Contents

1. SAP revision history

Version updated	Updated version number	Summary of changes	Author of changes	Date
Pre-1.0	1.0	Authorisation by study CI and senior statistician.	Katie Saxby	15May2020
1.0	1.1	Addition of Health Economics analysis	Dr Katerina Gousia	18Nov2020
1.1	1.2	Update to incorporate: 1) changes following review by independent statistician 2) resolution of comments 3) consistency check against revised version of the study protocol	Tracy Pellatt-Higgins	21Apr2021

2. Introduction

2.1 Background and rationale

Standard treatment of hypertension includes recommending changes in lifestyle and/or medication. Many people fail to control their blood pressure (BP) within normal ranges because they do not adhere to medication or adopt the lifestyle recommendations, particularly that of at least 150-minutes a week of moderate intensity activity. As little as 8-minutes of isometric (static muscle activity) exercise 3x weekly has consistently reduced BP in those with suboptimal BP under laboratory and home-based conditions. This success is probably linked to the very short duration and accessibility of isometric exercise (IE). No studies have assessed the feasibility of prescribing IE using the validated wall squat protocol as an alternative treatment option for Grade 1 hypertension in an NHS setting.

2.2 Study objectives

To determine the feasibility of delivering an IE intervention to Grade 1 hypertensives in a primary care NHS setting.

Primary Objectives:

- To assess if nurses/allied health professionals (e.g. health trainer, healthcare assistants, physiotherapists) can deliver isometric exercise prescriptions for Stage 1 hypertensive patients in a primary care NHS setting.
- Estimate the variance in BP change from baseline

Secondary Objectives:

- Evidence the fidelity of the study intervention with respect to healthcare professional delivery and patient completion of IE
- Estimate short (4-week) and medium-term (3 and 6-month) adherence rates to IE intervention
- Estimate recruitment and attrition rates at recruiting GP sites to inform future trials.
- Explore the willingness of GPs, secondary care clinicians and healthcare professionals to consider IE as a treatment option for patients, including barriers and facilitators for delivering and integrating this within an NHS care pathway for hypertension.
- Establish the acceptability of resource use and utility measures, the cost of the IE intervention and the feasibility to conduct a full cost-utility evaluation of delivering this intervention in an NHS setting to assist with future health economic analyses.
- Understand participant experiences of undertaking IE, adherence to the programme and continuation.

3. Study methods

3.1 Study design

Parallel group trial comparing standard intervention (lifestyle advice only) with prescription of IE intervention (lifestyle advice plus 3 IE per week). Allocation ratio 1:1.

3.2 Randomisation

Random permuted blocks will be used within stratification by age (18-49, ≥50 years) and centre, ensuring that treatments are balanced at the end of every strata block.

3.3 Sample size

A sample size of 100 participants will be used. With attrition estimated to be 20%, and 6.5% incomplete data, completed measures at 4-weeks will be 74, 37 in each arm. This is in line with the recommended sample size of 70 to estimate key parameters from external pilot RCTs (1). A sample size of 74 produces a two-sided 95% confidence interval with a width of 1.33 mmHg when the standard deviation is 4. This estimate of 4 has been taken from a previous study (N=24) (2).The sample size confidence interval has been calculated using Pass11 software (PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

3.4 Framework

No hypothesis test intended as feasibility study.

3.5 Statistical interim analyses and stopping guidance

3.5.1 Interim analyses

No interim analysis required.

3.5.2 Early stopping guidelines

No early stopping guidelines required for feasibility study. Any significant adverse effects will be considered by the PI and may result in termination of the study.

3.6 Timing of final analysis

The proposed date of final analysis, assuming an extension is granted, is 31/01/2022

3.7 Timing of quantitative outcome assessments

BP data collected at:

Baseline (day 1)

4 weeks (30-33 days)

3 months (+/- 7 days)

6 months (+/- 7 days)

4. Statistical principles

4.1 Confidence intervals and p values

Difference in blood pressure from baseline between isometric exercise group and control group will be estimated with 80% and 95% confidence intervals.

No adjustment for multiple testing is required.

4.2 Adherence and protocol deviations

The number of IE sessions completed will be measured and recorded. Completion of at least 8 of 12 sessions between baseline and the 4-week timepoint will be deemed adherence to the intervention.

The percentage of completed IE sessions in week 1 that meet the required target HR threshold will be calculated.

The percentage of participants that deviate from the protocol will be calculated to assess the fidelity of the IE programme.

The rate of healthcare professionals that pass the competency assessment after the half-day training session will be calculated.

4.3 Analysis populations

Per protocol analysis will be carried out on complete cases and will be used for progression criteria. Intention to treat analysis will be carried out as a sensitivity analysis at 4-weeks, 3-months and 6-months, using last observation carry forward to estimate missing values for participants with data recorded post-baseline and baseline observation carried forward for participants with only baseline data.

5. Study population

5.1 Screening data

Blood pressure and heart rate

Current medications

Pregnancy test

5.2 Eligibility criteria

5.2.1 Inclusion criteria

- Aged 18 or over
- Clinic Systolic BP 140-159 mmHg
- Home blood pressure readings of systolic BP 140-159 mmHg during screening period
- Participants able to give informed consent

5.2.2 Exclusion criteria

- Currently taking anti-hypertensive medication
- White coat hypertension, as evidenced by averaged home systolic BP <135 mmHg
- Inability to undertake study intervention (isometric exercise)
- Previous history of any of the following:
    - Diabetes mellitus (type 1 or type 2)
    - Ischaemic heart disease (myocardial infarction and/or coronary angina and/or coronary revascularization procedure)
    - Moderate or severe stenotic or regurgitate heart valve disease
    - Atrial or ventricular arrhythmia
    - Stroke or transient Ischaemic Attack
    - Aortic aneurysm and/or peripheral arterial disease
    - Uncorrected congenital or inherited heart condition
- Estimated glomerular filtration rate <45 ml/min (calculated using CKD-EPI or MDRD formulae, and taking most recent documented results)
- Documented left ventricular ejection fraction <=45% and/or left ventricular hypertrophy (by either echocardiography or standard ECG criteria e.g. Sokolow-Lyon
- Documented urine albumin:creatinine ratio >3.5 mg/mmol
- Inability to provide informed consent
- If female, pregnancy or currently breast feeding
- Enrolled in another Clinical Trial of an Interventional Medicinal Product or Medical Device or other interventional study
- Medical condition that, in the opinion of the investigator, would make the participant unsuitable for the study

5.3 Recruitment

Approximately 2-6 primary care sites in South East England will be included in the study. Recruitment will be competitive across all sites until the total target of 100 patients has been met.

5.4 Withdrawal/follow up

Levels of withdrawal will be recorded at 4-weeks and also at follow-up times of 3-months and 6-months.

Within 7 days of intended visit.

The number and times of withdrawal will be recorded. Participants will be asked for a reason to help inform the feasibility of the study but are not obliged to provide this.

Other withdrawal criteria are as follows:

- Participant choice
- Randomisation error
- Health and safety criteria (e.g. change in medical circumstances)
- Trial discontinued prematurely, this may occur as a result of a systematic safety concern or following steering committee decision

5.5 Baseline participant characteristics

Age

Sex

Diastolic and systolic blood pressures

Heart rate (bpm)

Height (cm)

Weight (kg)

Arm diameter (cm)

Medical history

Medication

Diet questionnaire

Quality of Life (EQ-5D-5L)

Exercise level (GPPAQ)

6. Analysis

6.1 Outcome definitions

Primary outcomes:

Change from baseline in systolic blood pressure (mmHg) between groups at 4-weeks, 3-months and 6-months. Estimate the variance in BP change from baseline to inform future study.

To assess if nurses/allied health professionals (e.g. health trainer, healthcare assistants, physiotherapists) can deliver isometric exercise prescriptions for Stage 1 hypertensive patients in a primary care NHS setting. This will be measured by calculating:

- the proportion of healthcare professionals that pass the post-training competency assessment
- the heart rates recorded in participant study diaries during week 1

Secondary outcomes:

Fidelity of the study interventions with respect to the healthcare professional delivery and patient completion of IE will be assessed by checking that the heart rate is within 95% of peak heart rate confidence intervals in at least two-thirds of all training sessions.

Short-term fidelity: proportion of participants completing a minimum of 8 of 12 IE sessions up to 4-week point.

Long-term fidelity: proportion of participants completing a minimum of two-thirds of all IE sessions up to 3-month and 6-month point.

Recruitment rates: Average number of participants recruited per week.

Withdrawal rate: Number of withdrawals from study up to 4-weeks, 3-months and 6-months.

Change from baseline in diastolic blood pressure (mmHg) between groups at 4-weeks, 3-months and 6-months

IE experience questionnaire responses at week 4.

QALYs: Quality-adjusted life years calculated from patients' responses to the EQ-5D-5L questionnaire over a 4-week, 3-month and 6-month periods.

Healthcare resource utilisation: Number of GP visits, number of nurse visits, number of other health professionals visits, number of A&E attendances, number of inpatient hospital admissions, number of diagnostic tests at 4 weeks, 3 months and 6 months.

Intervention costs: Staff costs as measured by the time cost of the training team and healthcare professionals, supplies and equipment necessary to implement the intervention.

Medication: Frequency per week in days, dosage per day (mg/ml), start and end date per medication at 4 weeks, 3 months and 6 months.

6.2 Analysis methods

Analysis of covariance (ANCOVA) using a fixed treatment effect to compare change from baseline in systolic blood pressure (SBP) between IE and control groups. Adjustment will be made for baseline values, centre, sex and age (18-49, $\geq$50 years). If 6 or more centres participate in the study, centre will be included as a random effect. This model will be used to estimate differences between the treatment arms and confidence intervals from the feasibility study. 80% and 95% confidence intervals will be calculated.

Exercise adherence will be compared with outcomes to inform compliance criteria in the full study. Plots of number of IE sessions completed against change in SBP from baseline will be used to illustrate any correlation. An additional ANCOVA of SBP will be performed adjusting for the number of IE sessions completed.

It is assumed that the conditional distribution of the systolic blood pressure is normal for the IE and control groups and the residuals are mutually independent. The distribution of the SBP and diagnostic plots will be used to check normality for each group. Residuals will be plotted against SBP to check that there is no apparent trend. If the data is not found to be normally distributed, the data will be transformed prior to analysis or a non-parametric approach will be used.

Sensitivity analysis will be carried out to explore whether an increase or decrease from baseline in responses to the diet questions is associated with the change from baseline in SBP. A secondary

sensitivity analysis will explore whether an increase or decrease in the GPPAQ measure is associated with the change in SBP from baseline.

Outcomes, demographic and baseline data will summarised to compare treatment arms. Means and standard deviations will be calculated for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables and frequencies and percentages for categorical variables.

6.3 Missing data

Participants who dropout of the study will be grouped based on the time they were lost to follow-up or withdrew, and means/medians at baseline and each time (for each treatment arm and overall) will be examined to explore whether there are systematic differences between those who dropout at specific time points and those who remain in the study. It is expected that attrition will be low and interpretation with respect to the missing value mechanism will be limited due to the small numbers within each group.

In the secondary analysis of intention to treat, missing values will be estimated using a combination of last observation carry forward and baseline observation carry forward (where only baseline data are available), this method assumes individuals remain at the same level as their last measurement after they are lost to follow-up or leave the study (LOCF/BOCF).

6.4 Additional analyses

6.4.1 Health economics methods

The health profile established from EQ-5D-5L will be converted into a utility using the validated mapping function to derive utility values for EQ-5D-5L from the existing EQ-5D-3L. These utilities will be multiplied by the time spent in each state to generate QALYs. We will present summary statistics of the QALYS (Mean, Standard Deviation) and we will detail the number and percentage of questionnaires returned and the number and percentage of missing items within the returned questionnaires.

Data on health care utilisation and medication collected at 4 weeks, 3 months and 6 months after the intervention for both arms, will be converted into costs with the use of the relevant reference and unit costs from local or national databases (PSSRU, NHS Agenda for Change Pay scales, electronic market information tool (eMIT)). We will present summary statistics of the costs (Mean, Standard Deviation) and we will detail the number and percentage of questionnaires returned and the number and percentages of missing items within the returned questionnaires.

The cost of the intervention will be calculated as the sum of the staff, supplies and equipment costs necessary to implement the intervention in a primary care setting. Staff costs will be measured as the time cost of training and healthcare staff required for providing or receiving training for delivering the intervention in a primary care setting. Supplies will be measured by the number of supplies multiplied by the unit cost of supplies such as paper required as part of the training or delivery of the intervention. Equipment costs will be measured as the number of pieces of

equipment multiplied by the unit cost, such as specialised equipment for measuring the specific knee angle. The cost of Personal Protective Equipment (PPE) will be measured to provide an estimate of implementing the intervention under COVID19 restrictions.

We will conduct an exploratory cost-utility analysis over 6 months to test for the feasibility of full cost-utility analysis in the final trial. We will calculate the incremental cost per QALY gain for the patients in the treatment group compared to the cost per QALY gain for the patients in the control group by dividing the average difference in cost between two groups by the average difference in QALYs between those groups. We will present the Incremental Cost Effectiveness Ratio (ICER) to represent the additional cost per unit of outcome gained.

6.5 Harms

Rates and nature of any adverse effects or serious adverse effects will be described as set out in the trial protocol.

6.6 Statistical software

The quantitative analysis will be conducted using Stata/IC version 16.1.

7. References

1. Teare MD et al. Sample size requirements to estimate key design parameters from external pilot randomised controlled trials: a simulation study. Trials. 2014 Jul 3;15:264.

2. Taylor KA, et al. Neurohumoral and ambulatory haemodynamic adaptations following isometric exercise training in unmedicated hypertensive patients. J of Hypertens. 2018;