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

IsoFIT-BP

FEASIBILITY STUDY PROTOCOL

Version 4 - 30 Sept 2021

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ISRCTN #: 13472393

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 the UK policy for Health and Social Care Research (Oct 2017), the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as required.

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 trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

Chief Investigator:

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

Name: (please print):

.....

Co-Chief Investigator:

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

Name: (please print):

.....

KEY TRIAL CONTACTS

Role	Person and Contact details
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Sponsor Role: Organisation legally responsibility for the conduct of the study. Organisation holding study insurance and indemnity.	East Kent Hospitals University NHS Foundation Trust Caroline Cowley Interim Research and Innovation Manager
Funder(s) Role: Providing funds for delivery of the study	National Institute for Health Research, Research for Patient Benefit, ref NIHR200485
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PROJECT MANAGEMENT GROUP

Role: Oversight of delivery of the study according to this protocol, to provide advice to the Chief Investigators and ensure the protection of rights and safety of study participants.

Name	Study Role	Organisation
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Dr Jim Wiles	Chief Investigator	Canterbury Christ Church University
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Mrs Rachel Borthwick	Research Facilitator	University of Kent
Miss Ellie Santer	Project Research Fellow	Canterbury Christ Church University

STUDY STEERING COMMITTEE

Role: Oversight of delivery of the study on behalf of the funder to ensure achievement of study objectives within agreed timelines. To ensure the protection of rights and safety of study participants.

Name	Job title	Organisation
Dr Pauline Swift (Chair)	Consultant Nephrologist	
Prof Ian Maynard	Head of School and Professor within the School of Sport, Rehabilitation and Exercise Sciences	University of Essex
Dr Tim Doulton	Consultant Nephrologist	East Kent Hospitals University NHS Foundation Trust
Prof Heather Gage	Health Economist	
Kate Bennett Eastley	Statistician	
Ms Victoria Barnett	Public member	Public member
Dr Pieter Kat	Public member	Public member
Prof Chris Farmer	Chief Investigator	University of Kent
Dr Jim Wiles	Chief Investigator	Canterbury Christ Church University
Miss Ellie Santer	Project Research Fellow (secretariat)	Canterbury Christ Church University

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ii. LIST OF ABBREVIATIONS

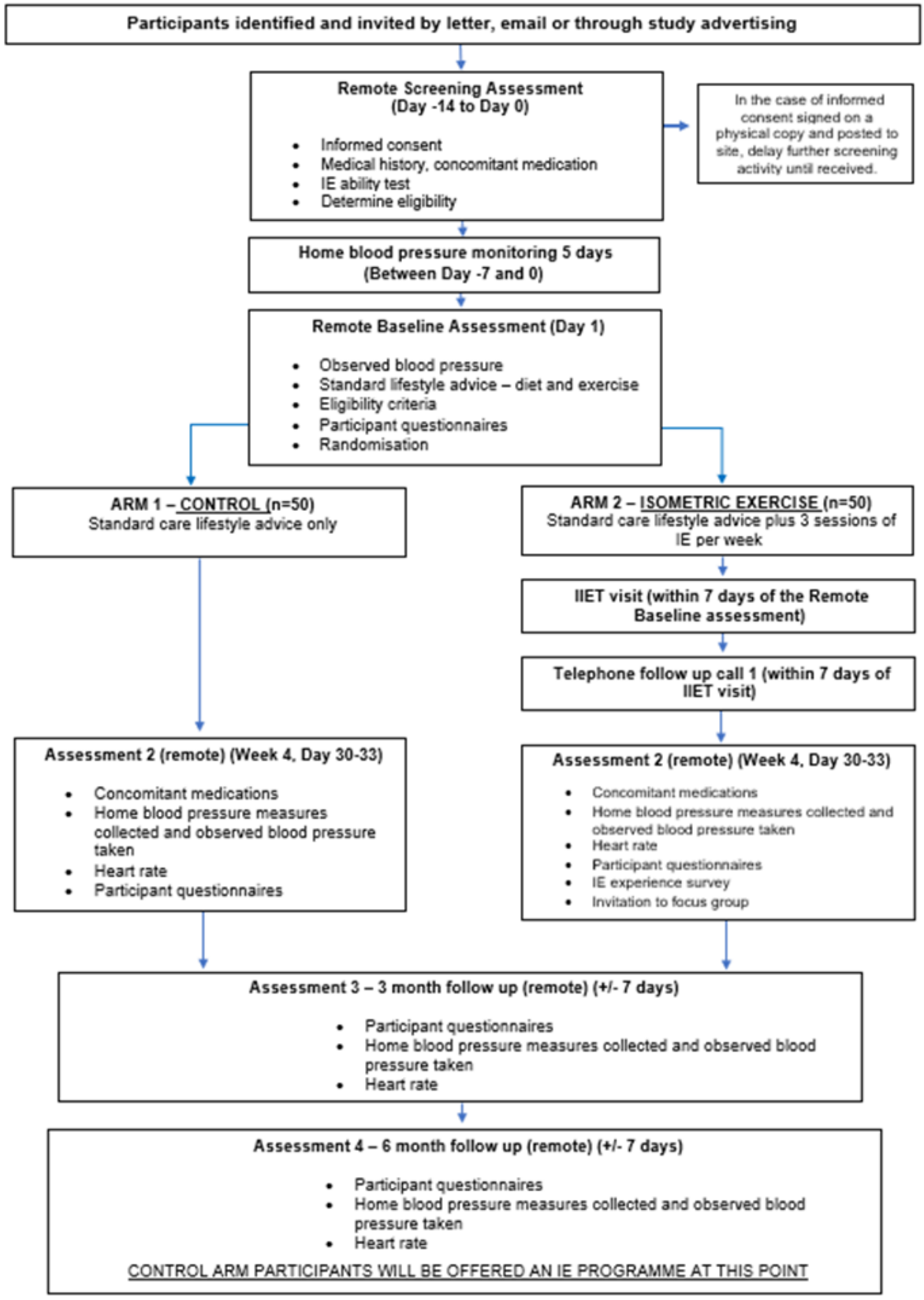
AE	Adverse Event
BP	Blood Pressure
CI	Chief Investigator
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IE	Isometric Exercise
IIET	Incremental Isometric Exercise Test
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
NHS	National Health Service
PHE	Public Health England
PI	Principal Investigator
PIS	Participant Information Sheet
PPE	Personal Protective Equipment
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File
SMG	Study Management Group
SSC	Study Steering Committee

iii. TRIAL SUMMARY

Full Study Title	Feasibility study to assess the delivery of a novel isometric exercise intervention for people with Stage 1 hypertension in the NHS
Short title	IsoFIT-BP
Trial Design	Randomised controlled feasibility study
Trial Participants	Patients with Stage 1 Hypertension who are not yet on anti-hypertensive medication and without any significant medical condition that would contraindicate their participation
Study intervention	Individually tailored wall squat isometric exercise programme completed three times a week over six months
Planned Sample Size	100 participants – 50 into each of a control and intervention arm
Participant duration in study	Six months
Study Objective	To determine the feasibility of delivering a personalised isometric exercise intervention for people with Stage 1 hypertension in an NHS setting
Primary Objectives	**Primary Objectives:** • To assess if nurses/allied health professionals (e.g. health trainer, healthcare assistants, physiotherapists, pharmacists) can deliver isometric exercise prescriptions for Stage 1 hypertensive patients in an NHS setting • To estimate the variance in BP change from baseline
Secondary Objectives	**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 to inform future trials • Explore the willingness of 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 cost and cost-utility 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- explore possible negative effects of COVID-19 on recruitment rates and participation. • To investigate the feasibility of using observed home blood pressure readings for remote monitoring

vi. KEY WORDS: Isometric exercise, exercise, hypertension, high blood pressure, general practice, feasibility study

vii. TRIAL FLOW CHART



1. BACKGROUND

Hypertension, or high blood pressure (≥140/90 mmHg) (1), affects 1 in 4 people in England and is the second largest risk factor for mortality after smoking (2). Furthermore, estimates indicate that the annual burden from conditions attributable to hypertension is over £2 billion (2) with long-term care following debilitating heart attack, stroke and vascular dementia often precipitated by hypertension costing substantially more (3).

National guidance for the treatment of hypertension is two-tiered: initial lifestyle advice (diet, weight management, exercise, alcohol intake etc.) and then anti-hypertensive medication if blood pressure (BP) remains elevated (if clinic BP is >180/120 mmHg at first encounter or is subsequently found to be ≥150/95 on home or ambulatory blood pressure monitoring antihypertensive medication is recommended alongside lifestyle change) (1). The goal of antihypertensive therapy is generally to reduce clinic BP to <140/90 mmHg, although recommended targets vary depending on age and co-morbidity. (1); however, up to 50% of people fail to achieve their target (5) mainly due to non-compliance (estimated 30%-50% failing to comply at 6 and 12 months, respectively) (6) with undesirable side effects of antihypertensive medication often cited in this context (4).

The importance of lifestyle changes (e.g. diet, exercise and weight loss) for patients with hypertension in the absence of other risk factors should not be overlooked (1). Exercise is associated with anti-hypertensive benefits (7-9) and can be as effective as medication in controlling BP. However, low adoption and high attrition rates are common (7, 10-11). To promote lifestyle exercise changes, patients need easily adopted, effective and manageable exercise interventions as a first line option for managing their BP.

Meta-analyses indicate that isometric exercise (IE) results in larger reductions in BP compared with aerobic exercise (8) and has great potential to treat hypertension (12), improve patient health and reduce mortality risk. We have shown that IE can lower BP in people with both normal (13) and high-normal (pre-hypertensive) (14) BP and is a potential effective lifestyle intervention for hypertension. IE involves holding a fixed position for a period of time: muscles are used but there is no movement, e.g. leaning against a wall in a seated position (Figure 1). Only 24 minutes of IE a week are required to achieve reductions in BP of 12/6 mmHg in pre-hypertensives, which can be easily carried out at home without costly equipment (14).

Figure 1. Isometric wall squat exercise

The importance of our findings is substantial considering a 10 mmHg reduction in systolic BP and 5 mmHg reduction in diastolic BP is associated with a 40% lower risk of stroke and 30% lower risk of mortality from heart disease and other vascular causes throughout middle age (15). Although we have consistently demonstrated that IE can lower BP (14, 16-18), interpretation of the results, along with the findings of others is limited by small participant numbers (13-14,18-25). Although IE may provide a new viable solution with respect to exercise for those with Stage 1 hypertension, evidence for the efficacy of IE is still not robust. Furthermore, this intervention has never been tested within an NHS setting, nor confirmed in any large randomised control trials.

This study will determine the feasibility of delivering an individually tailored IE training programme to patients with Stage 1 hypertension (defined as a clinic BP of 140-159/90-99 mmHg) for whom lifestyle changes would be recommended before treatment within an NHS setting.

2. RATIONALE

As the most common long-term health condition in the UK and a primary risk factor for mortality, hypertension is a serious health problem (2). With every 20 mmHg increase in systolic BP above 115 mmHg and 10 mmHg increase in diastolic BP above 75 mmHg, the risk of death from cardiovascular disease doubles (26). Public Health England (PHE) suggests that there is an opportunity to prevent more than 9,000 heart attacks and at least 14,000 strokes over three years with better detection and management of high BP, high cholesterol and atrial fibrillation (15). It has been further estimated that over ten years, 45,000 quality adjusted life years and £850m could be saved if England achieved a 5 mmHg reduction in population systolic BP (2). In 2007, the NHS and PHE announced a drive to prevent thousands of heart attacks and strokes but highlighted the need for research into innovative lifestyle modifications to lower BP (2). New personalised support for lifestyle changes, like our IE training prescription, delivered by primary care allied health professionals could support this drive without directly adding to GP workload.

Research suggests that IE can lower resting BP in people with hypertension enough to effect a clinically significant reduction in cardiovascular disease and all-cause mortality (14). In a randomised controlled trial, a long-term programme of aerobic exercise training failed to reduce BP (27). This may be due to poor adherence (67%) to the relatively high amounts of aerobic exercise recommended (27). Furthermore, other studies have demonstrated attrition rates as high as 50% during traditional aerobic exercise interventions (28). Use of IE to manage hypertension, supported by appropriate healthcare professionals, could provide a better option for patients and healthcare providers. Empowering patients to manage their condition is key and use of short, simple, personalised exercise that can be carried out at home may enable this.

IE offers distinct advantages over other forms of exercise (12) making it a better lifestyle treatment for hypertension. A frequently cited barrier to exercise is lack of time (11). Though aerobic exercise guidelines recommend ≥ 150 minutes per week (29), it has been demonstrated that adherence is better with shorter bouts of exercise (30). Our evidence-based IE programme can be easily prescribed by health care providers and is very simple to execute regardless of age or physical ability. It does not require costly equipment or access to specialist facilities, does not require specific clothing, and most importantly, is easily done at home. Furthermore, our personalised exercise ‘prescription’ ensures optimal IE intensity is achieved, helping to improve confidence, motivation and increasing patient’s adherence (11, 31).

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Overall aim: To determine the feasibility of delivering a personalised isometric exercise intervention for people with Stage 1 hypertension in an NHS setting.

3.1 Primary objectives

- To assess if nurses/allied health professionals (e.g. health trainer, healthcare assistants, physiotherapists, pharmacists) can deliver isometric exercise prescriptions for Stage 1 hypertensive patients in an NHS setting.
- To estimate the variance in BP change, to enable sample size calculation for a definitive randomised controlled trial.

3.2 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 to inform future trials.
- Explore the willingness of 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 cost and cost-utility of the IE intervention compared to standard care for Stage 1 hypertension.
- Understand participant experiences of undertaking IE, adherence to the programme and continuation. Additionally, explore possible negative effects of COVID-19 on recruitment rates and participation.
- To investigate the feasibility of using observed home blood pressure readings for remote monitoring

3.3 Outcome measures, endpoints and study progression criteria

Table 1 overleaf summarises the study endpoints and outcome measures. Table 2 describes the criteria determining progression to a follow-on study. The follow-on study will be a randomised, controlled efficacy study. This feasibility study will determine uncertain parameters needed to design a substantive trial: variance of the primary outcome measure needed for sample size calculation, ability to deliver the intervention as intended in an NHS setting recruitment rates and participant acceptability and compliance.

Table 1: Summary of study endpoints/outcomes

Objectives	Outcome Measure(s)	Endpoint(s)
Primary Objectives: • To assess if nurses/allied health professionals (e.g. health trainer, healthcare assistants, physiotherapists, pharmacists) can deliver isometric exercise prescriptions for Stage 1 hypertensive patients in an NHS setting	Qualitative data from healthcare professional focus groups Data from fidelity assessments: - Healthcare professional competency assessments - Heart rates from participant study diaries	Project month 11/12 Pre-recruitment healthcare professional training sessions – Month 3 Week 1 fidelity check. All training sessions
• To estimate the variance in BP change from baseline • Preliminary evidence of effect	Systolic blood pressure change from baseline. Estimate difference in systolic BP change from baseline between isometric exercise and control group with 80% and 95% confidence intervals.	Week 4, 3 and 6 months
Secondary Objectives: • Evidence the fidelity of the study intervention with respect to healthcare professional delivery and patient completion of IE	Healthcare professional competency assessment Observation at first Incremental Isometric Exercise Test (IIET) delivered Heart rate within 95% peak heart rate reference interval	Post-intervention training – project month 3 First patient, first IIET visit at each site Day 7-10 follow up phone call, week 4-Assessment 2
• Estimate short- (4-week) and medium-term (3- and 6-month) adherence rates to IE intervention	Proportion of participants completing two thirds of all IE sessions - data collected from participant diaries	Short-term =Assessment 2, Week 4 Medium term = Assessment 3 and 4, Month 3 and 6
• Estimate recruitment and attrition rates to inform future trials.	Average number of participants recruited per week Number of withdrawals from study	Project month 10 – end of recruitment period Last patient, last follow up call – project month 15
• Explore the willingness of 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	Healthcare professional remote focus groups and telephone interviews.	Project month 11/12 - end of the recruitment period
• To establish the feasibility of cost of a full economic evaluation in a definitive trial	Healthcare resource use data and quality-adjusted life years (QALYs)	Last patient, last follow up call – project month 15
• Understand participant experiences of undertaking IE, adherence to the programme and continuation-explore possible negative effects of COVID-19 on recruitment rates and participation.	Participant IE experience surveys Participant focus groups (remote) or telephone interviews.	Assessment 2 - week 4 Project month 7 and 11
• To investigate the feasibility of using observed home blood pressure readings for remote monitoring	Blood pressure data (observed and home readings) Evaluation of the participants ability to carry out the measure	Baseline Assessment, Day 1, Assessment 2, Week 4 , Assessment 3, Month 3 and Assessment 4, Month 6.

Table 2: Study progression criteria

Progression criteria	Measure(s) used	Assessment of criteria having been met
• Intervention can be delivered and carried out as intended	• Intervention fidelity assessments: • Healthcare professional training • Competency assessments • First patient per site observations • Training heart rates	• All healthcare professionals complete training, achieve the required competency and complete satisfactory first patient, first visit observations • Heart rate data indicate two-thirds of all training sessions achieve the optimal heart rate
• Required number of participants can be recruited	• Number of participants randomised to the study	• At least one participant per week per centre is recruited and randomised from Week 5 onwards resulting in 100 participants randomised.
• Study and intervention is acceptable to patients/healthcare professionals	• Participant focus groups – opinions and experiences of study, intervention and COVID-19 measures put in place • IE experience questionnaire • Study screening logs • Number of withdrawals from study and reason for withdrawal (although not obliged to provide this)	• Data provide evidence for acceptability and support for the study and the intervention including with COVID-19 measures introduced • Data support acceptability of intervention • Study screening and withdrawal logs will be reviewed to identify any themes for decline, withdrawal (although not obliged to provide these) and screen failures that may allow adaptation of study design to improve recruitment rates.
• Attrition and missing data • At least 70% of participants are retained and complete the IE sessions for 4 weeks • At least 70% of participants have complete outcome data at 4 weeks, 3 and 6 months	• Compliance with study visits • Completion of IE training – participant diaries • Number of withdrawals from study and reason for withdrawal (although not obliged to provide this)	• At least 70% of participants are retained and complete prescribed IE sessions for 4 weeks. If 70% cannot be retained, reasons for drop out will be reviewed. If appropriate the study design may be modified to reduce perceived barriers to reduce future drop-out rates provide this does not compromise the intervention. • If complete outcome data is not available for at least 70% of participants, reasons for missing data will be reviewed by the project team to assess whether the collection of outcome data can be improved.
• Adherence - completion of eight out of 12 sessions in first four weeks of study	• Number of IE training sessions completed – participant diaries	• At least eight out of 12 sessions in first four weeks are completed. Reasons for non-adherence will be recorded and used to adapt the study design to improve adherence rates where possible.
• BP data supports equal or decreased BP with IE intervention	• BP measurements from study visits	• The 95% confidence interval of the difference between treatment groups in systolic BP at 4 weeks includes the minimum clinically important difference of 2 mmHg.

4. TRIAL DESIGN AND SETTING

This study is a multi-centre randomised, controlled feasibility study of an isometric exercise intervention for patients with Stage 1 hypertension who are not yet taking anti-hypertensive medication carried out in NHS settings in the South East of England.

The study involves a 2-week screening period, after which eligible patients are randomised to receive an isometric exercise programme in addition to standard care advice for six months or continue with standard care advice alone. At the end of the follow up period, all participants will return to standard care and control participants will be offered an isometric exercise programme if they wish.

The study involves an initial screening telephone call (Day -14) and four follow-up telephone calls (assessments): at week 1, week 4, 3 months and 6 months. A single in-person visit will involve the intervention arm only in order to perform exercise testing (see section 7.2 below) and provide the 'at home' training plan (conducted within 7 days of the Baseline visit, Day 1). This group will also have an additional follow-up telephone call (conducted within 7 days of the in person exercise testing visit) to check how the participant is doing with their new exercise programme and to collect heart rate and blood pressure data to make safety and intervention fidelity checks. Patients will complete online questionnaires on diet, exercise and quality of life at all assessments. An IE experience questionnaire will be completed online at the week 4 visit and participants will be invited to attend an optional online focus group or telephone interview (see section 6 of this protocol for a detailed description of the study procedures and schedule).

5. PARTICIPANT ELIGIBILITY CRITERIA

5.1 Inclusion criteria

- Aged 18 or over
- Clinic systolic BP 140-159 mmHg
- Able to provide informed consent

5.2 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 regurgitant 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

6. TRIAL PROCEDURES

6.1 Recruitment

6.1.1 Participant identification

Approximately 2-10 NHS sites in South East England that provide care for people with hypertension will be included in the study. Recruitment will be competitive across all sites until the total target of 100 patients has been met. All participating sites will be required to participate in study training organised by the study team (refer to sections 6.2 and 7.1). In light of COVID-19 risk, it is proposed the intervention will now be delivered from sites based in different geographic locations as far as possible within the South East to avoid all sites being subject to localised lock down.

6.1.1.1 Full research sites
Sites will identify potential participants opportunistically and through searches of their patient databases, waiting lists, case records and referrals. Potentially eligible patients will be provided with a Participant Information Sheet (PIS) by post or email with a covering letter/email. The site research team can also phone potentially eligible patients to inform them of the study before sending the PIS to interested patients. They will then follow up the approached patients with a phone call to confirm that they have received the PIS and to ask if they would be interested in participating. After receiving a PIS by email or post and having had sufficient time (at least 24 hours) to consider the information, interested patients will be asked to contact the site research team to schedule a remote screening appointment. The screening assessment can also be performed at this same contact if the patient has sufficient time and is willing to do so, otherwise a separate remote telephone call for screening will be arranged.

6.1.1.2 Participant Identification Centres (PIC)
Patient identification centres will be used to recruit patients and invite them to attend another local site with capacity to deliver the study visits. PIC sites will identify potential participants opportunistically and through searches of their patient databases, waiting lists, case records and referrals. Potentially eligible patients will be provided with a PIS by post or email with a covering letter/email. PIC sites can also choose to notify potential participants by text message providing a link to the study website. The site research team can also phone potentially eligible patients to inform them of the study before sending the PIS to interested patients.

Interested participants will be given the contact details (telephone and email) of the study team who will then follow up interested participants with a phone call and/or email to confirm they have read the PIS on the study website or to send the PIS and to answer any questions about the study. After receiving a PIS by email and having had sufficient time (at least 24 hours) to consider the information, remote screening will be conducted by a research site closest to the participant's place of residence or by the study team. The screening assessment can also be performed at first contact by telephone if the patient has sufficient time and is willing to do so, otherwise a separate remote telephone call for screening will be arranged.

6.1.1.3 Study advertising to potential participants

The study can be publicly advertised with electronic and/or paper materials approved by the Research Ethics Committee and the Health Research Authority. The study will be advertised with posters and leaflets at the participating sites, pharmacies and hospitals, with electronic adverts on relevant websites, social media and local newsletters and print media. The public advertising materials will contain a link to the study website, which will have basic information about the study, the PIS and a list of participating research sites plus a team contact for each site. The adverts will invite any interested patients and direct them to the study website and register their interest with the study team who will share the PIS with them. The PIS will also be available on the study website for instant access. Once confirmed that the patient has read the PIS they will be pre-screened by telephone by the study coordinator or other trained project team members.

6.1.1.4 Study screening/enrolment recording

A study screening/enrolment log will be updated to document whether the patient was randomised into the trial, or was not eligible/declined (reasons should be documented). This log will contain the following anonymised data for participants that fail the screening period:

- age
- gender
- reason the participant did not meet the eligibility criteria for study trial participation.

6.2 Consent

The site Principal Investigator (PI) is responsible for the conduct of the research at their site; this includes the receiving of informed consent from participants. The PI takes responsibility for ensuring that any vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence. The PI must ensure that any healthcare professional delegated the duty of receiving informed consent from participants is duly authorised, trained and competent to perform this activity in accordance with this protocol. Anyone receiving informed consent for the study should have received study-specific training prior to recruiting any participants and will be encouraged to complete local NIHR CRN informed consent training online or in person. A medically qualified practitioner must confirm eligibility and sign the eligibility criteria checklist CRF (see Section 11.2). Written, informed consent must be received prior to the participant undergoing any study specific procedures. This includes the collection of identifiable data.

Potential participants will have received the PIS by email or post and been given at least 24 hours to consider the information. During the screening phone call (see section 6.3.1 below), a discussion about the research, detailing the nature, objectives and risks associated with the study will take place. This should include the following:

- discussion with the potential participant about the nature and objectives of the trial and possible risks associated with their participation
- confirmation that they have received the written PIS and if they have any questions
- explanation of the screening period, study visits and what the intervention involves, including a visit to an NHS site if allocated to the intervention arm

- where patients do not have electronic and/or internet access they will be asked to attend an NHS site for their observed blood pressure measurement(s)
- information about their data and how it will be kept confidential
- information about who is running the study and who will be responsible for the conduct and storage of data
- verbal agreement to take part in the study
- assessment of capacity.

Only patients with capacity should be included in the study. For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. A capable person will:

- understand the purpose and nature of the research
- understand what the research involves, its benefits (or lack of benefits), risks and burdens
- understand the alternatives to taking part
- be able to retain the information long enough to make an effective decision
- be able to make a free choice
- be capable of making this decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity).

Where patients are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected.

After the informed consent discussion, if the participant is still willing to take part in the trial then informed consent will be completed electronically. Alternative arrangements will be made as below for those unable to consent electronically, see section 6.3.1 below for consent process details. If the participant loses capacity during the trial, the original consent endures the loss of capacity providing that the trial has not significantly altered. Once a participant has consented to the trial, they will be allocated a unique Participant Identification Number (Participant ID). These details will be logged on the Study Screening/Enrolment Log. This document must remain at the investigator site at all times. Copies will only be collected by the central research team with participant names and personal information redacted.

6.3 Study visits and assessments

The following sections describe the assessments and visits conducted with participants. Table 3 overleaf summarises the schedule of events and assessments to be conducted at each time point. Healthcare professionals delivering the intervention will be provided with training on all study visits, assessments and procedures by the research team.

Table 3 – Participant schedule of events

		Study time point					
Assessment	**Remote Screening Assessment Day -14**	**Baseline Assessment Day 1 (remotely)**	**IIET visit (within 7 days of Baseline visit)**	**Follow up Telephone call – IE arm only (within 7 days of IIET visit)**	**Assessment 2 Day 28-33 (Remotely)**	**Assessment 3 Month 3 (+/- 7 days) (Remotely)**	**Assessment 4 Month 6 (+/- 7 days) (Remotely)**
Medical history	X						
Concomitant Medication	X	X		X	X	X	X
Consent	X						
Observed blood pressure and heart rate		X			X	X	X
IE ability test	X						
Incremental IE test and IE programme provided (for those randomised to intervention arm only)			X				
AE review				X	X	X	X
Diet questionnaire		X			X	X	X
Exercise questionnaire		X			X	X	X
Quality of life questionnaire		X			X	X	X
Collection of IE exercise diary (for those randomised to intervention arm only)				X	X	X	X
Collection of home blood pressure and heart rate readings	X (recorded between Day -7 and Day 1)	X		X	X	X	X
Health resource use questionnaire					X	X	X
IE experience questionnaire					X		

6.3.1 Remote Screening appointment

The patient will have been provided with an information sheet and given at least 24 hours to decide if they wish to enter the study.

During the remote screening appointment (phone/video call), informed consent will be discussed and provided electronically using Qualtrics software (refer to section 6.2 for consent procedures). The patient will be asked to enter the name of the person discussing consent with them, then they will be asked to tick each consent clause in the presence of the person taking consent. Finally, the patient will be asked to type in their name and date before submitting the form as a record of their consent Patients will be asked to provide informed consent prior to any further assessments taking place.

Access to an electronic device for remote visits and internet access of potentially eligible patients will be established at this point. Where the participant cannot consent electronically, written informed consent will still be discussed and a hard copy of the consent form sent in the post for completion by the participant. The remainder of the remote screening appointment will be rearranged once the written informed consent form is received via post and signed by the healthcare professional at this time. Written informed consent forms will be personally signed and dated by the patient as well as by the healthcare professional receiving consent.

A copy of the electronic consent form or the paper form if required will be provided to the patient, scanned or filed in the patient's health record and stored in the Investigator Site File at the local research site.

Patients who are eligible based on the information available at the screening visit and with consent to proceed, the following assessments will also be completed:

- Medical history and concomitant medication will be reviewed and recorded to ensure the individual meets the inclusion/exclusion criteria as far as possible prior to home blood pressure monitoring. Patients will be instructed how to perform an IE wall squat and asked to complete a single squat at approximately 120^{o} for 60 seconds to determine if they are able to perform the basic exercise. A protocol video will be provided to support the patients performing a 60 second isometric wall squat remotely.

If they successfully meet all screening criteria, patients will be sent an automated blood pressure device (Omron M3) and entered into a 2-week screening phase to monitor their blood pressure at home according to British Hypertension Society (BHS) and National Institute for Health and Care Excellence (NICE) guidelines using an automated device (1, 32). They will be given written instructions on how to use the blood pressure monitor and an electronic or paper diary to record home blood pressure measurements. They will measure their blood pressure for 5 consecutive days ahead of the baseline visit (day -7 to Day 0) and record their measurements in a daily diary. The patients should continue normal activities during the screening period. Patients will be made aware at the screening phone consultation that a final decision about their participation in the study will be made at the baseline visit as the results of the blood pressure monitoring may show that they are ineligible to take part.

6.3.1.2 Screening failures

Patients will fail screening in the following four ways:

1. failure to meet the eligibility criteria at remote screening assessment.
2. unable to perform a moderate IE wall squat for 30-60 seconds during their remote screening (see section 6.3.1)

3. Unable to perform a home-based blood pressure measurement
4. unable to complete the first 3 increments in their Baseline incremental isometric exercise test (IIET) – refer to Visit 1 below and section 7.2

6.3.2 Baseline Assessment- Day 1

At the baseline assessment, conducted remotely, the following assessments will be completed:

- past medical history – reviewed from screening visit
- current medication – reviewed from screening visit
- home blood pressure measurements recorded and assessed
- observed blood pressure measurement taken - this will help to ensure patients are using the correct technique and allow further instruction if required. At least three measurements will be taken at least 1 minute apart (1-2 minutes). Blood pressure will be recorded as the average of the last two readings (32).
- diet questionnaire completed (EPIC Norfolk FFQ or study adapted version of this questionnaire)
- exercise questionnaire completed (General Practice Physical Activity Questionnaire (GPPAQ))
- quality of life questionnaire completed (EQ-5D-5L).

The eligibility criteria will be reassessed using the home and observed blood pressure measures and any additional relevant information in order to proceed to randomisation. This assessment will be recorded using the eligibility checklist case report form (CRF) (see section 11.2 for data collection details). Baseline data will be collected and recorded in the study CRF (see section 11.2). A patient must not be randomised before the results of home blood pressure monitoring and any relevant tests required are performed e.g. a negative pregnancy test, if applicable. However, participants may still fail screening after randomisation, based on their inability to complete the first 3 increments of the IIET (see section 6.3.1.2 for screening failures). Patients who fail the screening period will not be randomised to the study.

Patients will then be randomised after confirmation of eligibility, refer to section 6.3.3 for further details. All participants will be provided with standard care advice in line with NICE guidelines for hypertension in adults (1) (see Appendix 16.12) covering the below information:

- assessment of diet and exercise pattern, appropriate advice will be offered
- assessment of alcohol consumption, guidance regarding safe levels of alcohol consumption
- discussion relating to avoiding coffee and other caffeine-rich products
- advice relating to reduction in dietary sodium and substitution with low sodium alternative
- advice and signposting regarding smoking cessation
- signposting regarding local groups promoting healthy lifestyle.

All participants will record their home blood pressure and heart rate readings in a home diary (blood pressure device, instruction sheet and diary provided to all) so it is ready for collection at each visit (remote follow up call). Home blood pressure monitoring will follow NICE (2019) and ESH/ESC guidelines. The protocol requires three consecutive measurements (separated by two minutes) always

using the same arm (use higher arm if >15 mmHg difference when first checked), to be taken in the morning and again in the evening for five days prior to each study visit (follow up call). In addition, participants in the intervention arm will also be asked to record their heart rate during exercise sessions using a heart rate monitor provided to them and asked to complete an exercise diary to record this and details of their training sessions. All participants will receive electronic reminders (1 per week for standard care advice to all and additional reminders for intervention arm participants of exercise sessions) to aid adherence to the standard care advice and training.

For participants randomised into the IE intervention arm, an in-person appointment will be arranged at the practice or in another NHS setting to undergo an Incremental Isometric Exercise Test (IIET) and receive a personalised IE programme within 7 days of the baseline visit. Control group patients will proceed directly to follow up assessment as detailed in section 6.3.4. If participants were identified through PIC sites or are attending a research site that is not a GP practice, a letter will be sent to the participant's GP (GP letter, version 1) informing them that the participant is on the trial.

6.3.2.1 IIET visit (intervention arm only) – within 7 days of baseline

An in-person visit at the practice/clinic will be conducted within 7 days of the baseline visit for the Intervention group only. Participants will be asked to complete an Incremental Isometric Exercise Test (IIET) as detailed in section 7 in person. Travel expenses will be provided to the participants to attend the IIET visit in person. On completion of the test, they will be asked to perform their exercise plan three times a week for the duration of the study (see section 7). Participants who fail to complete three stages of the IIET at this visit will not continue with any further study activities (section 7). Instead, they will be invited to attend participant focus groups and informed that they should return to their usual care and follow up provided by the healthcare professional/organisation overseeing their care. Patients will then be followed up as below in section 6.3.4. In cases where the research site has no healthcare professional staff capacity for the delivery of the IIET and support is not available from other sites, an appropriately trained member of the research team may assist by delivering the IIET visit.

6.3.3 Participant randomisation

Those that meet the inclusion criteria will be randomised to one of two groups in a 1:1 ratio. One hundred participants will be recruited; therefore, 50 people will be allocated to each group. Random permuted blocks will be used within stratification, ensuring that treatments are balanced at the end of every strata block. Participants will be allocated using a third party supplier of randomisation services (https://www.sealedenvelope.com/) for which healthcare professionals conducting the study visits will be provided with training and online log in details. This internet-based service allows investigators to randomise patients from anywhere in the world through a web browser. For randomisation, the healthcare professional conducting the study visit will need to provide details collected on the Baseline CRF.

6.3.4 Assessments – Follow up calls

6.3.4.1 Week 1 – follow up phone call (isometric exercise group only)

The participants will be contacted one week (between days 7 and 10) after the baseline visit by telephone. The following information will be collected:

- adverse events//issues with completion of isometric exercise

- compliance with isometric exercise
- self-recorded heart rate during IE sessions.

If the participant's heart rate readings recorded during training sessions are found to be outside of the specified range (see section 7.2 on IIET), then the participant will be instructed to alter their training as described in Section 7.4.

6.3.4.2 Assessment 2 - Week 4 follow up

All participants will receive a follow up call four weeks post-randomisation and be asked to provide the following data which will be recorded in the Assessment 2 CRF:

- current medication
- 3 home blood pressure measurements taken 10-15 minutes before the call
- observed blood pressure and heart rate (using the same protocol as screening visit)
- any AEs experienced
- diet questionnaire – as per baseline assessment
- exercise questionnaire – as per baseline assessment
- quality of life questionnaire (EQ-ED-5L)
- health resource use questionnaire

At this point, participants in the intervention group (isometric exercise) will also be asked to complete an IE experience survey and will be invited to take part in one of two remote participant focus groups, or alternatively a phone interview. Participants will be provided with a focus group information sheet about attending a focus group along with a reply slip which they will be asked to return to the project team in an addressed envelope if they are interested (refer to Section 6.4 for more details on the focus groups).

6.3.4.3 Assessments 3 & 4 – Month 3 and Month 6

All participants will receive a follow up call at Month 3 and Month 6 post-randomisation and asked to provide the following data which will be recorded in the follow up assessments 3 and 4 CRF:

- current medication
- 3 home blood pressure measurements taken 10-15 minutes before the call
- observed blood pressure and heart rate (using the same protocol as screening visit)
- any AEs experienced
- diet questionnaire – as per baseline assessment
- exercise questionnaire – as per baseline assessment
- quality of life questionnaire (EQ-ED-5L)
- health resource use questionnaire

Participant diaries will be collected after the Month 6 follow up, or earlier if the participant is withdrawn from the study sooner. At this point the data will be collected for heart rate during IE sessions and home blood pressure readings.

6.4 Qualitative data collection

During the study, we will ascertain the opinions and perceptions of the participants receiving the intervention to determine their experiences, as well as those of healthcare professionals in relation to the delivery and sustainability of the intervention in practice. Data will be collected by the central research team (grant holders) to explore the barriers and enablers that might influence implementation of this intervention beyond the feasibility study and to inform optimisation of the intervention delivery prior to a definitive study. Focus groups will be undertaken remotely via telephone or video call dependent on the participants' willingness to use group video call. It is acknowledged that when conducted via telephone call the non-verbal communication will be lost. However, there is the possibility for group video call, one-to-one video call or telephone group/individual communications. It is expected that each focus group will take approximately one hour.

6.4.1 Participant focus groups

In addition to the quantitative data collected through the IE experience survey at Follow up call 2, patients allocated to the intervention arm will be invited to take part in one of two remote participant focus groups or a telephone interview. Participants reaching the 4-week visit will be emailed an information sheet by the study team inviting them to attend a focus group and asking them to respond to the project team if interested.

A maximum of two focus groups will be run (held at Month 4 and Month 8 of the recruitment period) with 6-10 participants within each group. The study lay co-applicants, who have also helped design the topic guide for guiding focus group discussions, will assist with leading the focus groups.

All those who have expressed an interest will be placed in a pool of potential participants according to their age, gender and geographical area. If over-subscribed, we will select a sufficient number of people to participate from this pool, ensuring a spread of participants. Those who are selected to participate will be contacted using their preferred contact method specified on their reply slip - email or text message. Those invited will be informed of the dates of the focus groups and necessary arrangements made for their online attendance. A £15 shopping voucher will be given to participants to compensate for their time. Those who are not randomly selected to participate will be informed using their preferred contact method specified on their reply slip and will be thanked for offering to do so.

Focus groups will be used to enable an in-depth exploration of patients' views and experiences on the following topics:

- their opinions of the IE intervention
- their opinions of the IIET and delivery of the exercise programme
- their opinions of how easy it was to perform, keep to and fit into daily life
- how they felt about being part of the study
- whether they were happy with the number of visits and the assessments carried out
- how the study impacted on their time

- whether they would take part in future studies of this type
- what they think about the intervention as an option for patients regarding treatment choice
- experience of receiving the intervention in an NHS setting
- anything they would like to see changed in a future study of this type.

6.4.2 Healthcare professional focus group and interviews – intervention delivery

A single focus group with 6-10 individuals will be held remotely at the end of the recruitment period with healthcare professionals delivering the IE intervention from participating study sites. Invitations to participate in the focus groups will be sent to healthcare professionals by email, via their usual staff communications or directly from the project team. The invitation email will include the contact details of the project team member to respond to if interested in taking part. If there is a low response rate after two weeks, another invitation will be sent to encourage participation. Where any healthcare professional group is under-represented in the focus groups, individual interviews will be conducted to obtain the views of those key stakeholders.

This focus group will provide in-depth data to explore the feasibility of providing the IE intervention as part of standard NHS care services and to collect views and experiences of the following:

- opinions of the IE intervention
- whether they thought it would be of benefit to patients and improve patient treatment choice
- opinions of the training and education events
- opinions of the screening protocol, study visit and assessments carried out
- how they felt the study was received by patients
- things that they would change about the intervention or the study protocol
- how the study impacted on their time
- whether they would support future studies for an intervention of this type
- whether they think this intervention has the potential to become a standard care option
- comments on the delivery in an NHS setting
- barriers/enablers that might influence sustainability beyond the pilot study.

6.4.3 Focus Group Consent

All participants will be invited to take part in a focus group for the study at their 4-week Visit (remote follow up call). In addition, healthcare professionals delivering the intervention will be asked to attend a focus group at the end of the recruitment period (see section 6.4.4 below). All those attending the focus groups (patients and healthcare professionals) will be provided with information about the purpose of the focus group and will be asked to complete an online consent form ahead of the focus group. In all instances, a copy of the information sheet and electronic consent form will be given to the participant and another copy retained by the research team. Focus group participants will be asked for

their permission to digitally record the conversations but will be made aware that any comments they make will not be directly identifiable to them.

6.4.4 Healthcare professional focus group and interviews – stakeholder opinion

To understand the views of healthcare professionals not participating in the study or delivering the intervention, short interviews of 15-20 minutes will be conducted to generate views on wider perceptions of the intervention, the study itself, barriers or facilitators to the roll-out of the intervention more generally and general opinions of this approach to managing blood pressure in patients.

A general email invitation with an information sheet attached will be sent out by the local NIHR Clinical Research Network Kent, Surrey and Sussex networks to healthcare professionals across Kent, Surrey and Sussex to identify those interested in participating in a short interview. The invitation email will include the contact details of the project team member to respond to if interested in taking part. If interested, a convenient time will be booked to conduct the telephone interview. A confirmation email containing the interview time, dial in details and the information sheet will be sent to confirm the appointment. Participants will be asked to verbally consent to the interview and its recording prior to the start of the interview having read the information sheet provided at the time of invitation email. Where any healthcare professional group is under-represented, further email invitations sent out will be targeted accordingly to obtain the views of those key stakeholders.

6.5 Withdrawal criteria

The participant is free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where he/she may obtain further information about the trial.

Data collected up to the point of withdrawal will only be used after withdrawal if the participant has consented to this. This is explicitly detailed in the Participant Information Sheet. The right of a participant to refuse participation without giving reasons will be respected.

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.

6.6 End of trial

The trial will be completed when the last patient has completed their last visit at Month 6 (remote call). Throughout the study, data will be verified against CRFs and primary data sources (e.g. heart rate monitors). After the last patient, last assessment, trial data will then be locked. The CI will inform the HRA that the study has been completed.

Publications and reports will be prepared and published in the medical literature. Publications and lay summaries of the results will be shared with study participants.

On completion of publications, data will be anonymised and kept for future research in accordance with ethical approval and participant consent in compliance with general data protection regulation (GDPR) legislation.

6.7 Post trial care

On completion of the trial, all participants in the control arm of the study will be offered an isometric exercise training programme at the Month 6 assessment and followed up by phone one week later to check they are happy with their exercise programme. All participants (control and intervention) will be returned to the care of their general practitioner and/or normal care provider (e.g., hospital) in order to ensure appropriate management of their hypertension.

All participants who had received the intervention will be allowed to retain the equipment provided to facilitate ongoing isometric exercise (wall squat measuring device only, participants will be asked to return home blood pressure and heart rate monitors). Those participants who choose to be trained and receive an IE prescription following the control period will be provided with and allowed to retain a wall squat measuring device.

All participants will be provided with a lay summary of the study findings along with copies of publications resulting from the trial when the results are available.

7. STUDY INTERVENTION

The participant's normal care provider (GP or hospital where appropriate) will retain responsibility for the healthcare of the patient outside the research. Those participants randomised into the IE intervention arm will physically attend an exercise testing visit within 7 days of baseline in order to receive an individually tailored training programme (termed IE programme hereafter). To ensure each participant is provided with an IE programme at a personalised optimum intensity, they will undergo an incremental isometric exercise test (IIET) to determine the optimum knee angle at which to do their wall squat. Section 7.2 below describes how the IIET is conducted.

Participants will be instructed to perform their IE programme for 4 x bouts of 2 minutes in the appropriate squat position with 2-3 minutes rest in between each bout. They will perform this three times a week for the duration of the study. All participants in the intervention group will receive a training manual providing a summary of their IE prescription programme, detailed instructions for the exercise, IE training equipment (see Figure 2) and an exercise diary to record their exercise sessions and their heart rate (during their IE sessions). This is in addition to the weekly blood pressure monitoring diary received by all study participants (both control and intervention arms).

Figure 2 – Example of IE programme training equipment to achieve specified knee angle

7.1 Study Intervention Training

A healthcare professional at each full research site (not PIC sites) will be identified by the PI to deliver the IE intervention and conduct study visits. This person will receive a half-day training session on how to perform an IIET (section 7.2) and provide patients with an IE programme as well as study specific training (including consent and adverse event reporting). The training will include a written introductory pack, a training workshop on the IE programme, performing the IIET, a mock study clinic IIET visit and ongoing support.

This training will be conducted at Canterbury Christ Church University by the project team including assistance from the project lay co-applicants and members of the public for the mock clinic. During the healthcare professional training sessions all efforts will be made to maintain social distancing and reduce COVID-19 risk to attendees. Risk will be mitigated whilst completing the IIET through wearing appropriate PPE according to local practice procedures, the same that will be worn during the research visits. The training session will finish with an assessment to ensure each healthcare professional is delivering the IE programme competently. If they do not meet the required competency level, they will be provided with an additional one-hour individual session to achieve an adequate training level.

Each person attending the training session will be asked to complete a feedback form to evaluate the training provided, ascertain whether they feel confident with delivering the intervention and ask if they think any improvements could be made.

7.2 Incremental isometric exercise test (IIET) protocol

The incremental isometric exercise test (IIET) using the wall squat exercise is designed to determine a knee angle needed to elicit 95% of the peak heart rate (HRpeak) for this type of exercise (13-14). The test involves participants performing a maximum of five increments, each held for two minutes. The angle at the knee is reduced after each increment (135°, 125°, 115°, 105°, 95°) which progressively increases the difficulty (intensity) of the test (see Figure 3). The test is terminated either by the participant reaching the end of the five increments, or by not being able to continue due to fatigue. Average heart rate data from the last 30 seconds of each of the completed increments is then used to calculate a participant specific knee angle relative to 95% HR_{peak}, which will form their optimal training intensity for their IE programme.

At the end of each knee angle stage, the patients will be asked to rate their perceived exertion (RPE) score. The participant will be encouraged to complete as much of the test as they are able to. The test will finish when the participant either completes the five increments or is forced to stop due to maximal exertion (normally indicated as approximately 10 on the RPE scale). The healthcare professional delivering the IIET should maintain a good dialogue (providing as much encouragement as necessary) with the patient throughout, and ensure they stay calm and relax their breathing. They should also watch closely for any signs of physical distress and stop the test immediately if they feel the patient's health is at risk.

If participants are unable to complete the first 3 increments of the IIET, then a reliable knee joint training angle cannot be calculated and the participant will be classed as a screen failure. See IIET Visit, section 6.3.2 for procedure after screen failure.

On completion of the IIET, the healthcare professional will contact the study team who will calculate the optimum knee angle for the participant's IE programme using a dedicated software programme and data collected during the IIET.

Figure 3 – Images to show how the knee angle is determined in the IIET and the five incremental knee angles of the test (from left to right: 135°, 125°, 115°, 105°, 95°)

7.3 Assessment of the fidelity of the intervention and alteration of IE programmes

7.3.1 Intervention fidelity assessments

Throughout the study, several checks will be made to determine the extent to which the intervention is being delivered as intended and defined in the protocol (fidelity checks). This will be done at an intervention delivery level and patient level as below. Ongoing fidelity data will be reported to the Study Steering Committee for regular review.

Delivery level:

1. The healthcare professional or exercise specialist will complete a standardised training package and be required to meet a minimum competency level in delivering the intervention at end of the training.
2. A member of the project team will observe (and assist if requested) the first IIET delivered by each healthcare professional at each study site and the prescribed IE training knee angle checked. Post-observation feedback will be provided to the health care professional and any additional support given if required.
3. Healthcare professionals and participants involved in the study will have access to a ‘help-line’ (manned by a member of the project team) during normal working hours (9.00am-5.00pm) or email response within 24 hours in case of any questions or concerns.

Participant level:

1. Participant heart rate data recorded during training sessions in week 1 (collected at the Day 7-10 telephone check) will be checked by a member of the project team to ensure the participant is training to their optimum intensity (95% of the peak heart rate). If these data are outside the recommended range for optimum intensity the patient will be contacted and appropriate adjustments to their training angle made.
2. As part of the study analysis (refer to section 10.3), heart rate data from all exercise sessions conducted by intervention participants will be checked for optimum intensity (95% of the peak heart rate) and reported as part of the study findings.

7.4 Adjustment or alterations permitted to participant IE programme

The mean HR recorded during the last 30 seconds of the fourth/final bout of each IET session will be used to check whether a participant is working within their prescribed target heart rate range (THRR) calculated as: 76-111% of their 95% HR_{peak} value (33). Adjustments will be made at one time point only in the study. When collecting heart rate data at the Day 7 telephone call, if this HR value falls outside the range for two consecutive IE sessions during the first week of training, any necessary adjustment in knee joint angle will be interpolated based upon the participant's knee joint angle/heart rate relationship (previously calculated from the IIET). Accordingly, new settings for the Bend and Squat device's 'floor' and 'wall' arms will be calculated and communicated to the participant by a member of the project team. The target heart rate range will be recorded in the participant's IIET Visit CRF and healthcare professionals at study sites will be asked to check that readings recorded at Day 7 are within this range. If not, the site will contact the study co-ordinator for recalculation of the settings required for the participant and communicate these new settings to the participant by telephone.

8. ADVERSE EVENTS

8.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a study participant.
Serious Adverse Event (SAE)	Any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.2 Operational definition of (S)AEs for this study

Only AEs or SAEs which might have resulted (definitely or probably) from the study intervention, e.g. muscular injury in the leg as a result of IE, should be recorded in the study CRF and reported to the Study Co-ordinator as below.

8.3 Recording, reporting and follow up procedure for Adverse Events

8.3.1 AEs

AEs (see definition above) will be collected throughout the study and documented on the relevant CRF from randomisation until Month 6. These may be volunteered by the participant or discovered by the investigator or healthcare professional conducting study visits/follow-up telephone calls. All AEs should also be recorded in the participant's medical records. If an AE is reported by the patient, the relationship of the event to the study treatment or procedures should be assessed by the local PI, or a delegated sub-PI, nurse or healthcare professional.

8.3.2 SAEs

An exception to the above are SAEs (see definition above), which should always be recorded and reported to the Study Co-ordinator using the SAE reporting form. The form should be emailed to the study co-ordinator within 24 hours of the site team becoming aware of the event. For each SAE the following information will be collected:

- full details in medical terms and case description

- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to investigation), in the opinion of the local PI
- whether the event would be considered anticipated.

An acknowledgement of receipt will be sent to the site within 24 hours. The Study Co-ordinator will immediately inform the CI of any reported SAEs. The CI will review the SAE to confirm causality and expectedness. The CI will then report all SAEs to the Sponsor following local procedures. The Sponsor will report all SAEs to the Research Ethics Committee (REC) within the conditions of ethical approval. The Study Steering Committee will periodically review safety data to ensure patient safety throughout.

SAEs should be followed-up until resolution or a final outcome. All follow-up information should be added to the CRF and emailed to the Study Co-ordinator as soon as it becomes available. The SAE form and any email correspondence related to the SAE should be filed in the investigator site file and in the Trial Master File.

8.4 Reporting of pregnancies

Although isometric exercise can be undertaken in pregnancy, we have decided to take a conservative approach in this first feasibility study and are excluding any pregnant or breast-feeding patients. Any women of childbearing potential should agree to use a medically accepted method of contraception while they are participating in the study. Should a patient get pregnant during the study, the site should notify the Study Co-ordinator within 24 hours of becoming aware of the pregnancy. In case of a pregnancy while receiving study treatment, a patient should be withdrawn from the study.

9. STATISTICS AND DATA ANALYSIS

9.1 Sample size calculation

Review of current literature revealed few IE studies in a hypertensive population. These studies were small (n<25), conducted under different conditions to the proposed study, and showed low precision and large variability in estimates of the standard deviation (SD). A sample size of 100 participants, 50 per arm, will be used in the feasibility study. Allowing for 20% attrition and 6.5% incomplete data, 74 participants (37 in each arm) will have completed change measures at 4 weeks. This is in line with the recommended sample size of 70 to estimate key parameters from external pilot RCTs (35). A sample size of 74 produces a two-sided 95% confidence interval with a width of 1.33 when the standard deviation is 4. This estimate of 4 has been taken from a previous study (N=24) (14).The sample size confidence interval has been calculated using Pass11 software (PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

9.2 Planned recruitment rate

Feasibility data from three GP practices within Canterbury and Coastal Clinical Commissioning Group (CCG) indicated 4,949 patients with recorded BP in study range and not taking medication (data March 18-19). With a conservative estimate that 50% fit the full eligibility criteria and a 2.5% response rate to letter/email invitation, we estimate that recruitment of 100 participants will be achieved with four sites recruiting an average of one participant per week. Allowing for a slow start up in the first four weeks, a seven-month recruitment period is predicted. Furthermore, it is possible under current circumstances that COVID-19 may have a negative effect on recruitment.

9.3 Statistical analysis plan

9.3.1 Quantitative data analysis

Descriptive statistics will be used to assess primary and secondary process outcomes such as recruitment rates, adherence rates and completeness of data. Exercise adherence will be compared with outcomes to inform compliance criteria in the full study. In a definitive study, the primary outcome – change from baseline in systolic BP – will be analysed using analysis of covariance (ANCOVA), with a fixed treatment effect allowing adjustments for baseline values, centre, sex and age. This model will be used to estimate differences between the arms and confidence intervals from the feasibility study. 80% and 95% confidence interval will be calculated. Data from the IE experience questionnaires will be transferred to SPSS (v24) and analysed using descriptive statistics.

9.3.2 Qualitative data analysis

Thematic analysis of focus group/interview transcripts will be carried out using Braun and Clarke's (2013) six stage model using NVIVO v11 (36). The process involves the following stages:

1. Familiarization with the data: Transcribing data, reading and re-reading the data, noting down initial ideas.
2. Generating initial codes: Coding interesting features of the data in a systematic fashion across the entire data set, collating data relevant to each code.
3. Searching for themes: Collating codes into potential themes, gathering all data relevant to each potential theme.
4. Reviewing themes: Checking if the themes work in relation to the coded extracts (Level 1) and the entire data set (Level 2), generating a thematic 'map' of the analysis.
5. Defining and naming themes: Ongoing analysis to refine the specifics of each theme, and the overall story the analysis tells, generating clear definitions and names for each theme.
6. Producing the report: Selection of vivid, compelling extract examples, final analysis of selected extracts, relating back of the analysis to the research question and literature, producing a report of the analysis.

Drawing on Sweeney et al's (37) notion that the service user researcher unique perspective should be preserved rather than subsumed, the process will involve multiple members (including public co-applicants) of the project team. They will independently undertake stages 1-3 before joining together

to generate a consensus view of the themes, to refine and develop the themes and to produce a report of the analysis (stages 4-6). The findings will be fed back to respondents for validation or revision of the interpretations.

Inductive thematic analysis of focus group/interview transcripts will be carried out using NVIVO 11. The process will involve reading and re-reading the transcripts and noting down initial ideas. Then the transcripts will be coded. Data extracts will be collated within each code and then codes ordered into potential themes. Subsequently, these themes will then be reviewed and refined. Ongoing analysis will refine the specifics of each theme and identify any themes which have not previously been recognised. Deviant case analysis will be used to ensure that perspectives that diverged from dominant trends are not overlooked.

9.3.3 Health economic analyses

The aim of the health economics analysis is to establish the feasibility of a full economic evaluation of the IE intervention programme in the definitive trial. The economic analysis in this feasibility study will seek to determine the acceptability of resource use and utility measures in this setting, establish the cost of the IE intervention programme and conduct some preliminary modelling to explore potential cost effectiveness.

The definitive study will estimate the cost-utility of the IE intervention programme compared to standard care for high BP and will adopt an NHS and personal and social services perspective adhering to the guidance set out by NICE (38). We plan to use quality-adjusted life years (QALYs) as the primary outcome in the economic evaluation and 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 (38). We will collect data on quality of life and resource utilisation. Since QALYs are the primary outcome of the economic evaluation we plan to obtain utility values from patients' responses to each of the EQ-5D-5L at the beginning of the intervention and at 4 weeks, 3 months and 6 months after the intervention. The combination of answers to EQ-5D-5L will lead to a health profile that will be converted into a utility using the validated mapping function to derive utility values for the EQ-5D-5L from the existing EQ-5D-3L (39-40). These utilities will represent patients' overall quality of life and will be multiplied by the time spent in each state to generate QALYs.

Data on health and social care services utilisation will be collected at 4 weeks, 4 months and 6 months after the intervention for both arms. Data on the use of primary care services and medication profile will be collected from routine patient records from participant GP practices. We will also collect data from participants on the utilisation of social care and other community services, inpatient and outpatient hospital services and laboratory tests with the use of participant questionnaires. To establish the cost of the intervention we will collect resource data comprising time spent with healthcare professionals for intervention and follow up, plus resources and equipment. We will also identify relevant reference and unit costs from local or national databases (e.g. Personal Social Services Research Unit (PSSRU), NHS Agenda for Change Pay scales, electronic market information tool (eMIT) and British National Formulary (BNF)) to be used to convert resource use data into overall direct costs.

The data collected at the feasibility study will be used to test for clarity and ease of use and to determine completion rates. They will also be used to determine which costs are the most relevant for this study and to explore whether we can collect information on resource utilisation that cannot be collected from routine databases. We will use descriptive statistics for each arm of the trial to assess the acceptability of the data and indicate potential outliers. We will detail the number and percentage of questionnaires returned and the number and percentage of missing items within the returned questionnaires. This will highlight any discrepancies in the data, missing data and need for advanced modelling of outliers in the full trial. We will also conduct some preliminary modelling to explore potential cost effectiveness and value of further research.

10. DATA MANAGEMENT

10.1 Source data definition

For the purposes of this study, data entered directly onto the case report forms (CRF) will be considered as source data. Additional source documentation for this study will include the participant's medical record, any participant diaries and questionnaires completed and focus group/interview audio recordings and transcripts.

Where CRFs are then transmitted from recruitment sites to the study team, a copy should be retained in the Investigator Site File to ensure that the PI has a full account of what has occurred during the trial at his/her site.

10.2 Data collection and handling

Data will be collected throughout the study using paper case report forms (CRFs). A case report form is a form on which individual patient data required by the study protocol are recorded. Participant documents to be completed directly by the participants for example, the blood pressure diary, will now be available online for completion due to the requirement to remove as much physical contact as possible. However, provision will be made to ensure that no participant will be excluded based upon access to technology. The CRF data is used to perform statistical analysis for the study. Data will be collected by local research team members at participating sites from participants and participants' medical records using the following paper CRFs:

- Screening CRF – collect preliminary information required for eligibility checks (e.g. blood pressure, age) in order to confirm participant eligibility on completion of the screening period
- Baseline assessment CRF – baseline data collection
- IIET visit- IIET prescription data, heart rates
- Day 7 telephone call follow up CRF – capture intervention fidelity and safety data
- Follow up visit CRF – remote assessments 2, 3 and 4
- AE log CRF – capture any intervention related AEs
- SAE reporting CRF – refer to section 9 for details

- Withdrawal/loss to follow up CRF – to be completed if patient withdraws consent (refer to section 5.6) or has been lost to follow up
- Participant completed questionnaires and diaries
- IE programme alteration CRF.

10.3 Archiving

All essential documents and trial data will be held by the Sponsor for a minimum of five years after the end of the study. Investigator site files should be archived at the participating sites for five years and should not be destroyed until authorisation to do so has been received from the Sponsor.

11. MONITORING, AUDIT & INSPECTION

The study will be conducted in accordance with the current approved protocol, UK policy framework for health and social care research (41), other relevant regulations and standard operating procedures. Regular monitoring will be performed by the Study Co-ordinator to evaluate compliance with the protocol and accuracy in relation to source documents in accordance with the Study Data Management Standard Operating Procedure. Monitoring will verify that the study is conducted, and data are generated, documented and reported in compliance with the protocol and the applicable regulatory and national policy requirements (41). Any data issues in the CRF (such as missing data or data discrepancies) will be addressed by raising data queries for GP sites to resolve where possible. Monitoring may also be conducted by authorised representatives from the Sponsor, host institution and the regulatory authorities if required.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Research Ethics Committee (REC) review

The Chief Investigator has obtained approval from the London – Bromley Research Ethics Committee and the Health Research Authority (20/LO/0422) to undertake this study. The study must receive Confirmation of Capacity and Capability from participating GP recruitment sites. The study will be conducted in accordance with the UK Policy Framework for Health and Social Care Research March 2018 (41) and recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions (42).

12.2 Peer review

This study has been independently, externally peer reviewed by the funder, National Institute for Health Research (NIHR), Research for Patient Benefit scheme, as part of the funding application process.

12.3 Public and Patient Involvement (PPI)

Using an NIHR Research Design Service South East PPI grant, we formed a five-member patient group which met twice to develop the research questions and study design. The proposal was also

discussed at the 'Opening Doors to Research' group, a public group run by the Centre for Health Services Studies (CHSS) at the University of Kent.

The project benefits from having two public co-applicants working alongside the project team who will be fully involved in the project and the decision-making processes throughout. Their role is to assist with the project, including decision making, using their experiences and views as members of the public and their personal or professional experiences of GP services for hypertension.

We will seek additional PPI input from patients and the public through utilising participating GP practice Patient Participation Groups (PPGs), re-consulting with patients' groups formed to develop the project at application stage (detailed above) and the Opening Doors to Research group established at the Centre for Health Services Studies at the University of Kent.

Finally, independent PPI input into the progress of the study will be provided by two public members of the Study Steering Committee identified through local University of Kent, lead NHS trust and NIHR PPI channels.

The below demonstrates areas where PPI input is planned and will be key to the success of the project (this list is not exhaustive and new areas for input may arise):

- review of the documents during preparation for ethical approval and when amendments are made
- input into the interview/focus group questions for patients and healthcare professionals
- design of the patient experience survey
- design training materials for healthcare professionals delivering the isometric exercise intervention
- assist the training session and mock clinics for healthcare professionals delivering the intervention
- assist with the participant focus groups for the study
- contribute to monthly project management/steering meetings
- review of the project data, findings and progress
- contribute to dissemination to the public and lay audiences
- ensure a variety of Patient and Public Involvement in the project.

We will provide appropriate training to ensure PPI collaborators can be fully involved in the project – this will be discussed with each individual. Training in an overview of clinical studies, quantitative and qualitative data collection, data analysis and other topics will be offered through CHSS and through local NIHR CRN, INVOLVE UK and other relevant providers. Public co-applicants will receive training in focus group facilitation and qualitative data analysis and coding so they can fully contribute to data analysis.

12.4 Protocol compliance

All members of the study team, including researchers and health/social care professionals recruiting patients at sites will abide by this protocol. A protocol deviation is any non-compliance with the study protocol. Protocol deviations can reduce the quality or completeness of the data, make the informed consent form inaccurate, or impact a subject's safety, rights or welfare.

Accidental protocol deviations can happen at any time. Where a protocol deviation occurs, this will be reported as soon as possible to the Study Co-ordinator who will document the occurrence and any rectifying actions taken. These will be reviewed by the CI and reported to the Sponsor as per their guidelines. Deliberate deviations from the protocol or deviations which are found to frequently recur are not acceptable, will require immediate action and could potentially lead to a pause in recruitment and data collection pending resolution.

12.5 Data protection and patient confidentiality

Personally identifiable information will be utilised to conduct this research project, the lawful basis of which being to perform a task in the public interest through research to improve healthcare and services. As a publicly funded organisation, the Sponsor will ensure that all data used in this study is appropriate and within the legal basis for data processing and that all participants have agreed to take part in the research. The Sponsor will ensure necessary regulations are adhered to in link with local policies and procedures. To safeguard the rights of those participating in the study the minimum of personally identifiable information will be utilised. The Sponsor, the University of Kent and Canterbury Christ Church University will hold the data for this study in pseudo-anonymised form and service users will be notified of the Sponsor's policies under GDPR in the Participant Information Sheet. All GP practices recruiting participants for the study will be asked to complete the Organisation Information Document which will act as a site agreement and data processing agreement for the purposes of this study.

12.5.1 Collection and processing of data (including personal data)

All participants in the study will only provide information that is necessary to answer the study questions. The nature of this information will be clearly provided in the information sheet along with information regarding their right to withdraw at any time and that for service users, withdrawing will not affect any current or future care.

The information collected will include personal information such as age, gender and medical conditions, health and social care resource use. If interested in taking part in the focus groups, participants will be asked to provide the necessary contact information (emails and/or telephone numbers). A unique code will be assigned to each service user and will be used to label the relevant documentation and files (e.g. data, surveys, audio recordings and transcripts focus groups) to ensure anonymity. Once the unique code has been assigned to the documents, personal information that may enable the participant user to be identified will be removed. The research study sites recruiting participants will be the only organisation holding the master key to link participant study code to their name and medical records data. The project team will hold contact details shared by participants linked to their participant study code for contact purposes only and for taking part in a focus group. This will be stored separately to CRF data in a password protected file on a secure drive. Contact

details held by the project team will be destroyed at the end of the study, retaining only participant study code CRF's.

12.5.2 Storage of data and access (including personal data)

Any personal data will be stored on password-protected computers within a limited access folder on the university partner network with unique codes allocated to each service user. Personal information that may enable the service user to be identified will be removed from interview and focus group transcripts.

Electronic files with personal information will be password protected and stored on the university partner networks in folders that can only be accessed by the research team. These folders will not be transferred from the network onto personal computers. Data in paper form will be stored in locked filing cabinets in offices that are locked when unoccupied. Access to the data collected during the project (including any participant personal data) will be restricted to the research team, and data will not be shared with anyone else. This is possible by placing clear restrictions to individual access to files on the university partner networks. Any personal data will be destroyed on completion of the project. The coded data will be stored for five years following the completion of the study, when it will be destroyed.

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.

12.5.3 Analysis and reporting of data

All data will be coded, and the interview and focus group transcripts will be pseudo-anonymised before analysis. These will not be linked back to the personal data. The study team will ensure as far as possible that specific individuals and teams are not identifiable in written reports and that no quotes can be traced back to the persons concerned. However, while they will not be named, there is the potential that some participants (namely healthcare professionals delivering the intervention) may be identifiable to local staff or organisations working locally. While their data will be coded and anonymised as described, this potential risk will be fully explained to the professionals prior to obtaining consent. Care will be taken on how the data is reported, and those affected will see drafts of the report before wider dissemination.

12.6 Sponsorship and indemnity

The East Kent Hospitals University NHS Foundation Trust will act as the Sponsor for this study. Delegated responsibilities will be assigned to the Chief Investigators, Study Management Group, Study Steering Committee and the study sites taking part in this study. The Sponsor holds relevant insurance policies which apply to this study.

12.7 Amendments

Any substantial amendments to the protocol or other study documents may require review and approval by the REC before the changes can be implemented to the study. Where amendments are required, NHS HRA and REC procedures will be followed.

12.8 Access to the final trial dataset

Only the study team will have access to the full dataset throughout the study. A summary of findings will be reported to the participating research sites on completion of the study. Relevant data reports will be produced by the project team for the benefit of the Study Steering Committee which contain only pseudo-anonymised data.

Personal data collected in the course of the study will not be shared outside the research team in line with participant consent. Participants will be asked to consent for their data to be anonymised and retained once the study is completed for use in future unspecified research. The sharing of anonymised data with other researchers is of benefit to wider society in order to facilitate the following:

- assist with service provision improvements of benefit to the NHS
- enable new research questions to be answered in existing data
- share knowledge about best methods for data collection, linkage and analysis
- ensure that collected data are cleaned, well documented, with value added
- independently verify established research findings
- development and testing of new research methods
- use to best effect the gift of data made by study participants.

Data sharing represents an efficient use of public money and supports more timely scientific discovery. Anonymised data will be made available to researchers at universities, NHS organisations or other healthcare providers where the sharing of data has a clear defined purpose and its use will be of benefit to wider society (43).

13. DISSEMINATION POLICY

13.1 Dissemination policy

This research will lead to the following outputs: published guidelines for training and delivery of an home-based IE intervention for Stage 1 hypertensive patients in the NHS; data to inform sample size estimates for a substantive trial; a patented IE tool (Figure 2) and copyrighted training manual for the IE intervention delivery; the identification of barriers and enablers for delivering this intervention in the NHS; and a funding application and protocol for a substantive randomised controlled trial in the NHS to establish effectiveness and mechanisms of IE action in reducing BP in this population.

The results of the study will be disseminated through local, national and social media. We will present our results at national and international conferences (e.g. UKactive Summit) and publish findings in high-impact, open access peer-reviewed journals in the field where the project team's previous work has been well received (e.g. Hypertension, Journal of Human Hypertension, Journal of Hypertension, Journal of Applied Physiology, PLOS Medicine, British Medical Journal).

Study participants will receive a personalised report of their own results and a summary of study findings will also be sent to GP practices and local organisations (E.g. CCCCG, EKHUFT, Kent and Medway STP, Kent AHSN and NIHR CRN:KSS). The study final report will be submitted and a lay summary disseminated to a wider audience to create national impact by engaging with policy and national governing body organisations (e.g., PHE, NICE, National Centre for Sport & Exercise Medicine), third sector organisations (e.g. BHF, BHS) with the aim of understanding the evidence required to influence current hypertension treatment guidelines with respect to offering lifestyle interventions like IE as standard care and a tangible product that can be marketed in the NHS.

13.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship for report and publication outputs from this evaluation will be based on the following four criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work, an author should be able to identify which co-authors are responsible for specific parts of the work. All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged.

13.3 Intellectual Property Rights

An Agreement is in place between collaborating project partners outlining the rights with respect to IP used in the project. This Agreement does not affect the ownership of any Intellectual Property Rights in any Background or in any other technology, design, work, invention, software, data, technique, know-how, or materials which are not results. Each Party has granted each of the other Parties a royalty-free, non-exclusive licence to use its Background IP for the purpose of carrying out the Project. The Intellectual Property Rights in them will remain the property of the Party which contributed them to the Project (or its licensors).

All parties and each of its employees and students will have the irrevocable, royalty-free right to use any of the Results (except the following types of Result: results relating to the development, improvement, enhancement or modification of the P1vital Assessment Tools) for Academic and Research Purposes excluding research projects which are carried out by the Academic and Charitable Party with any third party and Clinical Patient Care.

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