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PROTOCOL

FULL/LONG TITLE

Programme on Adherence to Medication (PAM): A very brief nurse-led intervention, followed by a text message or a smartphone app to support medication adherence in people prescribed treatment for hypertension in primary care. A randomised controlled trial.

SHORT STUDY TITLE / ACRONYM

PAM trial

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Abstract

Background. Medication adherence can reduce morbidity, mortality, and health care costs associated with high blood pressure. However, many patients are non-adherent to prescribed medications, and thus remain under treated. Very brief advice during usual care consultations followed by ongoing digital intervention could provide highly tailored behavioural support for medication adherence. However, rigorous evidence about the effectiveness and cost effectiveness of behavioural interventions for medication adherence in primary care is limited.

Objectives. This study will evaluate the effectiveness and cost effectiveness of the Programme on Adherence to Medication (PAM) intervention, consisting of a very brief intervention facilitated by nurses or health care assistants followed by a text messages programme or smartphone app, in patients prescribed treatment for hypertension and high blood pressure in primary care. The study includes a process evaluation.

Methods. An individually randomised controlled trial recruiting patients treated for hypertension and high blood pressure in primary care practices in the UK. The Intervention group will receive the PAM intervention in addition to usual care and will be compared to usual care alone. Home blood pressure measurements and biochemical adherence will provide evidence for primary analysis. Questionnaires and practice level data will inform the cost effectiveness analysis.

Results. Recruitment to the trial will began in January 2021 and follow up of participants will be completed in August 2023.

Conclusion. The results of this study will enhance the evidence base of the effectiveness and cost-effectiveness of very brief intervention followed by digital support to improve medication adherence and decrease blood pressure in people prescribed antihypertensives in primary care.

Introduction

Hypertension is a global health challenge accounting for 8.5 million deaths worldwide from cardiovascular disease despite the availability of low-cost pharmaceutical treatment [1,2]. Hypertension is expected to affect 1.56 billion adults by 2025 [2]. In the UK alone, there are 14.5 million people diagnosed with Hypertension and many more are undiagnosed. About half of these hypertensive patients have high blood pressure (HBP) [3-5], and many have other accompanied health conditions, like Type 2 Diabetes and High Cholesterol increasing the risks for health complications associated with high blood pressure [3-6].

Adherence to pharmacological treatment is highly effective at reducing blood pressure, multimorbidity and mortality associated with hypertension [7]. However, many people do not take their medications as prescribed [8,9]. Medication non-adherence reduces the effectiveness of treatment, wastes healthcare resources, and leads to additional consultations, referrals, investigations, prescriptions, and hospital admissions. In England, non-adherence to treatment is estimated to cost the health service over £390 million per year [10]. A Cochrane review of interventions for medication adherence concluded that current interventions are complex, not effective, and trials are limited to non-rigorous evaluation [11]. NICE has recommended that novel and cost-effective interventions for medication adherence should be developed and rigorously assessed [12].

The clinical management of hypertension is one of the most common consultations in primary care. In England over 14% of primary care consultations are to treat hypertension [3]. Primary care practitioners have an important role in advising, encouraging, and supporting patients to adhere to their prescribed treatment, however their time is limited and expensive. Nurse led advice could potentially support patients with hypertension [13] and might be a cost-effective solution for primary care [14]. However, there is no evidence about effectiveness and cost-effectiveness to support adherence to blood pressure lowering medications [15,16].

A low-cost way to support treatment adherence is for practitioners to integrate brief or very brief behaviour change interventions (VBI) into routine consultations [12,17,18], and signpost patients to options for ongoing support [18,19].

Text messaging and smartphone apps are popular and low-cost mediums for regular communication in the UK population. During 2016, more than four in five adults (83%) used traditional mobile messaging services [20], and the number of downloaded apps worldwide

has reached 20 billion in 2020 [21]. Previous studies suggest that such interventions could potentially support medication adherence and might be feasible adjunct to primary care consultations, though the evidence of such interventions within the constraints of primary is weak [22-27].

To address this gap, we have developed a medication adherence behavioural intervention, facilitated by a nurse led VBI followed by a text messaging programme and a smartphone app, the PAM intervention. Our previous research suggests that PAM is feasible and potentially effective at supporting medication adherence and reductions in blood pressure in patients prescribed treatment for hypertension and high blood pressure, as an adjunct to usual care consultations [28]. The aim of this trial is to evaluate the effectiveness and cost-effectiveness of the PAM intervention to improve medication adherence and reduce blood pressure as an adjunct to usual care. The trial includes a process evaluation.

Methods

Trial design

The study will be two-parallel group multicentre individually randomised controlled trial of the PAM behavioural intervention with primary outcome measured at twelve months. This trial does not involve changes in current pharmacological treatment, and it will not introduce or use new medications (trial flow chart, Figure 1).

Participants and recruitment

We will recruit primary care practices across England and Wales to take part in this trial. Primary care practices will be eligible to participate if they have at least 250 eligible patients with hypertension and high blood pressure (HBP). With an average of over 6000 patients with hypertension per primary care registry most practices will be eligible. We will aim to recruit practices with a range of deprivation levels (defined by the Index of Multiple Deprivation derived from the practice post code) and proportionately at urban and rural areas.

Practices will need to have at least one eligible health care practitioner (i.e., nurse or healthcare assistant), who advice patients with hypertension during annual review, blood pressure checks, medication reviews, or similar consultations. To maximize generalisability, we have not specified additional practice-level eligibility criteria (for the list of practices, see supplementary file 1)

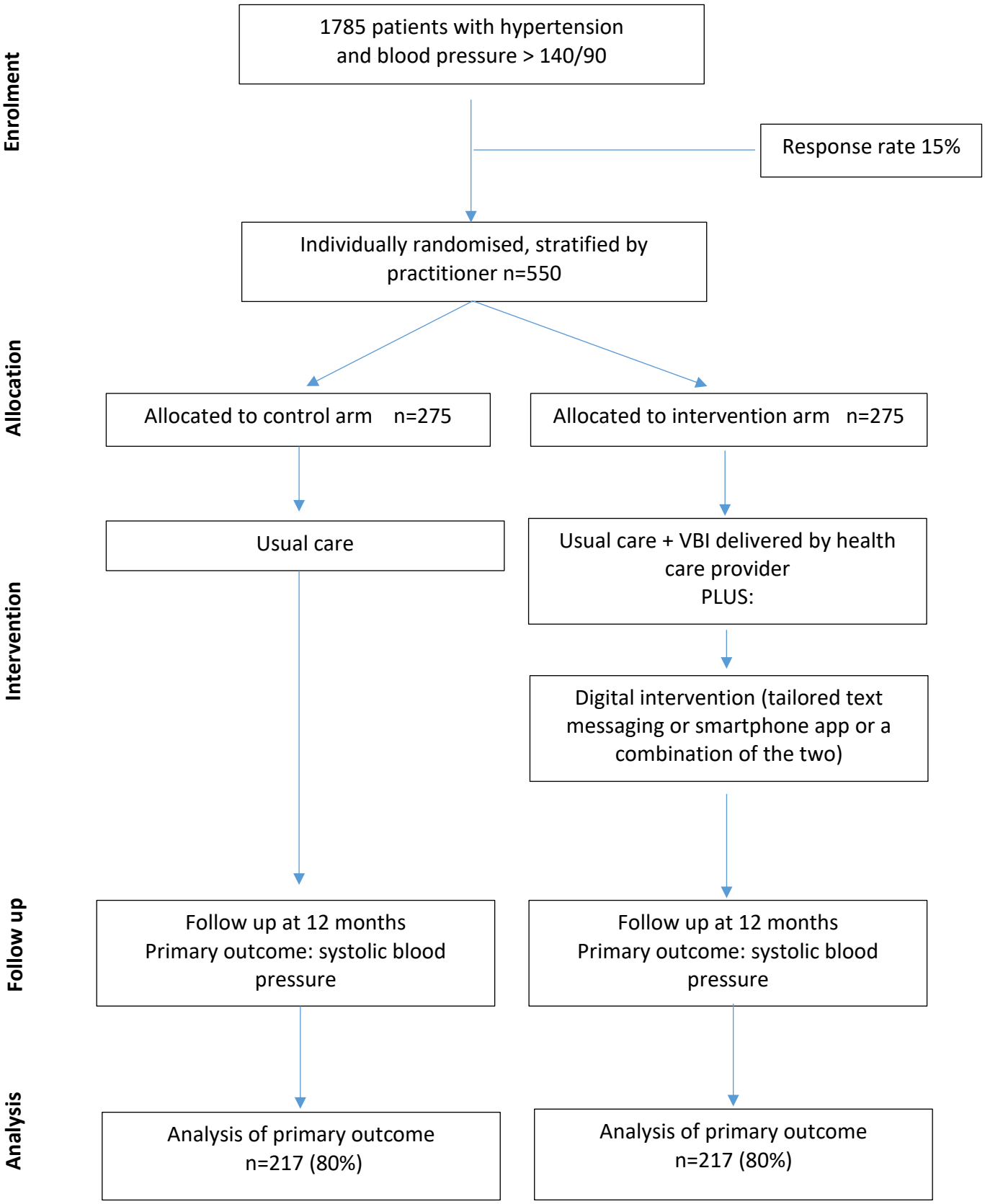

Figure 1. Trial flow chart

Participants will be eligible for inclusion if they: (a) have a diagnosis of Hypertension; (b) are prescribed at least one blood pressure lowering or antihypertensive medication (e.g. ACE inhibitors, beta blockers, calcium channel blockers, diuretics, alpha1 blockers, alpha2 agonists) for at least one month before study recruitment, as confirmed by practice records; (c) have poorly controlled BP (HBP, High Blood Pressure) as indicated by at least two sequential clinical measures (i.e. clinic readings of blood pressure >140/90 mmHg if under 80 years old and >150/90 mmHg if over 80 years old or home blood pressure readings >135/85 mmHg if under 80 years and >145/85mmHg if over 80 years) obtained during the preceding 12 months; (d) have a good understanding of English; (e) own and are able to use a mobile phone; and (f) have the capacity to provide informed consent.

Patients will be excluded if they: (a) have blood pressure > 200/100mm Hg, or postural hypotesion (>20mm Hg systolic drop), (b) have a diagnosis of dementia or other cognitive difficulties that could affect study participation; (c) have had a recent severe life-threatening event or are under treatment for another long-term health condition e.g. chemotherapy for cancer; (d) receive kidney dialysis; (e) take part in another medication adherence or digital intervention; (f) plan to move from the area in the next 12 months, (g) BP is not managed by their GP practice.

Eligible patients will be identified through practice database searches, conducted by a member of the practice staff, and checked for eligibility by the practice GP. Practices will invite patients in the trial opportunistically during usual care appointments, or with SMS text messages and postal invitations sent out in advance. All patients will be provided with written and verbal information and at least 24 hours to decide whether or not to participate. Strategies during trial uptake will aim to identify and address patients' beliefs about medicine prescribed for hypertension and treatment adherence. Patients will be asked to complete pre-screening questions self-reporting their beliefs about medication adherence. Those expressing an interest to participate will be followed up by phone calls by a member of the research team to address concerns and support trial participation. All patients will provide written informed consent before any trial procedures commence (participants invitation pack, supplementary file 2).

Randomisation and blinding

The practitioner will use an online webpage to randomly allocate patients in the intervention or the control group. Adults with hypertension and high blood pressure (>140/90mmHg if readings obtained at clinic appointment or >135/85mmHg if obtained by home BP readings) will be allocated randomly by a computer in a 1:1 ratio to receive the VBI followed by the digital intervention or usual care only. Stratification will be per health care practitioner only, using a method of random block size of 12. Although the allocation sequence will be concealed, once a participant is allocated, neither the health care practitioner nor the participant will be blind to group allocation.

Practitioners Training

Nurses or health care assistants will complete a three-hour training: on-line on their own followed by a meeting with a member of the research team. Practitioners will be asked to repeat the online training before they initiate the remote consultations.

The training is theory-based and informed by results from our previous medication adherence research in primary care [27,29-32]. The primary aim of the training is to address practitioners' beliefs about the underpinnings of treatment non-adherence, and to enable them to effectively facilitate medication adherence risk appraisals using shared decision-making strategies (the VBI). A secondary aim of the training is to address professional norms and provide practitioners with strategies to enable them signpost non-adherent patients to ongoing digital support (supplementary file 3).

Interventions

The PAM behavioural intervention is a theory and evidence-based intervention [27-34]. It consists of two-components: the VBI followed by a digital component. The VBI is facilitated by the practitioner remotely using telephone or video link. The VBI consist of risk appraisal information about adherence to prescribed antihypertensive medications, aiming to address patients' risk perception and enable intention to medication adherence.

The digital component of the intervention is delivered either by text messages or a smartphone app (the app is available on Android phones only). Participants who select the text message intervention will receive automated messages to switch to the app at least 4 times during the 12-month intervention. The digital interventions consist of highly tailored

advice aiming to address the mechanisms that underpin medication adherence behaviour change. Based on information obtained from participants themselves, participants will receive individually tailored messages designed to address one or both of intentional non-adherence (INA) and non-intentional non-adherence (NINA) reasons. INA is addressed with messages to reinforce necessity beliefs about medications (e.g., "even if you do not feel any different after taking each of your pills, you can keep your BP under control when you take all your meds as prescribed"), and to counter concern beliefs in a non-confrontational way (e.g. "your tablets support you to keep your blood pressure under control..."). NINA is addressed through (a) explicit (e.g., "do not forget to take your medication today: Ramipril, 2 tablets, 1.25mg, at 16:00") or implicit reminders. The content of the explicit reminders is updated should adjustments to the prescribed treatment made by the practice GP following the consultations. Other behaviour change strategies are included as appropriate (e.g., 'report whether or not the behaviour was performed'). Control group will receive usual care only. For more details about the intervention content and intervention procedures see supplementary file 4.

Outcomes and Outcome Measurements

Primary trial outcome – effectiveness

Intervention effectiveness will be evaluated by comparing the mean changes in systolic blood pressure together with the associated mean change in biochemically validated medication adherence between the intervention and the control group at 12 months.

Blood pressure measurement. Primary outcome measure for Blood Pressure will be obtained by the Home Blood pressure measurements at 12 months [35]. Blood pressure will be measured using validated automated electronic sphygmomanometers (A&D UA-611) with 30 memories function.

Participants will be posted a blood pressure monitor and a BP template after their baseline consultation and at 12-months. They will be asked to take twelve BP measurements over one week (two measurements over three mornings and over three evenings with two minutes gap between each measurement), record their BP readings on a template, and post the BP monitors with the blood pressure record to the research team.

Patients will receive guidance in a printed leaflet with information and a video demonstrating how to perform the BP measurement and will be asked to record the measurements on the

template, to ensure that accurate BP measurements are obtained (BP measurements, supplementary file 2). To improve completion of the remote measurements we will track the BP monitors, and we will contact those not completing the measurements as requested, to explore and address barriers in providing valid BP measurements. Two members of the research team blinded to group allocation will contact the participants to facilitate adherence to remote measurements.

BP readings recorded at the memory of the BP monitors will be extracted and included in the analysis as an objective outcome measure of BP. Home BP measurement will be obtained at the completion of the baseline remote consultation and at 12 months follow up. The anonymised data will be extracted by a member of the research team blinded to group allocation.

In addition, practice BP measurements before randomisation (as the baseline measure of the BP outcome) and the closest to the at 12 months follow up will be obtained by the practice records.

Blood pressure measurements extracted by the BP monitors and those obtained by clinic readings will be analysed separately. Primary measure of BP will be the Home BP measure extracted by the memories of the BP monitors, and secondary blood pressure measure will be the clinic BP measure at 12 months follow up.

Biochemical adherence measurement. Primary measure of medication adherence will be evaluated using biochemical analysis of urine samples at 12 months. Biochemical analysis is measuring the presence or absence of anti-hypertensive medication (or their metabolites where appropriate) during the past 12-24 hours from collection.

Patients will be posted a urine sample kit and a template at completion of the remote consultations and at 12 months. The template will prompt participants to report the name and the dosage (in mg) of all the medications they have been prescribed for hypertension. Participants will be asked to provide spot urine samples (10ml) early in the morning, record the name and the dosage (in mg) of all blood pressure lowering medications at the template, and post using special delivery the urine sample and the template to the laboratory for analysis on the same morning of sample collection. Similarly, to BP measurement, participants will receive guidance in a printed leaflet with information on how to provide valid measurements for analysis (supplementary file 2).

A biochemical test of the urine sample will be undertaken by liquid chromatography-tandem mass spectrometry (LC-MS/MS). LC-MS/MS is highly sensitive and at present is the most specific technique of biochemical testing of medication adherence. Biochemical medication adherence will be calculated by the number of daily doses of anti-hypertensive medications detected in the urine out of the number of daily doses of medications prescribed. Total adherence to antihypertensive medication will be defined if all daily prescribed doses (or their metabolites where appropriate) are detected in the urinalysis, partial adherence if fewer doses than prescribed are detected at analysis, and total non-adherence will if no prescribed antihypertensive medications are detected [28,36]. Anonymised data will be sent to the research team using encrypted internet files.

Medication adherence measurement. Secondary outcome measure of medication adherence will be evaluated using two single self-reported items at 12 months. The practitioner will obtain patients self-reported medication adherence at baseline during the remote consultation using two questions: 'how much of your prescribed medications have you taken in the last month?' with responses at a Likert scale from 0% to indicate non-adherence to 100% to indicate adherence; and 'how many days in the past week have you taken all your medications as prescribed' with Likert scale response from 0 days to indicate non-adherence to 7 days to indicate adherence. Follow up measurements will be obtained via questionnaires enclosed with patients 12-months measurement package.

Repeat prescription measurement. Tertiary outcome measure of medication adherence will be evaluated by repeat prescription data extracted by practice records for a duration of 3-months prior randomisation and at the 12 months. For a subsample of patients prescribed medications for Type 2 Diabetes and/or High Cholesterol, repeat prescription data for these medications will be obtained in addition to those prescribed for hypertension.

Repeat prescription outcome will be defined by the number of days of medication obtained by the participant. It will be calculated by the number of days the supply of medication was issued excluding the next prescription day, divided by the number of total days of the assessment period (i.e., 420 days) as per our previous trial. Per patient ratio will be adjusted per denominator prescribed period (28 or 56-day prescription). The overall adherence ratio will be calculated by averaging each patient's ratio divided by the total number of participants.

Assessment period at baseline will refer to the supply claimed by the participant for a period of 3 months before randomisation, and assessment period at follow up will refer to the last 3 months of the trial. Data for the repeat prescription measurement will be extracted by a member of the practice staff and sent to research team using encrypted internet files.

Biochemical adherence, self-reported measurements and refill prescription measures will be analysed separately, and the primary measure of the medication adherence outcome will be the biochemical adherence.

Secondary trial outcome – cost effectiveness

Cost effectiveness will be evaluated by estimating the age-related relative risk of having a cardiovascular event following the use of antihypertensive medications together with the associated reductions in blood pressure. Secondary cost-effectiveness measure will be the value for health, and tertiary measure will be the cost of the intervention for the NHS.

Risk Reduction of Cardiovascular Events. The relative reductions in cardiovascular events will be defined by the effect of the improved adherence to daily prescribed doses of anti-hypertensive medication together with the associated unites of reductions in blood pressure on the change in the age-related relative risk of cardiovascular events.

We will base and will build upon our model on previous models [37] to estimate the PAM intervention effect (i.e., changes in blood pressure and associative changes in daily adherence) on age-related relative risk reductions of CVD events assigning UK-specific values.

Value for Health. We will estimate value of health effects using the Quality-of-Life Adjusted years (QALYs) retrieved from the EQ-5D-5L quality of life questionnaire at trial-level [38] with a discount rate of 3%. To account for declining quality of life with age, QALYs will be estimated by assigning UK-specific health state evaluations to EQ-5D-5L profiles over time. To account for declining quality of life with age, we will account for multiplicative values of the UK age-specific utility estimate and the specific health state.

Intervention Economic Cost for the NHS. We will measure resource use, adverse events attributed to the intervention, and the cost of the intervention at trial-level to estimate the cost of the intervention for the NHS.

Resource use measurement. We will measure the use of resources for treatment via questionnaires. Participants will be asked to report their use of NHS services and facilities and

out-of-pocket health care expenditure. This includes consultations with practice staff hospital outpatients, hospital admissions, and attendance at accident and emergency facilities. They will be asked to self-report on health and hypertension-related work productivity loss to capture work productivity and time off work due to reasons related to hypertension. To estimate NHS and social services cost, they will be asked to report the medication prescription cost and medication management costs. Each collects data for the duration of the proceedings 6 months (for baseline questionnaire, see supplementary file 5).

Participants will be sent and asked to complete the Recourse use and EQ-5D-5L at baseline, at 6 month follow up, and at 12 months follow up.

Cost of the intervention treatment. To measure the intervention cost we will calculate the cost for the person who facilitates the training to the nurses; health care practitioner time spent training on and delivering the VBI and cost of text messaging programme/smartphone app. Data for practitioners training and the VBI are automatically recorded at digital log files transferred via encrypted internet protocols and at research team records at baseline. Data for the text messaging/ app will be recorded and extracted by digital log files during the 12 months.

Practice level data will include Index of Multiple Deprivation obtained by practice post code at baseline. We will also obtain publicly available data on number of patients with hypertension, practitioners and QOF achievements at baseline and at 12 months. This data will provide information about the implementation setting.

Tertiary trial outcomes – additional modifiable risk factors related to hypertension

Tertiary outcomes will be Haemoglobin A1c and/or full lipid profiles (for a subsample of patients with multimorbidity) [6], and additional lifestyle modifications related to hypertension (for all patients) [39-43].

Additional clinical outcomes. The trial will evaluate Haemoglobin A1c and full lipid profiles (triglycerides, cholesterol, HDL cholesterol, LDL cholesterol) at 12 months, for a subsample of patients who have been prescribed treatment for Type 2 Diabetes and/or High Cholesterol in addition to hypertension. Patients will be provided with finger prick tests and asked to collect home blood samples for each or both clinical outcome and post the samples to the laboratory for analysis. Measurements will be obtained at completion of baseline consultation and at 12 months.

Blood samples will estimate the levels of Haemoglobin A1c, or triglycerides, cholesterol, HDL cholesterol, LDL cholesterol in the blood during the past three months. Participants will receive guidance from the research team and a printed leaflet with information demonstrating how to perform the blood sample measurement, to ensure that valid measurements are obtained for analysis. To improve adherence to the blood sample remote measurements we will apply similar strategies reported for the other remote measurements. In addition, blood sample test results collected in clinic and closest to baseline and to 12 months follow up, for haemoglobin A1c and full lipid profile will be obtained.

Remote blood sample measurements and those obtained in clinic will be analysed separately. Remote measurement results will be the primary outcome measure and the clinic results the secondary outcome measure, for each of Haemoglobin A1c and full lipid outcomes. Clinic blood test results will be used to supplement missing values for remote blood test results, should the completion for the remote measurement be very low (<70%).

Additional lifestyle modifications. Changes in health behaviours related to hypertension will be measured at 12 months via 5 single items, one item measuring each of salt consumption (how often do you eat food high in salt i.e., more than 6g/ 1 teaspoon per day? with response at a Likert scale from 1 always to indicate high consumption of salt to 5 never to indicate low consumption of salt), alcohol consumption (how many drinks containing alcohol e.g. half a pint of beer or a small glass of wine, do you have on a typical day when you are drinking? with response at a Likert scale from 10 or more to indicate high consumption of alcohol to 0 to indicate low consumption of alcohol), diet (how often do you eat 5 portions of fruits and vegetables? A portion is equal to 80g. with response at a Likert scale from 1 daily to indicate healthy diet to 5 seldom to indicate low consumption of healthy diet and an additional response of 6 to indicate a response for not being able to eat fruits and vegetables), physical activity (how often do you exercise at a rate that raises your pulse and produce hard breathing? In younger people this might be running, cycling or sport, or brisk walking for older people. with response at a Likert scale from 1 daily to indicate physical activity to 5 seldom to indicate low levels of physical activity and an additional response item of 6 to indicate not being able to exercise due to disability), and smoking (do you smoke? with a response yes to indicate smoking behaviour or no to indicate non-smoking behaviour).

Sample Size Estimations

The randomisation ratio will be 1:1. A final sample size for analysis of 434 patients (217 per arm) will detect a 5-mmHg difference in systolic BP between groups at 12 months with 90% power (alpha = 0.05, 2-sided test) assuming a standard deviation of 16mmHg (this value is a conservative estimate based on a recent adherence trial [28]. A 5-mmHg difference in systolic BP is of clinical significance, being associated with a 20% reduction in major vascular events [41-43]. This sample size (N = 434 analysed) also gives 81% power to detect a smaller difference in systolic BP of 4.4 mmHg. Assuming 20% lost to 12-months follow-up, we will need to randomise 550 patients (275 per arm) in order to achieve total of 434 patients at follow up for analysis of the primary outcome. Full lipid profile will be analysed at a subsample of 42%, and glycated haemoglobin (HbA1c) at 35% of patients [28].

We estimate that 30% patients will have a BP above target in each practice, of whom 15% will meet criteria for invitation and 4% will attend remote consultations. Assuming an average 6000 adults with hypertension per practice registry, there should be at least 250 eligible patients per practice to achieve the per practice recruitment target.

Based on the feasibility trial [27], it is feasible to recruit on average six patients per month into the trial. So, to recruit 550 patients, assuming a six-month recruitment period per practice, would require 16 to 17 practices. However, to increase generalisability of the research and reduce the workload for each practice, we will recruit more practices. Therefore, we propose to recruit on average 50 practices across England and Wales, but still allow a six-month recruitment period per practice.

Statistical Analysis

Effectiveness

We will use an intention to treat approach, maintaining participants in the arm to which they were randomised regardless of whether or not they received the intervention. The main analysis will use analysis of covariance (ANCOVA) to compare the mean systolic BP at 12 months in the two arms and quantify this as a difference in means and 95% confidence interval, adjusting for baseline value, primary care practice, gender, and age. A similar approach will be used for the medication adherence outcome, similarly to the feasibility trial analyses [28].

Missing data will be handled using (i) multiple imputation and (ii) within a sensitivity analysis considering optimistic and pessimistic scenarios for the intervention effect size in those with missing data and incorporating baseline predictors of primary outcome missing status that are differential by arm. This analysis will be undertaken to examine the robustness of the main analysis result to the 'missing at random' (MAR) assumption. The aim is to adequately explore the impact of departures from the MAR assumption on the primary outcome results [44]. We will also conduct a Complier Average Causal Effect (CACE) analysis [45] by defining a 'compliant' per protocol population as only those participants who used the digital intervention for at least three months.

Pre-specified subgroup variables will be examined in relation to the primary outcome of Blood Pressure and will involve an initial test of differential intervention effect across the subgroup variable before summarising the intervention effect within subgroup categories. Subgroup variables will include age, gender, deprivation score (Index of Multiple Deprivation IMD 2007, derived from the patient's postcode [46]), geographical region (East of England, London, South-East of England, South-West of England, Yorkshire and Humber, and Wales) and health care practitioner. For the continuous moderators, such as medication adherence change the intervention effect observed in each subgroup will be estimated with a 95% confidence interval having an informative width of +/- 4.3 mmHg. All significance tests will be two-sided and assessed at the 5% level of significance. Data will be anonymised, and all identifiable information will be deleted before sent to trial statistician for analysis.

Cost-effectiveness

We will use the Markov model to estimate the long-term cost effectiveness of the PAM intervention compared with usual care. A within-trial economic evaluation will be conducted from the perspective of the public sector (NHS and social services), reporting incremental cost per mmHg reduction in blood pressure and QALYs gained over 12 months. We anticipate that the bulk of QALY gains will be achieved through avoided downstream cardiovascular events, therefore the trial data will be combined with prior data and inserted into the health economic model to generate a revised estimate of the incremental cost per QALY gained of the intervention over a lifetime horizon. Sensitivity analysis will examine the effect of different time horizons and reduced effectiveness of the intervention. The value of

information analysis will be repeated to ascertain the value of additional research on conclusion of this programme [37].

Process Evaluation

The trial includes an embedded process evaluation, with measurements of intervention engagement including measures of fidelity, and mechanisms of action [47].

Fidelity, VBI. Fidelity of the VBI will be measured using consultation audio-recordings. Practitioners will be asked to randomly select and audio-record at least three of their consultations. Consultation transcripts will be coded using a coding frame against the pre-scheduled consultation content as per online training, for each of the intervention or control group participants. The coding frame for the intervention group participants will include the pre-scheduled content for the VBI and the signposting to the digital component of the intervention, in addition to the control group coding frame.

Transcripts will be coded for frequency (giving a value of 1 if each content was facilitated as per training or value of 0 if each content was not facilitated as per training, total score of above 75% will indicate high fidelity, 50-75% medium fidelity or below 50 % low fidelity) and quality (giving a symbol of +++ if content was facilitated using shared decision making strategies, ++ if content was partially facilitated using shared decision making strategies or + if content was facilitated without the use of shared decision making strategies; shared decision making strategies will be indicated by the level of interactivity and patients' involvement during the remote consultation, and will be independently evaluated by transcript coders). Intervention and control group coding will be compared, and any additional codes will be extracted inductively, to inform the VBI intervention mechanism of action.

We will also measure completion rate of the theory-based training using objective proxy (e.g., frequency and duration of attending the online training) captured by digital log files. We will use a median split (e.g., total duration 45 min) to estimate completion (above 45 min) or non-completion (below of 45 min) of the online training, and we will also record completion of the in-person training with a member of the research team (45 min). Completion of the training will be defined when practitioners complete the online training and the in-person training before they initiate the real time remote consultations with the patients.

Engagement, digital intervention. We measure engagement using quantitative and qualitative data. We will use proxy measures of engagement with the digital content of the intervention using quantitative data captured by digital log files. We define intervention engagement using two quantitative variables; intervention use and intervention interactivity. Digital log files will be coded for frequency of intervention content use (giving a value of 1 if each content was received by the participant or value of 0 if content was not received) and interactivity with intervention content (giving a value of 1 if each interaction response to intervention content or the value of 0 if there was no interaction response to the intervention content). Variables will be combined to estimate engagement. We will use a generic framework to operationalise engagement; that is, engagement will be defined as high when more than 70% of the intervention content was marked as received or interacted with by the participant, medium when 50-70%, and low when less than 50% of the intervention was marked as received or interacted with by the participant for a duration of 3 months [32]. Total engagement will the digital component be calculated using log values (logging each participants engagement score to the total number of participants). Based on results from previous studies, we anticipate that engagement will be treated as a continuous variable [28,32].

We will further explore intervention engagement using qualitative data obtained by semi-structured telephone interviews (see below at mechanisms of action).

Engagement, intervention. Overall intervention engagement will be explored by synthesising data from the VBI fidelity and the digital intervention engagement. Total engagement will be defined as high (when all VBI comments were facilitated and participants were engaged in the digital component above 70%), medium (when all VBI comments were facilitated and participants were engaged in the digital component 50-70%) or low (when all VBI comments were facilitated, and participants were engaged in the digital component below 50%). Data will be coded independently by two researchers and any discrepancies will be resolved with discussion by a third researcher.

Intervention mechanisms of action

To evaluate the mechanism of action, hypothesised to underpin improvements in medication adherence, we will collect data by (a) patients' self-reported questionnaires measuring

intervention theoretical determinants, (b) consultation audio-recordings, and (c) in-depth telephone interviews with a subsample of practitioners and patients.

In addition, interviews with practitioners will aim to explore their views and their recommendations about the behavioural intervention and the implementation of the Very Brief Intervention (VBI) in practice.

Theoretical determinants measurements. The theoretical determinants of the intervention have been described in the programme theory (supplementary file 4), and these are: intention to medication adherence, non-intention to medication adherence, beliefs about taking medicine, beliefs about medication adherence, medication adherence affective attitudes, generic emotional state, medication adherence self-efficacy, medication adherence perceived behavioural control, and medication adherence social norms.

Intentional medication non-adherence and non-intentional medication non-adherence will be measured using the 5-item MARS [48]; 4 items measuring intentional non adherence and 1 item measuring non-intentional non-adherence (e.g., 'I forget to take my tablets, I take less of my tablets than instructed', with response at a Likert scale from 1 always to indicate high non-intentional non-adherence to 5 never to indicate low non-intentional non-adherence).

Beliefs about taking medicines will be measured using 10-item Beliefs about Medicine Questionnaire (BMQ) [49] (e.g., necessity beliefs 'my health at present depends on my medicine' with response at a Likert scale from 1 strongly agree to indicate strong necessity beliefs to 5 strongly disagree to indicate low necessity beliefs; and concern beliefs 'having to take medicines worries me' with response at a Likert scale from 1 strongly agree to indicate strong concern beliefs to 5 strongly disagree to indicate low necessity beliefs).

Beliefs about medication adherence will be measured using 3 single items ('if I were to take all my prescribed tablets every-day, it would do more harm than good' 'if I were to take all my prescribed tablets every-day, it would cause me unpleasant side effects', 'if I were to take all my prescribed tablets every-day, it would mean that my health depends on them' with Likert scale 1 agree to indicate strong negative beliefs about medication adherence to 3 disagree to indicate low negative beliefs about medication adherence'). Each of these items will be treated as continuous variables and included in the quantitative analyses.

Affective attitudes will be measured using 1 item ('taking my medications without missing a day is…', with a Likert scale 1 for pleasant, 2 for neither pleasant nor unpleasant, and 3 not pleasant)

Self-efficacy will be measured using 4 single items (e.g. 'I am confident that I can take all my prescribed tablets even if I am busy at home/ even if I am at a public place/ even if there is no one to remind me/ even if I am with friends or family', with Likert scale of 1 agree to indicate strong self-efficacy to 3 disagree to indicate low self-efficacy)

Generic emotional state will be measured using two single items (e.g., 'how much of the time during the past month have you felt calm and peaceful' with a Likert scale response from 1 all of the time to 3 none of the time, and 'how much of the time during the past month have you felt worried and troubled' with a Likert scale response from 1 all of the time to 3 none of the time)

Social norms will be measured using 1 item ('if they were prescribed tablets, most people whose opinion I value, would take all their prescribed tablets without missing a day' with a Likert scale of 1 agree to indicate high social norms to 3 disagree to indicate low social norms)

Perceived behavioural control will be measured using 1 single item ('do you believe that taking your medications as prescribed keeps your blood pressure under control' with a response yes to indicate high perceived behavioural control or no indicate low perceived behavioural control)

The MARS and the BMQ will be measured using self-reported questionnaires at baseline and at 12 months follow up for both intervention and control group to enable comparability. All other theoretical determinants that have been utilised to tailor the intervention will be measured at baseline and 12 months for the intervention group only. We will also measure automaticity using one single item at 12 months.

Consultation audio-recordings will be analysed thematically using a coding framework (as explained at fidelity VBI). Themes generated by the inductive analysis will inform recommendations about the mechanisms by which the content and the implementation of the VBI impacts on intervention effectiveness.

Interviews with practitioners will explore their perceptions about the behavioural intervention and its mechanisms of action. That is, their beliefs about reasons for treatment non-adherence and their ability to effectively facilitate medication adherence risk appraisal to non-adherence patients using shared decision-making strategies. Ten practitioners will be selected purposively to represent a range of practice IMD and geographical areas, and previous professional experience with research. Practitioner will be sent a brief overview of

the interview via email in advance and will be invited to one 30 minutes telephone interview. Data will be analysed thematically. Themes generated inductively will inform recommendations to improve practitioners training.

Interviews with patients will explore participants views about the hypothesised determinants of medication adherence (for both intervention and control group patients), and the intervention components and mechanisms of action (for the intervention group only). A subsample of 35 participants (20 intervention and 15 control) will be selected purposively and invited to one 45 minutes telephone interview. We will select patients to represent a range of demographics (e.g., age, gender), health conditions (e.g., hypertension only or co-morbidities), prescribed treatment (e.g., > 6 meds per day or < 6), geographical area, and IMD. An additional criterion for the selection of the intervention group participants will be the level of engagement with the intervention (low, medium, high engagement).

Participants who actively request to drop out from the trial or the intervention will be contacted and asked to attend a 20-min telephone interview. We will explore reasons for discontinuation and obtain recommendations for improvement (draft interview schedules, supplementary file 6).

Process evaluation analysis and synthesis

We will use a mixed methods analysis to generate evidence for the process evaluation [47].

Qualitative data. Interviews will be analysed using inductive thematic analysis [50]. Themes generated by the intervention group patients will be compared to those generated by the control group. Consultation audio-recordings will be coded against the framework with the intervention content to explore fidelity of the intervention. The programme theory will be used to guide qualitative data coding and analysis. Inductive approach will generate new themes to further inform intervention development and future research. A multi-perspective approach will intergrade findings into one analysis.

Quantitative data. ANCOVA will compare the mean change at the mechanisms of behaviour change (e.g., change on beliefs) in the two arms and quantify this as a difference in means and 95% confidence intervals. Multilevel regression analysis will explore the potential impact of the mechanisms of medication adherence on changing the primary outcome of blood pressure together with the associative changes in biochemical medication adherence. Subgroup variables will include continuous moderators; that is the theoretical determinants

and the engagement with the intervention. The intervention effect observed in each subgroup will be estimated with a 95% confidence interval. All significance tests will be two-sided and assessed at the 5% level of significance.

Data Management and Monitoring

The trial team will implement strategies to support adherence to procedures for uptake, retention, and completion of valid measurements at baseline and follow ups. Two members of the research team blinded to group allocation will contact non-responder participants to identify and address barriers to trial implementation procedures. They will aim to promote motivation and commitment to complete valid measurements based on the data collection forms specifying the requirements for analyses. To support retention in the trial or intervention, the researchers will contact those requesting to drop out from the trial, address their concerns and provide them with the opportunity to re-enrol in the trial.

All participants data will be anonymised. Two researchers will independently enter or code the data at a secure internet website hosted by the University of Cambridge and a third researcher will be double check data entry and coding.

Any identifiable data will be stored at the Secure Data Host Service (SDHS) and will be anonymised before analysis. The data manager and research team will ensure data are anonymized for forward data sharing with trial statistician. The anonymised data in will be hosted on a shared folder on a secure University of Cambridge Medical School Drive. Data will be extracted by the research assistants and double checked by the data manager. The lead author will ensure that GCP is applied to all procedures, supervise the trial team, and ensure that all data are anonymised before analysis. The data monitoring committee is independent of the Sponsor and have no competing interest. Adverse events and unintended effect of trial interventions or trial conducts will be recorded by the health care practitioners and will be recorded online at the electronic trial site file.

An independent trial steering committee will oversee the trial implementation procedures and will review and approve all trial modifications. Any major protocol modifications will be discussed within the research group and with the local ethics committee according to national and local guidelines. The participants will be informed of the modifications.

Sponsors

The University of Cambridge will act as the sponsor for this study. The Cambridgeshire and Peterborough Clinical Commissioning Group (CCG) is a co-sponsor.

Patient and Public Involvement

Study invitation packs (SIP), including the invitation letter, the PIS, and the consent forms, as well as the videos with trial implementation procedures have been reviewed by members of the PPI. Seven members of the PPI have provided comments during a PPI workshop and three by email. Comments have been addressed and integrated in the final versions of the documents. Two members of the PPI will review the SIP with the description about the remote consultations and remote measurements procedures. Three members of the PPI have pre-tested the intervention for a duration of one to three months, provided comments about intervention content and delivery mode, and made recommendations for improvement. PPI/E had provided comments during intervention development.

Practitioners online training has been reviewed by PPI members with nursing background who have provided comments for improvement before implementation.

Results and Dissemination Policy

The trial will complete data collection in March 2023. Following data cleaning, analysis will be implemented in April-July 2023 and results will be disseminated in August 2023. Primary care practices will disseminate anonymised results to the trial participants. The first author will be responsible for disseminating the results to practice practitioners, the public and other relevant groups including peer-reviewed publications.

Ethics approvals and consent to participate

The Cambridge East Independent Research Ethics Committee and the Health Research Authority have reviewed and approved this research project. REC reference 19/EE/0354

All participants have provided written informed consent to participate in the trial, and their data to be anonymised and published

Availability of data and material

All data is reported at the supplementary material. Additional data and material are available upon request to the first author.

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Trial Status

Protocol version is 1.0 and date 15 September 2021

The recruitment, first participant was recruited, 04/01/2021

The approximate date when recruitment will be completed, last patient visit, is 31/06/2022

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Abbreviations

VBI, very brief advice

Practitioners, nurses or health care assistants

Participants, patients with hypertension

SMS, short messaging service

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