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Stephen Sutton, Katja Beardsell, Debi Bhattacharya, James Brimicombe, Gianna Cadorna, Raquel Conceição, Anna De Simoni, Helen Eborall, Simon Griffin, Pankaj Gupta, Wendy Hardeman, Kevin Herbert, James Jamison, Jonathan Mant, Cecilia Mascolo, Efthalia Massou, Richard J McManus, Venus Mirzaei, Stephen Morris, Felix Naughton, Prashanth Patel, Andrew Toby Prevost, Sonia Shpendi, Amrit Takhar, Catalina Trama Alvarez, Miranda Van Emmenis, Joana Carvalho de Vasconcelos and Anamarija Veic

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Extended Research Article

Scalable low-cost interventions to support medication adherence in people prescribed treatment for hypertension in primary care: a research programme

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Abstract

Background: About 14.9% of people (9.9 million) registered with primary care practices in England and Wales are prescribed medication for hypertension. However, many do not take their medication as prescribed. To address this problem, we need scalable interventions.

Objective: To develop a scalable low-cost intervention to support medication adherence in people prescribed medication for hypertension in primary care, and to obtain precise and robust estimates of the effectiveness and cost-effectiveness of the intervention compared with usual care.

Design: Systematic reviews and meta-analyses; qualitative meta-synthesis; interviews and focus groups; expert consultations; pre-testing study; randomised feasibility trial; randomised controlled trial of effectiveness and cost-effectiveness; economic modelling.

Setting and participants: Primary care practices in England and Wales. Patients prescribed medication for hypertension with poorly controlled blood pressure.

Interventions: Very brief intervention delivered by a practice nurse or healthcare assistant followed by a digital intervention (text messaging programme or smartphone app).

Main outcome measures: Acceptability, feasibility, fidelity and cost of the interventions. Systolic blood pressure. Biochemical and self-reported measures of medication adherence.

Results: Our systematic reviews showed that both app-based and face-to-face interventions in patients with long-term conditions have a positive effect on medication adherence.

The meta-synthesis of published qualitative studies showed that: digital interventions to support medication use were perceived as acceptable and useful; a digital intervention would be more effective if it was personalised and tailored; barriers to using digital interventions included lack of interest, lack of confidence and lack of proficiency and experience in using the technology; digital interventions should be simple, easy to navigate and age-appropriate; patients wanted accurate information on their health condition, potential side effects of medication and health consequences of non-adherence; reminder notifications and a self-monitoring feature were perceived as helpful by some patients; some patients suggested that a digital intervention should enable them to communicate with pharmacies, but practitioners were concerned that this would increase their workload.

The interview and focus group study identified several barriers to adherence, including forgetting, unpleasant side effects and reluctance to medicate. A digital intervention to support medication adherence was acceptable to patients if it was user-friendly, the content was tailored to the user, and the privacy of user data was protected. Simple reminder messages for taking medication and reordering prescriptions were considered more useful by patients than those providing information on the benefits of medication or the consequences of non-adherence. Patients preferred to receive feedback on their adherence levels in the form of a simple graph, percentage score or statistic. Practitioners thought that it would be feasible to introduce a digital intervention to patients in a very brief face-to-face consultation.

In the pre-testing study, participants reported that the interventions we developed were easy to use and that they would recommend them to others. The feasibility trial showed that the combined intervention was acceptable and that a large cost-effectiveness trial was feasible. The main trial showed no difference between arms in systolic blood pressure or medication adherence at 12-month follow-up. The estimate (95% confidence interval) for the difference in means between arms in self-measured systolic blood pressure at 12 months was −0.61 mmHg (−3.05 to 1.82), $p = 0.62$ [for intervention vs. control (reference group)]. In the base case analysis, the intervention had a mean incremental cost-effectiveness ratio below the usual willingness-to-pay thresholds in the National Health Service in the United Kingdom. The probability of cost-effectiveness was between 77% and 80% at willingness-to-pay thresholds of £15,000, £20,000 and £30,000 per quality-adjusted life-year, but the confidence intervals are wide and cross zero, indicating some chance that the intervention could be less effective and more costly.

Limitations: The effectiveness trial was conducted during the COVID-19 pandemic. To reduce the risk of infection, the very brief intervention was delivered by telephone instead of face-to-face, and all study measurements were conducted

remotely. This may have led to lower response rates and data quality and lower effectiveness of the intervention. A significant proportion (24%) of participants did not have raised blood pressure at baseline, and self-reported medication adherence was high at baseline, which reduced the possible scope for an intervention effect.

Conclusions: The findings on effectiveness do not support the commissioning of the intervention in United Kingdom primary care. The cost-effectiveness findings are more equivocal, showing a high probability of being cost-effective at standard United Kingdom willingness-to-pay thresholds, but with some uncertainty.

Future work: Future research should address the challenge of identifying and recruiting people who are poorly adherent and have raised blood pressure and test the intervention in this group. Variants such as face-to-face delivery, adding a follow-up consultation or a purely digital version could also be investigated.

Study registration: This study is registered as CRD42017080150; CRD42020164049; ISRCTN12805654; ISRCTN74504989; ISRCTN82013652.

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Supplementary material can be found on the NIHR Journals Library article page (https://doi.org/10.3310/GJSS0929).

Supplementary material has been provided by the authors to support the article and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

The supplementary materials (which include but are not limited to related publications, patient information leaflets and questionnaires) are provided to support and contextualise the publication. Every effort has been made to obtain the necessary permissions for reproduction, to credit original sources appropriately and to respect copyright requirements. However, despite our diligence, we acknowledge the possibility of unintentional omissions or errors, and we welcome notifications of any concerns regarding copyright or permissions.

List of abbreviations

AI	artificial intelligence
BCT	behaviour change technique
BP	blood pressure
CEAC	cost-effectiveness acceptability curve
CEP	cost-effectiveness plane
CVD	cardiovascular disease
DDD	defined daily dose
EVPI	expected value of perfect information
GBP	Great British pound
GP	general practitioner
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
INMB	incremental net monetary benefit
MAR	missing at random
MARS	Medication Adherence Report Scale
MI	multiple imputation
PAM	Programme on Adherence to Medication
PPI	patient and public involvement
PSA	probabilistic sensitivity analysis
PSC	Programme Steering Committee
QALY	quality-adjusted life-year
REC	Research Ethics Committee
RCT	randomised controlled trial
SBP	systolic blood pressure
SMS	short message service
UC	usual care
VBI	very brief intervention
WS	workstream
WTP	willingness to pay

Plain language summary

About 15% of people (10 million) registered with primary care practices in England and Wales are prescribed medication for hypertension (high blood pressure). However, many do not take their medication as prescribed, which may harm their health and increases health service costs. To address this problem, we need low-cost interventions that can reach all the people who need them.

This research programme aimed to develop a new intervention to support people with poorly controlled blood pressure to take their hypertension medication as prescribed and to assess how well it worked and how much it cost compared with usual care only. The findings would inform a decision on whether to introduce the intervention in primary care practices in the United Kingdom.

We used a range of different research methods, including literature reviews, interviews and focus groups, and randomised controlled trials.

The intervention we developed has two parts: a very brief intervention delivered by a practice nurse or healthcare assistant by telephone, followed by a digital intervention (individually tailored text messages for up to 420 days or a smartphone app).

In the main trial, 537 participants received either the intervention or just usual care and were followed up 12 months later. The intervention was low cost, but it was not effective: the results showed no difference in blood pressure or medication adherence between the two groups at 12 months. Not all participants had raised blood pressure at the start of the study, and many were already taking their medication as prescribed; this may explain why the intervention did not work.

The findings suggest that the intervention should not be introduced in United Kingdom primary care practices before showing that it works in patients who do not take their medication as prescribed and have raised blood pressure.

Scientific summary

Background

Hypertension is a global health challenge accounting for 8.5 million deaths worldwide despite the availability of low-cost pharmaceutical treatment. About 14.9% of people (9.9 million) registered with primary care practices in England and Wales are prescribed medication for hypertension. However, many patients with hypertension do not take their medications as prescribed – 42% in the UK according to one study. Non-adherence to antihypertensive medication is associated with increased risk of suboptimal blood pressure (BP) control, complications and all-cause mortality, and increased healthcare costs.

Primary care practitioners have an important role in supporting patients to adhere to their prescribed medication. However, they lack time to provide ongoing support for adherence, and their time is expensive. A potential solution is for a practitioner such as a practice nurse to deliver a very brief intervention (VBI) during a consultation and to use a digital intervention such as text messaging or a smartphone app to support subsequent adherence.

About 96% of UK adults use a mobile phone, and in 93% of cases, this is a smartphone; the corresponding figures for those aged 65 and above are 88% and 77%. This suggests that digital interventions have the potential to reach the majority of this population. Digital interventions have several other advantages over traditional interventions: they can be fully automated; provide information that is highly tailored to the individual; be interactive; be available at any time; deliver support in real time; deliver support with high fidelity; and be easily updated.

Recent meta-analyses have reported promising findings for the effectiveness of nurse-led and digital interventions to improve medication adherence and reduce BP in people with hypertension. The interventions examined in these reviews varied widely in content and delivery, and the digital interventions that have been evaluated to date have not made full use of individual tailoring, interactivity and other features that may increase user engagement and potential effectiveness.

Objectives

The PAM programme (Programme on Adherence to Medication) aimed to develop and evaluate an intervention to support medication adherence that combines a VBI from a practice nurse or healthcare assistant with a digital intervention (text messaging programme or smartphone app). Such an intervention would be inexpensive to deliver, scalable and potentially cost-effective.

The objectives were:

1. To develop a scalable low-cost intervention to support medication adherence in people prescribed treatment for hypertension in primary care.
2. To evaluate the acceptability and feasibility of the intervention and the feasibility of conducting a (cost-) effectiveness trial.
3. To provide precise and robust estimates of the effectiveness and cost-effectiveness of the intervention compared with usual care (UC).
4. To develop an economic model of the cost-effectiveness of medication adherence interventions.
5. To inform a decision on whether to implement the intervention in primary care.

Methods

The target group is patients in primary care practices in England and Wales who do not take their antihypertensive medication as prescribed and have raised BP.

Methods used were:

1. Systematic reviews of randomised controlled trials of app-based (9 trials) and face-to-face interventions (20 trials) to support medication adherence, with random-effects meta-analyses.
2. A meta-synthesis of 30 published qualitative studies of adults taking medication for cardiovascular-related long-term health conditions (e.g. type 2 diabetes, hypertension) and/or healthcare practitioners who treat patients with cardiovascular conditions who were asked about their views and experiences of digital interventions to support medication adherence.
3. Interviews with 11 healthcare practitioners [6 practice nurses, 2 healthcare assistants, 2 practice pharmacists, 1 general practitioner (GP)] and 6 patients, and 4 focus groups, with a total of 14 patients, to gather views on the acceptability and content of digital interventions for medication adherence.
4. Expert consultations with 2 commissioners, 2 academics, 2 nurses, 2 patients and 10 GPs. Participants were e-mailed a description of the proposed intervention, a description of the proposed design of the randomised feasibility study and a link to an online questionnaire that asked their views on the delivery mode and content of the intervention and on the proposed feasibility study. Commissioners were asked about the evidence needed to inform a decision whether to commission the intervention.
5. Pre-testing study of early versions of the digital interventions to assess acceptability. The text messaging intervention was used by 22 patients with hypertension for 28 days, and four of them also used the smartphone app for an additional 28 days. Data were collected by weekly telephone interviews, questionnaires and log files showing how they had used the interventions.
6. Randomised feasibility trial to assess the feasibility and acceptability of the PAM intervention and the feasibility of conducting a large cost-effectiveness trial. Patients with hypertension who had raised BP and were non-adherent to their prescribed medication as indicated by their practice records and practice GP assessment were eligible for the study. One hundred and one eligible patients from nine general practices in the East of England and London were randomised to receiving the PAM intervention (N = 61) or UC only (N = 40).
7. Randomised controlled trial to estimate the effectiveness and cost-effectiveness of the PAM intervention to improve medication adherence and reduce BP compared with UC only, to inform a decision on whether to implement the intervention in primary care ('main trial'). A total of 573 eligible patients from 57 practices in England and Wales were individually randomised, stratified by practitioner, to the PAM intervention or control (UC only) and followed up at 12 months. The primary outcome was systolic blood pressure (SBP). The analysis was based on 537 participants.
8. Within-trial economic analysis of the cost-effectiveness of the PAM intervention compared with UC alone. The main cost-effectiveness measure was the incremental cost per quality-adjusted life-year (QALY) gained, and the analysis included extensive deterministic and probabilistic sensitivity analyses.

Results

Systematic reviews

1. The findings from the meta-analysis of app-based interventions showed that, at follow-up, patients in the intervention groups were more likely to self-report adherence to medication than those in the comparator groups [odds ratio 2.12, 95% confidence interval (CI) 1.64 to 2.75, n = 988, $p < 0.0005$]. None of the behaviour change techniques (BCTs) used in the interventions was significantly associated with intervention effect size.
2. In the meta-analysis of face-to-face interventions, statistically significant pooled effects were found favouring the intervention arm over the control arm for several Medication Event Monitoring System measures of adherence, for example, percentage of prescribed doses taken on time over a period of 3 weeks to 2 months [mean difference (MD) 9.34, 95% CI 4.36 to 14.33, n = 3,667, p = 0.0002]. We also found significant between-arm effects for a self-report measure of adherence (Morisky scale). The impact of BCTs on intervention effectiveness could not be estimated as the analyses were underpowered.

Taken together, these reviews supported our proposal to use face-to-face and digital components in the PAM intervention. However, we were unable to identify promising BCTs for potential inclusion in the proposed intervention.

Meta-synthesis of previous qualitative studies

The main findings from the meta-synthesis of published qualitative studies were: digital interventions to support medication use were perceived as acceptable and useful; a digital intervention would be more effective if it was personalised and tailored; barriers to using digital interventions included lack of interest, lack of confidence and lack of proficiency and experience in using the technology; digital interventions should be simple, easy to navigate and age-appropriate; patients wanted accurate information on their health condition, potential side effects of medication and health consequences of non-adherence; reminder notifications and a self-monitoring feature were perceived as helpful by some patients but unnecessary by others; some patients suggested that a digital intervention should enable them to communicate with pharmacies, but practitioners were concerned that this would increase their workload.

Interviews and focus groups with practitioners and patients

This study identified several barriers to adherence, including forgetting, unpleasant side effects and reluctance to medicate. A digital intervention to support medication adherence, either via text messages or smartphone app, was acceptable to patients, provided that it was user-friendly, the content was tailored to the user and the privacy of user data was protected. Simple reminder messages for taking medication and reordering prescriptions were considered more useful by patients than those providing information on the benefits of medication or the consequences of non-adherence, which were favoured by practitioners. Rather than messages of encouragement, patients preferred to receive feedback on their adherence levels in the form of a simple graph, percentage score or statistic. All the practitioners thought that it would be feasible to introduce a digital intervention to patients in a very brief face-to-face discussion during a primary care consultation.

Expert consultations

There was substantial similarity of views between the different stakeholders. They found the concept of a VBI delivered face-to-face by a healthcare practitioner acceptable. However, they felt that it was not feasible to address possible reasons for medication non-adherence in a VBI, and that the intervention should be limited to emphasising the importance of taking medication as prescribed and signposting the patient to a digital intervention.

Pre-testing study

Participants reported that the interventions were easy to use and that they would recommend them to other people. They were satisfied with the frequency of the messages and the content of the daily reminder and weekly query messages, but they were somewhat less satisfied with the content of the daily non-reminder (advice) messages. The response rate to the query messages was 100%, indicating a high degree of engagement.

Randomised feasibility trial

All 101 participants had their BP measured at baseline, and the vast majority provided a urine sample for chemical adherence testing. Participants were on average 65.8 years of age, 54% male, with a substantial minority (35%) from the most deprived areas, based on practice postcode. Baseline characteristics were similar in the two arms.

At 3-month follow-up, 83% of participants had their BP measured and provided a urine sample, and the percentage was similar in the two arms.

Ninety-two per cent of participants randomised to the intervention arm opted to receive text messages, and 8% opted to use the app. Ninety per cent responded to the tailoring questions which were administered digitally. Four intervention participants actively disengaged from the digital intervention by sending a STOP message. Seventy-two per cent continued to use the digital intervention for at least 1 month.

The post-trial interviews showed that intervention participants found the intervention to be acceptable. Participants were satisfied with the baseline and follow-up consultations and the study procedures, and there were no concerns among control participants about being randomised to this arm. Practitioners also confirmed that the study procedures and intervention were acceptable.

From baseline to follow-up, mean SBP reduced from 146.9 mmHg to 136.9 mmHg in the intervention arm compared with no change in the control arm (adjusted MD 9.2 mmHg, 95% CI 5.7 to 12.6), and biochemically measured adherence

increased to a greater extent in the intervention arm than in the control arm, suggesting that the intervention was potentially effective.

The findings from this trial showed that the intervention was acceptable to participants and that most offered the digital intervention used it, at least in the short term. The trial procedures were demonstrated to be practicable. Together with the findings on trial uptake and retention rates, this suggested that a large cost-effectiveness trial was feasible.

Main trial

Baseline characteristics were similar in the two arms. The majority of participants were recruited from practices in the East of England. Similar to the feasibility trial, 56% were male and mean age was 66.5 years. The vast majority categorised themselves as being of White ethnicity, but there was a range of deprivation levels, based on participant home postcode. Mean BP, obtained from practice records before randomisation, was 145/82 mmHg, again similar to the sample in the feasibility trial. Of participants, 75.8% had a BP reading above the accepted cut-off of 140/90 mmHg and 71.7% had a SBP reading above 140. We were, therefore, partially successful in recruiting a sample of participants who had a raised BP even though they were prescribed antihypertensive medication.

The estimate (95% CI) for the difference in means between arms in the primary outcome of self-measured SBP at 12 months was −0.61 mmHg (−3.05 to 1.82), $p = 0.62$ [for intervention vs. control (reference group)]. Thus, the estimated effect was very small, and the detectable effect size of 5 mmHg did not fall within the CI. The estimate for the difference in means between arms for SBP obtained from practice records was 1.04 mmHg (−1.56 to 3.65), $p = 0.43$.

Thus, the intervention appeared to have no effect on SBP. There was also no effect of the intervention on biochemically measured adherence. Of the 392 participants who provided a urine sample at follow-up, 388 (99.0%) were found to have at least one antihypertensive medication (or metabolite) in their urine. Based on the urinalysis, 94.3% of participants were categorised as 'fully adherent', 4.8% as 'partially adherent' and only 0.9% as 'non-adherent'. There was no difference in these percentages between trial arms.

Self-reported adherence at 12 months was also high, with no difference between trial arms. The mean score on the five-item Medication Adherence Report Scale questionnaire was 23.8 [standard deviation 1.7] out of a maximum score of 25 (based on 387 participants who provided 12-month data on this scale).

Of the intervention participants, 212 (77.9%) opted to receive text messages; 60 (22.1%) opted to use the app, and 39 of these became active users. On average, participants were satisfied with the combined intervention (VBI plus digital intervention) and thought that it was acceptable and effective. However, 61.0% used the digital intervention for less than 3 months, with the main reasons being not needing any further support and finding the messages annoying.

Economic analysis

The total mean intervention cost per patient was £30. In the base case analysis, the intervention was found to be cost-effective compared with UC, with a mean estimated incremental cost-effectiveness ratio (ICER) of £1231 per QALY gained (95% CI −£13,156 to £19,535) and mean incremental net monetary benefit (INMB) of £289 (95% CI −£498 to £1026) at a willingness-to-pay (WTP) threshold of £15,000/QALY. The INMB rose to £400 (95% CI −£643 to £1383) and £621 (95% CI −£933 to £2104) for £20,000/QALY and £30,000/QALY, respectively. The probability that the intervention is cost-effective was between 77% and 80% for these WTP thresholds.

Limitations

The effectiveness trial was conducted during the COVID-19 pandemic. To reduce the risk of infection, the VBI was delivered by telephone instead of face-to-face, and all study measurements were conducted remotely. This may have led to lower response rates and data quality and lower effectiveness of the intervention. A significant proportion (24%) of participants did not have raised BP at baseline, and self-reported medication adherence was high at baseline, which reduced the possible scope for an intervention effect.

Conclusions

The combination of a VBI delivered by a practice nurse or healthcare assistant and a digital intervention was acceptable to both patients and practitioners. However, although the feasibility trial showed promising results, the main trial showed no effect of the intervention on medication adherence or SBP at 12 months. The cost-effectiveness findings showed a mean ICER below the usual WTP thresholds, but the CIs are wide and cross zero, indicating some chance that the intervention could be less effective and more costly compared with UC only. The effectiveness findings do not support the commissioning of the intervention in UK primary care.

Future research should address the challenge of identifying and recruiting people who are poorly adherent. If it is feasible to recruit patients who are non-adherent to their prescribed antihypertensive medication and have raised BP, the intervention could be tested with the VBI delivered remotely or face-to-face. Variants such as adding a follow-up consultation or testing a purely digital version could also be investigated.

The economic model developed for this programme can provide the basis for future economic evaluations of similar interventions across a range of different conditions.

Study registration

This study is registered as CRD42017080150; CRD42020164049; ISRCTN12805654; ISRCTN74504989; ISRCTN82013652.

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Synopsis

Background and rationale

Hypertension is a global health challenge accounting for 8.5 million deaths worldwide despite the availability of effective low-cost pharmaceutical treatment.[1,2] About 14.9% of people (9.9 million) registered with primary care practices in England and Wales are prescribed medication for hypertension.[3,4] However, many patients with hypertension do not take their medications as prescribed. A meta-analysis involving 27 million patients found that the global prevalence of non-adherence to antihypertensive medication ranges from 27% to 40%.[5] Little information is available for the UK, though one study that used urine analysis reported a non-adherence rate of 41.6%.[6] Non-adherence to antihypertensive medication is associated with increased risk of suboptimal blood pressure (BP) control, complications and all-cause mortality, and increased healthcare costs.[5,7]

Primary care practitioners have an important role in supporting patients to adhere to their prescribed medication.[8] However, they lack time to provide ongoing support for adherence, and their time is expensive. A potential solution is for a practitioner such as a practice nurse to deliver a very brief intervention (VBI) during a consultation and to use a digital intervention such as text messaging, smartphone app or website intervention to support subsequent adherence.

According to a recent report, 96% of UK adults use a mobile phone, and in 93% of cases, this is a smartphone;[9] the corresponding figures for those aged 65 and above are 88% and 77%. This suggests that digital interventions have the potential to reach the majority of this population. Digital interventions have several other advantages over traditional interventions: they can be fully automated, provide information that is highly tailored to the individual, be interactive, be available at any time, deliver support in real time, deliver support with high fidelity and be easily updated.

Recent meta-analyses have reported promising findings for the effectiveness of nurse-led and digital interventions to improve medication adherence and reduce BP in people with hypertension.[10–19] The interventions examined in these reviews varied widely in content and delivery, and the digital interventions that have been evaluated to date have not made full use of individual tailoring, interactivity and other features that may increase user engagement and potential effectiveness.[20]

Hypertension is 1 of the 16 opportunities listed in recent guidance published by NHS England in their document *National medicines optimisation opportunities 2024/25*.[21] The specific wording is 'Identifying patients with hypertension and starting antihypertensives when appropriate'. Clearly, these are important goals. The emphasis in our research programme on finding better ways of supporting patients with hypertension to take their antihypertensive medication is complementary to this approach. Our proposal for a VBI, followed by a digital intervention, is consistent with NHS England's push for scalable, cost-effective digital solutions to support medicine use.[22]

Aims and objectives

This programme, which we refer to as Programme on Adherence to Medication (PAM), aimed to develop and evaluate an intervention to support medication adherence that combines a VBI from a practice nurse or healthcare assistant with a digital intervention (text messaging programme or smartphone app). The target group is patients in primary care who do not take their antihypertensive medication as prescribed and have raised BP. Such an intervention would be inexpensive to deliver, scalable and potentially cost-effective.

The objectives were:

1. To develop a scalable low-cost intervention to support medication adherence in people prescribed treatment for hypertension in primary care.
2. To evaluate the acceptability and feasibility of the intervention and the feasibility of conducting a (cost-) effectiveness trial.

3. To provide precise and robust estimates of the effectiveness and cost-effectiveness of the intervention compared with usual care (UC).
4. To develop an economic model of the cost-effectiveness of medication adherence interventions.
5. To inform a decision on whether to implement the intervention in primary care.

Structure of the programme

The programme consisted of five workstreams (WS):

Workstream 1: evidence to inform intervention development.
Workstream 2: operationalisation and pre-testing of interventions.
Workstream 3: randomised feasibility study.
Workstream 4: randomised controlled trial (RCT) of effectiveness and cost-effectiveness.
Workstream 5: economic modelling.
The relationship between the WSs is shown in *Figure 1*.

Changes to the programme

There were no changes to the research aims during the programme, but the COVID-19 pandemic significantly impacted on WS4 (and therefore WS5), leading to a long delay in starting the main trial and major changes in the trial procedures. This is described in the section on WS4. Also, we did not conduct a long-term economic analysis as part of WS5. Although we had originally planned to do this (see the health economic analysis plan in *Report Supplementary Material 1*), extrapolation beyond the end of the trial was not undertaken, because there was no significant difference in the primary outcome between groups at the end of the within-trial period.

Qualitative work to inform the grant application

To inform the original grant application, we organised two workshops to gather views from patients prescribed BP-lowering medication.

The first workshop took place in July 2015. Six women recruited from knitting and exercise groups took part in the discussion held at the Southern Grove Community Centre in East London. Their ages ranged from 65 to 75 years. The

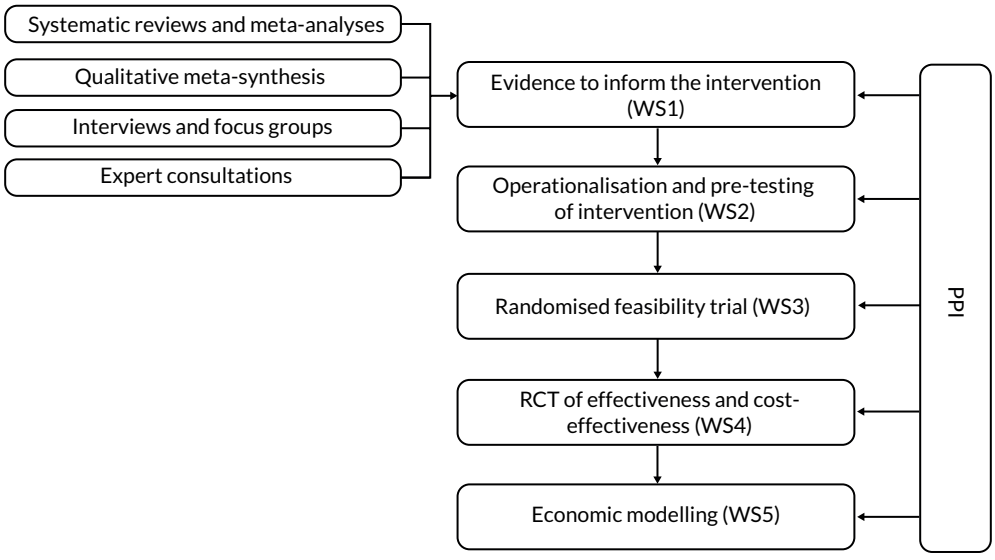

FIGURE 1 Research pathway diagram showing the structure of the programme. PPI, patient and public involvement.

majority were taking both BP- and lipid-lowering tablets. The workshop provided valuable insights into current use and attitudes to technology, unmet needs with tablet taking (to do with forgetting or deciding not to take tablets) and the potential of digital interventions to support medicine taking. Participants welcomed the idea of medication reminders and self-monitoring tablet taking through smartphones or computer tablets.

We held a second workshop in August 2015 at the Bromley-by-Bow Community Centre, East London, with a group of people recruited from a healthy lifestyle class. Six people (four men, two women), aged 65–74 years, including three of South Asian origin, took part. Most were on BP-lowering medication and statins. Only one had a smartphone. A consensus emerged that technology would slowly be incorporated into people's lives, and this was welcomed in the context of tablet taking. Participants liked the idea of using smartwatches to help with tablet taking because they felt that watches were more familiar to them than computers. Other findings confirmed our view that patients would be more likely to use a digital intervention if it was introduced to them during a brief consultation with a primary care practitioner.

A paper reporting this study was published in *Journal of International Medical Research*.[23]

Workstream 1: evidence to inform intervention development

The aim of WS1 was to collect evidence to inform the development of the intervention through a series of quantitative and qualitative studies.

Systematic reviews and meta-analyses

To complement our previously published meta-analysis of automated telephone interventions for medication adherence (Kassavou *et al.* 2018, *Health Psychology Review*[24]), we conducted a systematic review of RCTs to estimate the efficacy of app-based interventions to support medication adherence. We searched MEDLINE/PubMed, PsycINFO, CINAHL, EMBASE and Web of Science in November 2018 using a broad search strategy and identified nine relevant trials. Health conditions included cardiovascular disease (CVD), depression, Parkinson's disease, psoriasis and multimorbidity. Random-effects meta-analysis showed that, at follow-up (median 12 weeks), patients in the intervention groups were more likely to self-report adherence to medication than those in the comparator groups [odds ratio (OR) 2.12, 95% confidence interval (CI) 1.64 to 2.75, $n = 988$, $p < 0.0005$], suggesting that app-based interventions have a positive effect on medication adherence. We also coded the behaviour change techniques (BCTs)[25] used in the interventions but found that none of these was significantly associated with intervention effect size. We were, therefore, unable to identify any promising BCTs for inclusion in the digital interventions developed as part of this programme.

A paper reporting this study was published in *BMJ Open*.[26]

Since we also planned to include a face-to-face component in our proposed intervention, we conducted a second systematic review and meta-analysis of face-to-face medication adherence interventions for patients with long-term health conditions. We searched the following electronic databases in April 2019 and again in April 2020: Cochrane Central Register of Controlled Trials, EMBASE, PsycInfo, Web of Science, PubMed and Scopus. We included a total of 20 RCTs ($n = 3667$ participants) in the review. In a random-effects meta-analysis, we found statistically significant pooled effects favouring the intervention group over the control group for the following Medication Event Monitoring System measures of adherence: percentage of prescribed doses taken on time over a period of 3 weeks to 2 months [mean difference (MD) 9.34, 95% CI 4.36 to 14.33; $p = 0.0002$]; percentage of prescribed doses taken for a period of 1 week to 2 months (MD 5.63, 95% CI 1.62 to 9.64; $p = 0.006$); and for 1 month (OR 2.51, 95% CI 1.37 to 4.57; $p = 0.003$); percentage of days correct doses taken for 1 month to 14 weeks (MD 6.59, 95% CI 0.74 to 13.15; $p = 0.03$). We also found significant between-group effects for a self-report measure of adherence (Morisky scale[27]). The impact of BCTs on intervention effectiveness could not be estimated as the analyses were underpowered.

A paper reporting this study was published in *Annals of Behavioral Medicine*.[28]

Taken together, these reviews provided support for our proposal to use face-to-face and digital components in the PAM medication adherence intervention. However, no studies were identified that investigated whether using a VBI in combination with a digital intervention would have an additive or synergistic effect on adherence. We were also unable to identify promising BCTs for potential inclusion in the proposed intervention.

Meta-synthesis of previous qualitative studies

We conducted a meta-synthesis to assess and synthesise the existing qualitative evidence on the use of digital interventions to support medication adherence. We included qualitative studies of adults taking medication for cardiovascular-related long-term health conditions (e.g. type 2 diabetes, hypertension) and/or healthcare practitioners who treat patients with cardiovascular conditions who were asked about their views and experiences of digital interventions to support medication adherence. Five electronic databases were searched (CINAHL, EMBASE, PsycInfo, PubMed and Scopus). Medical subject heading terms and keyword searches were used across five categories: cardiovascular health condition (e.g. hypertension); medication (e.g. tablet); adherence (e.g. non-adhere*); digital intervention (e.g. smartphone); and qualitative method (e.g. interview). The initial search was conducted in February 2018, and it was updated in August 2023. In total, 7564 records were identified. Duplicate papers were removed, leaving 5694 papers. Title/Abstract screening was conducted by one author. Full-text screening was conducted by two authors. Conflicts were resolved through group discussion. Thirty papers were selected for inclusion in the review. We conducted a thematic analysis of the extracted data. The main findings were:

1. Patients identified both intentional and non-intentional (forgetting) barriers to medication adherence.
2. Digital interventions to support medication use were perceived as acceptable and useful.
3. However, some patients felt that the digital intervention would not be relevant to them as they already had an established routine or only had one prescribed medication but suggested that it could be relevant to others, for example, newly diagnosed patients.
4. Patients felt that a digital intervention would be more effective if it was personalised and tailored to their reasons for non-adherence and their preferences regarding the frequency and timing of the messages.
5. Common barriers to using digital interventions included a lack of interest, lack of confidence or lack of proficiency or experience in using the technology.
6. Usability was a salient theme. Digital interventions should be simple, easy to navigate and age-appropriate.
7. Patients expressed interest in receiving accurate information on their health condition, the potential side effects of medication and the health consequences of non-adherence. However, too much information could be burdensome for patients and could increase anxiety.
8. Reminder notifications were perceived as helpful by some patients but unnecessary by others who considered themselves to be adherent.
9. Similarly, there were mixed views on the inclusion of a self-monitoring feature. Some patients found it informative, while others found it unhelpful.
10. Some patients suggested that a digital intervention could be beneficial if it enabled them to communicate with pharmacies. However, practitioners were concerned that such a feature would increase their workload.

Interviews and focus groups with practitioners and patients

To gather views on the acceptability and content of digital interventions for medication adherence, we conducted face-to-face semistructured interviews with 6 patients and 11 healthcare practitioners who were involved in the care of patients with hypertension [6 practice nurses, 2 healthcare assistants, 2 practice pharmacists, 1 general practitioner (GP)], recruited from 4 practices in the East of England and East London. Patients were eligible to participate if they were prescribed medication for hypertension, were deemed non-adherent according to practice records and used either short message service (SMS) or smartphone apps. In addition, 4 face-to-face focus groups were conducted with a total of 14 patients recruited from 2 of the 4 practices. For the focus groups, the eligibility criteria were widened to include patients prescribed medication for type 2 diabetes and narrowed to ensure that participants were familiar with using smartphone apps.

This study identified several reasons for non-adherence, including: forgetting (forgetting to take medication, forgetting whether or not medication had been taken and forgetting to reorder a prescription in time), the experience or anticipation of unpleasant side effects and a reluctance to be reliant on medication. A digital intervention to support

medication adherence, either via SMS or smartphone app, was acceptable to patients, provided that it was user-friendly, the content was tailored to the user, for example, in terms of the frequency and timing of the messages, and the privacy of user data was protected. Simple reminder messages for taking medication and reordering prescriptions were considered more useful by patients than those providing information on the benefits of medication or the consequences of non-adherence, which were favoured by practitioners. Rather than messages of encouragement, patients preferred to receive feedback on their adherence levels in the form of a simple graph, percentage score or statistic. All the practitioners thought that it would be feasible to introduce a digital intervention to patients in a very brief face-to-face discussion during a primary care consultation, with two key provisos: they would need training to help them deliver the intervention within 5 minutes and a user-friendly template that could be incorporated in existing computer systems for inputting patient data to inform the subsequent digital intervention.

A paper reporting this study was published in *BMJ Open*.[29]

Expert consultations

Consultations were conducted with 2 commissioners, 2 academics, 2 nurses, 2 patients and 10 GPs. Participants were e-mailed a description of the proposed intervention, a description of the proposed design of the feasibility study (WS3) and a link to an online questionnaire with open-ended questions. The questionnaire asked their views on the delivery mode and content of the intervention and their views on the proposed feasibility study. Commissioners were asked about the evidence needed to inform a decision whether to commission the intervention. There was substantial similarity of views between the different stakeholders. They found the concept of a VBI delivered face-to-face by a healthcare practitioner to be acceptable. However, they felt that it was not feasible to address possible reasons for medication non-adherence in a VBI, and that the intervention should be limited to emphasising the importance of taking medication as prescribed and signposting the patient to a digital intervention.

Workstream 2: operationalisation and pre-testing of interventions

Informed by the findings from the WS1 studies outlined above, interpreted using our theoretical framework, and with additional patient and public involvement (PPI) input (see *Patient and public involvement*), we developed initial versions of the three intervention components: (1) a script for the VBI (together with training materials for the practice nurses and healthcare assistants who would be delivering it), (2) a 28-day tailored text messaging programme and (3) a smartphone app (see *Appendix 1* for the logic model). In preparation for WS3 (feasibility trial), we also developed an online system (the PAM online system) to guide the practitioner through the study processes of assessing the patient's eligibility, obtaining informed consent, collecting relevant data from the patient and entering this in an online questionnaire, randomising the patient to the intervention or control condition, and, for patients allocated to the intervention condition, prompting the practitioner to deliver the VBI.

We conducted a pre-testing study of the digital interventions to assess acceptability. Twenty-two patients with hypertension recruited from three practices in the East of England used the text messaging intervention for 28 days, and four of them also used the app for an additional 28 days. Data were collected by weekly telephone interviews, questionnaires and log files showing how they had used the interventions. Participants reported that the interventions were easy to use and that they would recommend them to other people. They were satisfied with the frequency of the messages and the content of the daily reminder messages and the weekly query messages (which asked whether they had taken all their medications as prescribed in the past week), but they were somewhat less satisfied with the content of the daily non-reminder (advice) messages. The response rate to the weekly query messages (participants were asked to reply 'yes' or 'no') was 100%, indicating a high degree of engagement.

This study was published in the journal *Pilot and Feasibility Studies*.[30]

The digital interventions were modified to incorporate or address participants' suggestions and recommendations. For example, users could text LESS to reduce the frequency of the non-reminder (advice) messages and MORE to increase the frequency again. The duration of the digital interventions was extended from 28 to 84 days in preparation for the randomised feasibility trial which had a 3-month follow-up period.

Six healthcare practitioners (practice nurses and healthcare assistants) tried out the PAM online system (incorporating the VBI script); minor changes were made as a result.

Workstream 3: randomised feasibility trial

The aims of this study were to assess the feasibility and acceptability of the PAM intervention and the feasibility of conducting a large cost-effectiveness trial. Patients with hypertension who had raised BP and were non-adherent to their prescribed medication as indicated by their practice records and practice GP assessment were eligible for the study. One hundred and one eligible patients from nine general practices in the East of England and London were randomised to receiving the PAM intervention (*N* = 61) or to UC only (*N* = 40). Unequal group sizes were used to obtain more information about participants' use and evaluation of the intervention. Participants were followed up at 3 months.

Participants attended their GP practice for the baseline consultation with a practice nurse or healthcare assistant and provided a urine sample for chemical adherence testing and had their BP measured before they were randomised. The same measurement procedure was used at 3-month follow-up.

A paper reporting this trial was published in *Nature Scientific Reports*.[31]

The main findings were:

1. In total, 3859 potentially eligible patients were identified from practice records and were sent invitations to participate in the trial. Of those invited, 599 patients responded to invitations (15.5% uptake rate), and the first 125 of these were booked in for, and attended, the baseline consultation. One hundred and one were confirmed eligible to participate and provided informed consent. The main reason for not being eligible was not owning or using a mobile phone, a criterion that was not assessed before the invitations were sent.
2. All 101 participants had their BP measured at baseline, and the vast majority provided a urine sample for chemical adherence testing. Participants were on average 65.8 years of age, 54% male, with a substantial minority (34.7%) from the most deprived areas (deprivation decile three or lower), based on practice postcode. Baseline characteristics were similar in the two arms.
3. At 3-month follow-up, 83% of participants had their BP measured and provided a urine sample, and this was similar in the two arms. The 17% attrition rate was likely an overestimate because nine participants were not invited for follow-up due to practices pausing consultations at the start of the COVID-19 pandemic.
4. Ninety-two per cent of participants randomised to the intervention arm opted to receive text messages, and 8% opted to use the app. Ninety per cent of intervention participants responded to the tailoring questions which were administered digitally. Four intervention participants actively disengaged from the text messaging programme by sending a STOP message. Seventy-two per cent continued to use the digital intervention for at least 1 month.
5. The post-trial interviews showed that intervention participants found the intervention to be acceptable. Participants were satisfied with the baseline and follow-up consultations and the study procedures, and there were no concerns among control participants about being randomised to this arm. Practitioners also confirmed that the study procedures and intervention were acceptable.
6. From baseline to follow-up, mean systolic blood pressure (SBP) reduced from 146.9 mmHg to 136.9 mmHg in the intervention arm compared with no change in the control arm (adjusted MD 9.2 mmHg, 95% CI 5.7 to 12.6). Although over 90% of participants were adherent to antihypertensive medication at baseline according to the urinalysis (which was contrary to the objective of recruiting participants who were non-adherent), this figure increased over the follow-up period to a greater extent in the intervention arm compared with the control arm. (Possible limitations of chemical adherence testing are discussed in a later section.)

The findings from this trial showed that the intervention was acceptable to participants and that most offered the digital intervention used it, at least in the short term. The trial procedures, including the identification and recruitment of eligible patients, the baseline consultation, the online system and the procedures for taking informed consent and

collecting data, were demonstrated to be practicable. Together with the findings on trial uptake and retention rates, this suggested that a large cost-effectiveness trial was feasible.

The intervention appeared to be potentially effective in terms of the effects on SBP and adherence. However, the trial was not powered to detect effectiveness.

Workstream 4: main trial

The main trial aimed to estimate the effectiveness and cost-effectiveness of the PAM intervention to improve medication adherence and reduce BP compared with UC, to inform a decision on whether to implement the intervention in primary care. The trial incorporated a process evaluation to assess intervention fidelity and to explore practitioners' and participants' experiences of delivering or receiving the intervention.

Impact of the COVID-19 pandemic

The COVID-19 pandemic had a significant impact on the programme, particularly on the main trial. Recruitment of practices commenced in February 2020. Recruitment of patients was planned to start in March 2020 but had to be delayed because of the COVID-19 outbreak. To reduce the risk of virus transmission, we modified the trial procedures so that the VBI would be delivered remotely by telephone or video call instead of in a face-to-face consultation, and all measurement would be conducted remotely (e.g. by sending BP monitors to participants' homes). These were major changes from the procedures used in the feasibility trial. We also reduced the target sample size for the trial from 764 to 542, based on our findings from the feasibility trial, and added a 6-month follow-up questionnaire to inform the economic modelling. These changes were approved by NIHR, the Programme Steering Committee (PSC), the study Sponsors, the Research Ethics Committee (REC) and the Health Research Authority.

We attempted to restart the trial in October/November 2020 but were unable to recruit any participants before the end of the year, mainly because of practice involvement in delivering the COVID-19 vaccination programme. However, we started recruiting participants in January 2021, 10 months after we had originally planned. To compensate for the long delay due to the COVID-19 pandemic and the subsequent lower-than-expected recruitment of practices and patients, we successfully applied for an 18-month no-cost extension to the programme.

Main trial methods

The design was a two-arm multicentre individually randomised controlled parallel group superiority trial of the PAM intervention versus UC only, with the primary outcome of SBP measured at 12 months. The setting was general practices in England and Wales.

Patients were eligible for inclusion if they: (1) had a diagnosis of hypertension; (2) had been prescribed at least one BP-lowering or antihypertensive medication for at least 1 month before recruitment to the study, as confirmed by practice records; (3) had poorly controlled BP as indicated by at least two sequential clinical measures (i.e. clinic readings of BP > 140/90 mmHg if under 80 years old and > 150/90 mmHg if over 80 years old or home BP > 135/85 mmHg if under 80 years and > 145/85 mmHg if over 80 years) obtained during the preceding 12 months or gaps in collecting repeat prescriptions (Continuous Measure of Medication Gaps > 0.20 for 12 months before recruitment); (4) had a good understanding of English; (5) owned and were able to use a mobile phone; and (6) had the capacity to provide informed consent.

Patients were excluded if: (1) they had BP > 200/100 mmHg or postural hypotension (> 20 mmHg systolic drop on standing); (2) they had a diagnosis of dementia or other cognitive difficulties that could affect study participation; (3) they had had a recent severe life-threatening event or were under treatment for a long-term health condition apart from hypertension, high cholesterol or type 2 diabetes (e.g. cancer); (4) they were taking part in another medication adherence intervention or digital intervention for behaviour change; (5) their BP was not managed by their GP practice; (6) their GP, practice nurse or healthcare assistant felt that it was not appropriate to include them.

Eligible patients were identified through practice database searches, conducted by a member of the practice staff, and checked for eligibility by a practice GP. Once identified, practices invited patients into the trial opportunistically during UC appointments or via text messages or postal invitations. Patients were provided with printed information about the trial, including a participant information sheet and consent form and given at least 24 hours to decide whether or not to participate. Those expressing an interest in participating by returning a reply slip were telephoned by a member of the research team to address any questions or concerns. A remote baseline consultation was then arranged between the healthcare practitioner and the participant and conducted by telephone.

During this consultation, eligible patients were individually randomised, stratified by practitioner, to intervention or control, using a randomisation programme that was integrated into the PAM online system. The intervention group received the PAM intervention plus UC; the control group received UC only.

The PAM intervention comprised two components: a VBI delivered by the practitioner by telephone, followed by a digital intervention (see *Report Supplementary Material 2* for a detailed description of the intervention and *Appendix 1* for the logic model).

Briefly, the digital intervention was delivered either by text messages or by a smartphone app; participants chose the mode of delivery. Participants received automated individually tailored messages or notifications for up to 420 days, at least one a day on most days, including query messages or notifications asking them to provide a response.

Participants were given several opportunities to stop the messages/notifications by sending a STOP message or notification to the system. Participants who opted to receive text messages were given several opportunities to switch to the app if they wished; however, app users were not invited to switch (or switch back) to receiving text messages.

The primary outcome was SBP measured at 12 months. Two sources of BP readings were available:

1. Self-measured at home by participants using a BP monitor provided by the research team; participants were asked to take 28 BP measurements over 7 days. (Originally, this was planned to be eight BP measurements over 2 days; the protocol was changed to comply with the updated guidelines for self-measured BP[32].)
2. Blood pressure readings extracted from practice records (one reading that was closest to 12 months post randomisation and no more than 9 months prior to this time point). The latter were used to replace any missing self-measured values.

Medication adherence was measured by chemical adherence testing of urine samples[33] and by self-report.[34–36] Information about medications used was collected on the post-baseline and 12-month follow-up questionnaires. Changes in antihypertensive medication between these two time points were examined using the defined daily dose (DDD), which is the assumed average maintenance dose per day for the drug used for its main indication in adults.[37]

For participants allocated to the intervention group, the 12-month questionnaire included questions about the use, acceptability, usefulness and perceived effectiveness of the two intervention components. Audio-recording of a sample of consultations was conducted to assess fidelity of delivery (see *Report Supplementary Material 2* for more details). For economic measures, see the later section on WS5.

We aimed to recruit a sample size of 542 patients (271 per arm) in order to follow up 434 patients (217 per arm) at 12 months, assuming that 20% would not provide SBP data at this time point. This would give 90% power to detect a 5 mmHg difference in mean SBP between arms, assuming a standard deviation (SD) of 16 mmHg (based on the feasibility trial) and using a two-sided t-test at the 5% significance level. A 5 mmHg difference in SBP is of clinical significance, being associated with a 20% reduction in major vascular events.[38–40]

Five hundred and seventy-three participants recruited from 57 practices (a mean of 10 per practice, range 1–26) were randomised into the trial between January 2021 and March 2022. This exceeded the target of 542 participants.

However, there were five post-randomisation exclusions (e.g. a GP from one of the practices who tried out the online system), and there were 31 participants for whom we were unable to obtain a completed consent form. The maximum final sample for analysis was, therefore, 537 (272 intervention, 265 control). See *Appendix 2* for the trial flow chart and *Report Supplementary Material 3* for the statistical analysis plan.

Main trial quantitative findings

Baseline characteristics were similar in the two arms (*Table 1*). The majority of participants were recruited from practices in the East of England. Similar to the feasibility trial, 56% were male, and mean age was 66.5 years. The vast majority categorised themselves as being of White ethnicity, but there was a range of deprivation levels, with 19% from the most deprived areas (deprivation decile three or lower) based on participant home postcode. Mean BP, obtained from

TABLE 1 Baseline characteristics by trial arm and overall

	Trial arm		
	Intervention, *N* = 272	Control, *N* = 265	Total, *N* = 537
Region			
East	61% (166/272)	63% (167/265)	62% (333/537)
London	2% (5/272)	2% (6/265)	2% (11/537)
North East	13% (35/272)	11% (30/265)	12% (65/537)
South East	7% (19/272)	6% (16/265)	7% (35/537)
South West	7% (20/272)	6% (17/265)	7% (37/537)
Wales	10% (27/272)	11% (29/265)	10% (56/537)
Sex			
Male	57% (155/272)	55% (146/265)	56% (301/537)
Female	43% (117/272)	45% (119/265)	44% (236/537)
Age	*N* = 272	*N* = 265	*N* = 537
Mean (SD)	66.9 (9.2)	66.0 (9.8)	66.5 (9.5)
Range	39–89	32–88	32–89
Ethnicity			
White	94% (234/250)	95% (231/244)	94% (465/494)
Black	0% (1/250)	2% (4/244)	1% (5/494)
Asian	3% (8/250)	2% (4/244)	2% (12/494)
Mixed	2% (5/250)	1% (3/244)	2% (8/494)
Other	1% (2/250)	1% (2/244)	1% (4/494)
Missing	8% (22/272)	8% (21/265)	8% (43/537)
Deprivation			
1–3 (most deprived)	19% (53/272)	18% (49/265)	19% (102/537)
4–7	37% (101/272)	38% (101/265)	38% (202/537)
8–10 (least deprived)	43% (118/272)	43% (115/265)	43% (233/537)
SBP	*N* = 262 (10 missing)	*N* = 258 (7 missing)	*N* = 520 (17 missing)
Mean (SD)	145.1 (14.6)	145.0 (14.2)	145.0 (14.4)

continued

TABLE 1 Baseline characteristics by trial arm and overall (*continued*)

	Trial arm		
	Intervention, *N* = 272	**Control, *N* = 265**	**Total, *N* = 537**
Median (IQR)	145 (136–154)	143.5 (136–152)	144 (136–154)
Diastolic BP	*N* = 262 (10 missing)	*N* = 258 (7 missing)	*N* = 520 (17 missing)
Mean (SD)	82.6 (11.4)	81.9 (10.3)	82.3 (10.8)
Median (IQR)	83 (75–90)	81 (75.8–90)	82 (75–90)
BP > 140/90			
Yes	78% (205/262)	73% (189/258)	76% (394/520)
No	22% (57/262)	27% (69/258)	24% (126/520)
Missing	4% (10/272)	3% (7/265)	3% (17/537)
SBP > 140			
Yes	74% (193/262)	70% (180/258)	72% (373/520)
No	26% (69/262)	30% (78/258)	28% (147/520)
Missing	4% (10/272)	3% (7/265)	3% (17/537)
Medication adherence	*N* = 272	*N* = 272	*N* = 272
'I forget to take my tablets' (1–5) Mean (SD)	4.4 (0.7)	4.4 (0.7)	4.4 (0.7)
'I alter the dose of my tablets' (1–5) Mean (SD)	4.9 (0.4)	4.9 (0.4)	4.9 (0.4)
High cholesterol (self-report)			
Yes	48% (127/264)	53% (137/258)	51% (264/522)
No	52% (137/264)	47% (121/258)	49% (258/522)
Missing	3% (8/272)	3% (7/265)	3% (15/537)
Type 2 diabetes (self-report)			
Yes	15% (39/264)	16% (40/258)	15% (79/522)
No	85% (225/264)	84% (218/258)	85% (443/522)
Missing	3% (8/272)	3% (7/265)	3% (15/537)

IQR, interquartile range.

practice records before randomisation, was 145/82 mmHg, again similar to the sample in the feasibility trial. Of the participants, 75.8% had a BP reading above the accepted cut-off of 140/90 mmHg, and 71.7% had a SBP reading above 140. We were, therefore, partially successful in recruiting a sample of participants who had raised BP even though they were prescribed antihypertensive medication.

Because of the changes to the trial procedures, we were not able to conduct chemical adherence testing prior to randomisation. However, we were able to measure self-reported adherence during the baseline consultation prior to randomisation. The findings showed that self-reported adherence was high. For example, the mean score on the first Medication Adherence Report Scale (MARS)[34] item ('I forget to take my tablets') was 4.4 (SD 0.7) on a scale from 1 (always) to 5 (never), and the mean score on the second MARS item ('I alter the dose of my tablets') was 4.9 (SD 0.4) on the same 5-point scale. This was contrary to our objective of recruiting non-adherent participants, although it is

possible that some participants may have exaggerated their adherence in the context of a telephone consultation with a practitioner (social desirability bias).

Blood pressure

Table 2 gives the means and SDs of the BP measures at 12 months and also shows that 511 participants (95%) had either a self-measured SBP measure at 12 months (based on multiple readings per participant) or a single practice-measured SBP measure. These participants were included in the main model for the primary outcome analysis. The estimate (95% CI) from this model for the difference in means between arms in self-measured SBP at 12 months was −0.61 mmHg (−3.05 to 1.82), $p = 0.62$ (for intervention vs. control (reference group)]. Thus, the estimated effect was very small, and the detectable effect size of 5 mmHg did not fall within the CI. The difference in means between arms for SBP obtained from practice records was 1.04 mmHg (−1.56 to 3.65), $p = 0.43$.

Primary outcome: sensitivity analysis

The primary outcome model assumes data to be 'missing at random' (MAR). A sensitivity analysis was applied to investigate the potential impact of this assumption on the intervention effect. For those participants with unobserved 12-month self-measured SBP, a quantity δ (a range of SBP values) was added to the −0.61 mmHg effect that was estimated from the model. This was done under three scenarios: in each arm individually and in both arms. δ was varied to range from −5 mmHg to 5 mmHg, centred on a δ of zero representing the main trial finding that makes the MAR assumption. The results are shown in *Figure 2*.

Under the first scenario, in intervention participants only, the quantity δ was varied from −5 mmHg up to a value of +5 mmHg, whereas for the control participants with unobserved SBP, it was set to zero. This caused departures from the −0.61 (−3.05 to 1.82) estimate. These are limited by the 25% (68/272) of intervention participants with missing 12-month self-measured SBP data. The results showed that, if the intervention participants with missing SBP had 5 mmHg lower SBP than expected, then the intervention effect would be estimated to be −1.86 mmHg, whereas 5 mmHg higher than expected would increase the effect size to 0.64 mmHg. In the second scenario, where 26% (68/265) of control participants had missing 12-month self-measured SBP data, these values changed to + 0.67 mmHg

TABLE 2 Blood pressure measurements at 12-month follow-up

	Trial arm		
	Intervention, *N* = 272	Control, *N* = 265	Total, *N* = 537
Systolic BP			
Self-measured	*N* = 204 (75%)	*N* = 197 (74%)	*N* = 401 (75%)
Mean (SD)	135.0 (11.9)	135.6 (13.1)	135.3 (12.5)
Practice measurement	*N* = 223 (82%)	*N* = 225 (85%)	*N* = 448 (83%)
Mean (SD)	137.9 (15.0)	136.9 (13.2)	137.4 (14.1)
Diastolic BP			
Self-measured	*N* = 204 (75%)	*N* = 197 (74%)	*N* = 401 (75%)
Mean (SD)	77.5 (8.5)	76.8 (8.0)	77.1 (8.3)
Practice measurement	*N* = 223 (82%)	*N* = 225 (85%)	*N* = 448 (83%)
Mean (SD)	78.9 (10.1)	78.2 (8.7)	78.6 (9.4)
Number (%) of participants with *both* a self-measure *and* a practice measure of SBP at 12 months	*N* = 166 (61%)	*N* = 172 (65%)	*N* = 338 (63%)
Number (%) of participants with *either* a self-measure *or* a practice measure of SBP at 12 months	*N* = 261 (96%)	*N* = 250 (94%)	*N* = 511[a] (95%)

a Included in the main model for the primary outcome analysis.

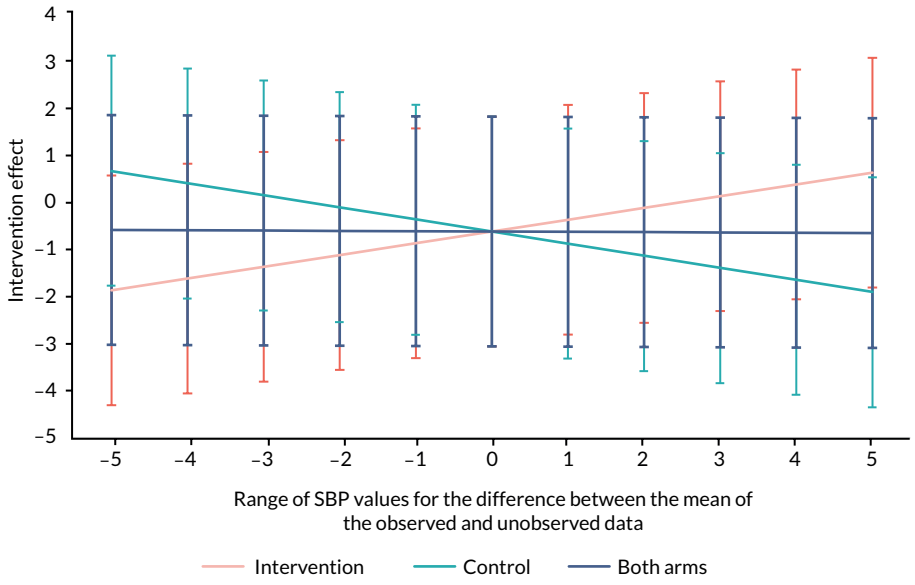

FIGURE 2 Sensitivity analysis for the MAR assumption in the primary outcome analysis. Vertical bars are 95% CIs for the intervention effect.

and −1.90 mmHg. In the third scenario, where both arms were subject to this sensitivity range, the values changed to −0.58 mmHg and −0.65 mmHg. The main model is seen to be robust to the MAR assumption because (1) the 95% CI bars for all three scenarios cross zero, confirming the non-statistically significant effect of the intervention on self-measured SBP, and (2) the estimated intervention effects remain small, lying within ±2 mmHg across the range.

Table 3 shows that there are no marked differences between arms in those with self-measured SBP at 12-month follow-up and those with missing self-measured SBP at this time point that would be expected to materially alter the results. No further sensitivity analysis was therefore undertaken.

Primary outcome: accounting for compliance

For the complier-average causal effect analysis, the estimate of the intervention effect was −1.58 (−7.83 to 4.68) mmHg. This was based on 106 intervention participants who used the digital intervention for at least 3 months. The SBP reduction of −1.58 mmHg may be an overestimate, as 'not needing any further support' was a main reason reported for not using the digital intervention beyond 3 months.

Primary outcome: subgroup analysis

The results of the subgroup analysis of the primary outcome are shown in *Table 4*. All of the CIs crossed zero, and interactions between each subgroup variable and arm were non-significant. Therefore, there is no statistical evidence against consistency of the intervention effect.

Changes in blood pressure

Additional, exploratory analyses ignoring trial arm showed that SBP reduced in the sample as a whole from baseline to 12-month follow-up [mean (SD) at baseline= 145.0 (14.2); mean (SD) at 12-month follow-up = 137.1 (14.0), $p < 0.001$, $N = 442$]. Of the 341 participants who had 'high' BP at baseline (> 140/90 mmHg), 45.5% moved to 'low' BP at follow-up; of the 101 participants who had 'low' BP at baseline, 33.7% moved to 'high' BP at follow-up, a statistically significant difference ($p < 0.001$). Similarly, of the 323 participants who had 'high' SBP at baseline (> 140 mmHg), 50.8% moved to 'low' SBP at follow-up; of the 119 participants who had 'low' SBP at baseline, 31.1% moved to 'high' SBP at follow-up ($p < 0.001$).

Medication adherence

As mentioned above, self-reported adherence before randomisation was relatively high. Self-reported adherence at 12-month follow-up was similarly high, with no difference between trial arms. For example, the mean score on the

TABLE 3 Characteristics of participants with and without a primary outcome by arm

	With self-measured SBP data *N* = 401		With missing self-measured SBP data *N* = 136	
	Intervention *N* = 204	Control *N* = 197	Intervention *N* = 68	Control *N* = 68
Region				
East	60% (122)	62% (123)	65% (44)	65% (44)
London	0% (1)	3% (5)	6% (4)	1% (1)
North East	13% (27)	11% (22)	12% (8)	12% (8)
South East	8% (17)	6% (11)	3% (2)	7% (5)
South West	8% (16)	8% (15)	6% (4)	3% (2)
Wales	10% (21)	11% (21)	9% (6)	12% (8)
Sex				
Male	56% (114)	54% (106)	60% (41)	59% (40)
Female	44% (90)	46% (91)	40% (27)	41% (28)
Age				
Mean (SD)	67.5 (8.7)	66.2 (9.3)	65.2 (10.5)	65.4 (11.2)
Ethnicity				
White	89% (181)	86% (170)	78% (53)	90% (61)
Black	0% (1)	1% (2)	0% (0)	3% (2)
Asian	2% (5)	2% (4)	4% (3)	0% (0)
Mixed	2% (4)	1% (2)	1% (1)	1% (1)
Other	0% (1)	1% (2)	1% (1)	0% (0)
Missing	6% (12)	9% (17)	15% (10)	6% (4)
Deprivation				
1–3 (most deprived)	20% (41)	18% (36)	18% (12)	19% (13)
4–7	33% (67)	38% (74)	50% (34)	40% (27)
8–10 (least deprived)	47% (96)	44% (87)	32% (22)	41% (28)

TABLE 4 Subgroup analysis of primary outcome

Subgroups	Intervention Mean SBP (SE); *N*	Control Mean SBP (SE); *N*	SBP difference in means (95% CI)	*p*-value for interaction between categories
Sex				
Male	134.9 (1.1) *N* = 114	133.3 (1.2) *N* = 106	+1.51 (−1.76 to 4.78)	*p* = 0.064
Female	135.0 (1.3) *N* = 90	138.2 (1.5) *N* = 91	−3.09 (−6.69 to 0.52)	
Age				
< 70	134.3 (1.1) *N* = 114	133.5 (1.0) *N* = 119	+0.83 (−2.34 to 4.00)	*p* = 0.13
≥ 70	135.8 (1.2) *N* = 90	138.7 (1.7) *N* = 78	−2.97 (−6.72 to 0.77)	

continued

TABLE 4 Subgroup analysis of primary outcome (*continued*)

Subgroups	Intervention Mean SBP (SE); *N*	Control Mean SBP (SE); *N*	SBP difference in means (95% CI)	*p*-value for interaction between categories
Region[a]				
East	132.9 (1.0) *N* = 122	134.0 (1.2) *N* = 123	−1.26 (−4.33 to 1.81)	*p* = 0.59
Rest	138.1 (1.4) *N* = 82	138.1 (1.5) *N* = 74	0.09 (−3.77 to 3.95)	
Deprivation decile				
1–5 (most deprived)	136.5 (1.5) *N* = 78	136.1 (1.6) *N* = 73	0.47 (−3.50 to 4.45)	*p* = 0.49
6–10 (least deprived)	134.0 (1.0) *N* = 126	135.3 (1.1) *N* = 124	−1.31 (−4.40 to 1.78)	

SE, standard error.
a Two categories are presented because 62% of participants were from the East of England.

Note
Other coding decisions are described in the statistical analysis plan (see *Report Supplementary Material 3*).

5-item MARS questionnaire[34] was 23.8 (SD 1.7) out of a maximum score of 25 (based on 387 participants who provided 12-month data on this scale).

Consistent with these findings, there was no effect of the intervention on biochemically measured adherence at 12-month follow-up. Of the 392 participants who provided a urine sample at this time point, 388 (99.0%) were found to have at least one antihypertensive medication (or metabolite) from a panel of 40 such medications in their urine. Of the 352 participants who returned a completed 12-month questionnaire and provided a urine sample, 94.3% were categorised as 'fully adherent' (all of the antihypertensives they reported taking were detected in their urine), 4.8% were categorised as 'partially adherent' (at least one, but not all, of the antihypertensives they reported taking were detected in their urine), and only 0.9% were categorised as 'non-adherent'. There was no difference in these percentages between trial arms.

Medication use

In the sample of 308 participants who provided antihypertensive medication use information on the post-baseline and 12-month follow-up questionnaires, mean DDDs increased by 4% over time from 2.74 (SD 1.91) to 2.85 (SD 2.02), but this was statistically non-significant ($p > 0.1$). There were no significant differences between trial arms at either time point or in change over time.

Duration of baseline consultation

Based on the timestamps automatically recorded by the PAM online system, the mean (SD) duration of the baseline consultations was 29.3 (36.6) minutes for intervention consultations and 20.4 (20.9) minutes for control consultations; the duration of the intervention consultations was much more variable. The difference in mean duration (8.8 minutes) is assumed to be the time taken to deliver the VBI, including the additional data collection that this required.

Fidelity of intervention delivery

Fidelity of delivery of the VBI was assessed by analysing the 55 audio-recorded consultations (27 intervention and 28 control). In all cases, the practitioner informed the participant which group they had been allocated to immediately after they had been randomised, as specified by the protocol. In the intervention consultations, the online system then prompted the practitioner to deliver the VBI, including emphasising to the participant the importance of taking all their medications as prescribed and explaining that the digital intervention that they would receive, whether via text messaging or smartphone app, would be personalised and tailored. However, this was done in only 52% (14/27)

of the consultations. As intended, no elements of the VBI were delivered in the control consultations, so there was no evidence of contamination. However, in a quarter of these consultations, the practitioner did not implement the online prompt to emphasise to the participant that they were still an important part of the study. It is not known how representative the audio-recorded consultations were of the full set.

Use of the digital intervention

Of the 272 intervention participants, 212 (77.9%) opted to receive text messages; one of these participants later switched to the app (which was available for Android phones only). Sixty participants (22.1%) initially opted to use the app, but eight of these who were iPhone (Apple Inc., Cupertino, CA, USA) users were switched to text messages. Of the 53 participants who initially opted for or were switched to the app, 14 either chose not to install it or tried and were unable to do so. Therefore, there were 39 active app users.

Of the 219 participants who opted for or were switched to text messages, only 5.9% did not reply to any of the 11 query messages (asking whether they had taken all their prescribed medications in the last 7 days) in the first 3 months of the programme, and a majority (56.6%) replied to six or more of the query messages during this time period. It was not possible to extract corresponding information for app users.

Of intervention participants, 73.9% used the digital intervention for at least 1 month, and 39.0% used it for at least 3 months (they could have used the text messaging programme for up to 420 days, and longer than this in the case of the app). In the 61.0% of intervention participants who stopped the intervention before 3 months, the main reasons given were 'I didn't need any further support' and 'The text messages were beginning to annoy me'.

Acceptability of the intervention

Based on ratings on the 12-month follow-up questionnaire, intervention participants on average were satisfied with the intervention and thought that it was acceptable and effective and provided useful information. Few participants said that they thought that there was any information not covered in the baseline consultation with the nurse that should have been (6.5%) or that there was any information not covered in the text messages/app that should have been (2.9%).

Outcomes not analysed or reported

There were several outcomes that were measured in the main trial but not analysed or reported here. Glycated haemoglobin and full lipid profile were measured in subgroups of participants who reported having type 2 diabetes or high cholesterol, respectively. Participants in these subgroups were sent finger prick test kits and asked to collect home blood samples and post these to a laboratory for analysis. However, response rates were low, and in some cases, the samples received by the laboratory could not be identified. We were unable to use the blood sample test results obtained from practice records because test dates were not provided due to an error in the design of the pro-forma that was completed by practice staff. We also decided not to report the findings from the Beliefs About Medicines Questionnaire, because they do not contribute to the interpretation of the main trial findings.

Main trial qualitative findings

To explore practitioners' and participants' experiences of delivering or receiving the PAM intervention, the following qualitative data were gathered: (1) semistructured interviews with 15 practitioners (all of them nurses), conducted on average 15 months after they had delivered their final baseline consultation; and (2) semistructured interviews with 44 participants, conducted on average 22 months after their baseline consultation, including those in the control group (N = 9) and the intervention group (N = 35). Separate interview guides were developed and tested for practitioners and participants. The interviews were conducted by research assistants/associates by telephone [or in one case by Zoom (Zoom Video Communications, San Jose, CA, USA)], audio-recorded and transcribed. Interviews with practitioners lasted 44 minutes on average; those with participants lasted 30 minutes on average.

Data analysis followed the steps of Braun and Clarke's thematic analysis.[41,42] Interview transcripts were read and reread for familiarisation with the data, noting down initial ideas. These were transferred to mind maps (separate for patient and practitioner data sets) to formulate into initial codes and an initial coding framework, which were discussed

as a team and imported into NVivo (QSR International, Warrington, UK) qualitative data-indexing software (version 12) [NVivo qualitative data analysis software. http://lumivero.com/products/nvivo/ (accessed 16 September 2025)]. All transcripts were then coded using NVivo, with refinement of the coding framework throughout the process. Key themes were defined, reviewed and refined (with different team members having different roles for the patient and practitioner data sets). Samples were coded by other team members – and discussions held – to check agreement and reliability of the coding framework and final themes.

Practitioners' experiences of delivering the very brief intervention

Practitioners described how an established practitioner–patient relationship facilitated delivery of and engagement with the VBI. Trust and continuity of care from such established relationships were thought to enhance patients' openness to a new type of consultation.

The VBI element was delivered by telephone. While practitioners recognised that this could improve access for many patients, most would have preferred to deliver it in person. This was particularly the case if there was not an established relationship.

Practitioners argued that delivering the VBI required effective communication skills in order to achieve a balance between adhering to the VBI structure while still providing information in sufficient depth and level and with appropriate language for each patient. A challenge noted was that if a patient required more information/explanation, in some cases the intervention could no longer be described as 'very brief'.

While practitioners were fairly positive about the intervention overall, they felt that the ability to adapt and tailor the VBI to the patient would enhance his or her engagement.

Participants' experiences

Participants who were interviewed were similar in demographic characteristics to the full sample.

Many participants struggled to recall the consultation in which the VBI had been delivered. Those who could remember, and who found it useful, appreciated the supportive tone and the clarity of information provided. Other participants, who considered themselves to be adherent to their medication, found it less helpful. Many were satisfied with remote delivery, but others noted a preference for in-person delivery.

The following summarises participants' views of the digital intervention:

Frequency and timing: some participants appreciated the ability to personalise the timing of the messages/notifications, but others appeared not to recall the option to do this being discussed in the baseline consultation. While many commented that the frequency of messages/notifications was appropriate, some had found them too frequent; annoyance at high frequency was given as a reason for stopping the intervention.

Accessibility: while the digital intervention was largely regarded as easy to understand and straightforward, some participants had struggled due to their level of literacy or digital literacy.

Message type: reminders were regarded as useful, but particularly for people taking multiple medications and at different times.

Message tone: participants varied in their views about the tone of messages/notifications, with some describing it as supportive and encouraging and others finding it patronising.

Usefulness: similar to the findings from the development phases, many participants commented that while the digital intervention was not useful for them personally, they could envisage it being useful for others; for example, people with a new regime of medication, multiple medications, memory problems or other impairments and/or busy lives. Suggestions for improvement included more personalisation and clearer instructions for dealing with technical difficulties.

Main trial: interpretation of findings

The main trial showed no effect of the intervention on SBP at 12 months. This is in contrast to the feasibility trial which found a positive effect of the intervention at 3 months, albeit in a small trial that was not powered for effectiveness. Possible explanations for the null finding include:

1. Contrary to our objective, a significant proportion (24%) of participants did not have raised BP at baseline, and self-reported medication adherence was high on average at baseline, which would have reduced the possible scope for an intervention effect. This is likely to be the main explanation for the null intervention effect, but additional factors may have contributed:
2. Lack of engagement due to the remote delivery of the VBI. Unlike in the feasibility trial, participants in the main trial had no face-to-face contact with the practitioner. This may have reduced the effect of the VBI, if not the digital intervention.
3. Low fidelity of the VBI intervention delivery. Analysis of the transcripts of the baseline consultations suggested that the VBI was delivered as specified in the protocol in only about half the consultations.
4. Insufficient exposure to the digital intervention. Intervention participants could have used the text messaging programme for up to 420 days, and longer in the case of the app. However, 61.0% of them stopped the intervention before 3 months. Many participants stopped the intervention because they felt that they did not need any further support. However, others could potentially have benefited from continuing with the intervention.
5. Because of the measurement schedule of the trial, we cannot rule out the possibility that the intervention had a short-term effect on adherence and SBP which dissipated by 12 months.

The findings from this trial appear inconsistent with the positive findings from previous trials as synthesised in recent meta-analytic reviews of nurse-led and digital interventions to improve medication adherence and reduce BP in people with hypertension.[10–19] The interventions examined in these reviews were heterogeneous, and none involved a very brief nurse-delivered telephone intervention followed by a digital intervention as investigated here.

The observed reduction in BP in the sample as a whole over the course of the trial may simply reflect regression to the mean without real underlying change. However, it may also partly reflect true change due to the experience of taking part in a trial that involved self-measurement of BP and objective assessment of medication adherence (Hawthorne-like effect). The reduction in SBP could not be explained by an increase in medication use.

Workstream 5: economic modelling

Overview of economic evaluation

The aims of this WS were to develop an economic model of the cost-effectiveness of medication adherence interventions and to evaluate the costs and cost-effectiveness of the PAM intervention compared with UC alone.

The analysis was based on patient-level data collected in the PAM main trial, including intervention costs, NHS resource use and health-related quality of life (HRQoL) assessed between baseline and 14 months post randomisation. A 14-month time horizon was used because intervention participants could receive text messages/notifications for up to 14 months; the extended time window also took account of the fact that the majority of 12-month follow-up questionnaires were returned by this time point. The outcome measure was quality-adjusted life-years (QALYs), which combine both the length of life and the quality of life and is consistent with National Institute for Health and Care Excellence recommendations for economic evaluations.[43]

The base case analysis was performed on data with missing values imputed using multiple imputation (MI) by chained equations and with adjustment for potential confounders, as described in *Appendix 3*. Cost-effectiveness estimates are also reported for the following scenarios:

A. With missing values imputed using MI, but with no adjustment for potential confounders.
B. Complete-case analysis (with no MI) with adjustment for potential confounders.
C. Complete-case analysis with no adjustment for potential confounders.

While it was planned in the health economic analysis plan (see *Report Supplementary Material 1*), extrapolation beyond the end of the trial was not undertaken because there was no significant difference in the primary outcome between groups at the end of the within-trial period.

Cost-effectiveness was expressed as the incremental cost per QALY gained and the incremental net monetary benefit (INMB),[43] as assessed using cost-effectiveness thresholds of £15,000, £20,000 and £30,000 per QALY gained. The time horizon was 14 months, as explained above. Given this time horizon, discounting was not applied to costs or outcomes in the base case analysis. The analysis took an NHS and Personal Social Services perspective, with all costs reported in 2023 Great British pound (GBP).

Full details of the methods used for the economic evaluation can be found in *Report Supplementary Material 1* and *Appendix 3*.

Findings from the base case (within-trial) analysis

National Health Service resource use costs and utility scores (base case imputed data) and estimates for CVD event excess healthcare costs are presented in *Tables 5* and *6*, respectively. While the inclusion of secondary care costs had been specified in the analysis plan, the collected trial data revealed that a high proportion of patients from both arms of the trial (> 80%) recorded no secondary care costs throughout the trial. This adversely impacted the imputation of missing data and could not be resolved through employing alternative imputation models. Given this and the low contribution to total costs, it was therefore decided to exclude these costs from the economic analysis.

Total running costs for the PAM intervention consisted of fixed periodic PAM intervention running costs of £23.01 per week (administrative staff costs) and £16.67 per month (server maintenance costs), resulting in a total annual PAM intervention cost of £1400.63. For patients who received the PAM intervention (n = 272), total running costs per patient for the trial period were £6.01. Patients in the PAM intervention group received notifications either via a

TABLE 5 National Health Service resource use costs and utility estimates, imputed estimates

	UC, costs per patient				PAM intervention, costs per patient			
	Mean	**SE**	**95% CI, lower**	**95% CI, upper**	**Mean**	**SE**	**95% CI, lower**	**95% CI, upper**
Healthcare costs[a]								
Primary care total cost	£53.5	£13.14	£27.35	£79.71	£73.82	£13.63	£46.77	£100.87
Antihypertension medication total costs	£11.63	£1.01	£9.63	£13.64	£12.95	£1.71	£9.55	£16.35
PAM intervention costs								
VBI	–	–	–	–	£6.75	–	–	–
Running costs	–	–	–	–	£6.01	–	–	–
Notification costs	–	–	–	–	£17.07	–	–	–
Total intervention costs	–	–	–	–	**£29.83**	–	–	–
Total costs[a]	**£65.17**	**£13.06**	**£39.14**	**£91.20**	**£113.60**	**£13.93**	**£85.95**	**£141.25**
Utility[a]								
Baseline utility	0.765	0.025	0.710	0.810	0.771	0.0237	0.724	0.818
6 months utility	0.767	0.024	0.718	0.816	0.769	0.0255	0.719	0.820
12 months utility	0.744	0.027	0.689	0.800	0.763	0.024	0.714	0.812
Total QALYs[a]	**0.759**	**0.022**	**0.714**	**0.805**	**0.768**	**0.023**	**0.722**	**0.815**

SE, standard error. Costs are in 2023 GBP.
a Imputed data. Mean and 95% CI estimates are calculated from the 20 imputed data sets.

TABLE 6 Cardiovascular disease event costs

CVD event costs		
Angina	£541.45	Age adjusted
Heart failure	£3690.73	
Myocardial infarction	£5088.90	
Stroke	£6684.10	
Dead	£6448.19	Non-vascular death, without previous CVD

smartphone app or via text messages. For those receiving notifications via the app, no costs above the running costs described above were applicable. Total cost for the 66,085 text notifications sent during the trial was £4123.70 (a cost of £0.06 per message sent).

The mean number of notifications sent in the within-trial period per patient who opted to receive text messages was 274, resulting in a total cost per patient of £17.07. Cost for the one-off nurse-led VBI at a mean duration of 8.8 minutes was £6.75. Total costs for the PAM intervention (VBI cost, running costs and notification costs) were therefore calculated to be £29.83 per patient.

Estimates for within-trial total costs and QALYs (imputed data) are also presented in *Table 5*. Total costs per patient (95% CI) were £65.17 (£39.14 to £91.20) for the UC group and £113.60 (£85.95 to £141.25) for the PAM intervention group. Mean utility scores remained broadly unchanged over the trial period for both the PAM intervention group (0.771 to 0.763) and the UC group (0.765 to 0.744).

Table 7 presents the results of the base case analysis – a decision tree model incorporating the within-trial costs (healthcare resource use and associated costs) and outcomes (QALYs) data, in addition to the expected costs and outcome impacts of health outcomes based upon the estimated CVD event risk (calculated as described in *Appendix 3*). For the short-term model, initial per-patient QALY estimates for each trial arm were derived via regression of imputed estimates, controlling for baseline utility and sex. Where required, CVD event multipliers were then subsequently applied to model their effect on HRQoL.

In the base case analysis, mean incremental costs for the PAM intervention were £42 (95% CI −£7 to £91), with mean incremental QALYs of 0.022 (95% CI −0.030 to 0.072). The mean incremental cost-effectiveness ratio (ICER) value was estimated to be £1231 per QALY gained (95% CI −£13,156 to £19,535) (see *Table 7*). The cost-effectiveness plane (CEP) for the 1000 Monte Carlo simulations is presented in *Figure 3*. The INMB for the PAM intervention versus UC at a threshold of £15,000/QALY was £289 (95% CI −£498 to £1026), indicating that, based on the point estimate, the PAM intervention was cost-effective in the base case analysis.

The INMB rose to £400 (95% CI −£643 to £1383) and £621 (95% CI −£933 to £2104) for £20,000/QALY and £30,000/QALY, respectively. The cost-effectiveness acceptability curve (CEAC) showed that for a cost-effectiveness threshold for a QALY of £15,000, the probability that the PAM intervention is cost-effective was 0.777 (0.782 and 0.792 for £20,000/QALY and £30,000/QALY, respectively) (see *Table 7*, *Figure 4*).

The expected value of perfect information (EVPI) at a willingness-to-pay (WTP) threshold of £15,000/QALY was £310.66, rising to £415.95 and £629.83 for £20,000/QALY and £30,000/QALY thresholds, respectively (*Table 8*). Population EVPI at £15,000/QALY is an estimated £1B for the estimated 34% of diagnosed hypertension patients with uncontrolled hypertension[44] among the approximately 9.9 million primary care patients prescribed treatment for hypertension in England and Wales.[3,4]

For scenario A, the mean ICER was £5688 (95% CI −£17,570 to £25,570), with mean incremental costs and QALYs of £58 and 0.024, respectively (see *Report Supplementary Material 4*, *Table 1* and *Figure 1*). The mean INMB for the PAM intervention versus UC at a threshold of £15,000/QALY was £306 (95% CI −£342 to £1002), indicating that the PAM

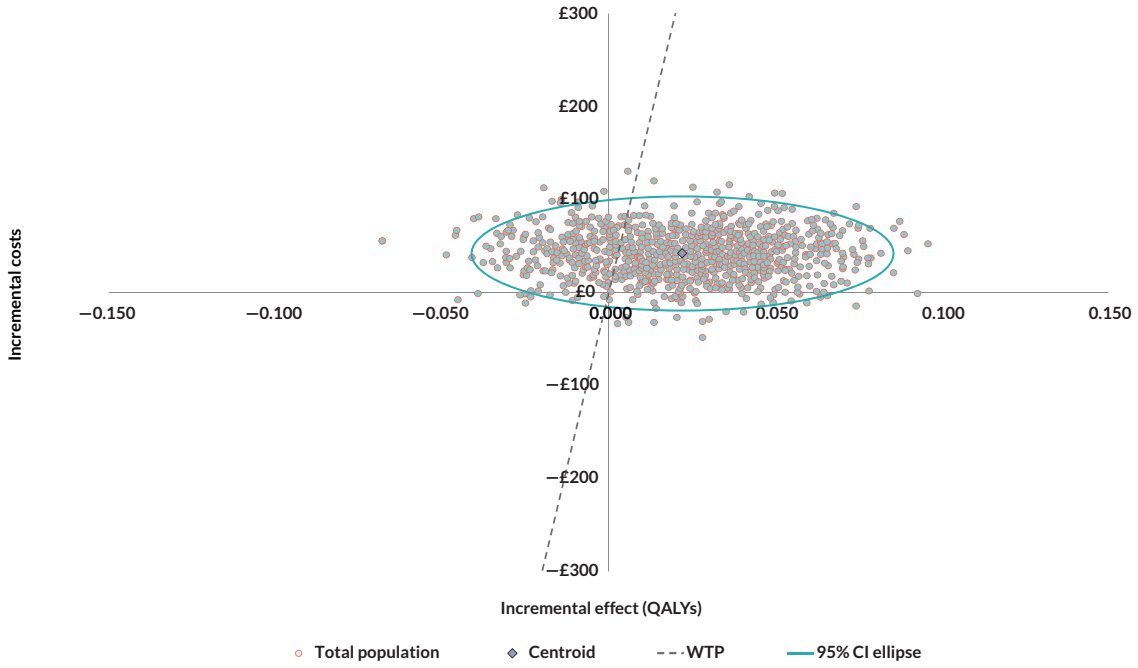

FIGURE 3 Cost-effectiveness plane, total population, base case. Note: Costs are in 2023 GBP. WTP threshold, £15,000 per QALY gained. Data include values imputed using MI, adjusted for potential confounders. Point estimates and 95% CIs were derived from 1000 Monte Carlo simulations (see text).

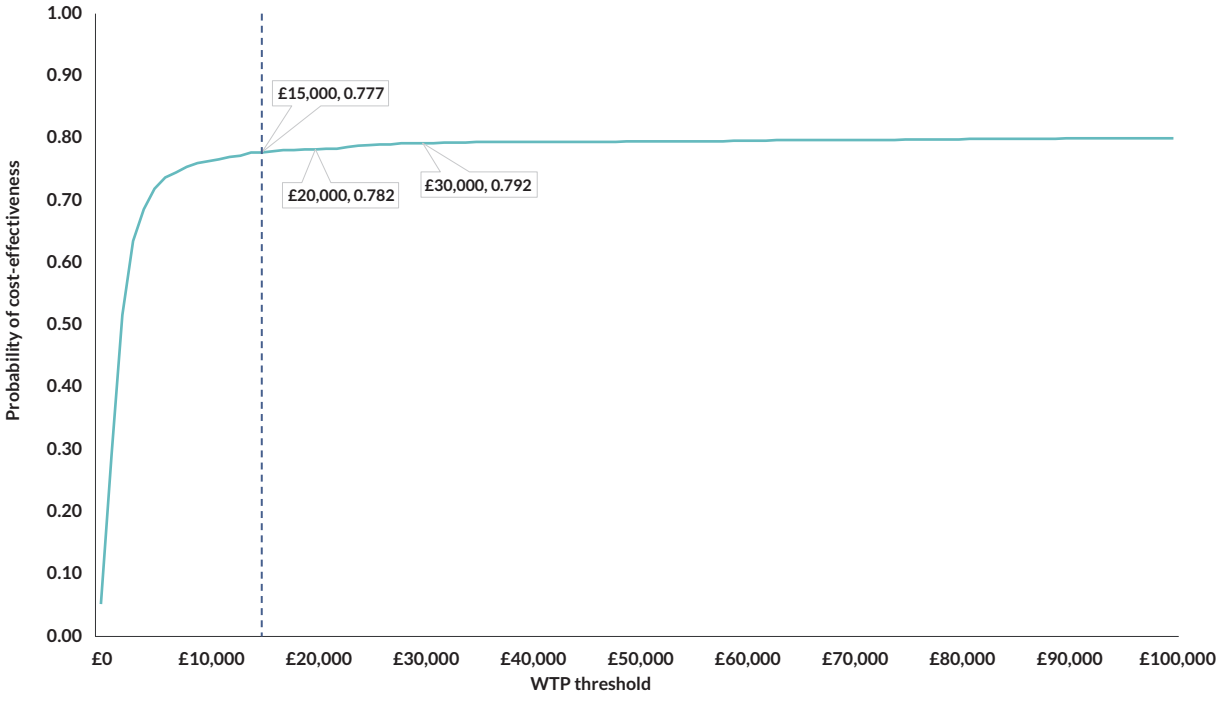

FIGURE 4 Cost-effectiveness acceptability curve showing the probability that the PAM intervention is cost-effective vs. UC at different values of the cost-effectiveness threshold for a QALY, base case. Note: Costs are in 2023 GBP. Data include values imputed using MI, adjusted for potential confounders. The probability PAM intervention is cost-effective is based on the QALYs gained and incremental costs and calculated across a range of cost-effectiveness thresholds for a QALY.

intervention was cost-effective in this scenario, rising to £428 (95% CI −£438 to £1356) and £671 (95% CI −£629 to £2064) for £20,000/QALY and £30,000/QALY, respectively. The CEAC showed that for a cost-effectiveness threshold for a QALY of £15,000, the probability that the PAM intervention is cost-effective was 0.815 (0.827 and 0.840 for £20,000/QALY and £30,000/QALY, respectively) (see *Report Supplementary Material 4*, *Figure 2*).

TABLE 7 Model outputs for PAM intervention vs. UC, base case[a]

Total trial population	Mean	SD	95% CI, lower	95% CI, upper
Total costs per patient, control	£235	£35	£192	£338
Total QALYs per patient, control	0.702	0.030	0.641	0.760
Total costs per patient, PAM	£277	£43	£208	£380
Total QALYs per patient, PAM	0.724	0.035	0.657	0.795
Incremental costs	£42	£25	−£7	£91
Incremental QALYs	0.022	0.026	−0.030	0.072
ICER (£/QALY)	£1231	£24,117	−£13,156	£19,535
INMB (WTP, £15,000/QALY)[b]	£289	£389	−£498	£1026
INMB (WTP, £20,000/QALY)[b]	£400	£517	−£643	£1383
INMB (WTP, £30,000/QALY)[b]	£621	£775	−£933	£2104
Probability of cost-effectiveness at £15,000/QALY	0.777			
Probability of cost-effectiveness at £20,000/QALY	0.782			
Probability of cost-effectiveness at £30,000/QALY	0.792			

Costs are in 2023 GBP.
a Point estimates and 95% CIs were derived from 1000 Monte Carlo simulations. The model was populated where available, using input parameters values randomly sampled from their respective uncertainty distributions.
b The INMB and the probability PAM intervention is cost-effective are based on the QALYs gained and incremental costs, and calculated at a cost-effectiveness threshold for a QALY of £15,000, £20,000 and £30,000.

TABLE 8 Expected value of perfect information, base case

WTP threshold (£/QALY)	£15,000	£20,000	£30,000
Maximum expected INMB	£1393.11	£1865.26	£2824.35
Expected INMB with perfect information	£1082.45	£1449.31	£2194.52
EVPI per patient	**£310.66**	**£415.95**	**£629.83**
Population EVPI	£1,045,698,442	£1,400,097,731	£2,120,007,948

Results for the scenario B analysis [complete-case analysis (with no MI) with adjustment for potential confounders] are reported in *Report Supplementary Material 4* (see *Table 2* and *Figure 3*). Scenario B mean incremental costs and QALYs were £42 and −0.012, respectively, resulting in a negative ICER value. The mean INMB for PAM intervention versus UC at a threshold of £15,000/QALY was −£216 (95% CI −£1007 to £598), indicating that the PAM intervention was not cost-effective in this scenario. The INMB fell to −£274 (95% CI −£1321 to £803) and −£391 (95% CI −£1944 to £1212) for £20,000/QALY and £30,000/QALY, respectively (see *Report Supplementary Material 4*, *Table 2*). The CEAC showed that for a cost-effectiveness threshold for a QALY of £15,000, the probability that the PAM intervention is cost-effective was 0.286 (0.293 and 0.299 for £20,000/QALY and £30,000/QALY, respectively) (see *Report Supplementary Material 4*, *Figure 4*).

Results for the scenario C analysis (complete-case analysis with no adjustment for potential confounders) are reported in *Report Supplementary Material 4* (see *Table 3* and *Figure 5*). Scenario C mean incremental costs and QALYs were £14 and −0.002, respectively, resulting in a negative ICER value. The mean INMB for PAM intervention versus UC at a threshold of £15,000/QALY was −£45 (95% CI −£124 to £35), indicating that the PAM intervention was not cost-effective in this scenario. The INMB fell to −£55 (95% CI −£162 to £53) and −£75 (95% CI −£237 to £90) for £20,000/QALY and £30,000/QALY, respectively (see *Report Supplementary Material 4*, *Table 3*). The CEAC showed

that for a cost-effectiveness threshold for a QALY of £15,000, the probability that the PAM intervention is cost-effective was 0.147 (0.169 and 0.188 for £20,000/QALY and £30,000/QALY, respectively) (see *Report Supplementary Material 4*, *Figure 6*).

Discussion

In our base case economic analysis, the PAM intervention has a mean ICER compared with UC that is below the usual WTP thresholds used in the UK. The probability of cost-effectiveness at WTP thresholds of £15,000, £20,000 and £30,000/QALY was between 77% and 80%. However, the CIs are wide and cross zero, indicating some chance that the intervention could be less effective and more costly compared with UC only. Similar findings were also obtained in the scenario using MI to account for missing values (but with no adjustment for potential confounders). The intervention was not cost-effective in the analyses involving complete cases only.

The main strengths of our analysis are that it was based on a RCT, with comprehensive assessment of HRQoL and resource use. However, these findings should be considered in the context of cost-effectiveness being based upon evidence of modest incremental cost and QALY gains.

A wider (societal) perspective would have provided insight into the impacts on patients, families and businesses, although it is uncertain how inclusion of these impacts would have changed the cost-effectiveness of the intervention at existing WTP thresholds.

The modelling approach made conservative assumptions with regard to the cost per patient for the intervention. There would be scope for reduction of per-patient running costs, via scaling of the intervention to all eligible patients nationwide. However, without robust information on costs escalation associated with a large-scale roll-out, it was not possible to model any potential cost savings in this area. Similarly, the current per text notification costs might also be reduced over time from their current level. If these costs were reduced, it would likely reduce the uncertainty surrounding the cost-effectiveness of the PAM intervention.

We have developed a model with which we were able to conduct a robust evaluation of a medication adherence intervention, with the capability for capturing key resource use, costs and outcome metrics over both the short and long terms. As such and with only moderate alterations, this model can provide the basis for future economic evaluations of similar interventions across a range of different conditions.

In summary, the PAM trial showed no effect of the intervention on medication adherence or SBP. Despite this, the accompanying economic analysis accounting for missing data showed that the PAM intervention is likely to be cost-effective under the current WTP thresholds, albeit with some uncertainty.

Patient and public involvement

Patients and the public were involved throughout the programme. In this section, we report what form their involvement took, at what stages it occurred and what impact it had.

Before we submitted the grant application, we engaged with two local patient representatives and INsPIRE (the local PPI group). Four patients reviewed a summary of our application. They emphasised the potential of digital interventions to support tablet taking through addressing the main reasons for non-adherence and the need to examine existing evidence and canvas expert opinion in developing the interventions.

In the original grant application, we named a PPI collaborator, who, among other activities, subsequently cowrote the PPI sections of our annual and checkpoint reports.

At the start of the programme, we recruited a pool of PPI representatives from several sources, including Addenbrooke's Hospital PPI panel, patient support groups based in Cambridgeshire, participants in our previous medication adherence studies, and the People in Research website. They were all people who took regular medication for long-term health conditions.

We also set up a PSC, which included an independent PPI representative.

From the outset of the programme, we used the NIHR INVOLVE national standards for public involvement as a guide for our PPI activities. These emphasise conducting research 'with' rather than 'on' patients and the public.

We kept a log of PPI activities and changes made to the programme as a result of these. The following is not an exhaustive list but highlights key examples of how PPI contributed to the programme.

Workstream 1

Patient and public involvement representatives reviewed various participant documents for the qualitative interviews, including the information sheet, invitation letter, poster, consent form, topic guide and visual materials. As a result of PPI input, we made a number of changes, simplifying the language and adjusting the vocabulary used to make the documents more accessible and patient-friendly. PPI contributors received detailed feedback on the changes made as a result of their input.

The PPI collaborator reviewed the manuscript for the qualitative interviews paper.[29] As a result of her feedback, we reworded several sections and added a new section in the methods, describing PPI input into the study.

Workstream 2

Obtaining recommendations for the intervention

We attended three Cambridgeshire-based peer support groups for patients with type 2 diabetes at which we obtained informal feedback from patients about what they would find useful and unhelpful in a digital intervention. One of the ideas we took forward was the suggestion of a 'snooze' button for the smartphone app.

During the intervention development stage, two PPI representatives joined one of our research team meetings to help us decide on the objectives of the PAM intervention, that is, what it should focus on and what was missing; they also provided ideas for message content.

Creating intervention content

At the University of Cambridge Science Festival 2019, members of the general public joined our interactive stall over the course of a day. We presented some example scenarios of patients who forget or intentionally skip their medication. We asked people to generate their own intervention messages and recommendations for smartphone app features to support medication taking. This activity yielded pages of example intervention content from people who either took regular medication themselves or were responsible for someone else's medication regimen as a carer. We collated these suggestions and adapted some for inclusion in the intervention. See our Science Festival blog here: www.spcr.nihr.ac.uk/news/blog/behavioural-science-group-at-the-cambridge-science-festival-2019.

One attendee shared some of the example patient scenarios with their health and social care students based in London and asked them to write intervention messages. We received around 30 messages from the students, which we added to the pool of suggested content. The messages included hard-hitting facts, practical advice and ideas for interactive components.

Pre-testing study

Patient and public involvement representatives reviewed all study documents for the pre-testing study: protocol, patient information sheet, consent form and advertising materials. Two PPI representatives trialled the 1-month text messaging programme and smartphone app, giving feedback on the acceptability and usability of the intervention. PPI representatives also tested the PAM online system and reported back on the usability, ease of navigation and any technical bugs. Following study completion, PPI representatives provided comments on a draft of the manuscript.

Workstreams 3 to 5

We obtained PPI feedback on the design of the feasibility study and all participant documents.

We held a PPI workshop in Cambridge to inform the design of the main trial. We obtained recommendations for maximising recruitment and retention of patients. Our topic guide and questions were based on the Patient and public involvement Intervention to enhance Recruitment and Retention in Surgical Trials (PIRRIST) guidance for chief investigators (www.phc.ox.ac.uk/forms/pirrist-guidance), which was coauthored by the PPI collaborator. PPI representatives reviewed all the participant materials (poster, information sheet, leaflet) as a group; the discussion between attendees added to the richness of the feedback. We made changes in response to their comments, such as simplifying the text and changing the layout.

The protocol for the main trial was reviewed before it was submitted for ethical approval. PPI feedback focused on the changes made to the study procedures as a result of COVID-19, including the acceptability of the remote consultations and the need for clear instructions for participants to take their own BP measurements.

Patient and public involvement representatives reviewed a draft resource use questionnaire, intended for use in the main trial. They answered questions related to the burden of completing the questionnaire, the anticipated accuracy of recall and how often they would be willing to complete the questionnaire. Their feedback directly informed how the questionnaire was administered in the trial, to maximise completion rates without compromising on recall accuracy.

The PPI collaborator edited a PAM study newsletter that was shared with patients and GP practices. She reworded sections to remove jargon and made sure that it was easy to understand the findings from a lay perspective. This improved the readability and quality of the newsletter.

The PPI collaborator attended the annual Programme Management Team meeting in March 2021 and contributed to discussions on the progress of the main trial. She shared with the team the PIRRIST PPI tool to aid recruitment and retention in trials which she coauthored. In addition, she provided advice to the team for future ethics amendments and funding extension applications, using her expertise as vice chair of a REC, emphasising the importance of PPI support for any proposed changes.

The PPI representative on the PSC participated in several PSC meetings prior to and during the main trial. He contributed to discussions around the development and maintenance of the PAM app, based on his extensive experience of mobile systems. He also trialled the PAM app on an Android tablet and provided detailed feedback on the usability and functionality of the app and suggested questions that end-users may have. He also made recommendations for the trial design, including the importance of recruiting patients and GP practices that represent the general population in terms of socioeconomic status.

We organised a dissemination event at the Cambridge Festival in April 2022 involving an expert panel discussion and invited comments and questions from the lay audience, which provided useful pointers on how to disseminate findings from the PAM main trial.

Equality, diversity and inclusion

Neither of our two systematic reviews of RCTs or our meta-synthesis of published qualitative research identified any papers that addressed equality, diversity and inclusion issues. As would be expected, the majority of studies were conducted in the USA, UK and other developed countries.

In our primary research studies, the target group was patients prescribed medication for hypertension with poorly controlled BP in primary care in England and Wales. Reflecting the prevalence of hypertension in the population, we therefore expected that our recruited samples would tend to be older than average and to comprise approximately equal numbers of men and women. This was indeed the case. We had the explicit aim of recruiting participants with a range of social deprivation, which we tried to achieve by recruiting practices partly on the basis of index of deprivation based on postcode. We were partially successful in this. For example, 35% of participants in the randomised feasibility study were from the most deprived areas (deprivation decile three or lower), though this fell to 19% in the main trial. Participants' ethnicity was not recorded in the feasibility trial, but in the main trial, the vast majority (94%) of

participants categorised themselves as being of White ethnicity, which indicates that minority ethnic groups were under-represented in the research. Clearly, this is an important issue that will need to be addressed in future research.

It should also be mentioned that the intervention we developed included a digital component (text messaging or a smartphone app). We, therefore, aimed to recruit participants who had a mobile phone and were familiar with this technology. Although the proportions of UK adults (and those aged 65 years and over) who use either a smartphone or a mobile phone capable of text messaging has increased rapidly in recent years, there are still many people in the population who would be unable to access or use the intervention we developed at the present time.

Climate, health and sustainability

These issues were addressed in the programme in three main areas:

1. Methods. In the main trial, the decision was made to deliver the VBI remotely (which was done by telephone in every case) and to conduct all study measurements remotely. This eliminated the need for participants to travel to their GP surgery or for research nurses to visit participants at home to collect BP and other measures. The changes in trial procedures were motivated by the aim of reducing the risk of COVID-19 infection. However, they had wider implications for sustainability.
2. Procurement. BP was the primary outcome measure in the main trial, so BP measurement was key to the programme. For this purpose, we purchased a large number of high-quality BP monitors. After the trial had been completed, all of these were reused by offering them to participants as partial recompense for taking part in the research or to local GP practices who accepted them gratefully.
3. Transport and travel. From the time of the first lockdown due to the COVID-19 pandemic through to the end of the programme, most meetings were conducted virtually, eliminating the need for any transport and travel. Similarly, dissemination has been predominantly virtual.

Brief reflections on the programme

In general, we were satisfied with the conduct, progress and achievements of the programme up to and including WS3. In the later stages of WS3, the COVID-19 pandemic emerged in the UK. This had a significant impact on the programme, particularly on the main trial. It led to substantial delays in the programme, requiring an 18-month no-cost extension. In addition, we modified the trial procedures so that the VBI would be delivered remotely by telephone or video call instead of a face-to-face consultation, and all measurement would be conducted remotely (e.g. by sending BP monitors to participants' homes). This required a number of compromises to be made. For example, it made it impracticable to obtain self-measured BP readings and urine samples for chemical adherence testing before randomisation. Pre-randomisation measures were limited to information that could be obtained from practice records and information that practitioners could obtain during the baseline consultation (e.g. self-report measures of medication adherence). Lack of face-to-face contact and remote measurement may have led to incomplete return of consent forms and lower response rates and data quality. Remote delivery of the VBI (by telephone) may have led to lower effectiveness because it made it more difficult to build rapport.

Limitations

The main limitations relate to the effectiveness trial which was conducted during the COVID-19 pandemic. To reduce the risk of infection, the VBI was delivered by telephone instead of face-to-face and all study measurements were conducted remotely. As noted above, this may have led to lower response rates and data quality and lower effectiveness of the intervention.

A further significant limitation is that, contrary to our objective, a significant proportion (24%) of participants in the main trial did not have raised BP at baseline, and self-reported medication adherence on average was high at baseline,

which would have reduced the possible scope for an intervention effect. As mentioned above, the changes in trial procedures made it impracticable to obtain self-measured BP readings and urine samples for chemical adherence testing before randomisation. It also appears that the eligibility criteria were not applied as strictly as we would have hoped, perhaps reflecting the general problems of remote communication between the research team and practice staff during the pandemic period.

Other limitations relate to the intervention. The app we developed was available for Android only, so iPhone users who opted to use the app had to be switched to text messages instead. There were also several periods of server downtime, during which the scheduled text messages were not sent. In some cases, this may have reduced participants' engagement with the digital intervention. More serious is the finding that the VBI was delivered as specified in the protocol in only about half the intervention consultations that were audio-recorded in the main trial, suggesting that the training programme we developed for practitioners and the screen prompts shown by the online system were inadequate.

The use of chemical adherence testing as well as self-report measures of medication adherence is a strength of our feasibility and effectiveness trials. However, although it represents an advance on previous work, there are limitations with this method. Participants knew in advance that they would be asked to provide a urine sample, and some of them may have increased their adherence temporarily. Also, the assay could detect whether a specific antihypertensive medication (or its metabolite) was present in urine, but it did not provide quantitative data that could be used to assess whether a participant was taking the prescribed dose of their medication.

A limitation of the qualitative component of the main trial is that the interviews with participants were conducted on average 22 months (range 14–32) after the baseline consultation. This may explain why many participants struggled to recall the consultation.

Implications for practice and policy

Our systematic review, published in 2020, showed that app-based interventions had a positive effect on medication adherence.[26] Since then, several reviews of app-based interventions to support adherence and/or reduce BP in patients with hypertension have been published, all of which have reported promising findings.[10,14,15,19] Such interventions are inexpensive and could be implemented on a wide scale.

Our development work suggested that the combination of a VBI delivered by a practice nurse or healthcare assistant and a digital intervention (text messages or smartphone app) was acceptable to both patients and practitioners in primary care, particularly if the digital intervention was easy to use, the content was tailored to the user, and the privacy of user data was protected. These and our other findings on the preferred features and content of digital interventions may be helpful to intervention developers.

However, although it was shown to be acceptable, feasible and inexpensive, the specific intervention we developed in this programme was not effective in increasing adherence or reducing BP. The findings suggest that the intervention should not be introduced in UK primary care practices at least before it is shown to be effective in patients who do not take their medication as prescribed and have raised BP.

Recommendations for future research

1. None of the recent reviews of app-based interventions have examined the extent to which intervention characteristics were associated with intervention effect size. Future studies and reviews should include a focus on intervention characteristics including BCTs. The same recommendation applies to studies and reviews of face-to-face interventions.
2. In our systematic reviews, no studies were identified that investigated whether using a nurse-led VBI (delivered face-to-face or remotely) in combination with a digital intervention would have an additive or synergistic effect on adherence. This should be addressed in future research.

3. In our feasibility and effectiveness trials, we used chemical adherence testing as well as self-report measures of medication adherence. Although this represents an advance on previous work, there are limitations with this method, as mentioned above. Given the widely acknowledged limitations of self-report measures of adherence, further development and refinement of chemical adherence testing is an important area for future research.
4. Future research should address the challenge of identifying and recruiting people who are poorly adherent to their medication. More specific targeting should be considered. For example, there is evidence that people who are prescribed three or more antihypertensive medications are more likely to be non-adherent.[6] If it is feasible to recruit patients who are non-adherent to their prescribed antihypertensive medication and have raised BP, the PAM intervention could be tested with the VBI component delivered either face-to-face (as in the feasibility trial) or remotely (as in the effectiveness trial). The effect of adding a follow-up consultation (e.g. after 3 months) could also be tested. Future research should also consider ways of adapting the interventions for more diverse populations, how best to introduce the interventions in the care pathway and how to sustain engagement over time.
5. A purely digital version of the intervention could also be developed and evaluated. The VBI, which is currently a separate, non-digital component, could be integrated into the app, for example, using videos, an AI-powered chatbot and avatars that could be created by the user or based on real health practitioners. It would be important to develop both Android and iPhone versions. The possibility of making the app part of, or available through, the NHS app could be explored.

Conclusions

The development work in this programme suggested that the combination of a VBI delivered by a practice nurse or healthcare assistant and a digital intervention (text messages or smartphone app) was acceptable to both patients and practitioners; particularly if the digital intervention was easy to use, the content was tailored to the user, and the privacy of user data was protected. The evaluation of the specific intervention we developed showed that it was acceptable and feasible, but, although the feasibility trial showed promising results for potential effectiveness, the main trial showed no effect of the intervention on medication adherence or SBP. Despite this, the economic evaluation showed that the PAM intervention is inexpensive and likely to be cost-effective under the current WTP thresholds, albeit with some uncertainty. The effectiveness findings do not support the commissioning of the intervention in UK primary care. Future research should address the challenge of identifying and recruiting people who are poorly adherent. If it is feasible to recruit patients who are non-adherent to their prescribed antihypertensive medication and have raised BP, the specific intervention we developed could be tested with the VBI component delivered either face-to-face or remotely; the effect of adding a follow-up consultation could also be tested. A purely digital version of the intervention could also be developed and evaluated. The economic model developed for this programme can provide the basis for future economic evaluations of similar interventions across a range of different conditions.

Additional information

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Programme Steering Committee

Keith Ridge (Chair, September 2017–March 2022).

Ronan O'Carroll (Member, September 2017–March 2022; Chair, March 2022–September 2024).

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Jennifer Bostock (May 2019–September 2024).

Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Data-sharing statement

All data requests should be sent to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

Ethical approval was obtained from the following RECs and from the Health Research Authority and Health and Care Research Wales:

West Midlands – Solihull REC (18/WM/0050) 7 March 2018.

London – West London and GTAC REC (18/LO/1959) 1 November 2018.

North East – Tyne and Wear South REC (19/NE/0018) 4 January 2019.

East of England – Cambridge East REC (19/EE/0354) 5 February 2020.

Information governance statement

The University of Cambridge is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, the University of Cambridge is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights, and the contact details for our Data Protection Officer here: www.information-compliance.admin.cam.ac.uk/data-protection

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJSS0929.

Primary conflicts of interest: Jonathan Mant was a member of the NIHR CTU Standing Advisory Committee (1 May 2017–1 May 2022).

Richard J McManus was a member of the HTA Clinical Evaluation and Trials Committee (1 October 2010–30 November 2015). He has worked with Omron to develop a telemonitoring system for BP. Consultancy and licencing fees for this were paid to Oxford University.

Stephen Morris is currently (2022–) a member of the SBRI Healthcare panel. He was formerly a member of the NIHR RfPB: under-represented disciplines and specialisms – Methodologists Committee (2023–5), the NIHR HS&DR

Programme Funding Committee (2014–6), the NIHR HS&DR Evidence Synthesis Sub Board (2016), the NIHR Unmet Need Sub Board (2019), the NIHR HTA Clinical Evaluation and Trials Board (2007–9), the NIHR HTA Commissioning Board (2009–13), the NIHR PHR Research Funding Board (2011–7), and the NIHR PGfAR expert subpanel (2015–9). He was also an associate member of the NIHR HS&DR Commissioned Board (2014–5) and associate member of the NIHR HS&DR Board (2015–8). His post is funded in part by RAND Europe, a non-profit research organisation. Morris is Deputy Director of Applied Research Collaboration East of England (NIHR ARC EoE) at Cambridgeshire and Peterborough NHS Foundation Trust.

Andrew Toby Prevost was a member of the NIHR COVID-19 Recovery and Learning Committee (1 June 2020–30 September 2020) and a member of the PHR Research Funding Committee (17 June 2014–15 June 2020).

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Publications

List of papers published from the programme

Holender A, Sutton S, De Simoni A. Opinions on the use of technology to improve tablet taking in > 65-year-old patients on cardiovascular medications. *J Int Med Res* 2018;**46**:2754–68. https://doi.org/10.1177/0300060518770578

Armitage LC, Kassavou A, Sutton S. Do mobile device apps designed to support medication adherence demonstrate efficacy? A systematic review of randomised controlled trials, with meta-analysis. *BMJ Open* 2020;**10**:e032045. https://doi.org/10.1136/bmjopen-2019-032045

Kassavou A, A'Court CE, Chauhan J, Brimicombe JD, Bhattacharya D, Naughton F, *et al.* Assessing the acceptability of a text messaging service and smartphone app to support patient adherence to medications prescribed for high blood pressure: a pilot study. *Pilot Feasibility Stud* 2020;**6**:134. https://doi.org/10.1186/s40814-020-00666-2

Kassavou A, Mirzaei V, Shpendi S, Brimicombe J, Chauhan J, Bhattacharya D, *et al.* The feasibility of the PAM intervention to support treatment-adherence in people with hypertension in primary care: a randomised clinical controlled trial. *Sci Rep* 2021;**11**:8897. https://doi.org/10.1038/s41598-021-88170-2

Van Emmenis M, Jamison J, Kassavou A, Hardeman W, Naughton F, A'Court C, et al. Patient and practitioner views on a combined face-to-face and digital intervention to support medication adherence in hypertension: a qualitative study within primary care. *BMJ Open* 2022;**12**:e053183. https://doi.org/10.1136/bmjopen-2021-053183

Akhter K, Sutton S, Mirzaei V, Kassavou A. A systematic review and meta-analysis of face-to-face medication adherence interventions for patients with long term health conditions. *Ann Behav Med* 2022;**56**:1218–30. https://doi.org/10.1093/abm/kaac010

List of other outputs from the programme

Armitage L, Kassavou K, Sutton S. *The Use of Mobile Device Applications to Support Medication Adherence: A Systematic Review with Meta-Analysis*. Conference poster at European Health Psychology Society (EHPS) Annual Conference, Galway, Ireland, 22 August 2018.

Kassavou K. *Medicines Adherence in Primary Care. Developing and Evaluating Low-Cost Digital Interventions to Support Medicines Adherence in Patients with Hypertension and Associated Comorbidities*. Presentation at CRN Eastern Primary Care Whole Team Event, 20 September 2018. The presentation discussed the evaluation of digital interventions in

primary care and provided evidence about the feasibility of recruiting primary care patients to such interventions. The presentation included evidence from our NIHR-funded studies of digital interventions for medication adherence and introduced the recruitment plan for the PAM programme.

Armitage LC, Kassavou A, Sutton S. *The Use of Mobile Device Applications to Support Medication Adherence: A Systematic Review with Meta-Analysis*. Conference poster at Royal College of General Practitioners Annual Primary Care Conference and Exhibition 2018, Glasgow, 4 October 2018.

Kassavou K, Akhter K, Mirzaei V, A'Court C. *Using Digital Interventions to Support Medication Adherence in Primary Care*. Workshop at Madingley Hall, Cambridge, Society for Academic Primary Care (SAPC), 24 January 2019. This was an interactive workshop with delegates of the SAPC regional meeting. The team presented early findings from the PAM programme and asked for feedback and suggestions for the proposed research.

A'Court C, Kassavou K. *Scalable Low-Cost Interventions to Support Medication Adherence in People Prescribed Medication for Hypertension in Primary Care*. Presentation at Madingley Hall, Cambridge. Society for Academic Primary Care (SAPC) South East Regional Meeting, 25 January 2019. We presented the aims, current progress and future direction of the PAM programme.

Kassavou K. *Developing and Evaluating Interventions to Support Adherence to Medicine Prescribed for Hypertension and Comorbidities in Primary Care*. Presentation at Primary Care Clinical Research Leadership Group, Fulbourn, Cambridgeshire, 31 January 2019. The aim of this presentation was to raise awareness about the potential for digital interventions to be a cost-effective adjunct to current practices. The presentation described the development of several digital interventions for medication adherence, including the PAM intervention, and presented evidence on the efficacy (based on reviews), acceptability (based on interviews) and feasibility (based on intervention data) of digital interventions in primary care.

A'Court C, Van Emmenis M, Kassavou K. *Taking Medication: Discovering Your Fête*. Dissemination event at University of Cambridge Science Festival, 24 March 2019. We held an interactive stall with family-friendly games, quizzes and prizes. We showcased the PAM programme and obtained recommendations from members of the public on specific elements of the intervention such as message content and app features. Read the blog here (www.spcr.nihr.ac.uk/news/blog/behavioural-science-group-at-the-cambridge-science-festival-2019) (accessed 16 September 2025).

Kassavou K. *Using Apps for Behaviour Change and Improving Treatment Adherence*. Presentation at NHS Cambridgeshire and Peterborough CCG Research Celebration Event, Jesus College, Cambridge, 1 May 2019. The aim of the presentation was to raise awareness of the potential use of smartphone apps as part of primary care services. The presentation described the use of digital interventions to support adherence to medical advice and highlighted the potential of apps to supplement current practices and improve adherence to prescribed medications. It presented literature review evidence and described the development of an evidence- and theory-based app to support medication adherence in primary care.

Kassavou K, Sutton S. *A Very Brief Face-to-Face Intervention, Followed by a Text Message or Smartphone App. PAM pre-testing study*. Conference poster at European Health Psychology Society (EHPS) Annual Conference, 2019, Dubrovnik, 6 September 2019.

Van Emmenis M, Eborall H, Jamison J, Sutton S. *Patient and Practitioner Views on a Digital Intervention Supporting Medication Adherence in Patients with Hypertension*. Conference poster at European Health Psychology Society (EHPS) Annual Conference, Dubrovnik. 6 September 2019.

Van Emmenis M, Eborall H, Jamison J, Sutton S. *Patient and Practitioner Views on a Digital Intervention Supporting Medication Adherence in Patients with Hypertension*. Conference Poster at Cambridge Institute of Public Health Annual Lecture, University of Cambridge, 21 October 2019.

A'Court C. *Assessing the Acceptability of a Text Messaging Service and Smartphone App to Support Patient Adherence to Medications Prescribed for High Blood Pressure*. Conference poster at Society for Academic Primary Care (SAPC) South East Regional Meeting, Madingley, Cambridge, 23 January 2020.

Kassavou K, Mirzaei V, Shpendi S, Brimicombe J, Chauhan J, Hafiz A, *et al. Programme on Adherence to Medication. Scalable Low-Cost Interventions to Support Medication Adherence in People Prescribed Treatment for Hypertension in Primary Care*. Presentation at Society for Academic Primary Care (SAPC) South East Regional Meeting, Madingley, Cambridge, 23 January 2020.

Kassavou K. *Development and Feasibility of the PAM Intervention: A Very Brief Face-to-Face Intervention Followed By A Text Messaging Programme or Smartphone App*. Conference presentation at Society of Behavioral Medicine (SBM) Annual Meeting, San Francisco, CA, USA, 3 April 2020. https://plan.core-apps.com/sbm_annual2020/event/fe17076fc42c1698fcb9ce68ffc926a5 (accessed 16 September 2025).

Kassavou K. *Programme on Adherence to Medication: A Very Brief Face to Face Intervention, Followed by a Text Messaging Programme or Smartphone App to Support Medication Adherence in People Prescribed Treatment for Hypertension in Primary Care. A Feasibility Randomised Controlled Trial*. Conference poster at University College London (UCL) Centre for Behaviour Change (CBC) Online Conference, 18 September 2020.

Kassavou K. *Assessing the Acceptability of A Text Messaging Service and Smartphone App to Support Patient Adherence to Medications Prescribed for High Blood Pressure. PAM Pre-Testing Study*. Conference poster at University College London (UCL) Centre for Behaviour Change (CBC) Online Conference, 18 September 2020.

Kassavou K, Mirzaei V, Brimicombe J, Chauhan J, Mascolo C, Sutton S. *Programme on Adherence to Medication: A Very Brief Face to Face Intervention, Followed by a Text Messaging Programme or Smartphone App to Support Medication Adherence in People Prescribed Treatment for Hypertension in Primary Care. A Feasibility Randomised Controlled Trial*. Abstract. University College London (UCL) Centre for Behaviour Change (CBC) Online Conference, 11 November 2020. https://osf.io/vfsgc/wiki/home/ (accessed 16 September 2025).

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Kassavou K, Mirzaei V. *How Digital Interventions Influence Our Health-Related Behaviours?* Presentation at Cambridge Science Festival, 3 April 2021.

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Appendix 1 Logic-model for the Programme on Adherence to Medication intervention (adapted from the trial protocol paper)

Problem

1. Many people who are prescribed antihypertensive medication in UK primary care have poorly controlled blood pressure because of suboptimal medication adherence
2. Healthcare practitioners have limited time to support adherence, and their time is expensive

Intervention

A VBI to support medication adherence, delivered remotely by a practice nurse or healthcare assistant, followed by a digital intervention (text messages for up to 420 days or a smartphone app)

Theoretical framework

Intentional/non-intentional non-adherence (INA/NINA)
Necessity-Concerns Framework
Self-efficacy Theory
Theory of Planned Behaviour
Theories of tailoring

Intervention strategies (od adherence/non-adherence to medication)

Forgetting
Intention
Necessity beliefs
Concerns beliefs
Self-efficacy
Affective attitudes
Subjective norm
Emotional state

Behaviour Change Techniques

Personalisation and tailoring (VBI and Digital)
Reporting whether behaviour was performed (Digital)
Goal setting (behaviour) (VBI)
Social support (unspecified) (VBI and Digital)
Social support (practical) (VBI)
Instruction on how to perform the behaviour (VBI)
Information about health consequences (Digital)
Information about emotional consequences (Digital)
Information about social and environmental consequences (Digital)
Prompts/cues (Digital)
Habit formation (Digital)
Credible source (VBI)
Social reward (Digital)
Distraction (Digital)
Verbal persuasion about capability (Digital)

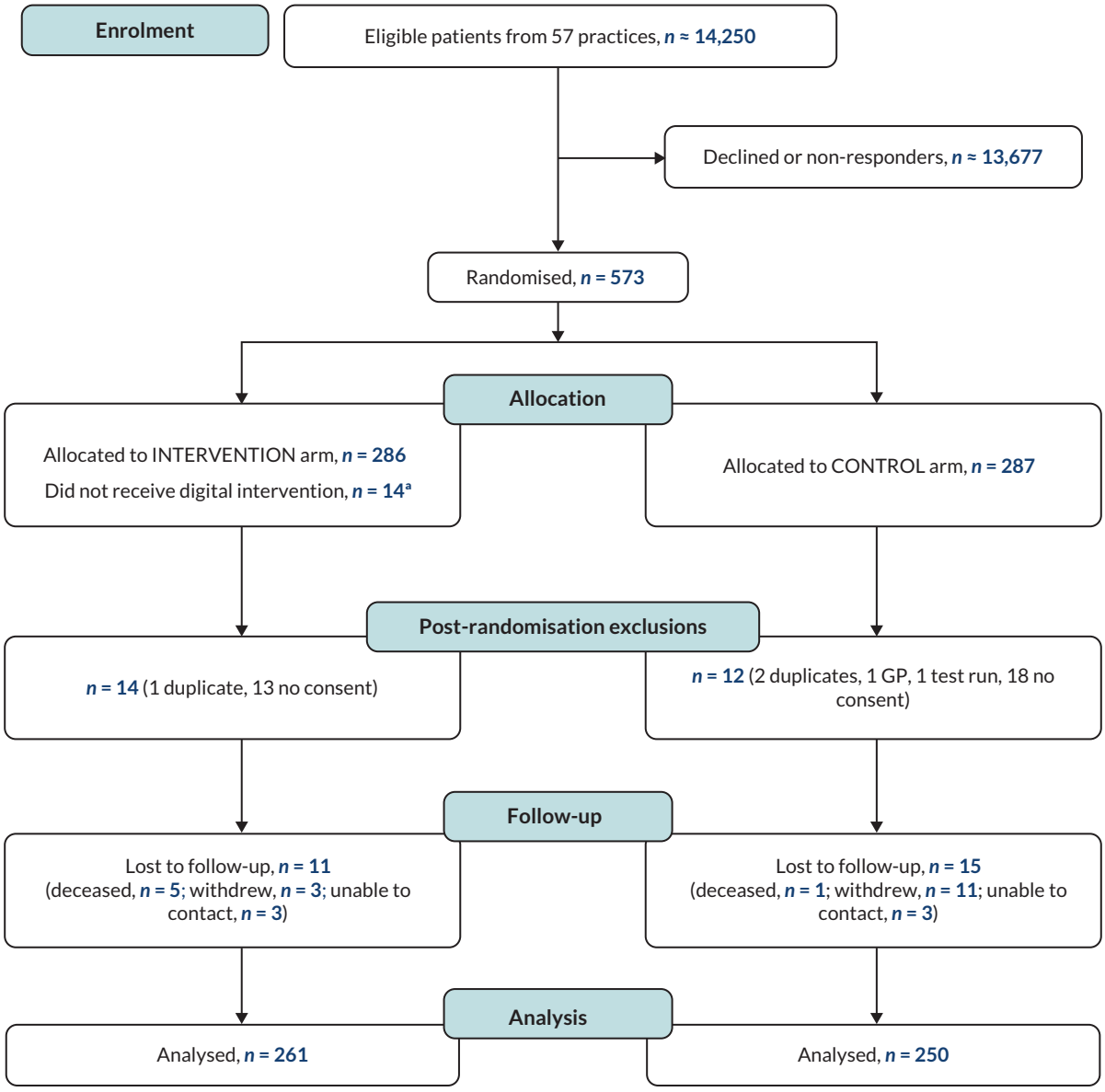
Behavioural outcome

Adherence to prescribed antihypertensive medication

Clinical outcome

Systolic blood pressure

Appendix 2 Trial flow chart for workstream 4: main trial



[a] Reasons for not receiving digital intervention: Did not install app (*n* = 11); iPhone user but was not switched from app to text messaging due to an administrative error (*n* = 2); Was not sent any text messages, reason unknown (*n* = 1).

Appendix 3 Details of methods for workstream 5: economic evaluation

Methods

Economic model

The health economic analysis adopted a UK NHS and Personal Social Services perspective for measurement of relevant costs. All costs were estimated in GBP for the cost reference year 2023, with the UK gross domestic product deflator[45] used to adjust costs to the reference year where required.

The base case model developed for the economic evaluation comprised a decision tree model for the within-trial period of 14 months. (A 14-month period was used because intervention participants could receive text messages/ notifications for up to 14 months; the extended time window also took account of the fact that the majority of 12-month follow-up questionnaires were returned by this time point.) The model, shown in *Figure 5*, consists of 'well', 'CVD event' (angina, heart failure, myocardial infarction and stroke) and 'dead' health states. It was configured to utilise characteristics and trial outcomes for individual patients to generate patient-specific expected costs and outcomes. From these, aggregated estimates were derived for the UC and PAM intervention trial arms.

The model was populated using individual patient characteristics, trial data (e.g. SBP, health resource use) and parameters identified and extracted to the model (e.g. healthcare costs, HRQoL, general population or CVD event mortality). Costs over and above those for UC (i.e. intervention costs) were applied for patients in the PAM trial arm (for details, see *Findings from the base case (within-trial) analysis*).

Within-trial risks for CVD events (angina, heart failure, myocardial infarction and stroke) were calculated for individual patients based upon their characteristics using Framingham Risk Score calculations (detailed below). Where unavailable from trial data, equation parameters were supplemented with trial arm-specific inputs to enable the calculation of outcomes for the within-trial time horizon of the model. For the 'dead' health state, ONS life tables were used to model the age-specific within-trial risk of death for each individual patient.[46]

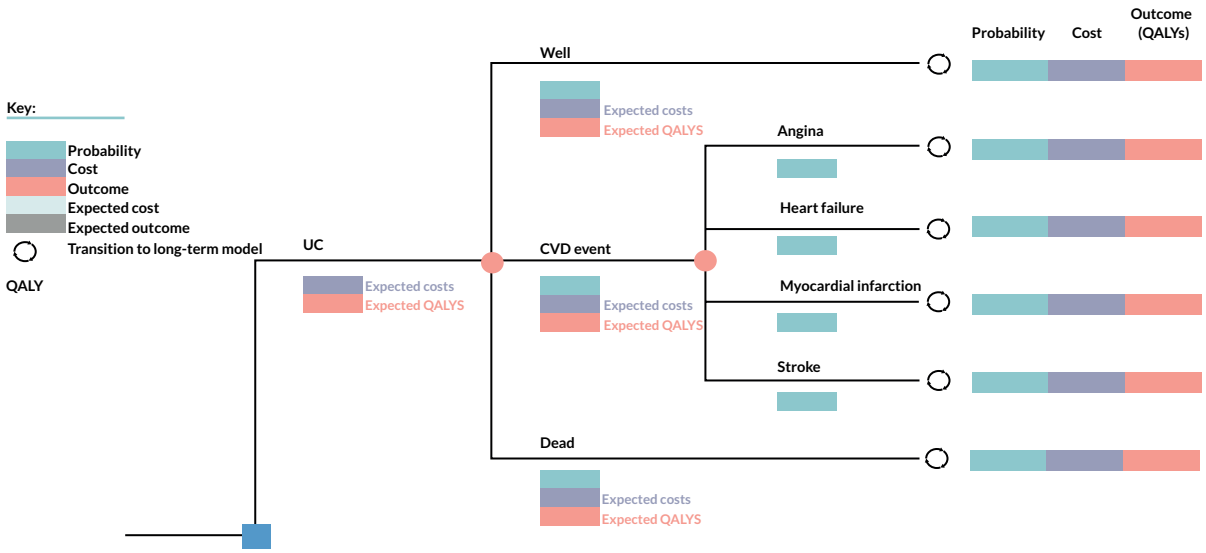


FIGURE 5 Short-term decision tree model, UC arm (the PAM intervention decision tree structure is identical, differing only by the input parameter estimates).

Expected costs and QALYs for each respective health state were calculated for each patient as a product of the probability of each health state and the total relevant cost for each. Total costs were then derived as a summation of the totals for each individual health state.

Cardiovascular risk estimation

Calculation of the mean 10-year risk for each patient, using the modified Framingham Risk Score.[47]

Framingham equation: females

$$\begin{aligned} RiskFactors &= (ln(\boldsymbol{Age}) * 2.32888) + (ln(\boldsymbol{Total\ cholesterol}) * 1.20904) \\ &\quad - (ln(\boldsymbol{HDL\ cholesterol}) * 0.70833) \\ &\quad + (ln(\boldsymbol{Systolic\ BP}) * \boldsymbol{SysBPFactor}) + \boldsymbol{Cig} + \boldsymbol{DM} - 26.1931 \end{aligned} \tag{1}$$

$$Risk = 100 * (1 - 0.95012e(RiskFactors)) \tag{2}$$

Framingham equation: males

$$\begin{aligned} RiskFactors &= (ln(\boldsymbol{Age}) * 3.06117) + (ln(\boldsymbol{Total\ cholesterol}) * 1.12370) \\ &\quad - (ln(\boldsymbol{HDL\ cholesterol}) * 0.93263) \\ &\quad + (ln(\boldsymbol{Systolic\ BP}) * \boldsymbol{SysBPFactor}) + \boldsymbol{Cig} + \boldsymbol{DM} - 23.9802 \end{aligned} \tag{3}$$

$$Risk = 100 * (1 - 0.88936e(RiskFactors)) \tag{4}$$

Abbreviations: Cig, cigarette smoking status; DM, diabetes status; SysBPFactor, antihypertension medication factor.

Where *Age* is the patient's age in years, *Total cholesterol* and *HDL cholesterol* are blood cholesterol levels (in mg/dL), *Systolic BP* (in mmHg), *Cig* and *DM* are binary variables for their current smoking and diabetes status, respectively, and *SysBPFactor* is an adjustment factor for their antihypertensive medication status. Where data are not available for specific risk factors from the trial, proxy values were used (e.g. UK population, age/sex-specific mean values). CVD event risk for each patient was converted to an annual CVD event probability, weighted for each type of CVD event (stroke, heart failure, myocardial infarction, angina) as measured in previous studies.[40,48]

Resource use and costs

The cost of NHS resource use was calculated for primary and secondary care services (*Table 9*) and for prescribed antihypertensive medications (*Table 10*), for each patient. Resource use data were collected at baseline and at 6 and 12 months from baseline using retrospective questionnaires covering the previous 6-month period. Unit costs were obtained from published sources,[49–51] inflated where appropriate to 2023 GBP using NHS Pay and Prices Indices.[49]

The summation of unit costs multiplied by the units of resource use across the 0- to 6- and 6- to 14-month trial periods was used to derive total within-trial costs.

In addition to costs applicable for UC, costs for patients receiving the PAM intervention included the cost of the VBI, running costs and notification costs (*Table 11*).

Total costs for the PAM intervention included a one-off VBI cost of £6.75. Running costs consisted of fixed periodic PAM intervention running costs of £23.01 per week (administrative staff costs) and £16.67 per month (server maintenance costs), resulting in a total annual PAM intervention cost of £1400.63. For patients who received the PAM intervention (n = 272), total running costs per patient for the within-trial period were £6.01.

TABLE 9 National Health Service resource use categories and unit costs included in the economic analysis

	Service	Unit cost	Details
Primary care	GP (surgery)	£35.00	Per surgery consultation lasting 9.22 minutes, without qualification costs
	GP (home)	£26.00	Primary care home visit cost after discharge from acute medical unit
	GP (remote)	£15.50	Telephone triage (GP-led)
	Practice nurse	£46.00	Unit cost per hour
		9.22	General practice consultation duration, minutes
		£7.07	Unit cost
	NHS psychologist/counsellor	£66.00	Band 7 clinical psychologist/counsellor (specialist). Cost per working hour
		30.00	Assumed duration, minutes (conservative estimate of session duration)
		£33.00	Unit cost
	NHS other service	£35.00	Assumed to be equal to the cost of a GP surgery consultation
Social care/ other	Social care	£35.00	Assumed to be equal to the cost of a GP surgery consultation
	Other service	£35.00	Assumed to be equal to the cost of a GP surgery consultation
Secondary care	Hospital stay	£1689.84	Weighted average: elective inpatients/non-elective long stay/ non-elective short stay, cardiac disorders
	Hospital attendance: accident and emergency	£312.49	Emergency care, national average unit cost
	Hospital attendance: outpatient	£167.31	Cardiology service
	Hospital attendance: day case	£735.09	Day case attendance, cardiac disorders
	Hospital attendance: other	£735.09	Assumed to be equal to day case attendance, cardiac disorders

TABLE 10 Antihypertensive medication unit costs

Medication	Unit price (per tablet) (£)	Medication	Unit price (per tablet) (£)
Amiloride	0.58	Lercanidipine	0.02
Amlodipine	0.01	Lisinopril	0.01
Atenolol	0.02	Losartan	0.01
Bendroflumethiazide	0.01	Methyldopa	0.07
Bisoprolol	0.01	Metoprolol	0.03
Bumetanide	0.06	Moxonidine	0.19
Candesartan	0.02	Nebivolol	0.03
Co-amilofruse	0.16	Nifedipine	0.17
Diltiazem	0.25	Olmesartan	0.05
Doxazosin	0.01	Perindopril	0.01
Enalapril	0.02	Prazosin	0.04

continued

TABLE 10 Antihypertensive medication unit costs (*continued*)

Medication	Unit price (per tablet) (£)	Medication	Unit price (per tablet) (£)
Eplerenone	0.10	Propranolol	0.02
Felodipine	0.02	Ramipril	0.01
Furosemide	0.01	Spironolactone	0.05
Hydralazine	0.04	Telmisartan	0.04
Indapamide	0.02	Valsartan	0.29
Irbesartan	0.03	Verapamil	0.04
Lacidipine	0.08		

TABLE 11 Programme on Adherence to Medication intervention costs

One-off costs	Unit cost	Duration, minutes	Total cost	Notes
VBI	£46.00	8.8	£6.75	Practice nurse, unit cost per hour
Running costs	**Unit cost**	**Cost period**	**Annual cost**	**Notes**
Administrative staff	£23.01	Weekly	£1200.63	Salary cost, per hour. Assumed 1 hour per week engaged in system administration tasks
Server maintenance	£16.67	Monthly	£200.00	Total server costs of £50/month, split between three active projects
Total within-trial costs, per patient			£6.01	
Notification costs	**Total cost**	**Number of units**	**Unit cost**	
Text message notification costs	£4123.70	66,085	£0.06	Cost per text message notification received, by participants using the text message service of the PAM intervention

The one-off cost for the VBI of £6.75 per patient was calculated from practice nurse costs of £46 per hour (see *Table 11*) and the MD in duration between the control and intervention consultations (8.8 minutes). Patients in the PAM intervention arm were able to receive notifications either via a smartphone app or via text messages. For those receiving notifications via the app, no costs above the running costs described above were applicable. Those patients who opted to receive text message notifications were sent a weighted average of 274 (95% CI 238 to 309) messages during the trial period. At a cost of £0.06 per message (total cost of £4123.70 for the 66,085 messages sent during the within-trial period), mean notification costs were calculated to be £17.07 per patient.

Utilities and quality-adjusted life-years

Health status was reported by individual patients at the baseline, 6-month and 12-month time points, using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L) descriptive system.[52,53] Each EQ-5D-5L health state was mapped to the corresponding EQ-5D-3L health state. Applying a formula to attached weights to each of the levels in each dimension based on valuations by a (UK) general population sample, a single summary index (utility value) was derived for each patient.[54] QALYs were calculated for each individual patient using an 'area-under-the-curve' approach, assuming a straight-line relationship between the utility score from baseline to 6 months and from 6 months to 12 months computed as the [(utility score at baseline + utility score at 6 months)/4] + [(utility score at 6 months + utility score at 12 months)/4]. Per-patient QALY estimates for each trial arm group were derived via regression of imputed estimates, controlling for baseline utility and sex. Where required, CVD event multipliers were then subsequently applied to model their effect on HRQoL, based on the Framingham equations described above.

Dealing with missing data

Multiple imputation was used to impute missing data for variables used to estimate CVD event risk (type 2 diabetes, smoking status, receiving medication for hypertension), costs (resource use and antihypertensive medication), and utility scores at baseline, 6-month and 12-month time points.

Multivariate normal regression was used to impute missing continuous variables and logistic regression for missing binary variables (type 2 diabetes, smoking status, receiving medication for hypertension). To account for skewed data, these variables were log-transformed prior to MI with multivariate normal regression. A total of 20 imputed data sets were generated, with patient age, sex and index of multiple deprivation status included in the imputation models as additional explanatory variables.

Statistical methods

Analyses were performed on an intention-to-treat basis. Raw mean (SD) resource use, total costs, utility scores and QALYs per participant were estimated for each randomised group; values were unadjusted with no imputation for missing data. MDs (95% CIs) between arms were also presented.

After accounting for missing data with MI, differences in mean costs and QALYs per group were calculated using regression analysis. Incremental costs and QALYs gained were both adjusted for patient age and sex, and for either baseline resource use costs (incremental costs) or baseline utility (QALYs gained).

Cost-effectiveness was evaluated relative to thresholds of £15,000, £20,000 and £30,000 per QALY. INMBs were calculated as the difference in mean QALYs per patient for the PAM intervention versus UC, multiplied by the cost-effectiveness threshold for a QALY minus the difference in mean costs per patient – a positive INMB indicating that the PAM intervention was cost-effective relative to UC.

For each of the 20 imputed data sets, 1000 bootstrap replications were run, with the results combined to calculate standard errors around mean values for the model inputs accounting for uncertainty in the patient-specific imputed values, such as the skewed nature of resource use and utility values, and sampling variation.[55] For each output variable, standard errors were used to calculate 95% CIs around the point estimates. The base case analysis was therefore performed using point estimate values for the bootstrap-generated model input parameters, plus those for the other relevant (non-patient-specific) input parameters. ICERs were calculated by dividing the incremental costs by QALYs gained. Results for all bootstrap replications were plotted on a CEP, with a 95% CI ellipse based upon a bivariate normal distribution plotted as a visual indicator of the CI about the mean ICER estimate (https://real-statistics.com/multivariate-statistics/multivariate-normal-distribution/confidence-ellipse/).

The EVPI – defined as the value of additional research that could be undertaken to fully address all uncertainty in the economic analysis – was estimated from the probabilistic sensitivity analysis (PSA) results by calculation of the difference between the maximum expected INMB value and the expected INMB value based upon current evidence.

All regression analyses were performed using Stata software, version 18 (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC), with the economic model and associated simulations conducted in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA).

Sensitivity analyses

A CEAC[56] showing the probability that the PAM intervention was cost-effective compared with UC at values of the cost-effectiveness threshold for a QALY ranging from £0 to £100,000/QALY was generated. This was based on the proportion of the bootstrap replications across all 20 imputed data sets with positive INMBs at each threshold value.[57] The probability that the PAM intervention was cost-effective at WTP thresholds of £15,000, £20,000 and £30,000 per QALY was also reported, based on the proportion of the bootstrap replications with positive INMBs at these values.

To account for overall uncertainty associated with the model input parameter estimates, a PSA using the base case assumptions was performed via 1000 Monte Carlo simulations, each of which randomly sampled from uncertainty distributions for both the bootstrap-generated model input parameters and for the other relevant (non-patient-specific)

input parameters. Beta distributions were used to model uncertainty around the utility values, and gamma distributions for costs parameters. Lognormal distributions were applied to the within-trial CVD event risk and measurements of SBP (see *Report Supplementary Material 4*). Cost-effectiveness was evaluated based upon PSA outputs, which included CEPs and CEACs.

In addition to the base case analysis (missing values imputed using MI, with adjustment for potential confounders, as described above), cost-effectiveness estimates were also reported for three other scenarios:

Scenario A: with missing values imputed using MI, but with no adjustment for potential confounders.

Scenario B: complete-case analysis (with no MI) with adjustment for potential confounders.

Scenario C: complete-case analysis with no adjustment for potential confounders.

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