Study Title:

A service evaluation of the implementation of HypertensIon-Plus – implementing a hypertension self-monitoring/management service in primary care

Internal Reference Number / Short title: The SHIP study

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Date: 21 December 2021

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

A Service evaluation of the HypertensIon-Plus Implementation – implementing a hypertension self-monitoring/management service in primary care

Protocol signature page

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator (Please print name)	**Signature**	**Site name or ID number**	**Date**

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1. KEY CONTACTS

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2. LAY SUMMARY

Hypertension Plus was developed to help patients measure their blood pressure (BP), send the results to the GP, and communicate about changes they could make to their treatment. Hypertension Plus reminds patients to measure their BP, and reminds patients and their GPs and other clinical staff when they need to take action.

The NIHR Applied Research Collaboration (Oxford and Thames Valley) is funding “A service evaluation of the implementation of Hypertension Plus” know as the “SHIP” study for short. The SHIP study will

explore how well Hypertension Plus works in GP surgeries, in particular how many patients choose to use it, how well their blood pressure is controlled, and what impact it has on the workload of GP practices.we will look at the impact on the cost of care, and how many prescriptions are issued.

The SHIP study will use anonymised routinely collected data, recorded by practices and patients in their routine care. We will compare data from patients who have chosen to useHypertension Plus with those who haven't. For those patients who use Hypertension Plus, we will compare results from before and after they start to use it. There is no way of the research team knowing who the patients are.

Summaries of the results will be shared with GP practices, patients and commissioners of care. The research team will publish the results in journals and present at conferences and share them in traditional and social media.

3. SYNOPSIS

Study Title	A Service evaluation of the HypertensIon-Plus Implementation – implementing a hypertension self-monitoring/management service in primary care		
Internal ref. no. / short title	The SHIP study		
Study registration	tbc		
Sponsor	University of Oxford Joint Research Office 1st Floor, Boundary Brook House Churchill Drive, Headington Oxford OX3 7LQ		
Funder	NIHR ARC Oxford and Thames Valley Radcliffe Primary Care Building Radcliffe Observatory Quarter Woodstock Road Oxford OX2 6GG Paula Wray Tel: 01865 289300 Email: arc_oxtv@phc.ox.ac.uk		
Study Design	Observational Service Evaluation		
Study Sites	GP practices		
Study Participants	Adult patients (>18y) with hypertension		
Sample Size	Anonymised records from approximately 60 practices		
Planned Study Period	From January 2022 for around 12 months with follow-up for 12 months following recruitment.		
	Research Questions	**Outcome Measures**	**Timepoint(s)**
Primary	Does Hypertension Plus lead to lower systolic blood pressure?	Systolic blood pressure	Over the first year of system use compared to year before and control patients
Secondary	Will people with hypertension use the Hypertension Plus system?	Proportion of hypertension register signing up for Hypertension Plus in first 6 months of implementation in each practice.	Over the first year of system use
	Does Hypertension Plus lead to lower diastolic blood pressure?	Diastolic blood pressure	Over the first year of system use compared to year before

	Does Hypertension Plus lead to better control of blood pressure?	Proportion controlled below target	Over the first year of system use compared to year before
	Does Hypertension Plus reduce practice workload?	Consultation rate recorded in clinic record before and after use of Hypertension Plus system	Over the first year of system use compared to year before
Intervention	Hypertension Plus system		
Comparator	We will use both interrupted case series (before/after) and difference of differences approaches meaning that the comparator is usual care without the use of Hypertension Plus. Practices that implement the system later will be used to as a further level of comparator.		

4. ABBREVIATIONS

ARC	Applied Research Collaboration
BAME	Black and minority ethnic
CI	Chief Investigator
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
EHR	Electronic Health Records
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
LTCs	Long term conditions
NIHR	National Institute for Health Research
NHS	National Health Service
RES	Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
QoF	The Quality and Outcomes Framework
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure

5. BACKGROUND AND RATIONALE

Hypertension is the key risk factor globally for death and disability and in the UK is the commonest long term condition currently recognised in over 8 million adults (14%).[1] The pre-eminence of hypertension in cardiovascular prevention arises from its association with the most costly conditions to treat in health systems, namely stroke, ischaemic heart disease, heart failure, and dementia. Blood pressure reduction is associated with significant reductions in cardiovascular risk: every 5mmHg systolic pressure reduction will reduce CHD rates by 20% and stroke rates by 10% but a large evidence base shows that system failure, clinical inertia and reduced patient adherence lead to sub-optimal use of proven interventions, notably antihypertensive medication.[2,3]

Key interventions which overcome all three issues, and have been shown to be cost-effective, are patient self-monitoring and self-management.[4,5] Both have the particular value of high patient engagement and increased self-efficacy plus engage clinicians to address medication changes, achieving improved blood pressure control mainly through better management of medication, and show these gains without adding to healthcare utilisation and therefore cost.

Patient self-monitoring and facilitated self-management of hypertension, has the further opportunity to act as a model for how greater patient involvement in care might be translatable into other important conditions that require monitoring and medication titration including diabetes, heart failure, asthma, and thyroid disease ie the major impact long term conditions for the NHS and patients.

This project builds on twenty years experience of self-monitoring/management of hypertension and will evaluate the implementation into primary care of a digital intervention developed specifically from this experience. The intervention has been developed by Omron, a blood pressure monitor manufacturer, and designed to be used by a wide group of people with hypertension and their practices.

The Applied Research Collaboration includes Omron as commercial partner, academics, general practice, NHS England, Academic Health Science Networks and perhaps most importantly, people with hypertension.

6. OBJECTIVES AND OUTCOME MEASURES

	Research Questions	Outcome Measures	Timepoint(s)
Primary	Does Hypertension Plus lead to lower systolic blood pressure?	Systolic blood pressure	Over the first year of system use compared to year before
Secondary	Will people with hypertension use the Hypertension Plus system?	Proportion of hypertension register signing up for Hypertension Plus in first 6 months of project	Over the first year of system use
	Does Hypertension Plus lead to lower diastolic blood pressure?	Diastolic blood pressure	Over the first year of system use compared to year before
	Does Hypertension Plus lead to better control of blood pressure?	Proportion controlled below target	Over the first year of sytem use compared to year before
	Does Hypertension Plus reduce practice workload?	Consultation rate recorded in clinic record before and after use of Hypertension Plus system	Over the first year of system use compared to year before
Exploratory	Further exploratory analyses will include sub groups (age, sex, deprivation, practice characteristics, individual CCG/PCN areas). We will also examine medication prescription and fidelity to the intervention using telemonitoring system data.		

7. STUDY DESIGN

This will be a service evaluation of the implementation of Hypertension Plus using interrupted case series and difference of differences to detect change in blood pressure and workload associated with the implementation of the Hypertension Plus system.

Anonymised data will be used to compare those using the intervention with historical data from themselves as well as from people not using the intervention.

Quantitative data will be extracted using electronic searches of practice computer systems, secure data transfer and the Omron Hypertension Plus system. Identifiable information will not be extracted.

7.1 The Hypertension Plus System

Hypertension Plus is a primary care remote hypertension management and medication titration platform. Based on workflow algorithms proven in randomised controlled trials through the TASMIN studies, and decision-support tools compliant with NICE guidelines. Hypertension Plus is intended to facilitate remote population health management, improving outcomes and increasing efficiency of hypertension management in primary care.

The system combines a web based dashboard for professionals, which both reads and writes data to the practice clinical system, with a mobile phone "app" which is downloaded by participating patients and used to upload blood pressure and other information.

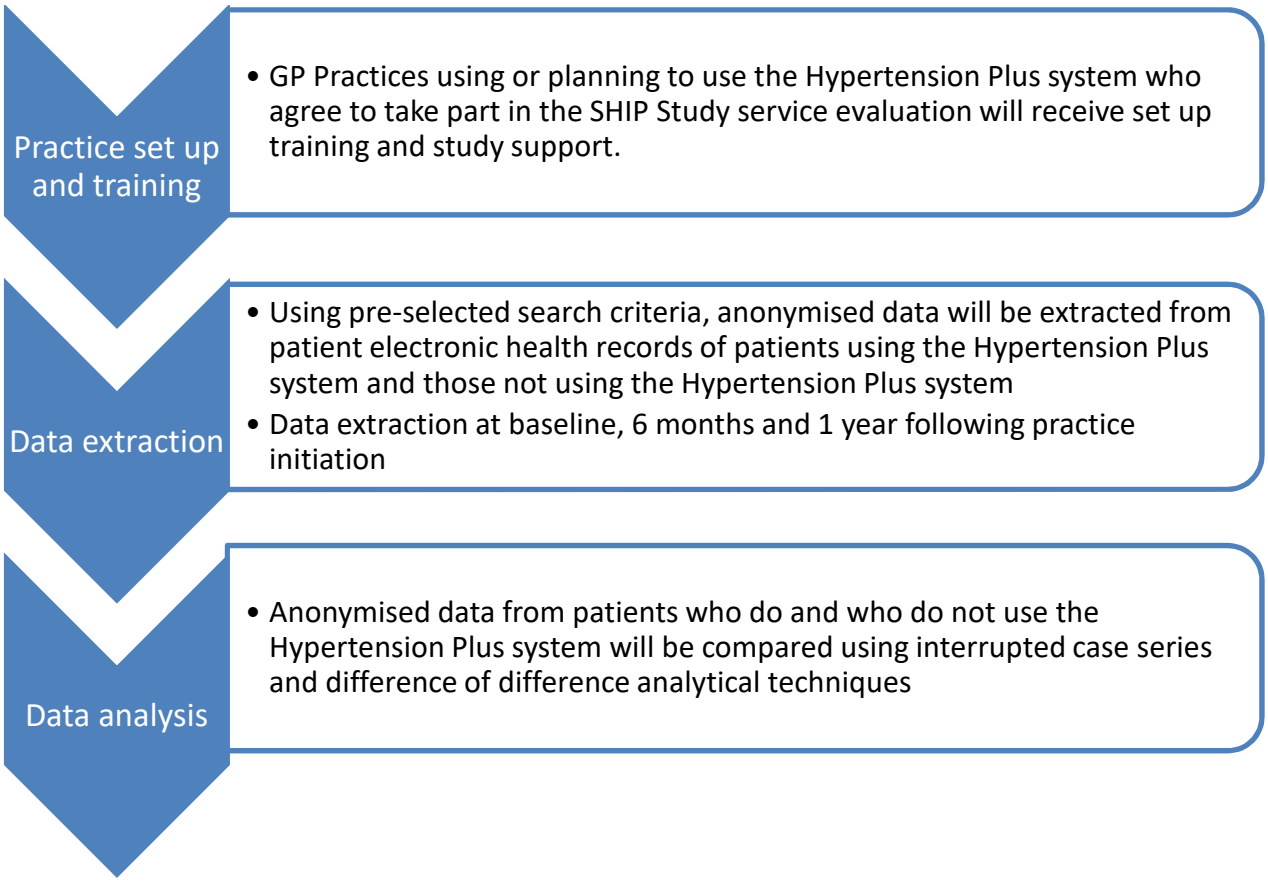
7.2 Implementation of the Hypertension Plus system

Implementation of the Hypertension Plus system is being led by Omron working with the National Association for Primary Care and Ernst & Young. They have a detailed implementation plan that has been developed independently comprising pre-implementation, implementation, initiation and maintenance phases. In undertaking this work they are working with the primary care networks and clinical commissioning groups that are implementing Hypertension Plus.

Once a primary care organisation has decided to commission Hypertension Plus (which is a paid for service), they will choose the practices to implement the system and these practices will work with the implementation group receiving training and initiation. The research team will be introduced to participating practices and research initiation will happen independently from the implementation.

The research team is working closely with the implementation to ensure that there is mutual understanding of the two types of activity.

Service evaluation procedures flow chart



8. PRACTICE IDENTIFICATION

8.1. Participating practices

We will work with approximately 60 GP practices (approximately 15 practices from each participating CCG) from areas that are taking part in the Omron Hypertension Plus first phase roll out and use a compatible Electronic Health Record (EHR) system. The precise number of practices will depend on the final number of practices in the first wave using an EHR system.

All participating practices must satisfy the following criteria:

- Practice is using (or planning to use) the Hypertension Plus telemonitoring system
- Utilises compatible EHR system
- Data available for the previous 2 years from practice recruitment are available

8.2. Exclusion Criteria: practices

- Practices that are not able to contribute data.

8.3. Study Patient Records

Outcome data for adult patients (>18 y) and on the hypertension register will be extracted from the EHR at each participating practice by electronic search and provided in an anonymised form to the analysis team.

Active users of the intervention will be defined as:

- Adults aged 18 years or above.
- Diagnosed with hypertension on practice hypertension registers whose baseline blood pressure is above 140/90mmHg on last recorded reading at baseline
- Registered users of the Hypertension Plus telemonitoring system with coded data in the clinical record identifying them as such

These will be compared to patients not using the system who are:

- Adults aged 18 years or above
- Diagnosed with hypertension on practice hypertension registers whose baseline blood pressure is above 140/90mmHg on last recorded reading at baseline
- With no record of using the Hypertension Plus telemonitoring system coded in the clinical record.

An exploratory analysis will examine people in the two groups above who have a blood pressure ≤140/90mmHg at baseline, with the same comparison between users and non users of the system.

9. PROTOCOL PROCEDURES

9.1. Practice Identification

Practices using (or planning to use) the Hypertension Plus system for their patients will be invited to participate in the service evaluation.

Practices that are eligible to take part in the service evaluation will be provided with a welcome pack which includes:

- Practice Information Leaflet
- Copy of the protocol
- Copy of regulatory approval documentation (if required)
- Instructions on how to complete the service evaluation activities

Site agreements will be in place with each practice and as part of the contracting process will include agreement from the practices, as Data Controllers, to provide the study team with anonymised data from the clinical records and the tele-monitoring system.

9.2. Screening and Eligibility Assessment

Not applicable

9.3. Informed Consent

No direct or active involvement will be required from consulting patients and we will not be seeking individual patient consent. Anonymised outcome data will be extracted from the EHR by automatic searches and from the Hypertension Plus system and provided in an anonymised form to the analysis team. This will apply to records of patients who have not opted out of use of their health records in research

Hypertension Plus is a commercial system which has passed separate regulatory approvals including GDPR and this evaluation is of the practice utilisation of the dashboard. Patients who use the system will do this via sign up outside of the service evaluation. We will seek permission of the Data Controller for access to anonymised data concerning utilisation of the system.

9.4. Randomisation

This is a service evaluation that does not include randomisation. Patients in participating practices will choose to use the Hypertension Plus system in conjunction with their health care professionals.

9.5. Description of study intervention and comparator

9.5.1. Description of study intervention

The study intervention is "Hypertension Plus". People using the system will use an app to send blood pressure readings securely to a central dashboard. Data will be recorded automatically in the clinical record via appropriate SNOMED codes allowing identification of active users. An active user will be someone with a record of having used the Hypertension Plus system in their clinical record with the appropriate SNOMED code. This definition will be regardless of how much use is made of the system and once labelled as having received the intervention, patients will be analysed in that group on an "intention to treat basis".

9.5.2. Description of comparator

Usual care – patients on hypertension registers not using Hypertension Plus for submitting home blood pressure readings ie those without a record of having used the system as defined by clinical (SNOMED) codes.

9.6. Data Extraction

Routinely collected retrospective data from people with a clinical code for hypertension registered in practices taking part in the Hypertension Plus implementation will be extracted at baseline and again at 6 and 12 months. This data will include:

- Age (years)
- Gender
- Ethnicity (White, Black, Asian, Mixed, Other)
- Smoking status (current, ex or non)

- Index of Multiple Deprivation
- Body mass index (kg/m^2)
- Total cholesterol (mmol/L)
- Systolic and diastolic blood pressure (clinic or home readings)
- Ambulatory blood pressure
- SNOMED codes for home blood pressure measurement (in order to identify system users)
- Past medical history:
    - Diagnosis of diabetes (Type 1 or 2)
    - Previous myocardial infarction or stroke
    - Diagnosis of chronic kidney disease
    - Estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2)
- Medication use
    - Statin treatment (drug type and dose)
    - Antihypertensive medication use (drug type and dose, defined daily dose)
    - Other current cardiovascular medication
- Electronic Frailty Index and/or characteristics making up the electronic frailty index [8]
- Health Economic Resource use including consultation rate, timing, personnel undertaking, referrals and admissions.

9.7. Sample Handling

Not applicable.

9.8. Early Discontinuation/Withdrawal of Participants

Not applicable.

9.9. Definition of End of Study

The end of study is the point at which all the study data has been received; i.e. the last data extraction has taken place and no further data queries are required.

10. SAFETY REPORTING

This service evaluation involves only analysis of anonymised retrospective data, so we do not anticipate any adverse effects.

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The plans for the statistical analysis of the study are outlined below. Prior to data lock and the final analysis, consideration will be made as to whether any further detail in a formal statistical analysis plan is required and if so then a SAP will be agreed before the analysis.

11.2. Description of the Statistical Methods

Exposures

The primary exposure will be use of the Hypertension Plus monitoring system, defined by SNOMED codes recorded in the clinical system compared to no use. The date on which the patients started using the system ("Time 0") will be extracted and patients will be classified as exposed from this date onwards. These patients will be classified as unexposed prior to this date. Where a practice or individual stops using the system, this will be classed as the end of exposure. Patients who never use the system will form the unexposed group.

Outcomes

Primary outcome: Systolic blood pressure (SBP) in mm Hg. Blood pressure readings will be extracted from the electronic healthcare record and from the Hypertension Plus system. Readings will be identified as having been taken by a healthcare professional in the clinic or by the patient at home. Readings derived from 24-hour ambulatory BP monitoring will be excluded. Values outside the range 70-250 mm Hg will be excluded.[6] Where multiple readings are recorded on a single day, the lowest value will be selected.

Secondary outcomes:

- Diastolic blood pressure (DBP) in mm Hg, extracted from the electronic healthcare record or the Hypertension Plus system in the same manner as SBP readings. Values outside the range 40-150 mm Hg will be excluded.
- Blood pressure control (binary variable) defined using SBP and DBP readings. Controlled BP will be defined as SBP <140 mm Hg and DBP <90 mm Hg for clinic readings or SBP <135 mm Hg and DBP<85 mm Hg for home readings. Uncontrolled BP will be defined as the presence of any clinic or home SBP or DBP reading above these thresholds.
- Primary care workload defined as the number of face-to-face and telephone consultations where hypertension or hypertension monitoring was listed as the primary problem. Sensitivity analyses will assess whether the addition of BP readings or antihypertensive treatment records to the definition of workload affects these results

Exploratory outcomes:

We will also evaluate the impact of the Hypertension Plus system on medication use in terms of number and dose of antihypertensive medication and other cardiovascular preventative treatment (statins, antiplatelets, anticoagulants). We will examine subgroups as listed below. We will investigate intervention fidelity in terms of adherence to the monitoring schedules.

Timeframe of outcome measurement

"Time 0" for exposed patients will be the date on which they start using the Hypertension Plus monitoring system. For unexposed patients "Time 0" will be the median date on which exposed patients in the same general practice started using the Hypertension Plus system. Longitudinal data for all

outcomes (BP measurements, consultation dates etc.) will be extracted from patient's electronic health record from the 12 months before and after "Time 0" for all patients.

Covariates

Covariates will be any factors that may confound the relationship between use of the Hypertension Plus system and the primary outcome which have been identified from our previous research.[4, 10] These are:

- Age (years)
- Gender
- Ethnicity (White, Black, Asian, Mixed, Other)
- Smoking status (current, ex or non)
- Index of Multiple Deprivation
- Body mass index (kg/m^2)
- Total cholesterol (mmol/L)
- Systolic and diastolic blood pressure (clinic or home readings)
- Past medical history:
    - Diagnosis of diabetes (Type 1 or 2)
    - Previous myocardial infarction or stroke
    - Diagnosis of chronic kidney disease
    - Estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2)
- Medication use:
    - Statin treatment (drug type and dose)
    - Antihypertensive medication use (drug type and dose, defined daily dose)
    - Other current cardiovascular medication
- Electronic Frailty Index and/or characteristics making up the electronic frailty index
- Health Economic Resource use including consultation rate, timing, personnel undertaking, referrals and admissions.

Covariates will be defined using the closest available electronic healthcare records data prior to "Time 0" for all patients, but within the previous two years. Otherwise this data will be regarded as missing.

Summary statistics and figures

Continuous covariate data and mean BP before "Time 0" will be summarised by the mean and standard deviations or median and inter-quartile range for non-normally distributed data. Normality will be determined through visual inspection of histograms and Q-Q plots. Binary/ categorical data will be summarised by mean and proportions. Summary statistics will be presented in tables overall and by exposure category.

Scatterplots of BP values over time will be produced, with exposed and unexposed groups denoted by different symbols.

Statistical modelling

Multilevel models and Difference-in-Differences (DiD) analysis will be used to describe changes in outcomes over time (12 months before and after "Time 0") and the effect of the introduction of the Hypertension Plus system. Difference-in-differences (DiD) allows comparison of differences in outcomes,

before and after an intervention, between groups.[7] Bias from unobserved fixed variables within each group is automatically accounted for in this type of analysis but bias from variables that affect allocation to the exposed an unexposed group must still be accounted for.

- Primary outcome (SBP) and secondary DBP outcome:

For the primary outcome (SBP) and secondary outcome of DBP, multilevel linear models will be used to model these outcomes over time, including a fixed linear effect for time relative to "Time 0" and random effects for patient and practice level average BP. The models will also include as fixed effects, an indicator for whether each BP was measured in the clinic or at home, an indicator for exposure and, to estimate difference-in-differences, interaction terms between the exposure and time period variable (initial model).

The addition of random effects for patient and practice level trends into the initial model will be considered by comparing models via the likelihood ratio test and Akaike Information Criterion (AIC), with terms retained if model fit is significant improved or the AIC is lower. Covariates will be included as fixed effects without selection once the initial model is finalised. To account for autocorrelation between BP measurements in the same individual, standard errors will be estimated using robust methods[9] and more specifically the Huber-White Sandwich estimator of the variance which can adjust for within-cluster correlation.

The effect of the Hypertension Plus intervention at 6 and 12 months will be estimated by comparing the estimated BP values in the exposed at unexposed groups at these time points, as derived from the models. These estimates, and estimates from the models will be summarised in tables including p-values and 95% confidence intervals.

Model assumptions will be checked by producing histograms of residuals and scatter plots of residuals against fitted values. If there is evidence of violation of assumptions, models will be refitted to log-transformations of SBP and DBP and assumptions re-checked.

- Secondary BP control outcome:

For the secondary outcome of BP control, a multilevel logistic regression model will be fitted to the BP control data, using the same steps as described above for the BP outcomes above.

- Primary care workload:

The number of primary care consultations occurring before and after "Time 0" will be totalled separately and modelled using a negative binomial model, including an offset term for person-time of follow-up (to account for potential loss-to-follow-up). This model will include an indicator for time before/ after "Time 0", an indicator for the exposure variable, and an interaction between these variables. Random effects for the patient and practice will also be included and robust standard errors will be estimated similar to other models.

Subgroup analysis

Analyses and modelling above will be repeated in the following subgroups:

- Men and women

- Age >65 years; >80 years
- Mean SBP before "Time 0" (>160 mm Hg)
- Previous history of myocardial infarction or stroke
- By CCG area
- Users of the system for at least 6months defined as coded data identifying use recorded in the clinical record at both baseline and between months 6-12
- People with baseline blood pressure ≤140/90 compared to those >140/90mmHg
- Deprivation score (High vs Low)
- Ethnicity

Sample size requirements for this study were determined through simulation, as there is little statistical literature for sample size requirements for multilevel modelling. Data was simulated for systolic BP measurements, nested within patients, nested within practices, with the same structure as that detailed in the statistical modelling section. Normal distributions for BP values and variances around patient and practice mean values were assumed (reflecting random intercept terms). A global mean BP of 148 mm Hg was assumed, with practice variation (standard deviation, SD) of 5 mm Hg about this mean. Within a practice, patient variation (SD) was assumed as 17 mm Hg and measurements within a patient were assumed to vary by 10 mm Hg (SD) about the patient mean. The effect of time was assumed to be 0, clinic BP measurements were assumed to be 5 mm Hg higher than home measurements and 25% of patients were expected to take up the Hypertension Plus system.

Assuming an effect size of -3 mm Hg (BP 3 mm Hg lower in patients using the Hypertension Plus system) and a minimum of 4 BP measurements for each patient, 1000 simulated datasets were created and multilevel models as described in the statistical modelling section were fitted to each simulation. This demonstrated that to achieve 90% power at the 5% significance level for the effect of the Hypertension Plus system, 100 patients each drawn from 8 general practices would be required for this study (800 patients in total, 91% power).

When assuming a smaller effect size (-1 mm Hg) or greater variation (practice SD=10 mm Hg, patient SD = 22 mm Hg or measurement SD = 14 mm Hg), the required sample size was 200 patients from 35 practices, 100 patients from 8 practices, 100 patients from 8 practices or 100 patients from 14 practices respectively. Combining all of these conservative assumptions led to a required sample size 300 patients drawn from 42 practices (12600 patients in total, 90% power).

Assuming an average practice size of 8000 people, a 14% prevalence of hypertension, and an uncontrolled hypertension prevalence of 30%, we expect 336 eligible patients per practice. Considering the scenarios above, that study power is more greatly influenced by the number of practices rather than the number of patients, and the possibility of withdrawal of up to 10% of practices. We anticipate that at least forty and up to approximately sixty practices will contribute, hence adequate power for the comparisons should be available.

12. Analytical populations

The primary analysis use data from all eligible patients. Analysts will not be blinded to the exposure status. Secondary analysis will be limited to patients in the exposed group who recorded BP measurements through the Hypertension Plus system on more than 3 occasions ("per-protocol" type analysis)

12.1. The Level of Statistical Significance

A 5% significance level will be used for all analyses/ tests.

12.2. Procedure for Accounting for Missing, Unused, and Spurious Data.

Due to the use of random effects models, missing data is only expected in covariate data. The primary analysis will use multiple imputation by chained equations to impute missing values, including the outcome(s) in the imputation model. Initially 5 imputed datasets will be created and estimates will be combined across imputations using Rubin's rules. Further imputations will be added if the Monte-Carlo error of estimates exceeds 10% of the corresponding standard error. Multiple imputation will only be employed if variables are missing in less than 20% of patients. For larger proportions of missing data, the covariate will be removed from analyses. Sensitivity analyses will be conducted using complete data only.

12.3. Potential biases

(Adapted from Parker et al In Press 2021)

The following table summarises key biases and the mitigation we propose.

Bias	Issues	Mitigation
(1) Confounding due to non-randomised design	a) Patients will not be randomised and there is likely to be variation in implementation between practices. b) Non-participating patients (comparator group) may be systematically different at baseline from those in the telemonitoring group. c) Practices who take part may be different to those who do not	a) Analysis will take into account area as similar implementation by area b) Use practices prior to implementation as comparators c) Within areas consider ordering effects This is an observational study so there is always the possibility of some residual confounding that can not be taken into account.
(2) Information bias	BP measured in the clinic and at home may be different due to white coat and masked effects leading to confounding in terms of change in BP .	a) In a linear mixed model this can be fully adjusted by adding the

		intervention/control in the analysis b) BP control rather than BP level in analyses
(3) High variability in the frequency of readings	Home readings can be several times per day or week whereas clinic readings tending to be 1-4x per year. Furthermore, attendance at clinic may be for some other reason meaning those who attend or not are different systematically	a) Primary analysis utilises all available data b) Consider sensitivity analysis using standardisation of readings over time. This means that we take bp values at fixed time points more specifically at 6 and 12 months with value closest to that time point being the one used for the analysis.
(4) Contamination of readings	Home readings can be coded as clinic readings. The automated importing of Hypertension Plus readings into the clinical record should avoid this but it is possible that home readings in the comparator group may also be contaminated as may be readings prior to the implementation period.	a) This may be a problem in both groups b) Hypertension Plus readings will be labelled as such
(5) Regression to the mean	People chosen on the basis of raised baseline readings are more likely to have subsequently controlled BP	Both intervention and comparison groups will be chosen using same attributes Consideration of need for matching.
(6) Measurement error	Both operator, system and monitor errors are possible	Operator errors may be more likely by patients but evidence of operator bias is more likely for clinicians. Most of these errors will be similar in both groups
(7) End digit preference	People tend to be more likely to record readings ending in zero	a. We will investigate prevalence in both intervention and comparator groups b. Adjusting for the control/intervention group in a mixed model should be

		able to take into account for potential differences in the magnitude of digit preference
(8) Withdrawal bias	Patients may not use the Hypertension Plus system consistently.	We will use intention to treat approach so individuals with any Hypertension Plus activity recorded will be assigned to intervention.

12.4. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Prior to the final analysis, we will consider if the analysis as described above is sufficient or whether a statistical analysis plan is appropriate and this will be finalised. Any subsequent changes to the statistical analysis plan will be described in the final report/ paper. Additional analyses conducted will be clearly specified as post-hoc.

12.5. Health Economics Analysis

The staff members' (clinical and technical) consultation time recorded on the clinical system setting up and delivering the service will be extracted and used to calculate the implementation costs. Medication quantities will be extracted from the clinical systems in addition. Time spent training and on other activity not recorded in the clinical system will be estimated.

The primary outcome of the health economics analysis will be the costs of NHS hypertension care including medical consultations and medications. The health economics resource use data will be extracted from GP's clinical routine data 12 months before and after the 'time 0'. Standardized unit costs will be obtained and combined with resource use data to calculate health care costs. Following the same analytical principles, summary statistics of health care costs will be presented, and the Difference-in-difference (DiD) modelling will be used to capture the effect of the implementation of Hypertension Plus using both before and after, and between the intervention and the no-intervention groups.

13. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

Data will be extracted from practice computer systems and secure data transfer and compiled in anonymised form following secure transfer from the practices. In addition, data will be directly downloaded from the Hypertension Plus system with permission of the relevant data controller. Data will be cleaned and compiled to make them comparable within practices.

13.1. Source Data

Source data is what is recorded in the patients' Electronic Health Records and/or the Hypertension Plus system.

13.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

13.3. Data Recording and Record Keeping

The participants will be identified by a unique study specific number and/or code in the dataset (SNOMED in the clinical record). The name and any other identifying detail will NOT be included in any study data electronic file.

The principal data source for this study will be anonymised routinely collected primary care data extracted retrospectively from participating general practices. All GP practices in the UK use a computerised medical system to maintain patient medical records. Data are entered into a patient's computerised medical system as coded data or free text. Coded data, anonymised at source, will be extracted from Electronic Health Records by automatic searches. All anonymised data from GP practices and from Omron via the Hypertension Plus system will be encrypted on transit and at rest. Data will be stored within the Department of Primary Care Health Sciences at Oxford University in a locked server facility and in a secure folder accessible only to researchers participating in the study or who have been granted access by the Principal Investigator.

Anonymised study data will be archived for at least five years in accordance with the PC-CTU's Archiving SOPs.

The Research Team has no roles in updating these clinical data recorded by clinicians as part of their consultation and care. The Research Team, however, maintains an auditable trail for all the stages of data processing to ensure the quality of data are not compromised by the processing.

14. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, relevant regulations and standard operating procedures.

14.1. Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

14.2. Study monitoring

Monitoring will be performed according to the study specific Monitoring Plan as identified within the risk assessment. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents.

15. Study Committees

Study Management Group (SMG)

The SMG is responsible for day to day management of the study and will monitor all aspects of conduct and progress, including Protocol; compliance, and the quality of the study itself. This group will meet on a monthly basis.

Study Advisory Committee (SAC)

The role of the SAC is to provide overall advice for the study on behalf of the Sponsor and the Funder and to ensure that the study is conducted according to the relevant regulations and local policies. The frequency of meeting will be determined by the SAC but likely to be four monthly.

16. PROTOCOL DEVIATIONS

A study related deviation is a departure from the approved study protocol or other study document or process or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

In the event of the inadvertent receipt of identifiable data, research team will notify the University of Oxford Data Breach team immediately (data.breach@admin.ox.ac.uk) in order to comply with procedures set out by the Information Commissioners' Office (ICO), as well as notifying the organsation from which the data was received.

17. SERIOUS BREACHES

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

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

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

18.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

18.3. Approvals

Following Sponsor approval the protocol will be submitted to the HRA and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

18.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the funder (where required). In addition, an End of Study notification and final report will be submitted to the same party.

18.5. Transparency in Research

This service evaluation will be registered on a publicly accessible database.

18.6. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be anonymised as soon as it is practical to do so. This is done at practice level prior to provision of data to the research team. Although multiple items will be extracted from individual clinical records, we have taken care to minimise the number of data items/variables that would be extracted. We do not believe that the data being requested would be sufficient, even in aggregate, to identify an individual. De-identification will ensure that it is not possible for research staff to link study data with data from other sources.

19. FINANCE AND INSURANCE

19.1. Funding

The study is being funded by NIHR via Applied Research Collaboration (ARC) Oxford and Thames Valley

19.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). Appropriate contractual arrangements will be put in place with all third parties.

20. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by NIHR ARC Oxford and Thames Valley. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

21. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

22. ARCHIVING

At the conclusion of the study, all essential documents and trial data will be archived for at least five years in accordance with the PC-CTU's Archiving SOPs. The Chief Investigator is responsible for authorising retrieval and disposal of archived material.

23. REFERENCES

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4. McManus RJ, Mant J, Franssen M, et al. Efficacy of self-monitored blood pressure, with or without telemonitoring, for titration of antihypertensive medication (TASMINH4): an unmasked randomised controlled trial. *Lancet* 2018; **391**(10124): 949-59.

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7. Zhou H, Taber C, Arcona S, Li Y. Difference-in-Differences Method in Comparative Effectiveness Research: Utility with Unbalanced Groups. *Appl Health Econ Health Policy* 2016; **14**(4): 419-29.

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9. Williams, R. L. 2000. A note on robust variance estimation for cluster-correlated data. Biometrics 56: 645–646.

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24. APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1.	2	21.12.2021	Richard McManus	**1. Lay Summary** Revision of lay summary to make it clearer. **2. 9.5.2 Description of comparator** Amended to make clearer that comparator is patients on hypertension registers**.** **3. 11.2 Description of the Statistical Methods – Covariates** References made to previous research and references added to protocol. **Subgroup analysis** Addition of 2 further subgroups – ethnicity and IMD. **4. 12.3 Potential biases** Updates to the mitigation columns to make these clearer

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).