Study Title: Prospective Register Of patients undergoing repeated OFfice and Ambulatory Blood Pressure Monitoring

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Conflicts of interest statement

All investigators declare that they have no conflicts of interest.

Confidentiality statement

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

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1. SYNOPSIS

Study Title	Prospective Register Of patients undergoing repeated OFfice and Ambulatory Blood Pressure Monitoring (PROOF-ABPM)	
Internal ref. no. / short title	PROOF-ABPM	
Study Design	Prospective, multi-centre observational cohort study	
Study Participants	Consecutive patients attending participating centres in Primary or Secondary Care or pharmacies for routine blood pressure screening.	
Summary	The aim of this study is to examine novel strategies for the diagnosis and management of hypertension using data from routine clinical practice. This will be achieved by setting up a Prospective Register Of patients undergoing repeated OFfice and Ambulatory Blood Pressure Monitoring (PROOF-ABPM) in Primary Care, Secondary Care and at pharmacies. Data contained within the register will include patient characteristics, repeated clinic and ambulatory blood pressure, clinical assessment data and subsequent admissions to hospital and mortality. The PROOF-ABPM will be unique in its consideration of multiple clinic blood pressure measurements in relation to ambulatory blood pressure readings taken in routine clinical practice.	
Planned Sample Size	1000	
Planned Study Period	01/05/2015-31/12/2017	
	Objectives	**Outcome Measures**
Primary	Establish the accuracy of the PROOF-BP prediction tool at predicting out-of-office blood pressure in routine clinical practice	The proportion of true positive, true negative, false positive and false negative classifications of hypertension according to out-of-office monitoring.
Secondary	Establish the accuracy of the PROOF-BP prediction tool compared to current strategies in routine clinical practice	Improvement in the classification of patients' hypertensive status of >10% or reduction in the utilisation of out-of-office monitoring of >20% compared to existing strategies.
	Establish the accuracy of the PROOF-BP prediction tool in different clinical settings (Primary Care, Secondary Care and pharmacies)	Difference in the proportion of patients correctly classified as hypertensive (according to out-of-office monitoring) by setting.
	Establish the accuracy of the PROOF-BP prediction tool in specific populations (older vs. younger patients, males vs. females, those at high cardiovascular disease risk	Difference in the proportion of patients correctly classified as hypertensive (according to out-of-office monitoring) by patient characteristic.

	vs. low risk, those taking antihypertensive medications vs. those not)	
	Examine whether the 'adjusted clinic blood pressure' generated by the prediction model predicts long term clinical outcomes (e.g. hospital admission with myocardial infarction or stroke, mortality) better than standard clinic blood pressure	Hazard ratio describing the association between adjusted clinic blood pressure and total mortality, cardiovascular mortality, hospital admission with stroke, myocardial infarction or heart failure.

2. ABBREVIATIONS

AUROC	Area Under the Receiver Operator Characteristic curve statistics
BP	Blood pressure
CPRD	Clinical Practice research Datalink
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
CTU	Oxford Primary Care and Vaccines Collaborative Clinical Trials Unit
DESCARTE	Decision rule for severe symptoms and complications of acute red throat in everyday practice study
ECG	Electrocardiogram
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital Episodes Statistics
ICF	Informed Consent Form
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NHS	National Health Service
NRES	National Research Ethics Service
ONS	Office for National Statistics
PI	Principal Investigator
PROOF-BP	PRedicting Out OFfice Blood Pressure in the clinic tool[1]
PROOF-ABPM	Prospective Register Of patients undergoing repeated OFfice and Ambulatory Blood Pressure Monitoring

R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RISP	Research Information Sheet for Practices/pharmacies
SOP	Standard Operating Procedure
UK	United Kingdom

3. BACKGROUND AND RATIONALE

High blood pressure (hypertension) is an important risk factor for cardiovascular disease,[2] a significant cause of morbidity and mortality worldwide. The diagnosis and management of hypertension depends on accurate measurement of blood pressure (BP) in order to target antihypertensive treatment appropriately and avoid unnecessary healthcare costs.[3] Traditionally, blood pressure measurement takes place in the physician's office (or clinic) in a Primary Care setting. However, it has long been recognised that 24 hour ambulatory blood pressure estimates true mean blood pressure more accurately because multiple readings are taken and it correlates better with a range of cardiovascular outcomes and end organ damage than clinic blood pressure.[4-6] Clinic blood pressure measurements frequently under/overestimate 24 hour ambulatory blood pressure and therefore may result in incorrect classification and hence subsequent management.[7, 8]

Depending on the direction of the error, such deviations can be defined as a 'white coat' or 'masked' effect.[9, 10] Patients with a significant white coat effect have higher clinic blood pressure than would be expected for the corresponding 24 hour ambulatory monitoring and are therefore at risk of over-treatment.[9] Conversely, patients with a significant masked effect have higher blood pressures with daytime or 24 hour ambulatory monitoring than would be expected for the corresponding clinic blood pressure. These patients are often underdiagnosed and potentially under-treated,[10] thereby leading to increased risk of target organ damage[11] and cardiovascular mortality.[12, 13]

In the UK, National Institute for Health and Clinical Excellence (NICE) guidelines now recommend out-of-office measurement (ambulatory or home monitoring) if blood pressure is raised in the clinic to confirm a diagnosis of hypertension.[14] Whilst this new method of diagnosis is considered cost-effective due to a reduction in misdiagnosis caused by white coat hypertension,[3] it still results in patients with true underlying hypertension identified by clinic blood pressure readings being sent for arguably unnecessary out-of-office monitoring and will not capture those patients with masked hypertension.

Work by this group[15] has shown that the change in clinic blood pressure over multiple readings is a significant predictor of the home-clinic blood pressure difference: a decrease in clinic blood pressure across multiple readings is associated with lower blood pressure when it is measured at home and *visa versa.* We have subsequently confirmed this effect using data from previous trials[16-19] and shown that, in combination with patient characteristics, this change can be used to accurately predict a patient's out-of-office blood pressure level.[1] Utilised as a triaging tool for out-of-office monitoring, the PROOF-BP prediction model permits detection of those patients with a possible white coat or masked effect on the basis of data available in a routine Primary Care clinic.

It is well know that blood pressure measurements made under controlled conditions in a research setting are not necessarily comparable to those made by a physician in routine clinical practice.[20-22] Differences occur for a variety of reasons, including the use of inadequate or uncalibrated devices,[23-25] suboptimal measurement techniques[26-28] and rounding bias (or last digit preference).[29, 30] Thus, a prediction model shown to be accurate in a research setting, is not guaranteed to work in routine clinical practice. Therefore, the PROOF-BP prediction tool needs to be prospectively validated in a clinical setting before it can be used for the diagnosis and management of hypertension in clinical practice.

The present study proposes to collect sufficient data from routine practice to prospectively validate the PROOF-BP prediction tool and better understand the relationship between blood pressures measured in different settings and how this relates to cardiovascular disease risk. This will be achieved by setting up a prospective register of patients attending a variety of healthcare settings for routine office and ambulatory blood pressure monitoring. The register will comprise of multiple clinic blood pressure readings, ambulatory blood pressure monitoring data, patient characteristics, medical history, clinical assessment data and prescribed medication. The registry will be complementary to existing blood pressure monitoring registries,[31, 32] many of which are based in specialist hypertension clinics around the world, but unique in its consideration of multiple clinic blood pressure readings taken in variety of healthcare settings. Indeed, although such data are routinely collected in clinical practice, there are no current databases which capture this information for research purposes. Even linked anonymised databases such as the Clinical Practice research Datalink (CPRD) do not collect all the information that will be captured within this database since data on individual clinic blood pressure readings are rarely captured on general practice or hospital computer systems.

4. OBJECTIVES AND OUTCOME MEASURES

Priority	Objectives	Outcome Measures
Primary objective	Establish the accuracy of the PROOF-BP prediction tool at predicting out-of-office blood pressure in routine clinical practice	The proportion of true positive, true negative, false positive and false negative classifications of hypertension according to out-of-office monitoring.
Secondary objectives	Establish the accuracy of the PROOF-BP prediction tool compared to current strategies in routine clinical practice	Improvement in the classification of patients' hypertensive status of >10% or reduction in the utilisation of out-of-office monitoring of >20% compared to existing strategies.
	Establish the accuracy of the PROOF-BP prediction tool in different clinical settings (Primary Care, Secondary Care and pharmacies)	Difference in the proportion of patients correctly classified as hypertensive (according to out-of-office monitoring) by setting.

	Establish the accuracy of the PROOF-BP prediction tool in specific populations (older vs. younger patients, males vs. females, those at high cardiovascular disease risk vs. low risk, those taking antihypertensive medications vs. those not)	Difference in the proportion of patients correctly classified as hypertensive (according to out-of-office monitoring) by patient characteristic.
	Examine whether the 'adjusted clinic blood pressure' generated by the prediction model predicts long term clinical outcomes (e.g. hospital admission with myocardial infarction or stroke, mortality) better than standard clinic blood pressure	Hazard ratio describing the association between adjusted clinic blood pressure and total mortality, cardiovascular mortality, hospital admission with stroke, myocardial infarction or heart failure.

5. STUDY DESIGN

Prospective, multi-centre observational cohort study recruiting patients from Primary Care, Secondary Care and pharmacies.

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

Consecutive patients attending participating centres in Primary or Secondary Care or pharmacies for routine blood pressure screening. These will include patients identified with raised blood pressure at routine NHS health checks in Primary Care, those referred (by their GP) to their local pharmacy for ambulatory blood pressure monitoring (as part of routine care) and those referred to Secondary Care with suspected hypertension, newly treated hypertension, resistant hypertension, secondary hypertension or other specialist conditions. Eligible patients will be invited to give informed consent to allow identifiable data to be collected for data linkage to external registries: the Office for National Statistics (ONS) mortality and Hospital Episodes Statistics (HES) databases via the Health & Social Care Information Centre's Data Linkage and Extract Service.

6.2. Setting

The register will be web-based to permit access from a variety of healthcare settings. Data collection procedures will be initially piloted in the hypertension clinic at University Hospitals Birmingham. Following successful role out in this clinic, other centres will be invited to contribute patient data to the registry. We will focus on recruitment of general practices within the NIHR Clinical Research Network and

pharmacies from the area covered by Sandwell and West Birmingham Clinical Commissioning Group, who currently offer an ambulatory blood pressure monitoring service for patients with raised clinic blood pressure referred from Primary Care.

6.3. Inclusion Criteria

- Male and female subjects
- Age ≥18 years
- Attending routine clinical practice for ambulatory blood pressure monitoring

6.4. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Lack of availability of basic clinical information
- Clinic blood pressure readings obtained on at least three occasions within the same visit not recorded

7. STUDY PROCEDURES

Procedures for data collection and individual patient consent are summarised in figure 1 in Appendix A and described in detail below.

7.1. Recruitment

Practices and pharmacies will be approached via the local NIHR Clinical Research Network. They will be responsible for producing a Research Information Sheet for Practices/pharmacies (RISP), which they will use to approach potentially eligible sites on the study team's behalf. General practices and pharmacies which are certified as having undergone training in Good Clinical Practice (GCP) will be targeted.

Patients attending each study site will be screened opportunistically, that is, potential patient records will not be screened prior to invitation to participate, but rather those attending routine clinical practice for ambulatory blood pressure monitoring will be approached by a member of the clinical care team and invited to give informed consent. Anonymised data will be collected for all patients approached and identifiable data will be collected in those giving informed consent.

7.2. Anonymised data collection

Anonymised data from all patients attending routine clinical screening clinics prior to ambulatory blood pressure monitoring will be collected and entered onto the study database by participating staff at each data collection site. Individual patient consent is not required for anonymised data collection and will not be sought, as is common in routine clinical audits and anonymised observational cohort studies.[33, 34] Participating centres from Primary Care will be given a data collection template to upload onto the practice database which will pre-populate with existing data from the patient's medical record and identify where new data is required from the patient's clinic visit. This template will have a report function which can be used by practice staff to enter data directly onto the study database or be emailed to the coordinating centre for central data entry. All sites will be provided with a Microlife Watch BP (or

equivalent) blood pressure monitoring device (or equivalent) to assist with the collection of multiple clinic blood pressure readings. This device takes a minimum of three clinic readings and automatically calculates an average. Both the individual readings and the averaged blood pressure can be viewed on the monitor after measurement. Current guidelines in the UK[14] and abroad[21, 35] recommend that 2-3 clinic readings are taken when screening for hypertension and thus collection of data for the minimum dataset required in the present study will not constitute a deviation from usual care (although documentation of these individual readings may incur additional time for which participating centres will be reimbursed, where appropriate). Instructions will be provided for clinic and ambulatory blood pressure monitoring (based on clinical guidelines)[14] but no formal procedure will be put in place for checking if measurement protocols have been adhered to; such flexibility will be allowed to reflect true clinical practice. A minimum dataset will be required for all eligible patients and include the following:

- Patient characteristics (age, sex, ethnicity, smoking status, height, weight)
- 3-6 clinic blood pressure readings
- 24 hour ambulatory blood pressure monitoring data
- Diagnosis of hypertension (yes/no)
- History of hypertension, cardiovascular disease, heart failure, diabetes, chronic kidney disease (stages 3-6) or atrial fibrillation (yes/no)
- Prescribed medication (type of antihypertensive, statin or antiplatelet therapy)

Where data are routinely collected and available, additional data relating to cardiovascular risk factors will be collected to permit sub-group analyses by risk group. These data will include:

- Additional patient characteristics (waist circumference, alcohol consumption)
- Clinic blood pressure readings on the right and left arm (6 readings)
- Follow-up clinic and 24 hour blood pressure monitoring data
- Blood analyses (renal and liver function, cholesterol profile, glucose, thyroid function, urate and gamma-glutamyl transferase, plasma renin levels)
- Albumin:creatinine ratio
- Other clinical investigations (ECG, cardiac MRI)

7.3. Identifiable data collection

Eligible patients will be invited to give informed consent to allow identifiable data to be collected for data linkage to external registries. The pre-specified identifiable information to be collected will be:

- Patient name
- Date of birth
- Current address
- Post code
- NHS number

For all consenting patients, study data will be linked to the Office for National Statistics (ONS) mortality register and Hospital Episodes Statistics (HES) database via the Health & Social Care Information Centre's Data Linkage and Extract Service. This service tracks patient events via the Hospital Episode Statistics and the Office for National Statistics death register, using NHS numbers and other identifiable information and will allow ascertainment of any hospital admissions and/or death status following enrolment into the study.

7.4. Informed Consent

Written and verbal versions of the Participant Information and Informed Consent will be presented to potential participants by the consulting healthcare team. This information will detail the exact nature of the study, what it will involve for the participant, the implications and constraints of the protocol and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The study participant will personally sign and date the latest approved version of the Informed Consent form before any study specific identifiable data collection is carried out. The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. The process of gaining informed consent will use methods established in the DESCARTE and Cough Complications Cohort (3C) studies.[36, 37] That is, eligible patients will be able to provide informed consent in one of three ways:

1. During clinic attendance, patients will be ask by participating staff if they would be willing to consider giving consent for identifiable data to be collected for data linkage purposes. Patients will be given an information sheet and consent form and if willing to do so, complete it during the clinic.
2. Those wishing more time to consider participation will be asked to take the information home and, if willing to participate, return a completed consent form during their next visit when they return the ambulatory blood pressure monitor.
3. Those forgetting to provide consent at either visit may return a signed consent form to the participating centre by post.

All participating centres will be expected to have undergone training in GCP. Where this is not the case, training of individual sites will be offered via the NIHR Clinical Research Network. Each participant will retain a copy of the signed Informed Consent and the original signed form will be retained at the study site. A copy of the signed form will be scanned and uploaded onto the study database.

7.5. Study database

Each data collection site will store their data locally using standard clinical systems and upload a copy of these data to a secure central database at the study coordinating centre (University of Oxford). Local staff will be trained to upload data and automated checks will be used to ensure data entry errors are kept to a minimum. Data will be entered into two separate study databases, one for anonymised data and one for identifiable data. A unique study identifier will automatically be generated for every patient entered onto the anonymised study database and this will be entered onto the database of patient identifiers for those patients giving informed consent (permitting linkage of identifiable and anonymised data). Double data entry will be employed for entry of the unique study identifier onto the database of patient identifiers to ensure accuracy. Both study databases will include secure login for staff at participating sites and facilities for manual entry of data and upload facilities for ambulatory blood pressure monitoring data consent forms (contained in .csv and .pdf files). These databases will be linked

to a study website with information about the project and other resources including the PROOF-BP prediction tool.

7.6. Data protection and storage

Identifiable data will be stored at each data collection site in accordance with data protection guidelines and NHS policy, and on the secure study database hosted by the coordinating institution (University of Oxford). The principle investigator will be responsible for the overall management and storage of the data within the registry. The data programmer from the Oxford Primary Care and Vaccines Collaborative Clinical Trials Unit (CTU) will be responsible for the management of the software; maintenance of backup regime and disaster recovery arrangements; ensuring duplicate files are kept to the minimum needed, controlling access rights, changing access rights promptly when the team changes and will report directly to the principle investigator on issues related to data security.

The study database will be managed according to Standard Operating Procedures maintained by the CTU. Access rights to data and applications software will be clearly defined and staff authorised to access personal data will be formally notified in writing of the permissible scope of their access. Data access will be limited to specific members of the research team (trained in data protection policy) including the principle investigator (as study guarantor), data manager and database programmer. For each database application, system users will be given a valid user system account name (username ID), and a password known only to that user to prevent unauthorised use of systems. Upon entering the database (for identifiable patient information), a confidentiality warning message will be displayed informing the user that the system contains confidential information and is for authorised users only. All data will be entered into the database through a reliably encrypted gateway.

All data used in analyses and published outputs will be anonymised. Applications for data sharing with researchers from other research organisations will be reviewed by the registry steering committee and decisions on access will be subject to satisfactory review of a study protocol. Data sharing will be accepted on condition that appropriate safeguards are detailed and the receiving organisation complies with the Data Protection Act 1998 or equivalent policies. Sharing of data will be subject strict data sharing conditions; 1) All data is store securely on a secure server at the collaborating research organisation; 2) Analyses will only be undertaken as agreed in the original proposal or by subsequent agreement of the registry steering committee; 3) All requests for further analyses must be agreed by the registry steering committee prior to such analyses going ahead; 4) All publications arising from the data must include at least one member of the registry steering committee in the publication authorship.

All data and study documentation will be stored for subsequent scientific validation and audit as required. Data will be archived following completion of the study in line with Good Clinical Practice guidelines and documents will be retained for a minimum of 5 years in line with the University Code of Practice for Research.

7.7. Discontinuation/Withdrawal of Participants from Study

All those giving informed consent for identifiable data collection will have the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Withdrawal of Consent

Patients wishing to withdraw from the study will be asked if they are willing for relevant data (already collected) to be used in the final analyses. The reason for withdrawal will be recorded in the CRF.

7.8. Definition of End of Study

The end of the study is the date of the last visit of the last participant, although outcome data will continue to be collected via the Health & Social Care Information Centre's Data Linkage and Extract Service for assessment of secondary outcomes.

8. STATISTICS AND ANALYSIS

8.1. Outcomes

The primary outcome of this study will be to define the accuracy of the PROOF-BP prediction tool in terms of the proportion of true/false positive/negative results in the general population attending routine clinical practice. Secondary outcomes will include assessment of model performance in different sub-groups – age (young vs. old), cardiovascular disease risk (high vs. low risk according to previous history and risk scores using data where available), those with Chronic Kidney Disease, Diabetes and across healthcare settings: Primary Care, Secondary Care and pharmacy settings.

In the longer term, linked data from the registry will be used to examine whether the 'adjusted clinic blood pressure' generated by the prediction model can better predict long term clinical outcomes (e.g. hospital admission with myocardial infarction/stroke and mortality) than standard clinic blood pressure. After the initial period of data collection is complete, the resources and funding required to continue ongoing data collection and follow-up will be reviewed. Where possible, patient accrual and data collection will continue and the study will become a research database permitting further investigations into blood pressure monitoring by a variety of means and cardiovascular disease risk factor data linked to cardiovascular disease morbidity and mortality in routine clinical practice.

8.2. Data analysis

A detailed analysis plan will be agreed by the study steering committee prior conducting any analyses. Briefly, data collected from the registry will be used to prospectively validate the PROOF-BP prediction tool. Descriptive statistics will be used, with hypertensive status defined according to ambulatory blood pressure measurements: The number of patients classed as true positives (sustained hypertensives), false positives (white coat hypertensives), true negatives (normotensives) and false negatives (masked hypertensives) will be used to calculate the sensitivity, specificity, positive predictive value and negative predictive value of the PROOF-BP prediction tool. Area Under the Receiver Operator Characteristic (AUROC) curve statistics will be used to examine the prediction model performance.

Chi-squared statistics will be used to compare the classification of patients' hypertensive status according to the prediction model and existing strategies[14, 35] for the diagnosis and management of hypertension. An improvement in patient classification of >10% or reduction in the utilisation of out-of-office monitoring of >20% will be deemed as successful validation. Where model validation is found to be unsuccessful, re-calibration will be explored.

Other secondary outcomes will be examined with chi-squared statistics comparing the classification of patients' hypertensive status across sub-groups (by setting, age group, sex, cardiovascular disease risk status, co-morbid conditions and treatment status). Linked data will be used to examine the association between the 'adjusted clinic blood pressure' (estimated from the PROOF-BP prediction model) and clinical outcomes. Such analyses will be conducted using Cox proportional hazards models after sufficient outcome data have been accrued.

8.3. Sample size

The proposed study will collect data on consecutive patients referred for ambulatory blood pressure monitoring in routine clinical practice. Based on the initial validation phase of the PROOF-BP prediction model, conducted using data from previous studies,[1] accrual of data from approximately 1000 patients would allow for estimation of hypertensive status with an accuracy of ±1-3%. In this previous data, 71% of patients were classed as true positives, 24% were classed as true negatives, 3% were classed as false positives and 2% were classed as false negatives. In population of 1000 patients it would be possible to estimate these rates with the following 95% confidence intervals: true positive 71% (68-74%), true negative 24% (21-27%), false positive 3% (2-4%) and false negative 2% (1-3%).

Approximately 182 patients would be required in each sub-group to examine the secondary outcomes proposed in the proposed study. This is based on a likelihood ratio test of two proportions detecting a 10% difference in the classification of hypertensive status between two sub-group populations (Secondary care vs. Primary care, Primary care vs. pharmacies, older vs. younger patients, high vs. low risk patients, etc.) with a significance level of 0.05 and power of 0.9. Assuming correct classification of 95% of patients in one group and 85% in the other, approximately 364 patients (182 in each group) would be required to demonstrate a significant difference. Thus, our recruitment target of 1000 patients should be sufficient to answer the secondary outcomes provided recruitment is appropriately distributed across clinic settings and patient characteristic sub-groups.

Sufficient funding is available to run the registry for an initial period of two and a half years. Recruitment of the sample size above should be achievable with recruitment of up to 10 Primary Care sites (each recruiting up to 25 patients), one Secondary Care site (recruiting up to 500 patients) and up to 10 pharmacies (each recruiting up to 25 patients). With patient attendance for routine blood pressure monitoring at individual sites likely to be significantly higher, these targets are eminently achievable. After the initial period of data collection is complete, the resources and funding required to continue data collection and follow-up will be reviewed. Where possible, patient accrual and data collection will continue, allowing the study to become a research database. This will permit longer term follow-up and further investigations into routine blood pressure monitoring by a variety of means and cardiovascular disease risk.

9. PATIENT AND PUBLIC INVOLVEMENT

Our lay patient advisor (Mr David Yeomans) has been engaged throughout planning of this study to ensure the project remains relevant and acceptable to the patients it is intended to help. Mr Yeomans forms an essential part of the study team and his expert advice will be sought for ongoing issues relating to the research protocol, acceptability of study documentation (patient information sheets, consent forms, study posters) and the ongoing management of the study. All Patient and Public Involvement expenses will be paid and reimbursed at INVOLVE rates, offered for both committee and preparatory work.

10. DATA MANAGEMENT

10.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations. Applications for data sharing with researchers from other research organisations will be reviewed by the registry steering committee and decisions on access will be subject to satisfactory review of a study protocol. Data sharing will be accepted on condition that appropriate safeguards are detailed and the receiving organisation complies with the Data Protection Act 1998 or equivalent policies. Sharing of data will be subject strict data sharing conditions; 1) All data is store securely on a secure server at the collaborating research organisation; 2) Analyses will only be undertaken as agreed in the original proposal or by subsequent agreement of the registry steering committee; 3) All requests for further analyses must be agreed by the registry steering committee prior to such analyses going ahead; 4) All publications arising from the data must include at least one member of the registry steering committee in the publication authorship.

10.2. Data Recording and Record Keeping

Each data collection site will store their data locally using standard clinical systems and upload a copy of these data to a secure central database at the study coordinating centre (University of Oxford). Data will be entered into two separate study databases, one for anonymised data and one for identifiable data. A unique study identifier will automatically be generated for every patient entered onto the anonymised

study database and this will be entered onto the database of patient identifiers for those patients giving informed consent (permitting linkage of identifiable and anonymised data). Double data entry will be employed for entry of the unique study identifier onto the database of patient identifiers to ensure accuracy.

A Case Report form (CRF) will be available to assist site staff in capturing all the data specified in the study protocol. The study CRFs will contain information about the patient's demographics (age, sex, ethnicity), blood pressure measurements, medical history, medication prescriptions and where collected, blood and urine measures. CRFs will also collect identifiable information about the patient (on a separate sheet) where individual patient consent is acquired.

CRFs will be used to guide data collection but will not be considered as the source document. Source data will be classed as the individual's medical records at each participating site. Study staff at participating sites may choose to collect data on paper/electronic CRFs and then enter data onto the study database. Other sites may choose to enter data from the medical records directly onto the study database. Flexibility in the method of data capture will be allowed to minimise the disruption for participating staff. Those choosing to collect data using paper/electronic CRFs will be responsible for subsequent storage and or secure disposal.

Every attempt will be made to minimise manual data entry. Where possible, data will be downloaded directly from clinical systems and then uploaded in the same format onto the study database. The nature of this study means that data should be accurate to that which has been collected on clinical systems, but the correctness or plausibility of such data are of less importance.

Administrative editing of the data will be permitted once the initial data entry is complete. This allows data to be changed in response to a query raised by entry personnel during initial data entry (if unsure of a value), or updates to data as a result of a query raised to Site (e.g. during data cleaning). All changes to data as a result of administrative editing are captured in the study audit trail and require a 'Reason for Change' discrepancy note to be saved within the system.

Relevant data validations (rules) will fire automatically as data entry is occurring. Rules will fire during initial entry (not administrative editing), after the form has been marked complete and saved. If the form is saved without change (i.e. no data entry error has occurred) then the rule will be committed to the system as a failed validation check. The study Data Manager will review the failed validation checks to determine if a query should be raised to Site.

11. QUALITY ASSURANCE PROCEDURES

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

12. PROJECT MANAGEMENT

The study will be run in collaboration with The Oxford Primary Care and Vaccines Collaborative Clinical Trials Unit (CTU) and overseen by the PROOF-ABPM coordinating centre at the University of Oxford. The principle investigator (James Sheppard) will coordinate the study and the CTU will provide trained staff to design and maintain the study database. The registry steering committee will meet every 6 months to

discuss the progress of the study and will include the core research team along with invited investigators from each recruitment and data collection site.

Individual sites will be responsible for providing staff to complete recruitment and data collection but will be reimbursed for costs incurred which do not directly relate to routine clinical care (i.e. patient recruitment and data entry). Costs will be reimbursed through a combination of NHS service support costs and standard research costs. The principle investigator will be responsible for the overall management and storage of the data within the registry. The data programmer from the CTU will be responsible for the management of the software; maintenance of backup regime and disaster recovery arrangements; ensuring duplicate files are kept to the minimum needed, controlling access rights, and changing access rights promptly when the team changes and will report directly to the principle investigator on issues related to data security.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Requirement for informed consent

Common Law states that anonymised clinical data collection is not within the control of the individual to whom the data relates (provided the data does not allow the individual to be identified) and is outside the scope of the 1998 Data Protection Act.[38] Thus, individual patient consent is not required for the anonymised data collection within this study, as has been the case in previous research studies of this nature.[33, 34]

The use of identifiable patient data, which comprises information about living people who can be identified from the data, or identified from combinations of the data and other information which the person in control of the data is likely to have, either now, or at some future time, does require individual patient consent under the 1998 Data Protection Act.[38] Informed consent will be sought from all patients attending routine clinics, health checks and pharmacies to undergo ambulatory blood pressure monitoring. Eligible patients will be asked for informed consent during the initial clinic visit to permit linkage of clinical data to ONS and HES outcome registries (death and hospital admissions). Up until the point of individual patient consent, identifiable patient data will only be available to healthcare professionals responsible for the care of the patient.

13.2. Participant Confidentiality

All data will be stored securely on an electronic study database in line with data protection guidelines and NHS policy. The study database will be managed according to Standard Operating Procedures maintained by the CTU. Access rights to data and applications software will be clearly defined and staff authorised to access personal data will be formally notified in writing of the permissible scope of their access. Data access will be limited to specific members of the research team (trained in data protection policy) including the principle investigator (as study guarantor), data manager and database programmer. For each database application, system users will be given a valid user system account name (username ID), and a password known only to that user to prevent unauthorised use of systems. Upon entering the database (for identifiable patient information), a confidentiality warning message will be

displayed informing the user that the system contains confidential information and is for authorised users only. All data will be entered into the database through a reliably encrypted gateway.

All data used in analyses and published outputs will be anonymised.

13.3. Declaration of Helsinki

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

13.4. Guidelines for Good Clinical Practice

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

13.5. Approvals

Approval will be sought to permit secure storage and use of routine patient data for research purposes. Permissions will be obtained for the use of both anonymised and identifiable patient data for linkage to national disease and mortality registries and Hospital Episode Statistics databases.

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval. Once ethical approval has been gained, local NHS Trust R&D approvals will be sought through the NIHR Clinical Research Network and University Hospitals Birmingham and Birmingham North. This will include applying for relevant permissions and letters of access to allow the research to be conducted in general practices, hospitals and pharmacies within the host NHS Trust.

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

13.6. Reporting

The PI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

14. FINANCE AND INSURANCE

14.1. Funding

This study is funded through a Medical Research Council Strategic Skills Post-doctoral Fellowship awarded to the PI. This funding will cover the costs of setting up and maintaining the study database and reimbursing general practice staff for data collection. Further funding for NHS service support costs have

been agreed in principle with the local NIHR Clinic Research Network to cover the costs of recruitment and gaining informed consent.

14.2. 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). NHS indemnity operates in respect of the clinical treatment which is provided.

15. 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 the Medical Research Council. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

All research outputs from this work will be published in peer-reviewed journals. Study findings will be presented at regional, national and international conferences to ensure maximum dissemination amongst academic and clinical colleagues. Where possible, local and national media will be engaged to bring the research findings to a wider audience. Relevant results will be made available for the next iterations of the NICE Hypertension guidelines and other relevant national guidelines. It is anticipated that these will support better patient-centred management plans for the diagnosis and management of hypertension and cardiovascular disease risk.

16. REFERENCES

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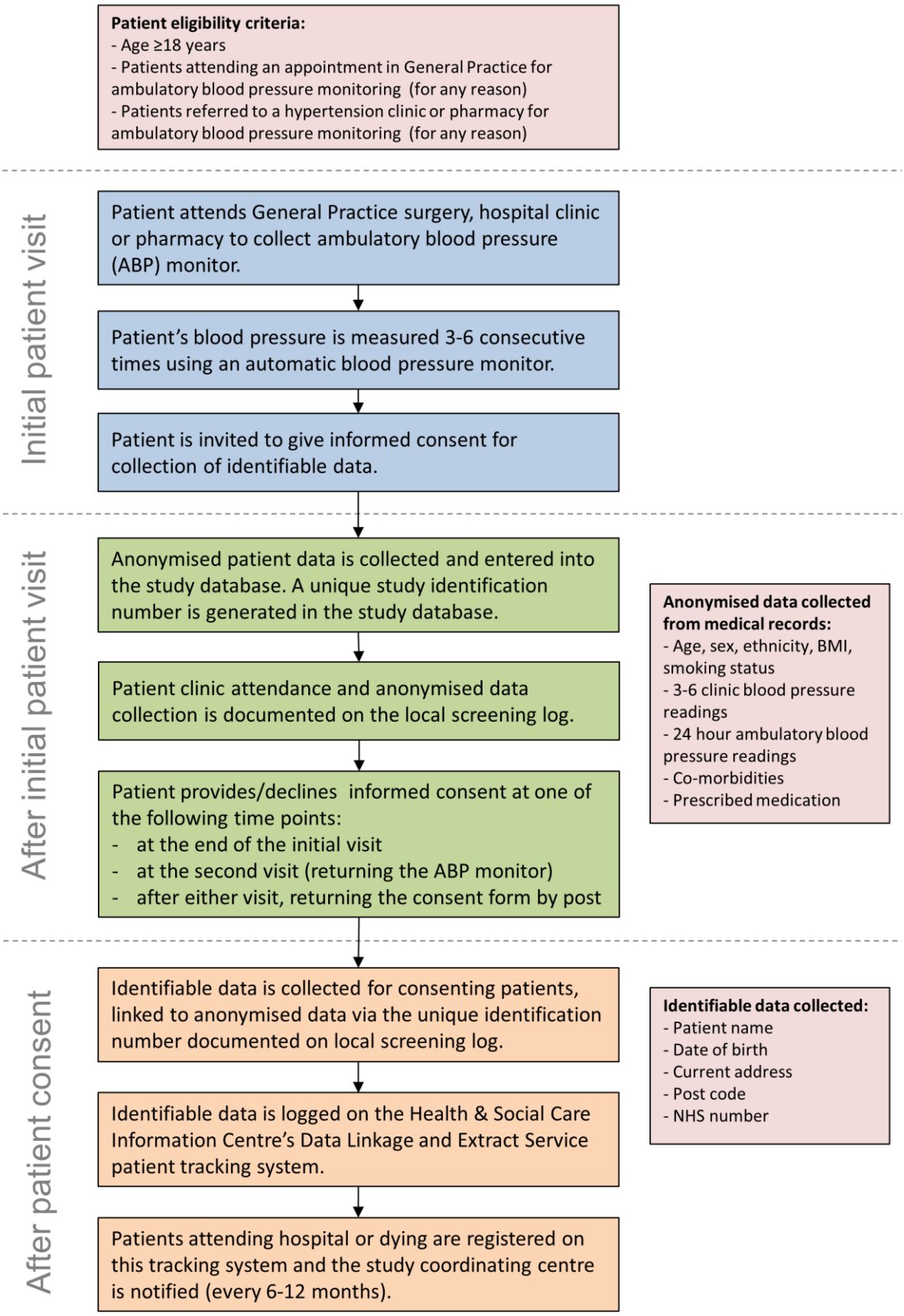
17. **APPENDIX A: STUDY FLOW CHART** (Figure 1. Data collection, consent)



18. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	V2	24/03/15	James Sheppard	Clarification that practices and pharmacies with training in GCP will be approached; Revision to consent procedure so that patients are not contacted by phone and asked for consent after the initial visit.