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Screening for Hypertension in the INpatient Environment (SHINE): A protocol for a Prospective Study of Diagnostic Accuracy among adult hospital patients

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Screening for Hypertension in the INpatient Environment (SHINE): A protocol for a Prospective Study of Diagnostic Accuracy among adult hospital patients

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ABSTRACT

Introduction

A significant percentage of patients admitted to hospital have undiagnosed hypertension. However, present hypertension guidelines in the UK, Europe and USA do not define a blood pressure threshold at which hospital inpatients should be considered at risk of hypertension, outside of the emergency setting. The objective of this study is to identify the optimal in-hospital mean blood pressure threshold, above which patients should receive post-discharge blood pressure assessment in the community.

Methods and Analysis

SHINE is a prospective diagnostic accuracy study. Patients admitted to hospital whose average blood pressure after 24 hours meets the study eligibility threshold (≥120/70mmHg) and who have no prior diagnosis of, or medication for hypertension will be eligible. At 8 weeks post-discharge, recruited participants will wear an ambulatory blood pressure monitor for 24 hours. Mean daytime ambulatory blood pressure will be calculated to assess for the presence or absence of hypertension. Diagnostic performance of in-hospital blood pressure will be assessed by constructing Receiver Operator Characteristic (ROC) curves from participants' in-hospital mean systolic and mean diastolic blood pressure (index test) versus diagnosis of hypertension determined by mean daytime ambulatory blood pressure (reference test).

Ethics and Dissemination

Ethical approval has been provided by the NHS Health Research Authority South Central – Oxford B Research Ethics Committee (19/SC/0026). Findings will be disseminated through national and international conferences, peer-reviewed journals and social media.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study to our knowledge to evaluate the diagnostic accuracy of a range of in-hospital blood pressure thresholds to identify the optimal blood pressure cut-off values for in-hospital hypertension screening.
- This is also the first study to our knowledge, to use real-time electronic algorithms to screen hospital inpatients' electronic blood pressure data.

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- Owing to the novel design of this study, the expected prevalence of hypertension at follow up is unknown and has therefore been estimated to calculate the sample size**.**

Patient and Public Involvement

The design of this study has been reviewed and supported by patient and public representatives who have provided input on the research questions, data analysis, informational material for public engagement and the burden of the follow up diagnostic testing from a patient's perspective. Their input lead to additional steps in data analysis, refining of the informational material and modification of the follow up plan to reduce patient burden.

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INTRODUCTION

Hypertension is the leading risk factor for death globally[1] with 12.8% of annual mortality attributable to hypertension.[2] A significant percentage of patients admitted to hospital have undiagnosed hypertension.[3,4] However, unless a person has severely elevated blood pressure, the clinical diagnosis of hypertension cannot be made in the in-hospital setting based on the UK, European or American Guidelines.[5–7] Indeed, increased blood pressure measurements in hospital are frequently dismissed and additional potential reasons for this include clinicians attributing increased blood pressure measurements to anxiety,[8] pain[9] or white coat hypertension.[10] However, evidence suggests that patients with elevated blood pressure recordings in hospital frequently remain hypertensive in the community.[11–17] Despite this, referral for community follow-up of these patients to determine the presence or absence of persistent hypertension is poor.[18–21]

Untreated hypertension is associated with a progressive increase in blood pressure that can become treatment resistant.[22] Therefore, hospital detection and timely management of hypertension offer an important intervention opportunity to address this major cause of morbidity and mortality.

In 2015, Oxford University Hospitals NHS Foundation Trust (OUHFT) introduced the NIHR-funded System for Electronic Notification and Documentation (SEND).[23] SEND is a tailored software application which links hospital bedside monitoring devices including blood pressure monitors, with a tablet computer for the manual recording of vital observations of patients.[24] Since this implementation, clinicians and researchers have been able to access and analyse patient observation data at a population as well as individual level. SEND has been used to record the vital observations of more than 200,000 patients so far and to link each patient's observations with their Electronic Patient Record (EPR).[24] This has paved the way for real-time and automated recognition of patients whose observations indicate they may be at increased risk of undiagnosed hypertension.

The objective of this study is to identify the optimal in-hospital mean blood pressure threshold, above which patients should receive post-discharge blood pressure assessment in the community.

METHODS AND ANALYSIS

We prepared this protocol following the STARD[25] guidelines.

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Study Design

This is a UK single-centre, prospective cohort diagnostic accuracy study. The study is due to commence in June 2019 and active follow-up will continue until May 2021.

Study Setting

Recruitment for this study will take place in Oxford University Hospitals NHS Foundation Trust (OUHFT), UK. Participants will be followed up in a community research clinic at 8 weeks (+/-4) following discharge from hospital to receive reference blood pressure testing. Participant timeline is shown in Figure 1.

Study Population

We will recruit participants aged between 18 and 80 years, whose mean blood pressure is between 120mmHg and 179mmmHg systolic and ≤109mmHg diastolic for any given 24-hour interval since their admission to hospital (index test). The mean blood pressure calculation must be based on a minimum of three blood pressure measurements taken over a minimum period of 24 hours with at least one blood pressure being recorded during night time hours (00:00 to 06:00) and at least one being recorded during day time hours (10:00 and 20:00).[26] Patients with an ICD10 code for hypertension or blood pressure lowering medication prescribed in their medication record will be excluded. Additional exclusion criteria include current, intended or recent pregnancy, cause for index admission being associated with end-organ damage related to severe hypertension (including but not limited to heart failure, myocardial infarction, stroke, hypertensive encephalopathy) and estimated glomerular infiltration rate of <30 ml/min. Full inclusion and exclusion criteria are provided in Table 1.

Inclusion Criteria	Exclusion criteria
Aged 18-80	Pre-existing diagnosis of hypertension or attending hospital with acute end-organ damage related to severe, undiagnosed hypertension.
Admitted to hospital for an acute or elective medical or surgical condition	Presence of atrial fibrillation or other pulse rate irregularity which means ABPM is not appropriate.
Have at least three in-hospital blood pressure recordings over a minimum of 24 hours for the index admission.	Currently pregnant, within 3 months post-partum or planning pregnancy during study period.
Identified by the blood pressure algorithm for any 24-hour interval to have a mean blood pressure which meets the eligibility thresholds.	Receiving treatments which might be used for the management of hypertension, e.g. beta blockers

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	for migraine, angiotensin-converting-enzyme inhibitors for renal disease.
Registered with a General Practitioner.	Diagnosed with terminal illness or cognitive impairment.
	Diagnosed with AKI on index admission or eGFR <30ml/min.
	Cause for hypertension being toxicology, medical or recreational e.g amphetamines and their derivatives or alcohol withdrawal syndrome.
	Post-discharge destination being another hospital or prison.
	Receiving concomitant chemotherapy.
	Already recruited to a separate hypertension study.

Table 1. Full inclusion and exclusion criteria

ABPM = ambulatory blood pressure monitoring, AKI = acute kidney injury,

Screening procedure

The identification of participants whose blood pressure exceeds the index test threshold will be automated using live, computerised algorithms. Blood pressure measurements in OUHFT are made using automated oscillometric devices and the BP monitor reading is entered manually using the SEND computer tablet before automated transfer to the electronic patient record by the SEND software app.[23] The identification of patients whose blood pressure measurements meet eligibility criteria will be computerised and automated. These automated systems for blood pressure documentation and evaluating study inclusion criteria are intended to ensure that the measurement of the index test is objective and thus the clinical staff who perform the blood pressure measurements can be considered blinded in the assessment of the index test. As this study is prospective in design they will not be aware of the result of the reference standard.

Participant sampling

Sampling will be stratified to ensure that there is representation of patients with a full range of in-hospital blood pressure profiles (according to pre-defined mean daytime systolic blood pressure, Table 2). Where there is insufficient study resource to enrol all recruitable patients, priority will be given to the strata with the least recruited patients. Recruitment will continue until the target recruitment number within each of the blood pressure intervals is achieved. The prevalence of each

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blood pressure profile among the hospital population will be recorded within a screening log during the study period.

Systolic blood pressure Interval	Target recruitment number
120-129	Approximately equal
130-139	representation of
140-149	participants recruited to
150-159	each of these systolic
160-179	bandwidth profiles
TOTAL	**200**

Table 2. Systolic blood pressure intervals against which recruitment will be stratified

Data Collection

Baseline data collection will be performed at the point of recruitment during the hospital admission, after the participant has provided informed, written consent. Custom-made baseline case report forms (CRFs) will be completed in the study data capture system for each participant by an appropriately qualified clinical researcher. The study data capture system will be electronic and accessible online. using a combination of data extracted from the EPR (e.g. diagnostic codes, current medications, serum haematology and biochemistry results and electrocardiogram) and participant self-report (e.g. ethnicity family history, previous prescribed medications for hypertension). Any extreme values entered into the electronic data capture system will be inspected. A data monitoring committee has not been convened since there is no concealed allocation to treatment in this cohort study. Frequency and procedures for auditing study conduct are determined by the study sponsor (University of Oxford) based on a proportionate approach to risks.

TEST METHODS

Index Diagnostic Test

The index test will be the first occurrence during the hospital stay of a cumulative mean 24-hour in-hospital blood pressure reading ≥130mmHg systolic or ≥80mmHg diastolic. By averaging a person's blood pressure measurements from the point of admission to the time of assessment by the algorithm, the chances of a person becoming eligible due to chance are reduced, in comparison to alternative, of assessing a person's eligibility based on 24 hour intervals of blood pressure

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measurements. The index test has been defined to reflect international consensus on the definition of stage 1 hypertension.[6,7]

Reference Standard Diagnostic Test

The gold standard diagnostic test for the presence of hypertension will be a daytime 24-hour ambulatory blood pressure threshold of ≥135mmHg systolic or ≥85mmHg diastolic, which is the current UK National Institute for Health and Care Excellence (NICE) diagnostic threshold for Ambulatory Blood Pressure Monitoring (ABPM).[5]

ABPM will be performed with each participant at 8 weeks (+/-4) following discharge from hospital using a validated automated Mobil-O-Graph ambulatory blood pressure monitor (IEM GmbH, Stolberg, Germany), calibrated to manufacturer standards. Should the participant have acquired a diagnosis of hypertension and initiated treatment for hypertension following hospital discharge but before they receive ABPM, they will not be eligible to proceed with ABPM. In this instance a participant will be regarded as being reference test positive, having acquired a clinical diagnosis of hypertension. The monitor will be programmed to measure blood pressure twice per hour during daytime hours (07:00 to 22:00), and once per hour during the night (22:00 to 07:00) for a period of 24 hours.[27] A minimum of 70% of the day time and 70% of the night time ABPM recordings must be successful in order to calculate the mean blood pressure for night and day and for the participant data to be analysed.[26] Where less than 70% of the recordings in any category are successful, the participant will be asked to wear the monitor for a further 24-hour period in order to collect adequate data. In the instance of two 24-hour episodes of ABPM not collecting sufficient data, the participant and their registered General Practitioner (GP) will be informed along with recommendation that the participant arrange an appointment with their GP for further evaluation of their blood pressure. The participant will continue to be followed up remotely through the online data capture system for up to 52 weeks from recruitment (Figure 1). Links to the questionnaires will be sent to participants by email and will collect data regarding blood pressure related health outcomes, the prescription of antihypertensive medications and repeat blood pressure measurements. At ten years, data will be obtained from the Office of National Statistics and Hospital Episode Statistics Databases regarding mortality and cardiovascular health related outcomes.

The fitting and removal of the ambulatory blood pressure monitor will be performed by a qualified clinical research nurse who is appropriately trained in the National Institute for Health's Good Clinical Practice and to perform ABPM. At the time of removal of the monitor, the electronic ABPM report will

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be downloaded to the study data capture system and interpreted by the research nurse. As the reference test procedure is objective through the use of an oscillometric, automated ABPM, the research nurse will not be blinded to the result of the index blood pressure test.

STATISTICAL METHODS

Sample size

Owing to the novel design of this study, estimates of expected prevalence of hypertension at follow-up have been used to calculate sample size. From a retrospective analysis of in-hospital OUHFT blood pressure data we estimate that 3000 patients per annum will be eligible for study inclusion (unpublished data). Previous studies have used an in-hospital blood pressure eligibility threshold (140/90mmHg) and revealed approximately that half of the patients with a blood pressure above the threshold have hypertension at follow up.[28,29] A lower rate of hypertension at follow-up is expected in this study owing to the lower eligibility blood pressure threshold of 120/70mmHg; a sample size of 200 has been derived to permit detection of a 20% rate of hypertension at follow-up with a 95% confidence interval width of approximately of ±5.36%.

Baseline characteristics

Clinical and demographic characteristics of the study population will be reported, including age, sex, presenting complaint, comorbidity and current treatments. Number of participants who complete each stage of the protocol will be reported, including those who complete successful ABPM, with reasons for failed testing where appropriate. Recruitment and study completion figures will be reported using a participant flow diagram. Interpretation of the ABPM result will be performed by researchers who are blind to the participant's index blood pressure test.

Index Test Performance

Diagnostic performance of in-hospital blood pressure will be assessed by constructing Receiver Operator Characteristic (ROC) curves from participants' in-hospital mean systolic and mean diastolic blood pressure (index test) versus diagnosis of hypertension determined by mean daytime ABPM (reference test). At first instance a complete case analysis will be performed by excluding patients without an observed test result. At the second instance, for patients with missing ABPM values, the data will be imputed. The two approaches will be compared and the number of cases with missing values will be reported, together with detailed description of the strategy for handling the missing data. The Area Under the Receiver Operator Curve (AUROC) will be calculated to estimate the discriminatory power of the diagnostic test.[30] Potential diagnostic blood pressure thresholds will

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then be identified from the ROC curve.[30,31] The diagnostic ability of each potential cut-off threshold will be evaluated using two-by-two tables[31] to compare sensitivity and specificity of each potential threshold. Confidence intervals will be reported for each value. Reproducibility of the index test and variability in diagnostic accuracy will be analysed using subsequent available periods of the hospital admission in which participants' mean in-hospital blood pressure values were at or above the recruitment threshold.

Subgroup Analyses

Logistic regression analyses will be performed to estimate whether the diagnostic performance of in-hospital mean blood pressure is influenced by participant baseline characteristics, including age, sex body mass index and comorbidity. Further subgroup analyses will include whether the index admission was scheduled or unscheduled and whether the admitting specialty was medical or surgical.

Additional analyses

Once the optimal thresholds for the in-hospital screening for hypertension have been identified, diagnostic accuracy of the thresholds at successive 24-hour intervals of patient admission will be estimated. Whilst the reference test for this study is based on the current UK diagnostic criteria for the diagnosis of hypertension, additional analyses will be performed using the European and American diagnostic thresholds for hypertension as shown in table 3.[6,7]

ABPM diagnostic thresholds for hypertension	European Society of Cardiology/European Society of Hypertension		American College of Cardiology	
	Systolic	Diastolic	Systolic	Diastolic
24-hour	130	80	125	75
Night	120	70	110	65
Day	135	85	130	80

Table 3, European Society of Cardiology/European Society of Hypertension[6] *and American College of Cardiology*[7] *diagnostic thresholds for hypertension.*

ETHICS AND DISSEMINATION

Ethics

This study (Protocol Version 1.7) has been given ethical approval from the NHS Health Research Authority South Central – Oxford B Research Ethics Committee (19/SC/0026). Any planned protocol modifications will receive further sponsor and ethical review and require approval prior to implementation. Any approved modifications will be communicated in the ISRCTN Registry where the

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study is registered. All participants will be required to give informed, written consent and will be advised that they can withdraw from the study at any time and without giving reason. Consent will be obtained by a trained clinical researcher.

We do not anticipate any harms from the use of ABPM, which is already a standard procedure for the diagnosis of hypertension in UK primary care and therefore this study does not carry any significant risk to participants. The measurement of ambulatory blood pressure among the participants of this study is in addition to usual care and may be considered beneficial if we detect the presence of undiagnosed hypertension earlier than may have otherwise been the case. If at any point a participant is found to have severely raised blood pressure, their responsible hospital care team or General Practitioner will be informed, following study Standard Operating Procedures, according to whether severely elevated blood pressure was observed in the hospital or community, respectively. Any adverse events which arise as a result of performing ABPM will be reported. The participant and their General Practitioner will both be informed of the ABPM result and any decision to initiate treatment will be made between the patient and their General Practitioner in line with standard care.

Data will be analysed by researchers based in the University of Oxford (Nuffield Department of Clinical Neurosciences, Nuffield Department of Primary Care Health Sciences and Institute of Biomedical Engineering).

Dissemination

Findings from this study will be disseminated through peer-reviewed journals, conferences, public engagement activities and online. Participants will be able to access results online.

Discussion

The SHINE study will be the first study to our knowledge, to evaluate the diagnostic accuracy of in-hospital blood pressure measurements on a continuous scale and therefore identify the optimal blood pressure cut-off values for in-hospital hypertension screening. In addition this will be the first study to our knowledge, which uses real-time electronic algorithms to screen hospital inpatients' electronic blood pressure data. The automated detection and subsequent treatment of previously undiagnosed hypertension has the potential to prevent the development of serious hypertension-related diseases.

The study is limited by uncertainty in the expected prevalence of hypertension at follow up, which has been used to estimate the required sample size.

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Author Contributions: PJW is the principal investigator. LCA, PJW, AJF, AM and LT made substantial contributions to the conception and design of the project. BL has contributed significantly to protocol development. TF provided advice on statistical methodology. All authors contributed to and revised the final manuscript.

Competing Interests

None declared.

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Figure Legends

Figure 1. Participant Timeline

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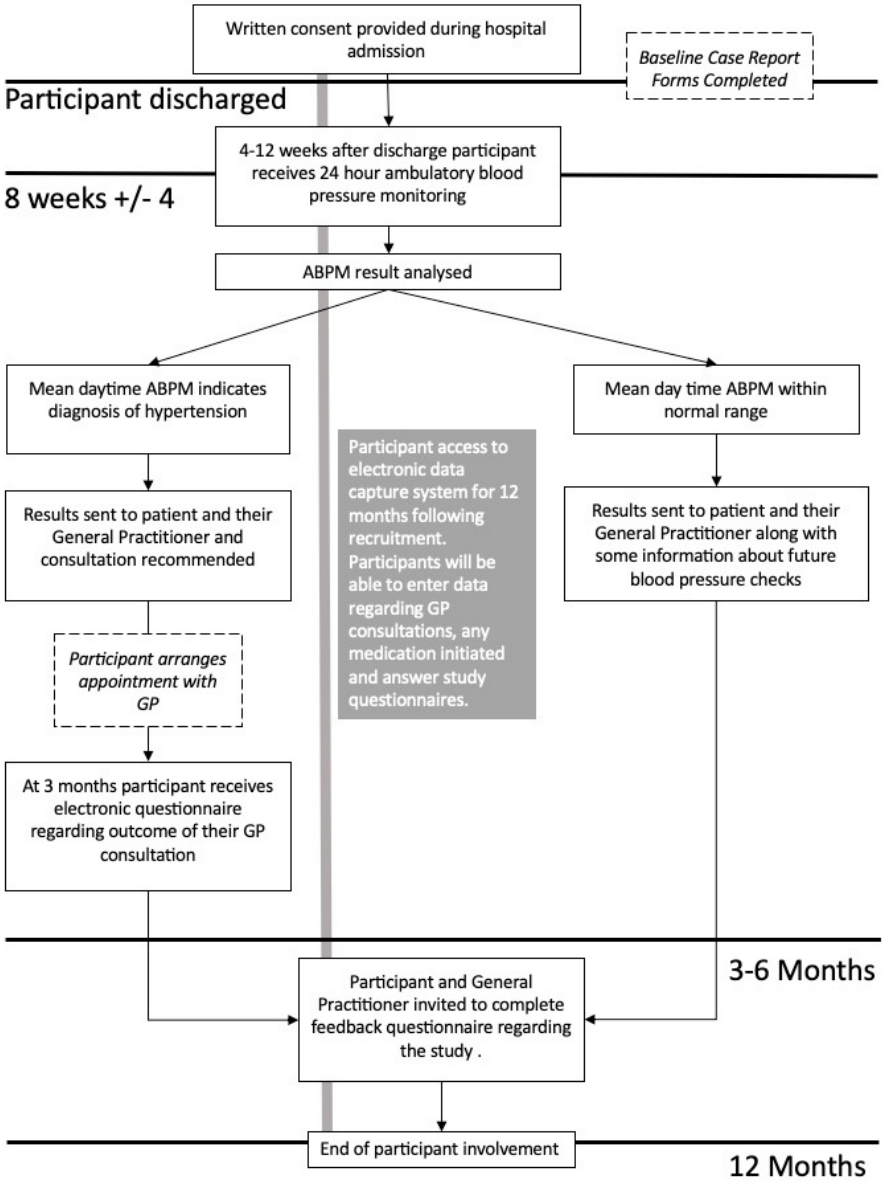

Figure 1. Participant Timeline

240x319mm (72 x 72 DPI)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	4
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
Participants	**6**	Eligibility criteria	5-6
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	6
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5
	9	Whether participants formed a consecutive, random or convenience series	6
Test methods	**10a**	Index test, in sufficient detail to allow replication	7
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	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	6
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OTHER INFORMATION			
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STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

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BMJ Open

Screening for Hypertension in the INpatient Environment (SHINE): A protocol for a Prospective Study of Diagnostic Accuracy among adult hospital patients

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ABSTRACT

Introduction

A significant percentage of patients admitted to hospital have undiagnosed hypertension. However, present hypertension guidelines in the UK, Europe and USA do not define a blood pressure threshold at which hospital inpatients should be considered at risk of hypertension, outside of the emergency setting. The objective of this study is to identify the optimal in-hospital mean blood pressure threshold, above which patients should receive post-discharge blood pressure assessment in the community.

Methods and Analysis

SHINE is a prospective diagnostic accuracy study. Patients admitted to hospital whose mean average daytime blood pressure after 24 hours or longer meets the study eligibility threshold for mean daytime blood pressure (≥120/70mmHg) and who have no prior diagnosis of, or medication for hypertension will be eligible. At 8 weeks post-discharge, recruited participants will wear an ambulatory blood pressure monitor for 24 hours. Mean daytime ambulatory blood pressure will be calculated to assess for the presence or absence of hypertension. Diagnostic performance of in-hospital blood pressure will be assessed by constructing Receiver Operator Characteristic (ROC) curves from participants' in-hospital mean systolic and mean diastolic blood pressure (index test) versus diagnosis of hypertension determined by mean daytime ambulatory blood pressure (reference test).

Ethics and Dissemination

Ethical approval has been provided by the NHS Health Research Authority South Central – Oxford B Research Ethics Committee (19/SC/0026). Findings will be disseminated through national and international conferences, peer-reviewed journals and social media.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study to our knowledge to evaluate the diagnostic accuracy of a range of in-hospital blood pressure thresholds to identify the optimal blood pressure cut-off values for in-hospital hypertension screening.
- This is also the first study to our knowledge, to use real-time algorithms to screen hospital inpatients' electronic blood pressure data.

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- Owing to the novel design of this study, the expected prevalence of hypertension at follow up is unknown and has therefore been estimated to calculate the sample size.

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INTRODUCTION

Hypertension is the leading risk factor for death globally[1] with 12.8% of annual mortality attributable to hypertension.[2] A significant percentage of patients admitted to hospital have undiagnosed hypertension.[3,4] However, unless a person has severely elevated blood pressure, the clinical diagnosis of hypertension cannot be made in the in-hospital setting based on the UK, European or American Guidelines.[5–7] Indeed, increased blood pressure values in hospital are frequently dismissed and additional potential reasons for this include clinicians attributing increased blood pressure values to anxiety,[8] pain[9] or white coat hypertension.[10] However, evidence suggests that patients with elevated blood pressure recordings in hospital frequently remain hypertensive in the community.[11–17] Despite this, referral for community follow-up of these patients to determine the presence or absence of persistent hypertension is poor.[18–21]

Untreated hypertension is associated with a progressive increase in blood pressure that can become treatment resistant.[22] Therefore, hospital detection and subsequent management of hypertension offer an important intervention opportunity to address this major cause of morbidity and mortality.

In 2015, Oxford University Hospitals NHS Foundation Trust (OUHFT) introduced the NIHR-funded System for Electronic Notification and Documentation (SEND).[23] SEND is a tailored software application which links hospital bedside monitoring devices including blood pressure monitors, with a tablet computer for the manual recording of vital-sign observations of patients.[24] Since this implementation, clinicians and researchers have been able to access and analyse patient observation data at a population as well as individual level. SEND has been used to record the vital-sign observations of more than 200,000 patients so far and to link each patient's observations with their Electronic Patient Record (EPR).[24] This has paved the way for real-time and automated recognition of patients whose observations indicate they may be at increased risk of undiagnosed hypertension.

The objective of this study is to identify the optimal in-hospital mean blood pressure threshold, above which patients should receive post-discharge blood pressure assessment in the community.

METHODS AND ANALYSIS

We prepared this protocol following the STARD[25] guidelines.

Patient and Public Involvement

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The design of this study has been reviewed and supported by patient and public representatives who have provided input on the research questions, data analysis, informational material for public engagement and the burden of the follow-up diagnostic testing from a patient's perspective. Their input led to additional steps in data analysis, refining of the informational material and modification of the follow-up plan to reduce patient burden.

Study Design

This is a UK single-centre, prospective cohort diagnostic accuracy study. The study is due to commence in November 2019 and active follow-up will continue until January 2022.

Study Setting

Recruitment for this study will take place in Oxford University Hospitals NHS Foundation Trust, UK. Participants will be followed up in a community research clinic at 8 weeks (+/-4) following discharge from hospital to receive reference blood pressure testing. Participant timeline is shown in Figure 1.

Study Population

We will recruit participants aged between 18 and 80 years, who have at least two blood pressure measurements taken during daytime hours defined as 07:00:00 to 21:59:59[26] and at least one blood pressure measurement taken during night time hours (22:00:00 to 06:59:59). To be eligible a patient's cumulative mean daytime systolic blood pressure must be between 120mmHg and 179mmmHg and cumulative mean daytime diastolic blood pressure ≤109mmHg for any given 24-hour interval since their admission to hospitalfollowing the first 24 hours of their admission (index test) - see TEST METHODS below for more details. The mean daytime blood pressure calculation must be based on a minimum of two blood pressure measurements made during day time hours. No lower eligibility threshold was set for the diastolic blood pressure in order that patients with isolated systolic hypertension would not be excluded. Patients with an ICD10 code for hypertension or blood pressure lowering medication prescribed in their medication record will be excluded. Additional exclusion criteria include current, intended or recent pregnancy, cause for index admission being associated with end-organ damage related to severe hypertension (including but not limited to heart failure, myocardial infarction, stroke, hypertensive encephalopathy) and estimated glomerular infiltration rate of <30 ml/min. Full inclusion and exclusion criteria are provided in Table 1.

Inclusion Criteria **Exclusion criteria**

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Aged 18-80	Pre-existing diagnosis of hypertension or attending hospital with acute end-organ damage related to severe, undiagnosed hypertension.
Admitted to hospital for an acute or elective medical or surgical condition	Presence of atrial fibrillation or other pulse rate irregularity which means ABPM is not appropriate.
Have at least three in-hospital blood pressure recordings with two performed during day time hours and 1 performed during night time hours, over a minimum of 24 hours for the index admission.	Currently pregnant, within 3 months post-partum or planning pregnancy during study period.
Identified by the blood pressure algorithm for any 24-hour interval to have a mean blood pressure which meets the eligibility thresholds.	Receiving treatments which might be used for the management of hypertension, e.g. beta blockers for migraine, angiotensin-converting-enzyme inhibitors for renal disease.
Registered with a General Practitioner.	Diagnosed with terminal illness or cognitive impairment.
	Diagnosed with AKI on index admission or eGFR <30ml/min.
	Cause for hypertension being toxicology, medical or recreational e.g amphetamines and their derivatives or alcohol withdrawal syndrome.
	Post-discharge destination being another hospital or prison.
	Receiving concomitant chemotherapy.
	Already recruited to a separate hypertension study.

Table 1. Full inclusion and exclusion criteria

ABPM = ambulatory blood pressure monitoring, AKI = acute kidney injury,

Screening procedure

The identification of patients whose blood pressure exceeds the index test threshold will be automated using live, computerised algorithms. Blood pressure measurements in the Oxford University Hospitals NHS Foundation Trust are made using automated oscillometric devices and the BP monitor readings (systolic and diastolic) are entered manually using the SEND computer tablet before automated transfer to the electronic patient record (EPR) by the SEND software app.[23] The identification of patients whose blood pressure measurements meet eligibility criteria will be computerised and automated. These automated systems for blood pressure documentation and

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evaluating study inclusion criteria are intended to ensure that the measurement of the index test is objective and thus the clinical staff who perform the blood pressure measurements can be considered blinded in the assessment of the index test. As this study is prospective in design they will not be aware of the result of the reference standard.

Participant sampling

Sampling will be stratified to ensure that there is representation of patients with a full range of in-hospital blood pressure profiles (according to pre-defined mean daytime systolic blood pressure, Table 2). Patients who are considered eligible according to the screening algorithm will be approached by a clinical researcher who will undertake a further screen of patient eligibility. Patients who are in significant or uncontrolled pain will not be recruited unless and until, their pain improves. Pain scales will be collected at baseline for all recruited participants. Where there is insufficient study resource to enrol all recruitable patients, priority will be given to the strata with the least recruited patients. Recruitment will continue until the target recruitment number within each of the blood pressure intervals is achieved. The prevalence of each systolic blood pressure interval among the hospital population will be recorded within a screening log during the study period.

Systolic blood pressure Interval	Target recruitment number
120-129	Approximately equal representation of participants recruited to each of these systolic blood pressure intervals
130-139	
140-149	
150-159	
160-179	
TOTAL	**200**

Table 2. Systolic blood pressure intervals against which recruitment will be stratified

Data Collection

Baseline data collection will be performed at the point of recruitment during the hospital admission, after the participant has provided informed, written consent. Custom-made baseline case report forms (CRFs) will be completed in the study data capture system for each participant by an appropriately qualified clinical researcher. The study data capture system will be electronic and accessible online. using a combination of data extracted from the EPR (e.g. diagnostic codes, current medications, serum haematology and biochemistry results and electrocardiogram) and participant self-report (e.g. ethnicity family history, previous prescribed medications for hypertension). Any

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extreme values entered into the electronic data capture system will be inspected. A data monitoring committee has not been convened since there is no concealed allocation to treatment in this cohort study. Frequency and procedures for auditing study conduct are determined by the study sponsor (University of Oxford) based on a proportionate approach to risks.

TEST METHODS

Index Diagnostic Test

The index test will be the first occurrence during the hospital stay of a cumulative mean daytime in-hospital blood pressure reading ≥135mmHg systolic or ≥85mmHg diastolic. The systolic blood pressure eligibility threshold has been defined as 10mmHg below the index test threshold to understand the frequency of true and false negatives in order to calculate sensitivity and specificity of the diagnostic test.

Blood pressure measurements from the point of admission to the time of assessment by the algorithm (every 24 hours at mifnight until day 10 of the admission or discharge, whichever occurred first) will be averaged to reduce the chances of a person becoming eligible by chance when compared to the alternative, of assessing a person's eligibility based on their mean day time blood pressure for any 24-hour interval. Thus, for each patient at each time of assessment, we will compute the cumuulative mean BP value using all the available daytime (7:00:00-21:59:59) BP readings. The cumulative mean is defined here to be the mean of the mean daytime BP values, the latter being calculated for each of the dats between the point of admission and the time of assessment. As the first occurrence of the test being passed is a necessary and sufficient condition, a patient will be recruited into the study even if their cumulative mean at discharge is below the indext test thresholds (≥135mmHg systolic or ≥85mmHg diastolic).

A day time definition was chosen as this study is being performed in a UK healthcare setting, where at present, night time measurements are not used the diagnosis of hypertension.[27] The index test has been defined according to the UK NICE Guideline definition of daytime hypertension.[27]

Additionally, a subgroup of participants will receive a research standard blood pressure assessment in hospital, performed according to the standard recommended by the UK NICE Guidelines.[27] The blood pressure will be measured using a validated and calibrated oscillometric device by a trained

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clinical researcher. Blood pressure will be measured with the patient seated and the arm outstretched and supported. Blood pressure will be measured in both arms and if a between-arm difference of ≥15mmgHg is found both measurements will be repeated. Where a difference persists, the arm with the highest measurement will be used for subsequent measurements. Two measurements will be taken in the selected arm; if the second measurement is substantially different from the first then a third measurement will be taken and the lowest of the second and third measurements will be recorded.

Reference Standard Diagnostic Test

The gold standard diagnostic test for the presence of hypertension will be a daytime 24-hour ambulatory blood pressure threshold of ≥135mmHg systolic or ≥85mmHg diastolic, which is the current UK National Institute for Health and Care Excellence (NICE) diagnostic threshold for Ambulatory Blood Pressure Monitoring (ABPM).[5]

ABPM will be performed with each participant at 8 weeks (+/-4) following discharge from hospital using a validated automated Mobil-O-Graph ambulatory blood pressure monitor (IEM GmbH, Stolberg, Germany), calibrated to manufacturer standards. Should the participant have acquired a diagnosis of hypertension and initiated treatment for hypertension following hospital discharge but before they receive ABPM, they will not be eligible to proceed with ABPM. In this instance a participant will be regarded as being reference test positive, having acquired a clinical diagnosis of hypertension. The monitor will be programmed to measure blood pressure twice per hour during waking hours for (07:00 to 22:00), and once per hour during the sleeping hours (22:00 to 07:00) for a period of 24 hours, according to the British and Irish Hypertension Society (BIHS) Standard Operating Procedure for performing ABPM.[26] Adjustments will be made for example, where a participant will be working a shift pattern during the period of wear. All participants will be asked to log their sleeping and waking times in an ABPM diary and these will be used to analyse the ABPM results. According to the BIHS Standard Operating Procedure for ABPM, minimum of 14 waking time ABPM measurements must be successful in order to calculate the mean daytime blood pressure. Where fewer than 14 of the waking time ABPM measurements are successful, the participant will be asked to wear the monitor for a further period in order to collect adequate data. In the instance of two episodes of ABPM not collecting sufficient data, the participant and their registered General Practitioner (GP) will be informed along with recommendation that the participant arrange an appointment with their GP for further evaluation of their blood pressure. The participant will continue to be followed up remotely through the online data capture system for up to 52 weeks from recruitment (Figure 1). Links to the

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questionnaires will be sent to participants by email and we will collect data regarding blood pressure related health outcomes, the prescription of antihypertensive medications and repeat blood pressure measurements. At ten years, data will be obtained from the Office of National Statistics and Hospital Episode Statistics Databases regarding mortality and cardiovascular health related outcomes.

The fitting and removal of the ambulatory blood pressure monitor will be performed by a qualified clinical research nurse who is appropriately trained in the National Institute for Health's Good Clinical Practice and to perform ABPM. At the time of removal of the monitor, the electronic ABPM report will be downloaded to the study data capture system and interpreted by the research nurse. As the reference test procedure is objective through the use of an oscillometric, automated ABPM, the research nurse will not be blinded to the result of the index blood pressure test.

The same subgroup of 50 participants who received a standardised research blood pressure assessment in hospital will receive a standardised research clinic blood pressure upon ABPM fitting. The procedure for measuring and recording the blood pressure will be exactly the same as described for the hospital setting, according to that recommended by the UK NICE Guidelines.[27]

STATISTICAL METHODS

Sample size

Owing to the novel design of this study, estimates of expected prevalence of hypertension at follow-up have been used to calculate sample size. From a retrospective analysis of in-hospital OUHFT blood pressure data, we estimate that 3000 patients per annum will be eligible for study inclusion (Mahdi, A, 2019; Prevalence of hypertension and undiagnosed hypertension in a large inpatient population). Previous studies have used an in-hospital blood pressure eligibility threshold (140/90mmHg) and revealed approximately that half of the patients with a blood pressure above the threshold have hypertension at follow-up.[28,29] A lower rate of hypertension at follow-up is expected in this study owing to the lower eligibility blood pressure threshold of 120/70mmHg; a sample size of 200 has been derived to permit detection of a 20% rate of hypertension at follow-up with a 95% confidence interval width of approximately of ±5.36%. Screening logs will be recorded for both the algorithm and the manual screening process to understand the prevalence of patients falling in each of the in-hospital blood pressure intervals against which recruitment will be stratified.

Baseline characteristics

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Clinical and demographic characteristics of the study population will be reported, including age, sex, presenting complaint, comorbidity, current treatments (including oral steroidal and non-steroidal anti-inflammatory medications), pain score (using an 11-point Likert scale where 0= no pain and 10 = maximum possible pain) for the preceding 24 hours to recruitment and the Six-Item State Anxiety Scale.[30] The number of participants who complete each stage of the protocol will be reported, including those who complete successful ABPM, with reasons for failed testing where appropriate. Recruitment and study completion figures will be reported using a participant flow diagram. Interpretation of the ABPM result will be performed by researchers who are blind to the participant's index blood pressure test.

Index Test Performance

Diagnostic performance of in-hospital blood pressure will be assessed by constructing Receiver Operator Characteristic (ROC) curves from participants' in-hospital mean systolic or mean diastolic blood pressure (index test) versus diagnosis of hypertension determined by mean daytime ambulatory systolic and diastolic blood pressure (reference test). At first instance a complete case analysis will be performed by excluding participants without an observed test result. At the second instance, for participants with missing ABPM values, the data will be imputed. The two approaches will be compared and the number of cases with missing values will be reported, together with detailed description of the strategy for handling the missing data. The Area Under the Receiver Operator Curve (AUROC) will be calculated to estimate the discriminatory power of the diagnostic test.[31] Potential diagnostic blood pressure thresholds will then be identified from the ROC curve.[31,32] The diagnostic ability of each potential cut-off threshold will be evaluated using two-by-two tables[32] to compare sensitivity and specificity of each potential threshold. Confidence intervals will be reported for each value. Reproducibility of the index test and variability in diagnostic accuracy will be analysed using subsequent available periods of the hospital admission in which participants' mean in-hospital blood pressure values were at or above the recruitment threshold.

Subgroup Analyses

Logistic regression analyses will be performed to estimate whether the diagnostic performance of in-hospital mean blood pressure is influenced by participant baseline characteristics, including age, sex body mass index and comorbidity, pain, anxiety and in-hospital prescriptions such as oral steroid medications and non-steroidal anti-inflammatory medications. Further subgroup analyses will include whether the index admission was scheduled or unscheduled and whether the admitting specialty was medical or surgical.

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Additional analyses

Once the optimal thresholds for the in-hospital screening for hypertension have been identified, diagnostic accuracy of the thresholds at successive 24-hour intervals of patient admission will be estimated. Whilst the reference test for this study is based on the current UK diagnostic criteria for the diagnosis of hypertension which concerns daytime blood pressure measurements only, there is increasing evidence in the literature to support the association between nocturnal hypertension and cardiovascular risk.[33,34] Therefore, additional analyses will be performed incorporating night time measurements and using the European and American diagnostic thresholds for hypertension as shown in table 3.[6,7]

ABPM diagnostic thresholds for hypertension	European Society of Cardiology/European Society of Hypertension		American College of Cardiology	
	Systolic	Diastolic	Systolic	Diastolic
24-hour	130	80	125	75
Night	120	70	110	65
Day	135	85	130	80

Table 3, European Society of Cardiology/European Society of Hypertension[6] *and American College of Cardiology*[7] *diagnostic thresholds for hypertension.*

ETHICS AND DISSEMINATION

Ethics

This study (Protocol Version 1.7) has been given ethical approval from the NHS Health Research Authority South Central – Oxford B Research Ethics Committee (19/SC/0026). Any planned protocol modifications will receive further sponsor and ethical review and require approval prior to implementation. Any approved modifications will be communicated in the ISRCTN Registry where the study is registered. All participants will be required to give informed, written consent and will be advised that they can withdraw from the study at any time and without giving reason. Consent will be obtained by a trained clinical researcher.

We do not anticipate any harms from the use of ABPM, which is already a standard procedure for the diagnosis of hypertension in UK primary care and therefore this study does not carry any significant risk to participants. The measurement of ambulatory blood pressure among the participants of this study is in addition to usual care and may be considered beneficial if we detect the presence of undiagnosed hypertension earlier than may have otherwise been the case. If at any point a participant

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is found to have severely raised blood pressure, their responsible hospital care team or General Practitioner will be informed, following study Standard Operating Procedures, according to whether severely elevated blood pressure was observed in the hospital or community, respectively. Any adverse events which arise as a result of performing ABPM will be reported. The participant and their General Practitioner will both be informed of the ABPM result and any decision to initiate treatment will be made between the patient and their General Practitioner in line with standard care.

Data will be analysed by researchers based in the University of Oxford (Nuffield Department of Clinical Neurosciences, Nuffield Department of Primary Care Health Sciences and Institute of Biomedical Engineering).

Dissemination

Findings from this study will be disseminated through peer-reviewed journals, conferences, public engagement activities and online. Participants will be able to access results online.

Discussion

The SHINE study will be the first study to our knowledge, to evaluate the diagnostic accuracy of in-hospital blood pressure measurements on a continuous scale and therefore identify the optimal blood pressure cut-off values for in-hospital hypertension screening. A recent systematic review indicates this will be the first study to use real-time algorithms to screen hospital inpatients' electronic blood pressure data.[17] The automated detection and subsequent treatment of previously undiagnosed hypertension has the potential to prevent the development of serious hypertension-related diseases.

The study is limited by uncertainty in the expected prevalence of hypertension at follow-up, which has been used to estimate the required sample size.

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Author Contributions

PJW is the principal investigator. LCA, PJW, AJF, AM, CR and LT made substantial contributions to the conception and design of the project. BL has contributed significantly to protocol development. TF provided advice on statistical methodology. All authors contributed to and revised the final manuscript.

Data sharing

Data will be made available as appropriate following review of the research proposal by the Kadoorie Centre for Critical Care Research and Eduction data access committee.

Competing Interests

PW and LT are the Chief Medical Officer and R&D Director for Sensyne Health and hold share options in the company. Their University departments receive research funding from Sensyne Health.

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Figure Legends

Figure 1. Participant Timeline

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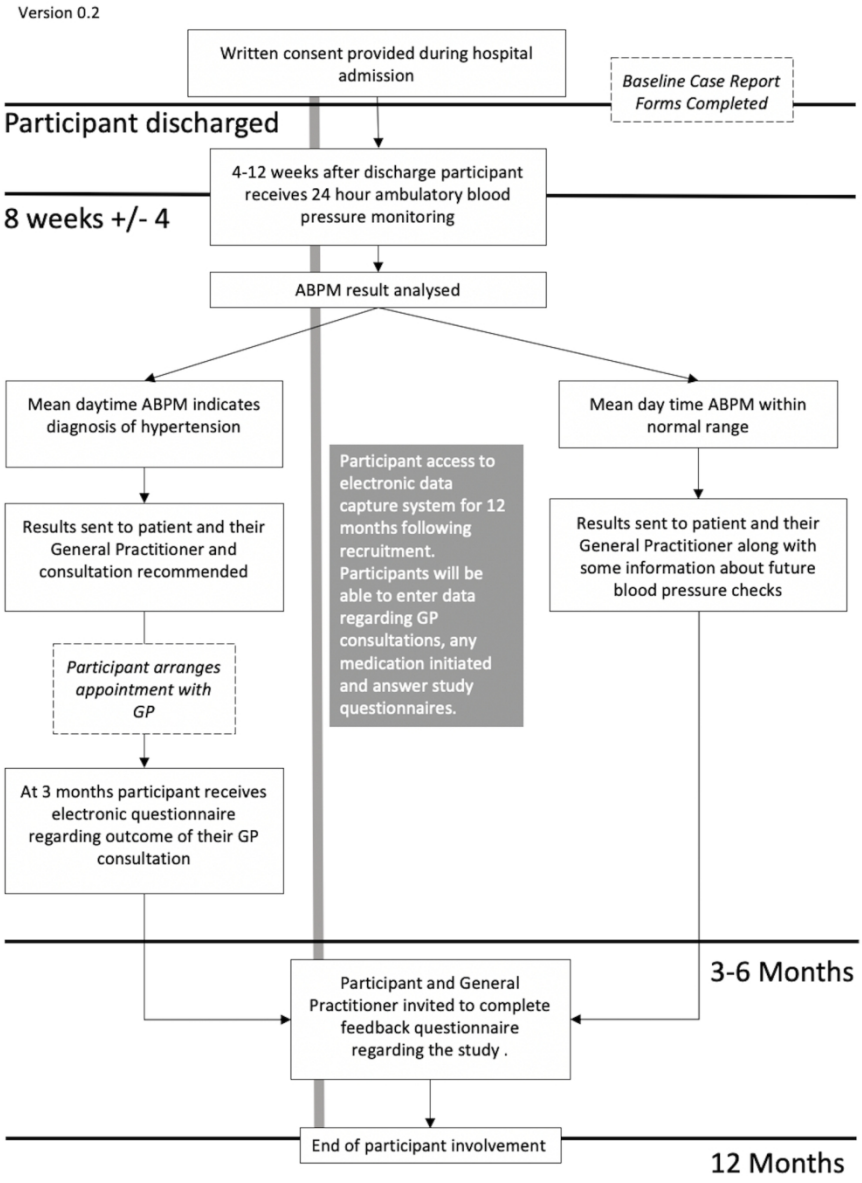

Figure 1. Participant Flow.

140x183mm (300 x 300 DPI)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	4
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
Participants	**6**	Eligibility criteria	5-6
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	6
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5
	9	Whether participants formed a consecutive, random or convenience series	6
Test methods	**10a**	Index test, in sufficient detail to allow replication	7
	10b	Reference standard, in sufficient detail to allow replication	7-8
	11	Rationale for choosing the reference standard (if alternatives exist)	8
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	7 and 10
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	8 and 10
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	6
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	8
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	9-10
	15	How indeterminate index test or reference standard results were handled	8
	16	How missing data on the index test and reference standard were handled	9-10
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	10
	18	Intended sample size and how it was determined	9
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Consort diagram not yet available as study protocol, but participant timeline available in figure 1.
	20	Baseline demographic and clinical characteristics of participants	9
	21a	Distribution of severity of disease in those with the target condition	9
	21b	Distribution of alternative diagnoses in those without the target condition	n/a
	22	Time interval and any clinical interventions between index test and reference standard	7
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	9
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	9
	25	Any adverse events from performing the index test or the reference standard	11
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	n/a
	27	Implications for practice, including the intended use and clinical role of the index test	10

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OTHER INFORMATION			
	28	Registration number and name of registry	n/a: in progress
	29	Where the full study protocol can be accessed	n/a: in progress
	30	Sources of funding and other support; role of funders	10

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STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

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