PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Screening for Hypertension in the INpatient Environment (SHINE): A protocol for a Prospective Study of Diagnostic Accuracy among adult hospital patients
AUTHORS	Armitage, Laura Catherine; Mahdi, Adam; Lawson, Beth K; Roman, Cristian; Fanshawe, Thomas; Tarassenko, Lionel; Farmer, Andrew; Watkinson, Peter J

VERSION 1 – REVIEW

REVIEWER	ALEJANDRO DE LA SIERRA UNIVERSITY OF BARCELONA HOSPITAL MUTUA TERRASSA SPAIN
REVIEW RETURNED	01-Sep-2019

GENERAL COMMENTS	1. Study population (page 5): Inclusion requires at least 3 BP values, only one required during daytime hours. Theoretically 2 night BP values and only 1 day BP value would be the basis for the comparison with mean daytime ABPM. 2. Study population (page 5) and reference standard diagnostic test (page 8): Daytime hours are different (10:00 to 20:00 for index test and 07:00 to 22:00 for reference test). 3. Exclusion criteria (pages 5 and 6): In addition to antihypertensive drugs, some receive BP-modifying drugs for a certain period of time (i.e. corticosteroids for COPD). This could theoretically increase BP values both during hospital stay and at the time of the ABPM. 4. Participant sampling (page 6, bottom): Stratification of sampling based on pre-dedined mean daytime SBP???. Is it a mistake?. Should it read mean in-hospital BP? 5. Reference standard diagnostic test (page 8): Definition of daytime BP is based on a fixed window. Needs to assure that all patients will be awake at these hours. Why don't using a custom window?. Mobil-O-Graph allows to customize periods based on patient's information. 6. Reference standard diagnostic test (page 8): Using a fixed daytime period makes unnecessary the prolongation of the ABPM procedure during the night. Night BP is not required for the study and nothing is written about a specific analysis based on night BP.

REVIEWER	Maxime Lamarre-Cliché University of Montreal Institut de Recherches Cliniques de Montréal
REVIEW RETURNED	23-Sep-2019

GENERAL COMMENTS	The SHINE protocol focuses on a very pertinent topic. Hospital blood pressure measurements are commonly used to diagnose and manage hypertension yet they have never been validated. The proposed study will attempt to link hospital blood pressure measurements to ABPM, an accepted gold standard. I have a few comments and, I hope, constructive criticism that could improve the study design. Why are the authors using daytime blood pressure as their diagnostic standard? 24 hour blood pressure being available, it would be pertinent to include nighttime measurements as they have been shown to be strongly associated to cardiovascular risk. Also using a full 24 hour schedule obviates the difficulties of defining when day and night start and end. The authors should probably not include patients in significant and uncontrolled pain. Standardized research grade blood pressure measurements should be performed in-hospital and at 8 weeks. Hospital blood pressure measurements are not standardized and they overestimate true blood pressure. The addition of a well performed measurements is not essential to this study but it is not much added work and it will greatly help the investigators understand their results. A discordance? When explaining the index diagnostic test, I noticed a threshold of 130/80. An eligibility criteria of 120/70 was stated otherwise in the protocol. I am not sur I understand how the hospital blood pressure will be estimated. How many days? Simple average? Weighted averages? Will some outlier measurements be excluded (e.g. a serie of 5 very high BP measurements over a panic attack)? Maybe an example would help. Reference Standard Diagnostic test. I suggest the investigators set their ABPM schedule to 30 minute intervals day and night as is usually recommended. In the statistical methods. I suggest the investigators keep track of their screening process and include in their publication the number of screens.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: ALEJANDRO DE LA SIERRA
Institution and Country:
UNIVERSITY OF BARCELONA
HOSPITAL MUTUA TERRASSA
SPAIN
Please state any competing interests or state ‘None declared’: NONE DECLARED

Please leave your comments for the authors below
Reviewer comment 1. Study population (page 5): Inclusion requires at least 3 BP values, only one required during daytime hours. Theoretically 2 night BP values and only 1 day BP value would be the basis for the comparison with mean daytime ABPM.

Response: Thank you, this is an important point for consideration. We have clarified our inclusion criteria to be at least 3 BP values, to include a minimum of 1 night time BP value and 2 day time BP values. This has now been clarified in the manuscript under the Methods and Analysis Subheading of ‘Study Population’.

Reviewer comment 2. Study population (page 5) and reference standard diagnostic test (page 8): Daytime hours are different (10:00 to 20:00 for index test and 07:00 to 22:00 for reference test).

Response: Thank you, we have changed the hospital day time hours to match those of the reference test and have updated the manuscript accordingly. Of note, the day time hours for the reference test will be adjusted on a per-participant basis to account for their logged sleep and wake times in their ambulatory blood pressure diary. We have now added this detail under the Test Methods subheading of 'Reference Standard Diagnostic Test'.

Reviewer comment 3. Exclusion criteria (pages 5 and 6): In addition to antihypertensive drugs, some receive BP-modifying drugs for a certain period of time (i.e. corticosteroids for COPD). This could theoretically increase BP values both during hospital stay and at the time of the ABPM.

Response: Thank you. We agree this is important; we will be collecting data on in-hospital prescriptions and all medications taken during the ABPM including corticosteroids and non-steroidal anti-inflammatories and will perform subgroup analyses to estimate the effect of these if possible. We have now added this detail to the manuscript under the Statistical Methods sub-headers of 'Baseline Characteristics' and 'Subgroup Analysis'.

Reviewer comment 4. Participant sampling (page 6, bottom): Stratification of sampling based on pre-dedined mean daytime SBP???. Is it a mistake?. Should it read mean in-hospital BP?

Response: Thank you for querying this; stratification will be based on mean daytime SBP as we are assessing the diagnostic performance of in-hospital daytime BP versus daytime BP measurements from the ABPM. However, patients are required to have at least 1 night time measurement in order that we can perform analyses for the diagnostic performance of night time BP also, given this is being associated increasingly with cardiovascular risk. We have now made this clearer in para 3 of the "index diagnostic test" section, p8.

Reviewer comment 5. Reference standard diagnostic test (page 8): Definition of daytime BP is based on a fixed window. Needs to assure that all patients will be awake at these hours. Why don't using a custom window?. Mobil-O-Graph allows to customize periods based on patient's information.

Response: Thank you; we will customise the window based on participant reported sleep and wake times and will also be asking them to log their sleep and wake times in an ABPM diary. We have now added this detail under the Test Methods subheading of 'Reference Standard Diagnostic Test'.

Reviewer comment 6. Reference standard diagnostic test (page 8): Using a fixed daytime period makes unnecessary the prolongation of the ABPM procedure during the night. Night BP is not required for the study and nothing is written about a specific analysis based on night BP.

Response: Thank you; we will be customising the day and night settings rather than using a fixed period and have added this detail to the manuscript. Details of the additional analyses to be performed for night time and 24 hour blood pressure are presented under the Statistical methods subheading of Additional Analyses and Table 3 and we have added further detail here. We believe it is important to collect data on night time blood pressure measurements as whilst, at present, these are not included in the assessment for blood pressure in the UK, night time measurements are taken into consideration in the rest of Europe[1] and America[2] and there is increasing literature to support the association between nocturnal hypertension and cardiovascular risk.[3,4]

Reviewer: 2
Reviewer Name: Maxime Lamarre-Cliche
Institution and Country:
University of Montreal
Institut de Recherches Cliniques de Montréal
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The SHINE protocol focuses on a very pertinent topic. Hospital blood pressure measurements are commonly used to diagnose and manage hypertension yet they have never been validated. The proposed study will attempt to link hospital blood pressure measurements to ABPM, an accepted gold standard.

Reviewer comment: I have a few comments and, I hope, constructive criticism that could improve the study design.
Why are the authors using daytime blood pressure as their diagnostic standard? 24 hour blood pressure being available, it would be pertinent to include nighttime measurements as they have been shown to be strongly associated to cardiovascular risk. Also using a full 24 hour schedule obviates the difficulties of defining when day and night start and end.

Response: Thank you very much for your helpful feedback and suggestions. We agree this is important and will perform analyses utilising the night time blood pressure data to evaluate the diagnostic performance of the index blood pressure threshold when international diagnostic thresholds for 24 hour ABPM are utilised. According to UK NICE Guidelines[5] at present however, only day time ABPM measurement are taken into consideration when making a diagnostic assessment and so as we are recruiting patients from a UK hospital setting we will conform to these guidelines for the reference test. We have made this clearer in the manuscript under the Test Methods subheading 'Index Diagnostic Test'.

Reviewer comment: The authors should probably not include patients in significant and uncontrolled pain.

Response: Thank you. Following identification of potential eligibility by the screening algorithm, patients will then be screened by a clinician researcher. Patients in significant and uncontrolled pain will not be considered suitable for approach. However, if their pain improves and they remain eligible for the study they will be approached at a later stage, as appropriate, during their hospital stay. In addition, Pain scales will be collected for all recruited participants We have now added this clarity to the manuscript under the Methods and Analysis subheading of 'Participant Sampling'.

Reviewer comment: Standardized research grade blood pressure measurements should be performed in-hospital and at 8 weeks. Hospital blood pressure measurements are not standardized and they overestimate true blood pressure. The addition of a well performed measurements is not essential to this study but it is not much added work and it will greatly help the investigators understand their results.

Response: Thank you. We very much value this suggestion and we have added this to the study.

Reviewer comment: A discordance? When explaining the index diagnostic test, I noticed a threshold of 130/80. An eligibility criteria of 120/70 was stated otherwise in the protocol.

Response: Thank you for identifying that this needs further clarity. The eligibility threshold is set lower than the index diagnostic test threshold in order that we can understand the frequency of true

negatives and false negatives and hence calculate the sensitivity and specificity of the index diagnostic test. We have now made this clearer in the manuscript under the Test Methods subheading of 'Index Diagnostic Test'.

Reviewer comment: I am not sur I understand how the hospital blood pressure will be estimated. How many days? Simple average? Weighted averages? Will some outlier measurements be excluded (e.g. a serie of 5 very high BP measurements over a panic attack)? Maybe an example would help.

Response: Thank you. We will use the cumulative mean of the mean day time BP values as the index test. Thus, for each patient at each time of assessment, we will compute the cumulative mean BP value using all the available daytime (7:00:00-21:59:59) BP readings. The cumulative mean is the mean of the mean day time BP values, up to the time of each assessment (every 24 hours). This detail has now been added to the Test Methods subheading of 'Index Diagnostic Test'.

Reviewer comment: Reference Standard Diagnostic test. I suggest the investigators set their ABPM schedule to 30 minute intervals day and night as is usually recommended.

Response: Thank you. The reviewer highlights international discrepancies. However we need to adhere to the recommended frequency according to the British and Irish Hypertension Society as this work will underpin further work in our UK clinical setting.

Reviewer comment: In the statistical methods. I suggest the investigators keep track of their screening process and include in their publication the number of screens.

Response: Thank you. We agree this is very important and have made careful plans to do this. We have added a sentence to make this clear in the manuscript under the Statistical Methods subheading 'Sample size'.

FORMATTING AMENDMENTS (if any)
Required amendments will be listed here; please include these changes in your revised version:
1. Figure/s should be in better quality:
-Please ensure that figures are a minimum of 300 dpi and a maximum of 600 dpi.

Response: Thank you, we have now uploaded the figure of 300dpi.

References

1 Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. J Hypertens 2018;36:1953–2041. doi:10.1097/HJH.0000000000001940
2 Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. J Am Coll Cardiol 2018;71:e127–248. doi:10.1016/j.jacc.2017.11.006
3 Fagard RH, Thijs L, Staessen JA, et al. Night–day blood pressure ratio and dipping pattern as predictors of death and cardiovascular events in hypertension. J Hum Hypertens 2009;23:645–53. doi:10.1038/jhh.2009.9
4 Tsioufis C, Andrikou I, Thomopoulos C, et al. Increased nighttime blood pressure or nondipping profile for prediction of cardiovascular outcomes. J Hum Hypertens 2011;25:281–93. doi:10.1038/jhh.2010.113
5 National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. NICE 2019. https://www.nice.org.uk/guidance/ng136 (accessed 16 Oct 2019).

VERSION 2 – REVIEW

REVIEWER	Alejandro de la Sierra Hospital Mutua Terrassa. University of Barcelona. Spain
REVIEW RETURNED	07-Nov-2019

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.