**Study Title:**  Reverse dipping in blood pressure and its impact on screening for hypertension in the clinic

**Internal Reference Number / Short title:** Impact of daily blood pressure patterns on detecting hypertension

**MS IDREC Ref:** R77097/RE001

**Date and Version No:** 16th July 2021, Version 1.0

|  |  |
| --- | --- |
| **Principal Investigator:** | Professor Lionel Tarassenko,Institute of Biomedical Engineering, Department of Engineering Science |
| **Investigators:**  | Doctor Shaun Davidson,Institute of Biomedical Engineering,Department of Engineering Science |
| **Sponsor:**  | University of Oxford |
| **Funder:** | National Institute for Health Research (NIHR) |
| **Principal Investigator Signature:**  |  |

There are no potential conflicts of interest to declare.

**Confidentiality Statement**

This document contains confidential information that must not be disclosed to anyone other than the authorised individuals from the University of Oxford, the Investigator Team and members of the Medical Sciences Interdivisional Research Ethics Committee (MS IDREC), unless authorised to do so.

**TABLE OF CONTENTS**

[1. SYNOPSIS 4](#_Toc77618322)

[2. ABBREVIATIONS 4](#_Toc77618323)

[3. BACKGROUND AND RATIONALE 5](#_Toc77618324)

[4. OBJECTIVES AND OUTCOME MEASURES 5](#_Toc77618325)

[5. STUDY DESIGN 6](#_Toc77618326)

[6. PARTICIPANT IDENTIFICATION AND RECRUITMENT 6](#_Toc77618327)

[6.1. Study Participants 6](#_Toc77618328)

[6.2. Inclusion Criteria 6](#_Toc77618329)

[6.3. Exclusion Criteria 6](#_Toc77618330)

[7. STUDY PROCEDURES 7](#_Toc77618331)

[7.1. Recruitment 7](#_Toc77618332)

[7.2. Screening and Eligibility Assessment 7](#_Toc77618333)

[7.3. Informed Consent 7](#_Toc77618334)

[7.4. First Visit 7](#_Toc77618335)

[7.5. Second Visit 8](#_Toc77618336)

[7.6. Discontinuation/Withdrawal of Participants from Study 8](#_Toc77618337)

[7.7. Definition of End of Study 8](#_Toc77618338)

[8. STATISTICS AND ANALYSIS 8](#_Toc77618339)

[8.1. The Number of Participants 8](#_Toc77618340)

[8.2. Analysis of Outcome Measures 8](#_Toc77618341)

[9. DATA MANAGEMENT 9](#_Toc77618342)

[9.1. Access to Data 9](#_Toc77618343)

[9.2. Data Handling and Record Keeping 9](#_Toc77618344)

[10. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES 9](#_Toc77618345)

[11. ETHICAL AND REGULATORY CONSIDERATIONS 9](#_Toc77618346)

[11.1. Declaration of Helsinki 9](#_Toc77618347)

[11.2. Approvals 10](#_Toc77618348)

[11.3. Participant Confidentiality 10](#_Toc77618349)

[11.4. Expenses and Benefits 10](#_Toc77618350)

[11.5. Annual Progress Report 10](#_Toc77618351)

[12. FINANCE AND INSURANCE 10](#_Toc77618352)

[12.1. Funding 10](#_Toc77618353)

[12.2. Insurance 10](#_Toc77618354)

[13. PUBLICATION POLICY 10](#_Toc77618355)

[14. REFERENCES 11](#_Toc77618356)

[15. APPENDIX A: SCHEDULE OF STUDY PROCEDURES 12](#_Toc77618357)

[16. APPENDIX B: AMENDMENT HISTORY 13](#_Toc77618358)

# SYNOPSIS

|  |  |
| --- | --- |
| **Long Study Title** | Reverse dipping in blood pressure and its impact on screening for hypertension in the clinic |
| **Short Study Title (to be used on participant-facing documents, if applicable)** | Impact of daily blood pressure patterns on detecting hypertension |
| **Internal ref. no.** | None |
| **Nature of Study Participants** | Healthy adults aged 21 – 69 years |
| **Intended number of participants** | 10 – 20 |
| **Planned Study Period** | 01 August 2021 – 31 October 2021 |
|  | **Objectives** | **Outcome Measures** |
| **Primary** | To investigate the ability of the Aktiia wrist-worn blood pressure monitoring device to capture distinct circadian BP profile phenotypes in systolic and diastolic blood pressure. | Presence of one of more of the widely recognised phenotypes in systolic blood pressure circadian pattern (i.e., `dipper’, `non-dipper’, or `reverse-dipper’ phenotypes). This assessment will be performed using a combination of classification rules in the literature and visual inspection of the averaged systolic blood pressure 24-hour profiles, averaged over the week of the study, for each participant. |

# ABBREVIATIONS

|  |  |
| --- | --- |
| ABPM | Ambulatory Blood Pressure Monitor |
| BP | Blood Pressure |
| CTRG | Clinical Trials & Research Governance, University of Oxford |
| CUREC | Central University Research Ethics Committee |
| DBP | Diastolic Blood Pressure |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| IBME | Institute of Biomedical Engineering |
| ICF | Informed Consent Form |
| MS IDREC | Medical Sciences Interdivisional Research Ethics Committee |
| PI | Principal Investigator |
| PIS | Participant Information Sheet |
| PPG | Photoplethysmogram |
| REC | Research Ethics Committee |
| SOP | Standard Operating Procedure |
| SBP | Systolic Blood Pressure |

# BACKGROUND AND RATIONALE

Blood pressure measured by a cuff (sphygmomanometer) in the clinic is often used to screen for hypertension (high blood pressure), a condition associated with long term cardiovascular complications (Prospective Studies Collaboration 2002, Rodgers et al. 2004). UK guidelines state that potentially hypertensive patients detected using cuff measurements in the clinic should have the diagnosis confirmed by 24-hour ambulatory blood pressure monitoring (ABPM) at home (Krause et al. 2011). However, the initial clinical cuff measurement used to screen for hypertension fails to account for the natural variability of blood pressure, including its circadian (daily) variability. Thus, some potentially hypertensive patients may be missed by screening.

The typical circadian profile of blood pressure (BP) involves a nocturnal decrease, followed by a morning ‘surge’ in blood pressure and higher levels during the day, known as a `dipping’ pattern (due to the night-time dip in BP) (Hermida et al. 2002, Davidson et al. 2020). However, some individuals experience nocturnal hypertension, where blood pressure is elevated at night compared to its values during the day (known as a `reverse-dipping’ pattern). This `reverse dipping’ pattern is known to be a powerful marker of adverse cardiovascular prognosis, with a reported prevalence of 3% to 39% depending on age, sex, and co-morbidities.

Patients with ‘reverse-dipping’ patterns may have blood pressures indistinguishable from those of normotensive (normal BP) patients during clinic hours when cuff measurements are taken by doctors or nurses in General Practice (Cuspidi et al 2017, Hermida et al. 2007). Thus, these patients are at a high risk of being missed by the traditional screening process in primary care.

We are investigating the use of a CE marked, cuffless, wrist-worn blood pressure monitoring device (Aktiia) to establish individual 24-hour BP profiles. This device uses a photoplethysmogram (PPG) sensor to estimate BP using a pulse wave analysis technique in a non-invasive and non-disruptive manner (using the measurement of visible light reflection at the wrist) (Vybornova et al. 2021). If this device can be shown to capture an individual’s BP profile accurately, it will enable nocturnal hypertension to be detected with minimal burden to the patient (compared to, for example, ABPM). This, in turn, would allow for preventative steps such as prescribing anti-hypertensive medication to be taken, potentially at bed time, with the aim of improving outcomes for these patients (reduction of risk of adverse cardiovascular events such as strokes).

# OBJECTIVES AND OUTCOME MEASURES

|  |  |  |
| --- | --- | --- |
| **Objectives** | **Outcome Measures**  | **Timepoint(s) of evaluation of this outcome measure (if applicable)** |
| **Primary Objective**To investigate the ability of the Aktiia wrist-worn blood pressure monitoring device to capture distinct circadian BP profile phenotypes in systolic and diastolic blood pressure. | Presence of one of more of the widely recognised phenotypes in systolic blood pressure circadian pattern (i.e., `dipper’, `non-dipper’, or `reverse-dipper’ phenotypes). This assessment will be performed using a combination of classification rules in the literature and visual inspection of the averaged systolic blood pressure 24-hour profiles, averaged over the week of the study, for each participant. | After 1 week of data gathering for each participant |

# STUDY DESIGN

This is an observational study that will involve the participant wearing a wrist-worn blood pressure monitoring device (Aktiia) for a week while otherwise behaving as normal. Each participant will visit the lab for 30 minutes at the beginning of the trial to be fitted with the device, have it calibrated, and be given instructions. Each participant will return to the lab for 10 minutes after one week to return the device.

The Aktiia device will gather data using a PPG sensor and provide estimates of systolic blood pressure (SBP) and diastolic blood pressure (DBP) to an app on the participant’s smartphone (or a smartphone provided by the research team). These estimates will be entered either by the participant into a Nexus365 OneDrive for Business spreadsheet provided to them by the research team or by the research team at the Instititue of Biomedical Engineering (IBME) at the end of the week’s home monitoring, when the Aktiia device is returned.

# PARTICIPANT IDENTIFICATION AND RECRUITMENT

## Study Participants

10 – 20 Healthy volunteers aged 21 – 69 years.

## Inclusion Criteria

* Participant is willing and able to give informed consent for participation in the study.
* Healthy adults, Male or Female, aged 21 to 69 years.

## Exclusion Criteria

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

* Individuals outside of the specified age range.
* Individuals suffering from tachycardia or atrial fibrillation.
* Individuals suffering from diabetes or renal dysfunction.
* Individuals who are pregnant.

# STUDY PROCEDURES

## Recruitment

It is expected that the majority of volunteers will be friends, family and colleagues of the research team, who will be directly approached. Graduate students affiliated to the University of Oxford may also be approached.

## Screening and Eligibility Assessment

Participants will be asked if they meet any of the exclusion criteria after being approached as part of the recruitment process.

## Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects 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, and with no obligation to give the reason for withdrawal.

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. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site (Institute of Biomedical Engineering).

## First Visit

Initial study set up will occur at the Institute of Biomedical Engineering. The participant will be given an information sheet (attached to this application), which will be discussed, and the participant will be asked to initial each part of the consent form to ensure understanding. Basic demographic information (age and gender) will also be taken.

The participant will then be provided with an Aktiia device. This device is a CE marked, cuffless, wrist-worn blood pressure monitoring device. They will be asked to install the Aktiia app on their smartphone (or provided with a smartphone for the duration of the study, if preferred) and guided through pairing the Aktiia device with the smartphone and calibrating the device using an Aktiia provided blood pressure cuff. They will also be instructed on the process of viewing their blood pressure measurements in the app. After this process, they will be asked to wear the device on their wrist for a week, apart from when showering, bathing, or swimming. Systolic and diastolic BP measurements will be entered daily into a Nexus365 OneDrive for Business spreadsheet either by the participant or by the research team at the IBME at the end of the week’s home monitoring, when the Aktiia device is returned (second visit). The first visit will have an approximate duration of 30 minutes.

## Second Visit

After one week, the participant will return to the Institute of Biomedical Engineering and the device will be unpaired and data deleted from their smart phone. This visit will have an approximate duration of 10 minutes.

## Discontinuation/Withdrawal of Participants from Study

Each participant has 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:

* Pregnancy
* Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
* Significant protocol deviation
* Significant non-compliance with study requirements
* Withdrawal of Consent

Withdrawal from the study will result in exclusion of the data for that participant from analysis. The reason for withdrawal will be recorded in the Case Report Form.

## Definition of End of Study

The end of study is the date of the last visit of the last participant.

# STATISTICS AND ANALYSIS

## The Number of Participants

The number of participants was not set due to a power calculation or for statistical significance but was decided upon as a convenience sample based on the anticipated target population and time available to complete the study. Our goal for this data is to obtain illustrative blood pressure profiles for a range of individuals, rather than make inferences about an overall population.

## Analysis of Outcome Measures

Typically, classification of SBP profiles in the literature is performed using the day-night SBP ratio (Hermida et al. 2007, Cuspidi et al. 2017). This can be expressed as:

$$\%∆SBP=\left(\frac{\overbar{SBP\_{day}}}{\overbar{SBP\_{night}}}-1\right)×100$$

And patients are typically classified:

* **Dipper:** If %∆SBP < -10%
* **Reverse-dipper:** If %∆SBP > 10% (or 5% or 0%, depending on the study)
* **Non-dipper:** Otherwise

The exact definition of ‘night’ and ‘day’ varies between studies (Taylor et al. 2015). For this study, we intend to use the following definitions:

* **Day-time:** 9:00 am – 5:59 pm (clinic hours)
* **Night-time:** 11:00 pm – 6:59 am

This provides 2-hour gaps between ‘day’ and ‘night’ time where participants may be awake or asleep and ensures the ‘day-time’ definition encompasses clinic hours where SBP could be assessed using a cuff.

# DATA MANAGEMENT

## Access to Data

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

## Data Handling and Record Keeping

Paper consent records will be collected from participants at the lab and placed in a locked filing cabinet directly after study set-up. Data will be entered into a Nexus365 OneDrive for Business spreadsheet provided directly and specifically to the participant. This data will then be collated and stored on a secure, password protected server at the IBME. At the end of each data gathering period, data will be deleted from the participant’s device. We will use a participant identifier number of research data instead of a participant name. No list of participant names against numbers will be retained.

# QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, relevant regulations and standard operating procedures.

# ETHICAL AND REGULATORY CONSIDERATIONS

## Declaration of Helsinki

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

## Approvals

The protocol, informed consent form, and participant information sheet will be submitted to the MS IDREC, and the Department of Engineering Science for written approval.

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

## Participant Confidentiality

The study staff will ensure that the participants’ anonymity is maintained. The participants will be identified only a participant ID number on all study documents and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

## Expenses and Benefits

There are no payments for taking part in this study.

## Annual Progress Report

The PI shall submit on request, a Progress Report to the MS IDREC with a copy to CTRG.

# FINANCE AND INSURANCE

## Funding

This study is funded by a National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC) Grant.

## Insurance

The University of Oxford 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).

# PUBLICATION POLICY

The results of the study will be documented in full in technical reports and shared with the whole project team. 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 the source of funding for the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

# REFERENCES

1. Prospective Studies Collaboration. (2002). Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *The Lancet*, 360(9349), 1903-1913.
2. Rodgers, A., Ezzati, M., Vander Hoorn, S., Lopez, A. D., Lin, R. B., Murray, C. J. L., & Group Comparative Risk Assessment Collaborating. (2004). Distribution of major health risks: findings from the Global Burden of Disease study. *PLoS medicine*, 1(1), e27.
3. Krause, T., Lovibond, K., Caulfield, M., McCormack, T., & Williams, B. (2011). Management of hypertension: summary of NICE guidance. *BMJ*, 343.
4. Hermida, R. C., Ayala, D. E., Fernández, J. R., Mojón, A., Alonso, I., & Calvo, C. (2002). Modeling the circadian variability of ambulatorily monitored blood pressure by multiple-component analysis. *Chronobiology international*, 19(2), 461-481.
5. Davidson, S., Villarroel, M., Harford, M., Finnegan, E., Jorge, J., Young, D., ... & Tarassenko, L. (2020). Vital-sign circadian rhythms in patients prior to discharge from an ICU: a retrospective observational analysis of routinely recorded physiological data. *Critical Care*, 24(1), 1-13.
6. Cuspidi, C., Sala, C., Tadic, M., Gherbesi, E., De Giorgi, A., Grassi, G., & Mancia, G. (2017). Clinical and prognostic significance of a reverse dipping pattern on ambulatory monitoring: an updated review. *The Journal of Clinical Hypertension*, 19(7), 713-721.
7. Hermida, R. C., Ayala, D. E., & Portaluppi, F. (2007). Circadian variation of blood pressure: the basis for the chronotherapy of hypertension. *Advanced drug delivery reviews*, 59(9-10), 904-922.
8. Vybornova, A., Polychronopoulou, E., Wurzner-Ghajarzadeh, A., Fallet, S., Sola, J., & Wuerzner, G. (2021). Blood pressure from the optical Aktiia Bracelet: A 1-month validation study using an extended ISO81060-2 protocol adapted for a cuffless wrist device. *Blood Pressure Monitoring*, 30, 000-000.
9. Taylor, K. S., Heneghan, C. J., Stevens, R. J., Adams, E. C., Nunan, D., & Ward, A. (2015). Heterogeneity of prognostic studies of 24-hour blood pressure variability: systematic review and meta-analysis. *PloS one*, 10(5), e0126375.

# APPENDIX A: SCHEDULE OF STUDY PROCEDURES

|  |
| --- |
| **Procedures** |
| **Visit 1 –** **Set Up** | **Visit 2 – Return** |
| **Minutes** | **Minutes** |
| Informed consent | 3 |  |
| Demographics | 1 |  |
| Eligibility assessment | 1 |  |
| Explanation of Device | 10 |  |
| App Installation | 5 |  |
| Device Calibration | 5 |  |
| Guidance on Recording Data | 10 |  |
| Check of Data |  | 5 |
| Deletion of Data |  | 5 |

# APPENDIX B: AMENDMENT HISTORY

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Amendment No.** | **Protocol Version No.** | **Date issued** | **Author(s) of changes** | **Details of Changes made** |
|  |  |  |  |  |