Hearables

Ear Electrocardiography (ECG) and Photoplethysmography (PPG) for real-time detection of cardiac arrhythmias

Version 1.0 30/10/2023

MAIN SPONSOR: Imperial College London
FUNDERS: UKRI award for the Centre for Doctoral Training in AI for Healthcare
STUDY COORDINATION CENTRE: ICTEM Building 4th Floor, Hammersmith Hospital, London W12 0HS

IRAS Project ID: 318229
REC reference: xxx

Protocol authorised by:

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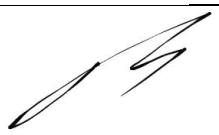
Dr Patrik Bachtiger		30/10/2023
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Study Management Group

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Study Coordination Centre

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Clinical Queries

Clinical queries should be directed to Professor Nicholas S. Peters who will direct the query to the appropriate person.

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Funder

This work is supported by the UKRI award for the Centre for Doctoral Training in AI for Healthcare (Grant No. EP/S023283/1).

This protocol describes the **Hearables** study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

ACM	Accelerometer
BP	Blood Pressure
COPD	Chronic Obstructive Pulmonary Diseases
CVD	Cardiovascular Disease
ECG	Electrocardiogram

ECM	Electret Condenser Microphone
EEG	Electroencephalogram
PAT	Pulse Arrival Time
PPG	Photoplethysmogram
PTT	Pulse Transit Time
ACM	Accelerometer
BP	Blood Pressure
CVD	Cardiovascular Disease
ECG	Electrocardiogram
ECM	Electret Condenser Microphone
EEG	Electroencephalogram
PAT	Pulse Arrival Time
PPG	Photoplethysmogram
PTT	Pulse Transit Time

KEYWORDS
Arrhythmias; electrocardiography; photoplethysmography; hearables; cuffless blood pressure, continuous real-time monitoring

STUDY SUMMARY

TITLE	Hearables: Ear Electrocardiogram (ECG) and Photoplethysmogram (PPG) for real-time detection of cardiac arrhythmias
DESIGN	Prospective observational study
AIMS	To evaluate qualitative and quantitative performance of ear ECG and PPG for real-time detection of arrhythmias against gold standard investigations.
OUTCOME MEASURES	Primary: - Arrhythmia detection and classification from Ear-ECG and Ear-PPG. Secondary: - Signal quality of Ear-ECG in different configurations, evaluated against 1-lead 'Rhythm strip' ECG at rest - Ear-ECG and Ear-PPG artefacts removal for continuous real-time monitoring. - Feasibility of estimating blood pressure from features extracted from simultaneous ear-ECG and ear-PPG signals
POPULATION	50 healthy patients and 50 patients with an established diagnosis of cardiac arrhythmias.

ELIGIBILITY	Inclusion Criteria	Aged > 18, no upper age limit Able to give informed consent; Healthy and diagnosed with cardiac arrhythmias.
	Exclusion Criteria	No abnormal ear anatomy
DURATION	9 months	

1. INTRODUCTION

1.1 BACKGROUND

Gold standard diagnosis of Cardiac Arrythmias:

Cardiac arrythmias, also known as abnormal heart rhythms, such as atrial fibrillation are a leading cause of morbidity and mortality worldwide. Left untreated the effects of arrythmias can be detrimental to an individual's quality of life and become a significant risk factor for stroke, heart failure, cognitive decline, hospitalisation, and death [1]. The lifetime risk and risk factor burden of arrythmias increases with an aging population meaning the increased risk of mortality and morbidities poses an ever-expanding burden to patients and healthcare systems worldwide. In 2019 around 18 million people died from CVDs and 85% of those deaths were due to heart attack or stroke [2], a large proportion of which was contributed by cardiac arrythmias. However, if detected early most people with an abnormal heart rhythm can lead a normal life.

The impact of cardiac arrythmias on patients is based on multiple factors, resulting in a wide variation of clinical presentation varying from palpitations, fatigue, light-headedness, chest discomfort, and alerted consciousness to no symptoms at all. In addition to this the duration of each arrythmia is dependent on individual physiology and anatomy, meaning some arrythmias occur randomly i.e., paroxysmal [3].

Gold standard techniques to detect arrhythmias revolve around 12-lead ECG recording, either in the form of a single 12-lead ECG or via continuous ECG recording device known as a Holter monitor for 24 hours or longer. However due to the variability in presentation and symptoms of cardiac arrythmias per an individual, the success in obtaining a clinical diagnostic ECG evidencing an arrythmia is low. In this instance more invasive diagnostic tools such as a cardiac event recorder can be implanted into patients to record electrical cardiac activity over a longer period. There is therefore a need for better non-invasive portable continuous ECG monitoring solutions.

Extensive research has been conducted on mobile self-monitoring ECG devices, such as KardiaMobile [4]. However, although these devices allow for remote monitoring,

they are heavily reliant on patient self-administration to be manually initiated. There is therefore an ongoing need for passive and continuous real-time arrhythmia detection systems.

Current wearable technologies:

Current wearable technologies have focused on recording cardiac activity either electrically through ECG or optically through PPG. So far, these technologies have been implemented in chest straps, smartwatches, and handheld devices [5]. These digital devices provide recreational recordings which must be manually initiated and require the subjects to be still at the time of recording. Moreover, most of these devices need a clinician to analyse the recordings to assess the presence of arrhythmias.

Recent developments in wearable technology have opened up the potential for identifying various physiological signals (including EEG, ECG, and PPG) by placing standard medical grade sensors in the ears, referring to them as "Hearables" [6]-[7]. Considering that people are largely used to wearing earplugs and the head being in a more stable position than the arms in everyday activities, the ears provide a unique location for AI-enabled 24/7 cardiovascular monitoring.

Hearables: Ear-ECG and Ear-PPG

Previous works [6]-[7] have discussed the biophysics and feasibility of recording ECG from the ears. Different head locations and the ear canal were validated against standard Lead I ECG (ECG from the arms) in terms of the morphology (amplitude and duration) of the characteristic waves (P, QRS and T) relative to the R-peak [7]. Ear-ECG was also used to detect an abnormal heartbeat caused by ventricular bigeminy [8], a type of arrhythmia where each heartbeat is quickly followed quickly by another twin (ectopic beat), generated by premature ventricle contraction. In all these cases however, the identification of the characteristic waves was possible only after averaging across multiple cardiac cycles [7], thus not allowing real-time monitoring. This is because the amplitude of ear-ECG is about 50 times smaller than a standard Lead I ECG, thus resulting in a much smaller Signal to Noise Ratio (SNR).

Ear PPG has also been shown to be far more sensitive than finger PPG to amplitude variations that arise from respiration, thus allowing for a better measurement of respiratory rate [9]. Furthermore, a significant delay has been evidenced between earlobe pulse oximetry and pulse oximetry on the hand or the foot for detection of hypoxemia (low levels of blood oxygen) [10]. Previous work showed that in a study of 14 healthy volunteers in-ear PPG compared with the current standard of care - the finger clip - the ear sensor shows non-inferiority and potential superiority with regard to detection of a mean blood oxygen delay (the time it took from detecting minimal

blood oxygen change in the ear to detecting minimal blood oxygen in the finger) reduction of 12.4 seconds, thus being faster at identifying acute desaturation [11]. Furthermore, ear PPG breathing waveforms have also been used to identify breathing disorders such as chronic obstructive pulmonary disease (COPD) and train a model able to distinguish those subjects against healthy and subjects with pulmonary fibrosis [12].

The estimation of blood pressure from the ears has been attempted in some preliminary works, by employing in-ear cuff-based systems with inflatable balloons [13], microphone and PPG signal from a single ear [14], as well as by positioning two PPG sensors, one in each ear and exploiting the PTT (i.e. the time necessary for the blood pressure wave to travel between two arterial sites) between the left and the right ear [15].

1.2 RATIONALE FOR CURRENT STUDY

In the future sensors in the ear-region either as a standalone system or integrated with other third parties' earbuds, may provide the opportunity to monitor the heart health in an unobtrusive, comfortable, and continuous way. This project sets out to explore the feasibility of recording ECG from the ears in real-time and use features extracted from ear-ECG and ear-PPG waveforms to detect cardiac arrhythmias. As discussed above, characteristic waves from ear-ECG could only be extracted after averaging across multiple cardiac cycles. From this work we aim to test both in-ear and outside of the ear (mastoid) electrodes to identify which configuration allows to consistently extract timings of the characteristic waves in real-time, and capture morphological changes. From the simulated cardiac electrical potentials on the head described in [7], and from the heart rate variability study in [16], we hypothesise that a signal recorded from the mastoid will be stronger in amplitude, and less prone to artefacts, compared to the signal recorded from inside the ear-canal.

It is also important to assess the quality of the signals during normal daily activities to fully exploit the potential for continuous ear ECG/PPG monitoring. Previous work has shown the presence of artefacts caused by jaw clenches [6], jaw-movements (chewing, talking) and walking [17]. The proposed denoising method [18] has been evaluated on ear-EEG signals and on a small cohort (12 subjects). In this study, we aim to further improve a series of different artefacts related to both head movements, jaw movements (talking and chewing) as well as full body movement (walking). The artefact signals will also be captured by some external sensors, such as an ECM and a 3-axis ACC, as described in [18]. Multiple approaches in the literature have been investigated to remove motion artefacts in standard ECG signals, such as adaptive noise cancellation (ANC), independent component analysis (ICA) and empirical mode decomposition (EMD) as well as deep learning architectures in more recent years.

Ear-ECG is a novel method to record ECG with a much lower SNR, further investigation is required to select the optimal artefacts removal solution. Our hypothesis here is that artefacts which cause more internal motion within the ear-canal (such as talking and chewing) will be better captured by the ECM, while head and full body movements will be better characterised by ACC.

As part of the clinical study, we will also investigate the feasibility of estimating blood pressure from ear ECG and PPG signals using information such as Pulse Arrival Time (PAT). ECG signals are electrical and hence arrive instantaneously to the measurement site, while PPG signals are related to the blood flow and will naturally have a delay. This delay (i.e. PAT) has been found to be negatively correlated with blood pressure. Previous works discussed above [13]-[15] have attempted to estimate blood pressure from the ears, however the current approaches were often tested on small healthy cohorts, and lack generalisation to unseen and pathological subjects. There is therefore scope in the literature to exploit the multimodality of the Hearables and extract information from both ear ECG and PPG signals to estimate BP. As part of the protocol, patients will be asked to perform some slow deep breaths, which result in the activation of the parasympathetic nervous system, dilation of blood vessels, and consequent reduction of the overall BP [19]; as well as immersing their hand in cold water < 4 ºC (cold pressor test), which on the contrary triggers a vascular sympathetic activation, thus increasing BP [20]. BP will also be monitored intermittently with a standard medical grade cuff-based device (already in use in the hospital) and those values will be used as ground truth and for calibration. Then, domain-specific features will be engineered to encode information related to blood pressure.

The data generated in this pilot feasibility study would allow scaling to prepare for larger research projects, aiming to move to remote monitoring of patients. Beyond the use for monitoring already diagnosed patients, the algorithms developed in this study will also allow to diagnose arrhythmias at the time of onset, providing both clinical and health economic benefits, expanding the clinical and consumer market of wearable health technology towards more personalised health.

2. STUDY OBJECTIVES

Objectives:
Primary:
- Detection and classification of arrhythmias from Ear-ECG and Ear-PPG waveforms

Secondary:
- Evaluate qualitative and quantitative performance of different configurations of ear-ECG against a gold standard 1-lead ‘Rhythm strip’ ECG.

- Removal of artefacts caused by common daily activities (head movements, talking, chewing, walking) towards a continuous ECG/PPG monitoring solution.
- Feasibility of estimating BP from features extracted from simultaneous ear-ECG and ear-PPG signals.

Hypotheses:

When tested on patients in real-world settings:

- Physiological signals recorded from the ears (Ear-ECG, Ear-PPG) can be used for arrythmia detection and diagnosis.
- Signals from ECM and ACC sensors can be used to remove artefacts in Ear-ECG and Ear-PPG signals, thus paving the way towards continuous monitoring solutions.
- Relevant features such as PAT can be extracted from simultaneous Ear-ECG and Ear-PPG signals and used to estimate BP non-invasively in real-time.

3. STUDY DESIGN

Prospective observational study of 50 healthy patients, and 50 with a pre-existing diagnosis of by cardiac arrhythmias. The study sample size of n = 100 is based entirely on feasibility. Patients with an already diagnosed cardiac arrythmia will be approached either on the hospital ward or during their outpatient visit at Imperial College NHS Trust by a clinical member of the research team. Patients will first be asked if they are happy to be approached for participation in this research study by the clinical team directly involved in their care. Identified participants will be provided with a clear explanation and patient information sheet detailing the study. Only after patients express having had adequate time to read and understand the study, they will be asked to provide written informed consent in person. Please see full details of obtaining informed consent in sub-heading '8.2 consent' below. After informed consent has been completed, participants will then be set up with Ear-ECG and Ear-PPG sensors.

Hearables: Ear-ECG and Ear-PPG sensors

Some off-the-shelf medical grade electrical and optical sensors will be placed in and around the ears, as shown in Figure 1. Two small silver-cup current standard-of-care EEG electrodes are placed in each mastoid with medical-grade gel to allow connectivity. Both the conductive gels and electrodes are already used in the NHS for standard of care EEG. In addition to this, two in-ear earpieces with a cloth electrode attached to a self-expanding foam [6] (the one used for commercial earplugs) are placed inside each ear canal. On the left ear, external sensors (ECM and ACC) are attached to the foam [18], and an additional PPG sensor (MAX30101 from Maxim Integrated) is attached to the back of the ear with adhesive medical tape.

ECG and PPG waveforms will be sent via Bluetooth to a secure laptop and visualised in real-time to spot any potential disconnections at the time of recording. At the end of each recording, the signals will be immediately uploaded to a secure repository. The in-ear sensor will be single-use and disposed of after use on a patient, thereby posing no infection control risk.

3.1 RECORDING PROTOCOL

The estimated setup time to place the ear sensors and electrodes is approximately 5 mins. In addition to being connected to the Ear-ECG and Ear-PPG sensors, the patient will also be connected to a gold standard single-lead ECG monitoring equipment, and a BP cuff in the arm, already in use on the hospital ward as part of their standard of care.

After setup, each patient will start the recording protocol following instructions visualised on a screen. The participants are required to be sitting up for the duration of the recording and follow the instructions on the screen, apart from the “walking” activity (if able and willing), where they will walk freely closely followed by a doctor and walking assistance if needed. In the event a patient is not mobile or has been medically deemed not safe to walk, this step will be skipped.

The instruction on the screen will be both written and visualised in a video for which the participants will be asked to mimic as closely as possible. The protocol lasts for a total of 12 mins plus breaks (reaching a maximum of 15 mins), with the activities described in Table 1. Patients will have allocated breaks between each activity. This has not been fixed, but rather left up to each person to ensure longer breaks if needed. However, a minimum break of 10 seconds will be guaranteed between tasks. If at any point the patient is uncomfortable or wishes to cease the activity early, the sensors will be safely removed, and the study ceased.

All data recorded will be sent via Bluetooth to a research laptop. All data will be pseudo-anonymised, with individual Study ID. There will be no linkage to any identifiable patient information.

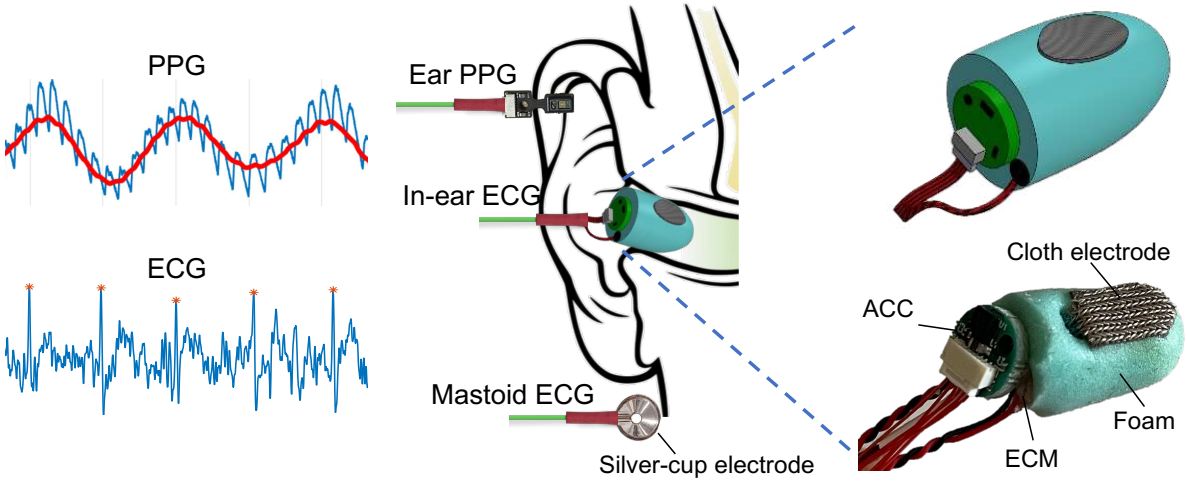

Figure 1. (a) Electrodes and sensors placement in the left ear including behind the ear PPG, silver-cup electrodes in mastoid and in-ear memory-foam earpiece, where accelerometer (ACC) and microphone (ECM) are attached. In the right ear the silver-cup electrode and another earpiece with ECG cloth electrode will be placed.

Table 1. Recording protocol. Total duration: 12 mins with breaks. The thick black lines correspond to instances where the blood pressure is measured from the cuff.

Baseline	Artefacts				Baseline	Blood pressure	
Relax	Head motion	Talking	Chewing	Walking	Relax	Slow breathing	Cold-pressor test
	Up-down and left-right head swing	Counting aloud up to 60	Chewing gum or simulate chewing	Walking freely (with assistance if needed)		Deep slow breaths	Immerse hand in 4ºC cold water
2 min	1 min	1 min	1 min	1 min	2 min	2 min	2 min

3.2 STUDY OUTCOME MEASURES

Primary:

Arrhythmia detection and classification from Ear-ECG and Ear-PPG:

- HRV and morphological features extraction;
- Identification of the timings of the characteristic waves (P, QRS, T);
- Arrhythmias classification accuracy.

Secondary:

1) Performance of different ear-ECG waveforms in different placements of the ear against a gold standard 1-lead 'Rhythm strip' ECG
- SNR in different ear configurations;
- Correlation of estimated heart rate (HR) and heart rate variability (HRV) features;

- Correlation of RR, PR and ST intervals;

2) Artefacts removal evaluation in Ear-ECG and Ear-PPG:
- Power reduction from artefact-corrupted signal to denoised signal;
- Recovery of ECG characteristic waves (P, QRS and T) masked by presence of artefacts.

3) Blood pressure continuous monitoring from ear-ECG and ear-PPG
- Expected trend of increasing and decreasing blood pressure depending on the haemodynamic state;
- Mean Absolute Error between estimated and BP cuff measures.

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

No pre-registration evaluations are required.

4.2 INCLUSION CRITERIA

- Age >= 18 (no upper limit)
- Able to give informed consent
- Healthy control patients and patients with a diagnosed cardiac arrythmia

4.3 EXCLUSION CRITERIA

- Abnormal ear canal anatomy

4.4 WITHDRAWAL CRITERIA

Participants are free to withdraw their consent from the study at any point.

5. ADVERSE EVENTS

This is a minimal risk study. There are no 'side effects' or contact hazards. Each ear sensor is for use by a single patient. All electrodes and contact gels have been medically graded and are already used in the NHS.

The electrodes will not interfere with any implanted medical devices the participant may have or cause any harm to the participant during the study. Patients are free to stop the study at any time during their participation.

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded.

5.3.2 Serious AEs

An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, relapse and death due to established medical conditions, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
RGIT@imperial.ac.uk
CI email (and contact details below)
n.peters@imperial.ac.uk
Fax: xxx, attention xxx
Please send SAE forms to: xxx
Tel: 07946579930 **(Mon to Fri 09.00 – 17.00)**

6. ASSESSMENT AND FOLLOW-UP

The recruitment for the study will end when the requisite number of 50 healthy participants and 50 patients with diagnosed arrhythmias has been achieved. The study will end when the last trial participant performs the last data collection (i.e. "last subject, last assessment").

INCIDENTAL FINDINGS

Incidental findings are highly unlikely during this study, as ECG/PPG signals are being recorded from patients with already diagnosed arrythmias. In the unlikely event of the study team making an incidental finding, they will notify the team in charge of the patient's care immediately.

There will be no follow-up for patients once they have participated in the study.

7. STATISTICS AND DATA ANALYSIS

Data will be analysed using statistical libraries and packages in Python. Analysis will be conducted by E.O. on a daily basis, in collaboration with cardiology clinical research fellows with appropriate access privileges (including honorary Imperial NHS contract).

In order to assess the accuracy of arrhythmia classification, we will extract features from the ear ECG and PPG recordings, specifically pertaining to HRV and morphological characteristics. These extracted features will be used to train various classifiers, including Decision Trees, Support Vector Machines, Bayesian models, and Neural Networks.

To evaluate the effectiveness of the two ear-ECG recording positions (mastoid and in-ear) in comparison to the standard-of-care Lead I configuration, two primary metrics will be employed. The initial metric involves assessing the precision, recall, and F1 score for accurately identifying the R-peak's location [16]. The second metric is the Signal-to-Noise Ratio (SNR), where the noise is due to both the smaller amplitude of the ear-ECG as well as the additional physiological signals such as EEG, EMG and more, which are inevitably measured when recording ECG from the ears. Since in this study we are interested in the ECG information only, we will estimate the SNR by comparing these ear signals with standard of care simultaneously recorded Lead I ECG.

With regards to artefacts removal, two metrics will be used: recovery of the characteristic waves (previously masked by the presence of the artefact) and reduction in power spectral density of the corrupted signal in the frequency of the artefacts. Indeed, we expect the artefacts to increase the power spectrum of the signal in specific frequency ranges, overlapping with the ones of the characteristic waves [15].

Finally, to assess the accuracy of the blood pressure estimation model we will calculate the mean absolute error (MAE) between the predicted blood pressure derived from ear-ECG/PPG features and the actual measurements obtained from the cuff. We will also investigate whether a personalised calibration helps in reducing this error. We will also look at the expected trends of blood pressure changes with respect to the baseline, depending on the current haemodynamic state.

Data Protection, Security and Compliance

Prior to commencement this study be reviewed and obtain approval from the Imperial College Healthcare NHS Trust Data Protection Office. Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

REDCap (Research Electronic Data Capture)

All nonidentifiable patient study data will be collected using a REDCap (Research Electronic Data Capture) database, with a unique nonidentifiable study ID for each participant.

During enrolment, the following data (where available) will be captured by the investigator from the electronic health record and stored on the REDCap database:

- Age
- Ethnicity
- Comorbidities
- Past medical history including cardiac arrhythmias
- BMI (height and weight)
- Medication
- Electrocardiogram monitoring
- Blood pressure

Hearables Data Security

The only data recorded will be digital ECG and PPG waveforms. Data will not be identifiable to the patient (i.e. not associated with an NHS number, date of birth or other identifier). Data recorded will be sent via Bluetooth to a password protected research laptop stored in a locked cabinet in a restricted building, only assessable to the study team. Information will then be periodically uploaded to securely store the data onto an encrypted folder on Imperial College NHS trust servers and computers. Data will be stored for a minimum of 10 years once the study is completed, in accordance with Imperial College policy.

Missing Data

The study design and nature of the variables collected makes missing data unlikely. To avoid introducing bias into the dataset by removal of participants with any missing data, all participants will be retained; missingness any variable will entail the affected participant not being included only in the analyses specifically relevant to that variable. Access to shared primary and secondary care electronic health records should make missing data retrievable in most cases. Details of any missing data will be explicitly described in any reports or publications.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the xxx Research Ethics Committee (REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected.

Inpatients will be given minimum 24 hours to decide whether or not to take part in the study. The research team will aim to obtain full consent within 72 hours of the patient receiving the patient information sheet. Outpatients instead will be provided with the patient information sheet prior to their clinical appointment and only after having the time to read the study patient information sheet and ask necessary questions, the patient will be recruited into the study post clinic. Patients will be given a minimum of the duration of their appointment to decide whether or not to take part in the study. This alternative is provided to eliminate the necessity for patients to make an additional trip to the hospital solely for the purpose of participating in the study data collection. If patients are still not sure in that timeframe, patients can be offered a telephone consultation to obtain informed consent by a member of the research team to call back in 48h after discharge from their outpatient appointment.

After the participant has entered the study, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. Data will be collected according to the data protection act 2018 in line with the general data protection regulation (GDPR).

Paper consent forms and questionnaires will be held in a secure room (swipe card access only) inside a locked cabinet (key only accessible to the study team) at Imperial College Healthcare NHS Trust (ICHNT). At the end of the study these consent forms will be securely collected and transported by a member of the research team and held in secure physical storage at ICHNT.

This study involves multiple layers of data protection. First, pseudonymised login details will be generated for each participant by the research team, thereby mitigating the need for the entry of personal identifiable data. The unique study ID for each participant will only be identifiable by the principal investigator using an encrypted master key held in a password protected file on NHS servers, linking the study ID to the NHS numbers. Data will be automatically transferred to a secure research laptop, where it will be password-protected and only accessible to the research team. All data transferred to the research laptop via Bluetooth will be stored under the Study ID. When not in use, the laptop will be stored in a secure room (swipe card access only) inside a locked cabinet (key only accessible to principal investigator) at site. After the study period, data and all appropriate documentation will be stored for a minimum of 10 years, according to Imperial College policy.
The study data will be collected using a REDCap (Research Electronic Data Capture) database, with a unique study ID for each participant (only identifiable by the principal investigator using an encrypted master key held in a password protected file on NHS servers). Patients will be allocated a de-identified study ID number, derived from a key that processes NHS numbers algorithmically. This key will be kept secure in a password encrypted file (accessible only to principal investigator). Study participant data will therefore not be identifiable unless researchers revert study ID's to NHS number.

No data received by research laptop will be identifiable to the patient (i.e. not associated with an NHS number, date of birth or other identifier). At the end of the study, all data will be stored in accordance with Imperial College Healthcare NHS Trust policy on secure Trust computers.

Upon completion of the study, data will be accessible to the co-investigators only, no data will be transferred to other additional third parties.

8.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

This study is funded through an award held by Edoardo Occhipinti, supported by the UKRI award for the Centre for Doctoral Training in AI for Healthcare (Grant No. EP/S023283/1). Participants will not be paid for joining the study. Investigators will receive no direct or indirect payments for conducting the study.

8.7 AUDITS

The study may be subject to audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the Imperial College & Trust, 4th Floor ICTEM, Hammersmith Hospital, London, W12 0HS.

10. PUBLICATION POLICY

Results from this study will be submitted for publication in peer-reviewed medical journals with authors as per the listed investigators. Results may also be discussed in internal reports and presented at scientific conferences.

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