The measurement of Vital Signs by LifeLight software in comparison to standard of care – Development

The VISION-D study

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PHT Study Reference: PHT/2018/25

Sponsor: Xim Ltd.

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Date: 19/09/2018

Chief Investigator: Professor A. Chauhan
Portsmouth Hospitals NHS Trust

<table>
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<th>Version</th>
<th>Date</th>
<th>Authors</th>
<th>Changes</th>
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<tr>
<td>1.0</td>
<td>19/03/2018</td>
<td>Thomas Jones, Melissa Kapoor, Carole Fogg, Laurence Pearce</td>
<td>N/A</td>
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<td>Elaine Baddeley</td>
<td>Change of PI from Thomas Jones to Emily Heiden</td>
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<td>19/09/2018</td>
<td>Emily Heiden, Elaine Baddeley</td>
<td>Update to protocol to include approaching potential participants from local GP practices</td>
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Key Trial Personnel

Chief Investigator: Professor A. Chauhan
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Principal Paediatric Investigator: Dr Catherine Tuffrey
Investigator: Sharon McCready
Paediatric Investigator: Paediatric Nurse (Andrew Gribbin)
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Patient Representative: PHT Patient Research Ambassadors (PRA) Group
Study Methodologist: Carole Fogg
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Study Design: Melissa Kapoor, SEHTA
Device Advisor: Joe Booth, The Clinical Trial Company
Sponsor Representative: Laurence Pearce, CEO, Xim Ltd
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# 1. Study synopsis

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<th>Title</th>
<th>The measurement of Vital Signs by LifeLight software in comparison to standard of care – Development; the VISION-D study</th>
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<tbody>
<tr>
<td>Sponsor</td>
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<tr>
<td>Design</td>
<td>Prospective observational non-invasive study</td>
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<tr>
<td>Population</td>
<td>Inpatients, outpatients, staff and healthy participants – adults and children</td>
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</tbody>
</table>
| Sample size | Maximum 2000 patients  
Approximate proportions of population groups:  
- 33% inpatients  
- 33% outpatients  
- 33% Healthy controls  
Approx. 25% of participants will be children 3 – 16 years old |
| Study duration | Approximately 30 minutes per participant |
| Planned Trial period | 12 months |
| Early stopping criteria | The study will be stopped by the sponsor once the LifeLight app reaches acceptable accuracy |
| Primary Objectives | To develop the LifeLight heart rate, respiratory rate, SpO2 and blood pressure algorithms. |
| Secondary Objective | To evaluate the impact of variables other than vital signs on the accuracies of the LifeLight vital signs estimates, e.g. age, gender, temperature, health condition, medication, skin tone and ambient lighting. |
2. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ADE</td>
<td>Adverse Device Event</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>GCP</td>
<td>Good clinical practice</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>HRA</td>
<td>Health Research Authority</td>
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<tr>
<td>ICA</td>
<td>Independent Component Analysis</td>
</tr>
<tr>
<td>ICH</td>
<td>International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use</td>
</tr>
<tr>
<td>ILS</td>
<td>Immediate Life Support</td>
</tr>
<tr>
<td>MEWS</td>
<td>Modified Early Warning Score</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
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<tr>
<td>PEWS</td>
<td>Paediatric Early Warning Score</td>
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<tr>
<td>PHT</td>
<td>Portsmouth Hospitals NHS Trust</td>
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<td>PIS</td>
<td>Participant Information Sheet</td>
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<tr>
<td>PI</td>
<td>Principal Investigator</td>
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<tr>
<td>PPG</td>
<td>Photo-plethysmography</td>
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<tr>
<td>QA</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedures</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
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3. Lay Summary

One of the key ways to understand how a patient’s illness is affecting them is by measuring ‘vital signs’. These include the patient’s blood pressure, how fast their heart is beating, how much oxygen they have in their blood and how fast they are breathing. These measurements are usually done by healthcare staff with different pieces of equipment, which take time to put on and use, and which can be uncomfortable for patients. This can lead to measurement of vital signs not always being done when they are required, or taking up a lot of healthcare staff time, meaning there is less time available for other caring activities. Some patients are asked to monitor their medical conditions at home using this equipment, but the time and effort required to do this may mean that they are less likely to do this as required. In addition, there may be patients who might benefit from self-monitoring, but the equipment is too cumbersome or expensive to be available for everyone who needs it, when they need it.

LifeLight is a computer program (“app”) which can be used on any smartphone, tablet or computer that contains a camera. The app uses data from looking at a person’s face to calculate the vital signs – it looks at the colour of a person’s facial skin and measures very small changes in colour because we believe that this could be an effective way of measuring vital signs. The app is still under development, which means that it is still “learning” the best match between the information it collects from the face and the values of vital signs measured using the standard equipment. The app should become more accurate in calculating the vital signs as it sees more and more information.

So far the app has seen data from a small number of healthy people and patients in doctor’s surgeries only. To make it more accurate for people of different ages, illnesses, skin tones etc., the app needs to see a large amount of information from lots of different types of people with normal vital signs done at the same time.

To do this, we will recruit around people who are attending a hospital, either as an inpatient, an outpatient, a friend/relative of a patient, or a member of hospital staff. The exact number will depend on how quickly the app “learns”. We will take their vital signs using the app and compare the results to vital signs measured in the normal way. The measurements we take in the hospital will be made under very specific conditions so we can develop the app to make it as accurate as possible.
4. Background and rationale

a. Assessment of vital signs

Assessment of vital signs is an essential part of any clinical assessment and is undertaken regularly on patients accessing healthcare services. The accuracy of these measurements is of vital importance as decisions regarding the urgency of medical review and subsequent management are often influenced by these measures.

The measurement of vital signs as part of normal medical care requires a level of medical / nursing skill or patient training. Observations can be altered by stress or anxiety making the results less representative of the patient’s clinical state. This is particularly recognised in the measurement of blood pressure but stress also alters heart rate and respiratory rate, especially in people who may become stressed by the handling required for these measurements.

Regular community or home monitoring of vital signs can be useful in the older population and those with long-term conditions but standard of care methods can be labour intensive for health care providers, and complex, inconvenient and uncomfortable for individuals.

LifeLight is software which allows completely non-invasive measurement of these observations with no requirement for clinical skill or training. It can currently be used on a laptop or mobile device (tablet or smartphone) with integral camera. The use of mobile telephone technology is now commonplace in society so adults and children alike are likely to be accepting of this as a non-threatening method of measurement, thus reducing the impact of anxiety on the results. LifeLight therefore has potential application both within the health care system, particularly in children and in emergency settings, and in non-healthcare settings such as schools, nursing homes and at home (including for personal use for self-monitoring of vital signs such as blood pressure). It may also be useful in settings where direct access to health care is limited, as a part of a telemedicine service or to improve the quality of research in studies that are conducted in peoples’ homes such as studies using patient reported outcome measures.

This is a preliminary study to improve the accuracy of the LifeLight software in measuring heart rate, blood pressure, oxygen saturation and respiratory rate in inpatients, outpatients and healthy people in comparison to standard of care.

b. Standard of care measurement of vital signs

A variety of methods and devices are available for the measurement of vital signs. In this study, we will use methods and technology that are currently in routine use on adult and paediatric wards within PHT, which are non-invasive but accepted to be accurate enough for use in other research studies and in clinical settings, including GP surgeries. We will use new, calibrated vital sign equipment, using the same model for all data collection to ensure standardisation of data collected.
c. LifeLight

LifeLight software measures physiological vital signs through a method called photo-plethysmography (PPG) which is a low-cost and non-invasive means of detecting cardiovascular blood volume pulse (BVP) through small changes in reflected light from the skin surface. Although PPG is conventionally conducted with a dedicated infrared light source, it has been shown that the technique can be extended to detect BVP from the face using just reflected ambient light [1,3].

Working without the need for custom hardware, the LifeLight app uses a camera situated within a laptop computer, a tablet or a mobile phone to capture a live video of the subject, and a face-tracking algorithm detects the presence of a human face in the image. Once the subject’s face is detected, a rectangular region of interest (ROI) is selected (usually the forehead) and a matrix of values captured representing the red, green and blue values of each pixel within the ROI from each frame of video. The video is not stored or transmitted; the colour values from each frame are worked out and then the video data is deleted. For the purposes of the trial, optional video data may be transmitted if adult participants consent as detailed below.

A software method called Independent Component Analysis (ICA) is used to combine signals detected from the red, green and blue channels in order to eliminate noise and interference, and derive a plethysmographic signal. Next, the signal is turned from time domain into frequency domain using a method such as Fourier transformation, so that the various frequencies associated with pulse and respiration can be isolated from other general ambient noise such as artificial lighting.

After 30-60 seconds of data collection, mean values for pulse and respiration can be established. Subsequent algorithms finally derive oxygen saturations and blood pressure from the received data.

Once the measurement process completes, the calculated values are presented on the recording device display. During this study, values will not be presented to research staff to avoid confounding the results of standard measurements.
5. Patient and Public Involvement (PPI)

The study team is committed to ensuring that Public and Patient Involvement (PPI) is embedded throughout the study. The study design was discussed with the PHT PPI Facilitator and representatives of PHT Patient Research Ambassadors Group (PRA) were consulted in the production of study documentation, for example the Lay Summary and Patients Information Sheets. Representatives of this group will be invited to join the study steering committee to ensure patient representation while the study is being conducted. The PRA group will be asked to assist with dissemination of results following the completion of the Validation study to follow this.
6. Objectives

a. Primary objective

To develop the LifeLight heart rate, respiratory rate, SpO2 and blood pressure algorithms. This will allow progression to the next study which will validate the accuracy of the app once developed.

b. Secondary objective

To evaluate the impact of variables other than vital signs on the accuracies of the LifeLight vital signs estimates, e.g. age, gender, temperature, health condition, medication, skin tone and ambient lighting.
7. Study Design

a. Overview

This is an observational, non-invasive study. Participants will twice undergo concurrent measurement of their vital signs using 1. Measurement instruments as per standard of care, and 2. LifeLight software on a tablet.

Measurements will ideally be performed concurrently by two members of staff, or consecutively by one staff member where this is not possible. LifeLight values will not be displayed in order to avoid confounding.

Data will be used to “train” the algorithms to estimate the vital signs more accurately. The accuracy with which the algorithms estimate the test dataset will be monitored at regular intervals during the training dataset collection period. The study delivery process will be responsive to this learning curve to increase the likelihood that the pre-determined accuracies for each vital sign estimation algorithm are achieved by study end.

b. Duration of participant participation

Participants will be enrolled in the study for the duration of their study assessment, which will be approximately 30 minutes per participant assessment.

c. Definition of the start and end of the study

The start of the study will be the first assessment of the first participant and the end of the study will be the last assessment of the last participant.

d. Potential benefits for participants

There is no immediate benefit to participants from this study. Any clinically significant abnormalities found in the participants’ vital signs measured as per standard care techniques as part of this study will be referred to an appropriate clinician.
8. Study facilities

a. Study site

Data collection will take place in multiple locations across Queen Alexandra Hospital in Portsmouth. For example, inpatient measurements may take place while the inpatient is sitting in their hospital bed, and outpatient, staff and healthy participant measurements may take place in vacant consulting rooms or other private locations.

b. Clinical team involved in the trial

The study will be conducted by adult and paediatric nursing staff trained by and under the direction of the Principal Investigator and Paediatric Principal Investigator as applicable. They may be assisted by clinical trial assistants. Participants recruited from GP practices will be approached by members of the research team from the Queen Alexandra Hospital. All staff involved in data collection will have received Good Clinical Practice training.
9. Recruitment and withdrawal of participants

a. Recruitment

The study will be advertised by email and in team meetings to Trust staff. Posters will be put up in staff areas, and public recruitment posters will be put up in public areas. Staff will be contacted by email and stands in public areas of the hospital will recruit visitors. Inpatients will be approached by study staff during their stay and outpatients will be approached while waiting for an outpatient appointment. Members of the study team will be available to discuss the study with any interested individuals who approach the information stands, email or phone study staff, or people waiting in the hospital outpatient departments. Parents/guardians will be approached in the case of paediatric potential participants. Potential participants will also be approached in the community within local GP practices.

b. Participant Information Sheet

A participant information sheet (PIS) will be given to potential participants and parents/guardians will be given a parent information sheet. Age appropriate PIS for younger and older children will be provided. The PIS have been developed in collaboration with the PHT PRA group whose opinions were sought on the appropriateness and accessibility of the content. No minimum time delay between approach and consent will be in place due to the simple and non-invasive nature of the study but recruitment will not be attempted until potential participants have understood the information sheet.

c. Screening

i. Informed consent / assent

The aims of the study and all procedures to be carried out will be explained to potential participants or parents / legal guardians of potential participants under 16 years old. Written and verbal information will be given to children under 16 years at a level appropriate to their understanding including an age appropriate PIS. The participant or parent / legal guardian will be given the opportunity to ask about details of the trial. All participants or parents / legal guardians will sign and date the informed consent form before any study specific procedures are performed. Informed assent will be collected from children where appropriate.

The following will be emphasised:

- Participation in the study is entirely voluntary.
- Refusal to participate involves no penalty or loss of medical benefits.
- The participant may withdraw from the study at any time.
- The participant is free to ask questions at any time to allow him or her to understand the purpose of the study and the procedures involved.
- There is no direct benefit from participating.

The adult consent form includes an optional element regarding the level of video data collection.
Paediatric recruits will all be fully pixelated. Three options will be available for adults:

1. Fully pixelated data without any video data uploaded (default option)
2. Video data with identifying features obscured
3. Full face video

The consent form will be signed and dated by a member of the study team. A copy will be printed and kept in the Trial Site file.

d. Inclusion and exclusion criteria

i. Inclusion criteria

The participant must satisfy all the following inclusion criteria to be eligible for the study:

1. Sufficiently conversant in the English language to satisfy 3.
2. Able and willing to comply with all study requirements.
3. Able and willing to provide written informed consent to participate (including by parent or legal guardian if under 16 years old).

ii. Exclusion criteria

There are no exclusion criteria.

e. Withdrawal of a participant

A participant has the right to withdraw from the study at any time and for any reason, and is not obliged to give his or her reasons for doing so. The participant may withdraw/be withdrawn from further study procedures at any time in the interests of the participant’s health and well-being, or for any of the following reasons:
• Significant protocol deviation.
• Participant non-compliance, intentional or non-intentional, with study requirements.
• An adverse event (SAE, ADE), which requires discontinuation of the study involvement or results in inability to continue to comply with study procedures.
• Any other reason that may compromise the safety of the participant or the integrity of study data in the opinion of the investigator.

The reason for withdrawal from during the study visit will be recorded. For all SAEs/ADEs, appropriate follow-up visits or medical care will be arranged, with the agreement of the participant, until the AE has resolved, stabilised or a non-study related causality has been assigned. Any data collected prior to withdrawal will be included in the final analysis unless consent for this is withdrawn.
10. Study Procedures

Following informed consent, the study staff member will complete a very brief set of demographic and medical history questions, limited to the presence or absence of medical problems and treatment for them, and a set of pre-measurement observation questions. Background luminosity will be measured using a handheld lux meter. The staff member will then prepare for and take concurrent LifeLight and standard of care method measurements of the participant’s heart rate, blood pressure, respiratory rate and oxygen saturations for a 60-second measurement period. Best efforts will be made to adhere to the LifeLight measurement conditions listed in Appendix B. LifeLight and manual measurements will then be repeated following the initial observations. Once measurements are concluded, the study staff member will complete the post-measurement observation questions.

a. Demographic and medical history

The following demographic and medical information will be collected by the study staff on the CRF:

- Age
- Gender
- Ethnic background
- Background light
- Height and weight using height meter and scale or from patient’s notes where measurement is not possible
- Temperature, measured using standard of care temperature probe
- Skin colour by six point scale (a card with the scale on will be available to each nurse)
- Current diagnosis of any medical conditions that might impact on skin perfusion and pigmentation and cardiovascular processes, including:
  - Liver conditions
  - Anaemia
  - Renal failure
  - Skin conditions
  - Hypotension
  - Cardiovascular conditions
  - Respiratory conditions
- Prescription of medications for any of the above medical conditions.

b. Pre-measurement observational questions

The study staff will record pre-measurement observational questions on the CRF, including:

- Is there visible sweat on the participant’s face? [yes / no]
- Does the participant have facial hair covering the skin on their cheeks? [yes / no]
- Does the participant have a tattoo, jewellery (not including earrings), birthmark, scar or other feature on their face? [yes / no]
- Is there visible (heavy) foundation / concealer make-up on the participant’s cheeks and/or forehead? [yes / no]
The participant will also be asked to declare whether they are wearing foundation / concealer, as it may not be visibly obvious.

c. Measurement of vital signs using LifeLight

LifeLight will be used to measure vital signs using a tablet (Samsung Galaxy Tab S3). This device will be held approximately 1 metre away from the subject and angled towards the face. Where height and weight data are not available, blood pressure will not be estimated. Controls and instructions on the device will start and stop the measurement, which should last 60 seconds. The LifeLight measurements will be stored automatically on the device until it has internet connectivity, and not revealed to the study staff or participant. When the tablet has internet connectivity, data will be uploaded to the secure Xim database. Identifiable information will not be included with this stored data, and transmitted data is encrypted.

d. Standard of care measurement of vital signs

The participant’s heart rate, respiratory rate, blood pressure and oxygen saturations will be measured using standard of care methods during the same 60 seconds as they are measured using LifeLight. The following standard of care method set-up procedures will be performed before the measurement period begins:

- Placement of a standard clinical automatic sphygmomanometer with appropriately sized cuff (width at least 2/3 of upper arm length) on the participant’s upper arm for blood pressure measurements.
- Placement of a standard clinical finger clip sensor for oxygen saturation measurements on the finger opposite to the sphygmomanometer.

The study nurse will announce when the 60 second measurement period begins and ends, guided by the timer on the Lifelight software (to ensure the two sets of measurement methods are concurrent). He / she will manually count observed inspirations during the 60 second period.

The second staff member will operate the automatic sphygmomanometer at the start of the 60 second measurement period. During the remaining measurement period, he / she will observe the oxygen saturation measurements and note the average result ensuring the oximeter is picking up an appropriate waveform. The respective standard of care measurements will be written onto the CRF.
e. Post-measurement observational questions

Once measurements are concluded, the member of staff performing the LifeLight recording will complete the post-measurement observational questions on the tablet device, including:

- Did the participant move during the measurement period? [a lot / a little / no]
- In what position was the participant during the measurement period [lying / sitting / standing]
- Was the participant wearing glasses during the measurement period? [yes / no]
- Was the participant’s hairstyle covering the skin on their cheeks and / or forehead during the measurement period? [yes / no]
- Was the participant wearing an item that obscured their face during the measurement period, e.g. headscarf? [yes / no]
- Did the software report “Face not found” at any time during the measurement period? [yes / no]
11. Assessment of safety

Safety of the participants will be assessed by analysing the frequency, incidence and nature of adverse events and serious adverse events arising during the period of study participation, which will end when the post-measurement questionnaires are completed.

a. Definitions

i. Adverse Event (AE)

An adverse event (AE) can be defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device. This study comprises standard measurements of vital signs, a medical history and a non-contact piece of medical equipment. AEs are therefore not going be collected with the exception of SAEs and ADEs as below because any AEs that occur will be unrelated to the study.

ii. Serious Adverse Event (SAE)

An SAE is an AE during the study visit that results in any of the following outcomes, whether or not considered related to the study procedure.

- Death (i.e., results in death from any cause at any time)
- Life-threatening event (i.e., the participant was, in the view of the investigator, at immediate risk of death from the event that occurred). This does not include an AE that, if it occurred in a more serious form, might have caused death.
- Persistent or significant disability or incapacity (i.e. substantial disruption of one’s ability to carry out normal life functions).
- Hospitalisation other than that for which the patient was originally admitted, regardless of length of stay (if applicable), and even if it is a precautionary measure for continued observation. Hospitalisation (including inpatient or outpatient hospitalisation for an elective procedure) for a pre-existing condition that has not worsened unexpectedly does not constitute a serious AE.
- An important medical event (that may not cause death, be life threatening, or require hospitalization) that may, based upon appropriate medical judgment, jeopardize the participant and/or require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic reaction requiring intensive treatment in an emergency room or clinic, blood dyscrasias, or convulsions that do not result in inpatient hospitalization.
- Congenital anomaly or birth defect.

There are not expected to be any SAEs associated with this study. However, in the unlikely event that any events do occur, the participant will be with a medically trained professional who will act appropriately to ensure the participant is safe and treated (if required) immediately.
If any unknown medical conditions are discovered during the manual observations taken as part of this study, appropriate action will be taken to ensure the participant is cared for. In urgent cases arising in a hospital, the Trust’s emergency care services can be utilised as appropriate.

### iii. Adverse Device Event (ADE)

An Adverse Device Event is an adverse event related to the use of an investigational medical device (from ISO/FDIS 14155) i.e. the LifeLight system.

#### b. Reporting procedures for AEs

In the event of an adverse event occurring in this study, an adverse event report form will be completed and, if necessary, it will be reported to the on-duty clinical research fellow or research physician who will investigate and act as appropriate. The Sponsor will be informed when the AE is assessed as having potential to cause harm to the participants.

#### c. Reporting procedures for SAEs

In order to comply with current regulations on SAE reporting to regulatory authorities, the event will be documented accurately and notification deadlines respected. SAEs will be reported to the Principal Investigator immediately when the study team becomes aware of their occurrence, as described in the relevant trust SOP. Copies of reports will be forwarded to the Sponsor. SAEs will be reported to the ethics committee(s) if there is a clinically important increase in occurrence rate, an unexpected outcome, or a new event that is likely to affect safety of trial participants, at the discretion of the Chief Investigator.

#### d. Reporting procedures for ADEs

Device deficiencies will be recorded in the specially designated section of the CRF. The following details are required for documentation purposes:

- The participant’s study ID number
- Date of the occurrence of the event
- Consequences for the participant, if any.
12. Analysis and Statistical considerations

a. Endpoints of the study

- Heart rate
- Respiratory rate
- Oxygen saturation
- Blood pressure

b. Overview of the statistical aspects of the study

The overall objective of the data analysis is to collect data in order to improve the accuracy of the LifeLight system.

c. Sample size

The sample size of the study will depend on the incremental improvement in accuracy of the LifeLight system. In order to ensure recruitment is proportional, sample size will not be pre-specified as the algorithm development will not be predictable prior to enrolment. The Sponsor will update the study teams on the accuracy of the algorithm, and the study will end when accuracy is acceptable. Sample size is estimated to be up to 2000 participants.

d. Interim analyses

The LifeLight algorithm will be updated on a biweekly basis as LifeLight data is matched with anonymised standard of care data. Accuracy of the algorithm will be measured against collected data. If the algorithm accuracy exceeds the Sponsor’s minimum standard at interim analysis then the study will be stopped.
13. Quality control and quality assurance procedures

a. Monitoring
Monitoring will be performed by the Sponsor according to ICH Good Clinical Practice (GCP). Following written standard operating procedures, the monitors will verify that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The investigator site will provide direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the Sponsor and inspection by local and regulatory authorities.

b. Modification of the protocol
No amendments to this protocol will be made without consultation with, and agreement of, the Sponsor. Any amendments to the trial that appear necessary during the course of the trial must be discussed by the investigator and Sponsor concurrently. If agreement is reached concerning the need for an amendment, it will be produced in writing by the Chief Investigator and will be made a formal part of the protocol following ethical and regulatory approval (NRES-REC SOPs – Version 5.1 March 2012: http://www.hra.nhs.uk/wp-content/uploads/2013/08/NRES_SOPs_v5.1_2012.03.14.pdf).

An administrative change to the protocol is one that modifies administrative and logistical aspects of a protocol but does not affect the subjects’ safety, the objectives of the trial and its progress. An administrative change does not require UK ethical committee or regulatory approval.

The investigator is responsible for ensuring that changes to an approved trial, during the period for which regulatory and ethical committee(s) approval has already been given, are not initiated without regulatory and ethical committee(s)’ review and approval except to eliminate apparent immediate hazards to the subject.

c. Protocol deviation
Any deviations from the protocol will be documented in a protocol deviation form and filed in the site trial master file.

d. Audit and inspection
The QA manager may perform internal audits to check that the trial is being conducted, data recorded, analysed and accurately reported according to the protocol, approved SOPs and in compliance with ICH GCP. The internal audits will supplement the external monitoring process and will review processes not covered by the external monitor.

The Sponsor, trial site and ethics committee may carry out audit to ensure compliance with the protocol, GCP and appropriate regulations. GCP inspections may also be undertaken by the regulatory authority to ensure compliance with protocol and national regulations. The Sponsor will assist in any inspections.
e. Serious breaches
A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree: the safety or physical or mental integrity of the trial participants; or the scientific value of the trial.”
In the event that a serious breach is suspected, the Sponsor will be informed as soon as possible and in turn will notify the NHS REC within 7 days.

f. Study progress
The progress of the trial will be overseen by the Chief investigator.

g. Dissemination
Results of the study will be disseminated via paper submissions to relevant journals and conferences. A lay summary of the results will be produced in collaboration with the PHT PRA group. The study team will explore with this group other avenues and formats for the dissemination of the study findings to ensure as wide a public audience as possible, for example through co-produced public talks, articles in community communications and social media.
14. Ethics

a. Participant Confidentiality
The study staff will ensure that the participants’ anonymity is maintained. The participants will be identified only by initials and a participant’s ID number on the CRF 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 practicable to do so.

b. Ethics
No study activity will take place prior to review of the study and associated documents by the REC and HRA assessors or prior to a favourable opinion and confirmation of capacity and capability being received from the host NHS Trusts.

The measurements from this study are only being taken for the purposes of developing the LifeLight software. Results of the vital signs measurements taken will only be acted upon if they are clinically significant and warrant further investigation. For inpatients, vital signs measured using the standard of care equipment will be entered into the “VitalPAC” electronic observations record for use by the clinical care team responsible for the patient.

The study will not be initiated before the protocol and all study relevant material such as the informed consent forms and PIS have received approval / favourable opinion from the REC, and the respective NHS R&D departments. Any changes to protocol or relevant study documents will be approved by the Sponsor. Should an amendment be made that requires REC approval, as defined by REC as a substantial amendment, the changes will not be instituted until the amendment has been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC is notified as soon as possible and an approval is requested. Minor amendments as defined by REC as non-substantial amendment, may be implemented immediately, and the REC informed at a later time.

Patients who are already enrolled in other research trials will be invited and allowed to participate in the study if they so wish.

c. Informed Consent
It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each person participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study using the PIS. Participants will record their willingness to participate on the informed consent form.

The process for obtaining participant informed consent will be in accordance with the REC guidance, GCP and any other regulatory requirements that might be introduced.
d. Declaration of Helsinki

The study will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the Good Clinical Practice Guidelines, the protocol and applicable local regulatory requirements and laws.
15. Data handling and record keeping

a. Data handling
Data collected by the LifeLight app will be transmitted directly to Xim Ltd. Data from the CRFs will be transcribed into a study specific database which will be held securely on PHT computers and will be password controlled. Anonymised, password-protected data from the database will then be electronically sent to Xim Ltd. for matching with respective LifeLight data.

b. Record keeping
The investigators will maintain and retain appropriate medical and research records and essential documents for this trial in compliance with GCP and regulatory and institutional requirements for the protection of confidentiality of participants. The Chief investigator, co-investigators, study nurses and representatives of the sponsor will have access to records. The investigators will permit authorised representatives of the Sponsor, regulatory agencies and the monitors to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

c. Source data and case report forms (CRFs)
All protocol-required information will be collected in CRFs designed by the Investigators. Source documents are original documents, data, and records from which the participant’s CRF data are obtained. For this study these will include, but are not limited to, participant consent forms and CRF entries. CRFs will be considered source data as they will be the site of the original recording of data including medical and demographic history, medication records, vital signs and adverse events. All source data and participant CRFs will be stored securely.

d. Data protection
The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the Sponsor.
16. Financing and insurance

a. Financing
The study activities occurring at PHT and its responsible trial sites will be funded by a Phase 2 SBRI Healthcare Award, which has been secured by Xim Ltd.

b. Insurance
PHT has a specialist insurance policy which would operate in the event of any participant suffering harm as a result of involvement in the study on a site under their responsibility. The sponsor has arranged for insurance for research activity that takes place in GP practices.

c. Compensation for time
This study will recruit inpatient, outpatient, staff and healthy visitors of Queen Alexandra Hospital, Portsmouth and patients and staff attending NHS GP surgeries. The study visits will last for approximately 10 - 30 minutes and will not involve any invasive procedures. Participants will therefore not be offered financial compensation for participation in this study.
### Appendix A - Normal range of observations within age cohorts

<table>
<thead>
<tr>
<th>Age</th>
<th>Heart Rate</th>
<th>Respiratory Rate</th>
<th>Systolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12 months</td>
<td>110-160</td>
<td>30-40</td>
<td>70-90</td>
</tr>
<tr>
<td>12-24 months</td>
<td>100-150</td>
<td>25-35</td>
<td>80-95</td>
</tr>
<tr>
<td>2-5 years</td>
<td>95-140</td>
<td>25-30</td>
<td>80-100</td>
</tr>
<tr>
<td>5-12 years</td>
<td>80-120</td>
<td>20-25</td>
<td>90-110</td>
</tr>
<tr>
<td>12-18 years</td>
<td>60-100</td>
<td>15-20</td>
<td>100-120</td>
</tr>
<tr>
<td>18-75 years</td>
<td>50-90</td>
<td>12-20</td>
<td>110-220</td>
</tr>
</tbody>
</table>

Adapted from the Royal College of Physicians National Early Warning Score system[1] and the University Hospitals Southampton NHS Foundation Trust Paediatric Assessment chart
Appendix B - User guide

It is important that the trial data are collected under conditions that support the development of the LifeLight algorithms. These conditions are informed by research literature [2, 3, 4] and include:

- Minimal participant motion, to avoid face-tracking errors, PPG signal registration errors, and fluctuations to the PPG signal itself (movement alters blood flow to the head and face).
- Facial skin surface area maximised, to give the software the best chance of locating a patch of facial skin from which to measure RGB data.
- Lighting adequate to illuminate the facial skin detected by the measuring device camera.
- Avoidance of persons other than the participant being viewable by the tablet camera, to prevent the software measuring somebody other than the participant.
- Measurements made exactly concurrently with the standard of care measurements, for optimal algorithm training despite natural fluctuations in participant vital signs.

In light of these conditions, study staff should:

- Hold the tablet as still as possible, and at a distance of about 1 metre from the participant, and angled towards their face.
- Request participants to keep as still as possible during the measurement period, and ask them specifically to refrain from moving their head, talking or chewing.
- Ask participants to remove any garments (hats, scarves, etc.) and arrange hair (including fringe) so that facial skin is not grossly obscured. This excludes instances where garments or other features are of a sensitive nature, e.g. worn for religious purposes.
- Make best efforts to ensure that the software view of the participant is well illuminated, including by turning on more lights, opening window blinds, and re-positioning the participant.
- Ensure that, where possible, the trial takes place in a vacant space dedicated to the trial or that there is a wall or other inanimate object behind the participant that prevents other people coming into the line of sight of the camera (participant re-positioning may be required). The study nurse and assistants should also take care to position themselves so that they are not in the line of the sight of the camera.
- Ensure accuracy in data entered in the medical history and demography, pre-measurement observation questions, and post-measurement observation questions.
- Start the standard of care measurements when the LifeLight stopwatch reads 60.0s, and stop the measurements when the stopwatch reads 0.0s.
- If the “Face found” icon changes to “Face not found” icon during measurement period, record this in the post-measurement question answers.
- Charge the tablet when it is not actively being used, so that the device can be powered by its battery rather than main power supply. This should reduce the risk that the device poses a trip hazard.
- Reboot the tablet if the software crashes or freezes.
- Contact the Sponsor if and when the tablet device or software malfunctions or fails.

When these conditions are not achieved during the trial, because it was impractical to do so or because of participant non-concordance, the study nurse should indicate so in their answers to the post-measurement observation questions.
Appendix C – Escalation protocol

Participants in the study will be having vital sign measurements taken which may reveal unrecognised underlying medical problems, most likely hypertension. As the study lasts less than 30 minutes and so such issues cannot be dealt with as part of the study, an appropriate escalation route is required. This will be divided into inpatient participants, healthy controls, outpatient participants and participants recruited from GP practices.

a. Inpatients

Vital sign measurements for inpatients will be recorded in their vital sign records, e.g. VitalPAC for adults. If the vital sign measurements result in an escalation of the participant’s Early Warning Score (EWS) then the clinical team will be alerted, either the participant’s nurse or doctor, for further action if required.

b. Healthy controls

The table below gives ranges for escalation of vital signs in cases which are not expected. Participants who have vital signs within the “GP” range should be advised to attend their GP to discuss the results of their tests. Participants who have vital signs in the “Urgent care” range will be advised to attend the Urgent Care department for assessment and possible treatment. If vital signs are better on repeat testing then advice relevant to the improved results will be given.

<table>
<thead>
<tr>
<th>Vital sign</th>
<th>GP</th>
<th>Urgent Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen saturation</td>
<td>&lt;92%</td>
<td>&lt;92%</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&gt;160 systolic and &gt;90 diastolic</td>
<td>&lt;90 systolic, &gt;180 systolic or &gt;110 diastolic</td>
</tr>
<tr>
<td>Heart rate</td>
<td>&lt;40, &gt;120bpm or irregular (without known AF)</td>
<td>&lt;40, &gt;120bpm or irregular (without known AF)</td>
</tr>
</tbody>
</table>

If both sets of a participant’s results are within the “Urgent Care” range, the study staff member is concerned about the participant or the appropriate route of escalation, the on-call research fellow should be contacted between 08:00 and 20:00 on bleep 0076, and the PI or CI should be contacted via switchboard outside of these times.

c. Outpatients

In the event that participants are recruited prior to outpatient clinic appointments and vital signs are abnormal, the clinician that they are due to see should be alerted as to the results of the measurements. If this is not possible or the participant is recruited following an appointment then the escalation plan in section b. should be followed.
d. Participants recruited from GP surgeries

In the event that a participant recruited from a GP practice are found to have results outside the normal range, the health care professional due to see the participant will be informed. When a participant is not due to see a health care professional their results will be documented on a results card and the participant will be encouraged to discuss the results with their GP. If the results are within the urgent care range the duty GP will be informed.
Appendix D - References

1) Royal College of Physicians (2015), “National Early Warning Score with explanatory text”
2) Kumar et al. (2015), “Contact-free camera measurements of vital signs”
3) Poh et al. (2014), “Non-contact, automated cardiac pulse measurements using video imaging and blind source separation”