Full title of trial	Development of a robust and reliable pulse oximeter for use by frontline healthcare providers caring for children with pneumonia in low-income countries: clinical usability testing in children aged 0-59 months at Great Ormond Street Hospital, London
Short title	Lifebox Project
Version and date of protocol	Version 1.6, 26th January 2017
Sponsor:	Lifebox Foundation
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Funder (s)	Bill and Melinda Gates Foundation
Investigational Devices	AH-MX handheld pulse oximeter and Lifebox A2 oximeter probe prototype
Sites(s)	UK site: Great Ormond Street Hospital

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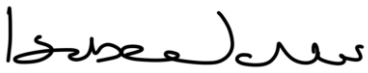
Signatures

The Chief Investigator and the Sponsor have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005' 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

26th January 2017

Chief investigator



Isabeau Walker

Signature	Date
	26th January 2017

Sponsor Representative

Kristine Stave

Signature	Date

Contents

List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GOSH	Great Ormond Street Hospital
IB	Investigator Brochure
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

1 Trial personnel

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2 Summary

Objectives:

The primary objective is to determine the proportion of oxygen saturation measurements obtained within 60 seconds when the oxygen saturation is measured by expert users and by trained healthcare workers using the redesigned Lifebox oximeter and probe for children aged 0-59 months

The secondary objective is to provide further description of the 'usability' of the redesigned oximeter and probe in children aged 0-59 months by healthcare workers, to assess how well children tolerate the probe, and the difference in time to a stable oximetry reading for expert users and healthcare workers in different settings, or for different ages of children.

Type of study:

Mixed methods observational usability testing

Study design and methods:

This observational usability testing involves three types of data collection from three sites in the UK, Malawi and Bangladesh. This protocol relates specifically to the UK testing at Great Ormond Street Hospital.

Expert usability testing: the probe and oximeter will be used by an expert on 204 stable children (i.e. not physiologically unstable or admitted to a high-dependency or intensive care unit) of different ages and with varying illness states. Children will be purposefully recruited from inpatient wards to meet age criteria by a clinical researcher. Following consent, an oxygen saturation measurement will be done by the expert user. An independent observer will note the condition of the child, along with other key demographic, performance and clinical features and the time to successful measurement of oxygen saturation.

Healthcare provider usability testing: the probe and oximeter will be used by healthcare providers on healthy or mild systemically ill patients (i.e. with a normal oxygen saturation, i.e. >94%). Children will be purposefully recruited from inpatient wards to meet age requirements by a clinical researcher and pre-screened for their oxygen saturation. 17 healthcare workers will be assessed for their performance with the prototype probe. Each HCW will undertake an oxygen saturation measurement on 12 children (maximum 204 children at Great Ormond Street Hospital). An independent observer will note the condition of the child, along with other key demographic, performance and clinical features and time to successful measurement of oxygen saturation.

Usability Questionnaire: HCW will be asked to complete a usability questionnaire to collect quantitative and qualitative feedback about the oximeter and probe usability. The questionnaire will be completed following the usability testing by all the healthcare providers.

Study duration per participant:	Healthcare providers are the main study participants and will be involved in the study between 1 and 4 hours, with each healthcare provider taking 12 oxygen saturation measurements. Children will be involved in the study intermittently for up to 80 minutes. Children will be assessed for recruitment and consented prior to each measurement.
Estimated total study duration:	4 weeks
Planned study sites:	Great Ormond Street Hospital [single-site]
Total number of participants planned:	17 healthcare providers, and up to 408 children aged 0-59 months
Main inclusion/exclusion criteria:	The study will be conducted in the inpatient wards of Great Ormond Street Hospital, with recruited healthcare providers and children aged 0-59 months. *Inclusion:* - Children aged 0-59 months in an inpatient ward at Great Ormond Street Hospital - Healthcare provider working on an inpatient ward at Great Ormond Street Hospital *Exclusions:* - Children aged >59 months - Children in critical condition - Guardians lacking capacity to give informed consent for their child - Guardians unable to speak English
Statistical methodology and analysis:	We will calculate the proportion of readings that meet the target product profile requirement of 95% stable readings within 60 seconds. We will describe the time to stable reading, looking at the median time and inter-quartile range. We will compare these descriptive statistics between patient age groups, expert and healthcare provider participants, and with measurements from sites in Malawi and Bangladesh. We will describe differences between these sub-groups using t-tests. Qualitative questionnaire data will be analysed using an inductive thematic approach.

3 Introduction

3.1 Background

Pneumonia is the leading infectious cause of death in children under five and causes an estimated 935,000 deaths every year. Most deaths occur in sub-Saharan Africa and Southeast Asia. The outcomes for children with pneumonia can be improved through appropriate treatment and better case management using the WHO Integrated Community Case Management guidelines (ICCM) and Integrated Management of Childhood Illness (IMCI) guidelines.

Severe pneumonia is associated with hypoxemia, and peripheral oxygen saturation (SpO_2) of less than 90% is associated with increased mortality. The WHO guidelines use this measure to differentiate pneumonia where the child needs referral for oxygen therapy and parenteral antibiotic treatment, from basic treatment which can be managed safely in the community with oral antibiotics. Hypoxemia can be detected non-invasively with a pulse oximeter. Routine screening for hypoxemia provides an opportunity for improved case management, referral and treatment decision making, and has been shown to improve outcomes in children with pneumonia in developing countries. Despite being in widespread use in high-income settings, the uptake of pulse oximeters in low-income countries has been limited due to cost, durability and lack of systems to support this essential technology.

The Lifebox Foundation was formed in 2011 to improve access to pulse oximeters in developing countries following the inclusion of pulse oximetry in the 2009 WHO Guidelines for Safe Surgery. These oximeters, designed in collaboration and with end-users from developing countries in mind, have received good feedback from anaesthetists, paediatricians and healthcare workers in developing countries. However, there are some key areas for improvement that are required to make suitable for use in routine paediatric pneumonia care. This includes the need to improve the reusable oximeter probe for neonates and infants, to reduce the time taken to obtain a reading when the oximeter is used for repeated spot checks, and to improve the battery life and resilience to power fluctuations.

The problem of probe design in children is common to all regions and all users, both expert and non-expert. The solution in high-income settings is to use single-use disposable oximeter probes with an adhesive strip, costing $10-15 each, making this approach not sustainable in resource-poor settings. A re-designed oximeter and paediatric probes, optimised for use in routine care at all levels of the healthcare system, is an important step to improving pneumonia diagnostics and care.

3.2 Preclinical data

In order to ensure that any re-designed oximeter and probe is fit for purpose, a process of Human-Centred Design has been used for the re-design. Human Centred Design is an iterative creative process to problem solving where end-user engagement is embedded into all stages of the product design. Crucially this approach will help to ensure that the end-product will be context appropriate and reflect the specific requirements of healthcare workers who will be using the oximeter. To date we have conducted focus group discussions (FGDs) with healthcare providers in Malawi and Bangladesh, and elicited feedback from a group of international experts in pulse oximetry about the re-designed paediatric probe and oximeter. This feedback has led to changes and modifications in the design of the probe, with two rounds of prototypes developed prior to the one being taken forward to usability testing.

3.3 Rationale

This project aims to design an upgraded pulse oximeter and re-usable probes specifically for children aged 0-59 months, suitable for use in all healthcare settings. A target product profile (TPP) produced through expert consultation by the Bill and Melinda Gates Foundation forms the baseline for the re-design. It specifies the required performance, functional, design and stakeholder needs, with a focus on the design of the interface between the probe and the patient (i.e. how the probe is attached to the child). In the formative work for this study, we have gone through a human centred iterative design process, engaging with end-users in developing countries and international experts, to produce a redesigned probe and oximeter. We are now undertaking final usability testing to ensure that the redesigned oximeter and probe meet the TPP in a range of children and in three different sites with different levels of training of healthcare workers (Great Ormond Street Hospital, district hospitals and community hospitals in Malawi and Bangladesh). This clinical investigation plan relates to the study proposed at Great Ormond Street Hospital only, but the results obtained will be pooled with results from other sites.

Hypothesis: *the redesigned probe and oximeter will perform according to the target product profile of achieving 95% of measurements within 60 seconds.*

Feedback from end-users to date has highlighted that measurements can take between 2-15 minutes in some settings, such as with agitated children in rural community healthcare settings in low-income countries. Therefore, achieving 95% of measurements within 60 seconds would constitute a significant improvement in paediatric pulse oximetry for use in a wide range of settings.

3.4 Assessment and management of risk

This study is categorised as: Type A = No higher than the risk of standard medical care.

Pulse oximetry is a non-invasive measurement that is routinely done in Great Ormond Street Hospital, by all levels of healthcare providers. It poses no risk to the patient, and all measurements taken during the study will be done by either experts or healthcare providers with a minimum required training.

4 Objectives

Primary:
The primary objective is to determine the proportion of oxygen saturation measurements obtained within 60 seconds when the oxygen saturation is measured by expert users and by trained healthcare workers using the redesigned Lifebox oximeter and probe for children aged 0-59 months

Secondary:
The secondary objective is to provide further description of the usability of the redesigned oximeter and probe in children aged 0-59 months by expert users and healthcare workers:

- Is this pulse oximeter probe easy to use by an expert and by healthcare providers?
- Does this oximeter provide a reliable reading when used by an expert and by healthcare providers?
- Is the probe well tolerated by the child?
- Is there a difference in the time taken to obtain a stable oximetry reading by the expert user compared to healthcare providers in different settings, or for different ages of children?

5 Study design

This is an observational usability study. 'Usability' is a broad concept defined by the international standard ISO 9241-11 as:

The extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency and satisfaction in a specified context of use.

There is no specific statistical test for usability. We have defined usability in this study as a measure that is clinically relevant, that is, the proportion of oxygen saturation measurements obtained within 60 seconds by any level of healthcare worker. This measure is taken from the TPP and is the parameter by which the redesigned probe and oximeter will be deemed a success, that is, for a target of 95% of measurements to be obtained within 60 seconds.

Time taken to obtain a reading is only one dimension of usability so we will also be using a mixed questionnaire with quantitative and qualitative data for feedback from end-users based on use failure modes effect analysis (U/FMEA) - this data will be important if we find a low proportion of measurements meet the TPP, to understand the barriers to effective use. These data will be interpreted together to give a broader conclusion of usability, alongside our primary end-point. We will collect additional observational data on the number of repositions of the oximeter probe, the quality of the waveform (used to judge whether a measurement is stable) and condition of the child.

There will be two different types of usability clinical testing performed in this stage, assessing slightly different usability criteria, initially with expert users and then by healthcare providers with a range of training and experience. The primary analysis for the timed outcome of usability will be a pooled analysis from all the participating sites, stratified by expert user and healthcare provider. As the oximeter and probe should be appropriate for different settings, albeit with different levels of staff training, this will provide us an overall measure of usability.

Expert usability testing: the probe and oximeter will be assessed on a range of children, including different ages and with varying illness states (excluding those who are critically ill). Children will be purposefully recruited from inpatient wards at GOSH to meet age criteria by a clinical researcher. The attending guardian will be given study information and asked for informed consent. Following consent, the expert user will take an oxygen saturation measurement. An independent observer will note the condition of the child, along with other key demographic, performance and clinical features, and the time to successful reading.

The end point for a successful reading is defined as the time from when the probe is placed on the child to when the reading is stable (one full screen of a stable pulse waveform); the user says 'STOP' at this point. The time for the successful reading, and the total time taken to obtain a reading including the number of attempts to obtain the reading will be recorded.

Healthcare provider usability testing: the probe and oximeter will be assessed on healthy or mild systemically ill patients (with a normal oxygen saturation, i.e. >94%). Children will be purposefully recruited from inpatient wards at GOSH to meet age requirements by a clinical researcher, who will pre-test children to ensure that their oxygen saturation is above 94% at the point of recruitment. Healthcare providers will be purposefully recruited in each site to have a range of pulse oximeter

experiences and qualifications. Healthcare providers and attending guardians will be given study information and asked for informed consent.

Following consent, the healthcare provider will take an oxygen saturation measurement. An independent observer will note the condition of the child, along with other key demographic, performance and clinical features, and time to successful measurement.

The end point for a successful reading is defined as the time from when the probe is placed on the child to when the reading is stable (one full screen of a stable pulse waveform); the user says 'STOP' at this point. The time for the successful reading, and the total time taken to obtain a reading including the number of attempts to obtain the reading will be recorded.

Usability Questionnaire: A usability questionnaire, which will provide a subjective rating of a product's usability, will be used to gather quantitative and qualitative measures of the new probes usability from the healthcare providers. The questionnaire will be conducted following the usability testing.

6 Selection of Subjects

6.1 Inclusion criteria

Child participants:

- Inpatients (or child awaiting surgery on pre-operative ward) in Great Ormond Street Hospital
- Aged 0 - 59 months
- Clinically stable (as judged by the ward sister and medical team)
- Guardian (parent or adult with legal responsibility for the child) present
- Written informed consent from the guardian

Healthcare providers:

- Healthcare provider employed at Great Ormond Street Hospital who are trained in the use of pulse oximetry
- Written informed consent from the healthcare worker

6.2 Exclusion criteria

Child participants:

- Unstable or critically unwell patients (as judged by the ward sister and medical team)
- Parents (or adult with parental responsibility) who are not able or willing to give informed consent
- Parents (or adult with parental responsibility) unable to speak English well enough to understand study methods or consent form
- For part (2) of the study (usability of the probe by healthcare workers), patients with oxygen saturation 95% or below will be excluded

Healthcare providers:

- Healthcare provider who are not trained to use a pulse oximeter
- Healthcare provider who have not given written informed consent

7 Recruitment

Child participants:
Recruitment of children will be purposeful; to ensure a range of ages (0-59 months old) are included in the study. Children will be recruited from inpatient wards at GOSH, by the clinical researcher with the assistance of the ward sister. We will ask the ward sister to identify patients in the four different age categories who are stable and whose parents (or adult with parental responsibility) are present on the ward. We will ask the ward sister to hand out patient information leaflets to the guardian, and the research team will only approach potential participants if they are happy to be approached. Basic patient demographic data will be collected from the electronic patient notes. Data from other sources will not be required.

Healthcare providers:
Recruitment of healthcare providers will be purposeful, to ensure a range of experiences with pulse oximetry are included in the study. Any nurse employed at Great Ormond Street Hospital who is trained to use pulse oximetry will be eligible to participate in the study. We will approach nurses on each ward in the hospital and hand out study healthcare worker information. Any nurse who is willing to participate will be asked for informed consent.

8 Study procedures and schedule of assessments

8.1 Informed consent procedure

It is the responsibility of the clinical researcher to obtain written informed consent from each subject prior to participation in the study, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. No study procedure will be conducted prior to taking consent from the participant. Consent will not denote enrolment into the study. The signed consent form will be retained at the study site and a copy placed in the medical notes.

Child participants:
A member of the research team will approach the responsible clinical team for potential participants. Having identified a potential patient, the nurse responsible for the patient will make the initial approach to the child and provide the guardian with an information sheet. Only after this point will a member of the research team then approach the parent to ask for informed consent, provided the parent is happy to be approached, making it clear that participation will have no impact on the child's ongoing care and is entirely voluntary. Guardians will have the opportunity to ask questions to the research team prior to consent being taken. Children will be given a picture to illustrate how a pulse oximeter is used to measure the oxygen saturation levels in the body. The picture has also been designed to provide a colouring-in activity for the child

Healthcare providers:
A member of the research team will approach the ward sister of each inpatient ward with written study information. We will ask for volunteer nurses to take part in the study and arrange in advance a suitable time for this to happen, at the convenience of the nurse and research team. Potential participant nurses will be given information sheets by the research team and have the opportunity to ask questions to the research team prior to consent being taken

8.2 Baseline assessments

All children will be assessed for their age and clinical condition; children who are critically unwell will not be included in the study. Children with oxygen saturations of <95% will not be measured by the healthcare providers.

8.3 Definition of end of study

The study will be completed at the end of recruitment. There will not be any follow-ups of the healthcare providers or children involved in the study. We anticipate the recruitment to take a maximum of 4 weeks.

8.4 Discontinuation/withdrawal of participants and 'stopping rules'

The study will stop recruitment if the first 25 readings obtained by the expert user are deemed unreliable according to clinical criteria (i.e. unable to obtain a stable oxygen saturation reading within 5 minutes of application of the probe in a cooperative child). In this situation the redesigned probe and oximeter will be considered 'unusable'.

9 Name and description of Investigational Device

The study involves the use of the AH-MX pulse oximeter manufactured by Acare Technology Co Ltd (Taiwan), and a new prototype pulse oximeter probe manufactured for use with the AH-MX pulse oximeter, the Lifebox A2 pulse oximeter probe (MHRA Class 11b device).

Pulse oximeters are comprised of two parts: the oximeter monitor and the oximeter probe. There is no change in the intended use of the pulse oximeter.

1. The AH-MX Pulse Handheld Pulse Oximeter monitor

The existing Lifebox pulse oximeter is the AH-MX Handheld Pulse Oximeter manufactured by Acare Technology Co Ltd in Taiwan.

The AH-MX handheld pulse oximeter is intended for continuously monitoring or spot checking peripheral oxygen saturation (SpO2) and pulse rate (PR) for adult, paediatric or neonatal patients. This device can be used in institutions or units with health care capability. This includes outpatient departments, emergency rooms and departments of internal medicine in hospitals, ordinary departments in clinics, nursing hospitals and community medical institutions. It may also be used in the home.

The AH-MX pulse oximeter has been CE marked according to the following safety standards:

Safety: IEC 60601-1:2012-Ed.3.1 (EN 60601-1:2006/A1:2013)
EMC: IEC 60601-1-2:2007-Ed.3.0 (EN 60601-1-2:2007/AC:2010)
Pulse Oximeter consensus standard: (EN)ISO 80601-2-61:2011

<u>Modifications to the AH-MX Pulse Oximeter</u>
The AH-MX pulse oximeter monitor has been modified for this project (AH-MX v3)
There have been no changes to the hardware of the oximeter. The oximeter will be powered by 3 commercially available AA alkaline batteries for the study. There has been no change to the intended use of the oximeter

The software in the AH-MX oximeter has been upgraded to allow the oximeter to respond more quickly and more reliably at low perfusion in children 0-59 months. No oxygen saturation readings will be taken for clinical care during the study and there are no safety hazards associated with the upgraded software in this device.

2. Lifebox A2 Pulse oximeter probe

The project team has designed a new prototype pulse oximeter probe for children 0-59 months (the Lifebox A2 probe), intended for use with the AH-MX pulse oximeter. This probe is the focus of this usability testing study. The probe has been designed to fit on the foot of infants, and the finger of older children and adults.

The Lifebox pulse oximeter prototype probes are manufactured with the intent to make them suitable for human use. The materials chosen are all currently in use as part of FDA and ISO cleared devices. The outer shell is of a polycarbonate / acrylonitrile butadiene styrene (ABS) blend and the pads are silicone. These materials are identical to those used in the Nellcor DS100a which has been in use globally for 25 years. The cable jacket is made of a polyurethane that has been FDA cleared and met ISO requirements in the Envisen Bridge FQ series of sensors which are also sold under EnviteC and Bluepoint brands.

While the prototypes as assembled have not yet been subjected to a biocompatibility test, historical experience is that if only known biocompatible materials are used, the device will meet the requirements.

Electrical safety of the sensors in all pulse oximeters is provided in the monitor. For the purpose of the study at GOSH the oximeter will be powered by 3 commercially available AA alkaline batteries.

10 Recording and reporting of adverse events and reactions

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject where the trial medical device is used and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	Any untoward and unintended response in a subject where the trial medical device is used, which **is related** to the medical device. *This includes uses outside of protocol (including misuse and abuse of product)*
Serious adverse event (SAE), serious adverse reaction (SAR) or unexpected serious adverse reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results in death • is life-threatening • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect
Important Medical Event	These events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'.
Unexpected adverse reaction	An adverse reaction the nature and severity of which is not consistent with the information about the device in question set out in the investigator's brochure relating to the trial in question.

SUSAR	Suspected Unexpected Serious Adverse Reaction

10.2 Recording adverse events

All adverse events will be recorded in the child's medical records following consent. If the clinical researcher suspects that the subjects' clinical condition has been affected by the oxygen saturation measurement, then they will record and report this as an unexpected adverse event. All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event. All adverse events will be recorded until the oxygen saturation observation is completed.

10.3 Assessments of Adverse Events

Each adverse event will be assessed for the following criteria:

10.2.1 Severity

Category	Definition
Mild	The adverse event does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

10.2.2 Causality

The assessment of relationship of adverse events to the pulse oximetry measurement is a clinical decision based on all available information at the time of the completion of the measurement. The following categories will be used to define the causality of the adverse event:

Category	**Definition**
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

10.2.3 Expectedness

Category	Definition
Expected	An adverse event that is classed in nature as serious and which is consistent with the information about the pulse oximeter and probe listed in the Investigator Brochure **or clearly defined in this protocol.**
Unexpected	An adverse event that is classed in nature as serious and which is not consistent with the information about the pulse oximeter and probe in the Investigator Brochure

10.2.4 Seriousness

Seriousness as defined for an SAE in section 10.1. Collection, recording and reporting of adverse events (including serious and non-serious events and reactions) to the sponsor will be completed according to the sponsor's guidelines.

10.3 Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the medical notes. The CI will submit a serious adverse event notification and send this to the sponsor within one working day of becoming aware of the event. The CI will respond to any SAE queries raised by the sponsor as soon as possible.

All SUSARs will be notified to the sponsor immediately (or at least within one working day). The sponsor will notify the REC and MHRA of all SUSARs. SUSARs that are fatal or life-threatening will be notified to the MHRA and REC within 7 days after the sponsor has learned of them. Other SUSARs must be reported to the REC and MHRA within 15 days after the sponsor has learned of them.

10.4 Annual progress reports

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The CI will prepare the APR.

10.5 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI and Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

10.6 Notification of Serious Breaches to GCP

A "serious breach" is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the study
(b) the scientific value of the study

The study sponsor will notify the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with the study or the protocol relating to the study, within 7 days of becoming aware of that breach. The sponsor will be notified immediately of any case where the above definition applies during the study.

11 Data management and quality assurance

11.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998. All data collected will not bear the subject's name or other personal identifiable data. A study assigned patient and healthcare provider ID will be used for identification.

11.2 Data collection tools

Data collection will be done using Android tablets for the observational data and with paper forms for the usability questionnaire. These data collection tools have been developed for the purpose of this study, but are based on the Systems Usability Scale and tools developed by the Malaria Consortium for evaluating pulse oximeter performance. The tools have been piloted with the study team and will be piloted with end-users prior to implementation.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the electronic form.

11.3 Data handling and analysis

All observational data will be collected using ODK Collect on an Android tablet. Validation rules will be in-built in the ODK Collect form on the tablet (i.e. not allowing input of invalid values). The tablet will be password protected and the data uploaded to a secure server, which only study personnel can access, with password and username protection. Data will be downloaded as a CSV file and converted to a Stata file. All electronic data will be stored on secure University servers, accessed on password protected computers.

The usability questionnaire will be collected on paper. Quantitative answers will be entered into an Access database and exported into a Stata file. Qualitative data will be analysed directly from the paper forms, with specific quotes transcribed into Microsoft Word. All paper data will be stored in locked cabinets in the Lifebox office.

12 Record keeping and archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. All paper data will be archived in a locked cabinet in the Lifebox offices, and all databases and electronic data will be stored on secure University and Lifebox servers.

The CI is ultimately responsible for the secure archiving of essential trial documents and the study database. All essential documents will be archived for a minimum of 5 years after completion of the study. Destruction of essential documents will require authorisation from the Sponsor.

13 Statistical Considerations

13.1 Outcomes

13.1.1 Primary outcomes

The primary outcome in the study is the proportion of measurements in which a stable oxygen saturation reading was obtained within 60 seconds of placing the pulse oximetry probe by all healthcare providers. This will be measured in both expert users and healthcare providers and the results pooled

13.1.2 Secondary outcomes

Secondary study outcomes include:

- The difference in the time to a stable oximetry reading for expert users compared to healthcare providers in different settings
- The difference in the time to a stable oximetry reading for children of different age
- Qualitative evaluation of the usability of the probe and oximeter
- The fit of the probe on the child's hand or foot
- The child’s tolerance for the probe

13.2 Sample size and recruitment

13.2.1 Sample size calculation

To calculate 95% of measurements being stable within 60 seconds (as per the target product profile) with 2.5% precision and 95% confidence intervals requires 292 measurements. This is calculated using the standard formula to calculate a sample size for estimating a proportion:

$n >= (Z^2 \times p(1-p))/e^2$ [1]
(Z = confidence interval; p = expected true proportion; e = desired precision, half the desired CI width)

$n >= (0.95^2 \times 0.95(1-0.95))/0.025^2$
$n >= 292$

The FDA HF/UE guidance and IEC 62366 state that at least 15 participants should be included from each identified user group interacting with the device. We intend to include 17 trained healthcare workers from a high-income setting, and 17 from each of two low-income settings where there is a high burden of disease in children, and where the Lifebox pulse oximeter is supplied. Each end-user will take 12 measurements (3 from each of four different age-group stratifications of children). This gives a total of 204 measurements from each user-type in each setting. In addition to our pooled primary analysis, this will give us enough power to conduct pooled stratified analyses by site and age group.

The primary outcome will be a pooled analysis from all the participating sites, stratified by expert user and healthcare provider. Studying this number of healthcare workers will give the study sufficient power to undertake sub-group analysis by site and by age of the children assessed.

A summary of the stratified analyses is presented in the table below:

Primary Analysis	**GOSH**	**Malawi**	**Bangladesh**	**Total (2 sites)**	**Total (3 sites)**
Healthcare providers	204	204	204	408	612
Expert users	204	204	204	408	612
All measures	408	408	408	816	1,224
Sub-Analysis					
Neonates (HCW + expert)	102	102	102	204	306
Infants (HCW + expert)	102	102	102	204	306
Toddler (HCW + expert)	102	102	102	204	306

1. For an online calculator: http://epitools.ausvet.com.au/content.php?page=1Proportion&Proportion=0.95&Conf=0.95&Precision=0.025&Population

Child (HCW + expert)	102	102	102	204	306

*shaded cell indicates sufficient power

13.2.2 Planned recruitment rate

We estimate that for 3 healthcare providers to take 12 oxygen saturation measurements will take up to one day. The expert will be taking oxygen saturation readings in parallel. Therefore, allowing for healthcare provider availability and patient turn-over on the inpatient wards, we anticipate recruitment to take a maximum of 3 weeks.

13.3 Statistical analysis plan

13.3.1 Primary outcome analysis

We will calculate the proportion of readings that meet the target product profile requirement of 95% stable readings within 60 seconds. Differences in the proportion of successful readings will be compared between the expert and healthcare providers, between different age groups of children, and between the UK, Bangladesh and Malawi. This will be done using chi^2 tests. All descriptive analyses will be done using Stata 14.

13.3.2 Secondary outcome analysis

We will describe the time to stable reading, looking at the median time and inter-quartile range. We will compare these descriptive statistics between patient age groups, expert and healthcare provider participants, and with measurements from Malawi and Bangladesh. We will look for statistical differences between these sub-groups using t-tests. Descriptive analysis of the observational data on usability, including correct positioning and number of re-positions of the probe, will be conducted. Qualitative questionnaire data will be analysed using an inductive thematic approach.

13.3.3 Sensitivity and other planned analyses

We will collect limited data on the number of children in whom we were unable to take measurements, recording their age and clinical condition to compare with those who we were able to take a measurement. We will compare the age distribution between the two groups, to give an indicator of age-bias in successful measurements.

13.4 Name of Committees involved in trial

There will be structured oversight and reporting of the project. A Project Management Group (PMG), chaired by the CI will be overseeing the study. This committee will also serve the function of the Data Monitoring Committee, with expertise in observational studies and statistics.

We have set up a project advisory group composed of international experts in pulse oximetry who have given input into the design and monitoring of the project and will be invited to provide feedback on the redesigned oximeter probe. They will be given regular updates on the progress of the study, and will act as an independent advisory committee.

We have also involved the GOSH Patient and Public Involvement and Engagement (PPI/E) Team, for input into the study documents, and will feedback results from the study.

14 Direct Access to Source Data/Documents

The investigators will permit study-related monitoring, audits, REC review, and regulatory inspection, providing direct access to study documents. Study participants will be informed of this during the informed consent discussion.

15 Ethics and regulatory requirements

The sponsor will ensure that the study protocol, patient information sheet and consent form have been approved by the MHRA, HRA and research ethics committee, prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation. Within 90 days after the end of the study, the CI will ensure that the REC and MHRA are notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study. The CI will supply the Sponsor with a summary report of the study, which will then be submitted to the MHRA and REC within 1 year after the end of the trial.

16 Monitoring

The sponsor will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly. The degree of monitoring will be proportionate to the risks associated with the trial. A trial specific oversight and monitoring plan will be established for studies. The trial will be monitored in accordance with the agreed plan.

17 Finance

The study is funded by the Bill and Melinda Gates Foundation [grant code: OPP1133291]. The CI and all co-investigators declare no competing financial interests.

18 Insurance

The Lifebox Foundation has purchased Clinical Trials Liability Insurance from CFC Underwriting. The sum insured is £5,000,000 for any one claim and in the aggregate. The basis is claims occurring during the period of the insurance. The period of insurance is for 5 years from the start of the trial.

Great Ormond Street Hospital provides clinical negligence insurance cover for harm caused by GOSH employees under the NHS indemnity scheme.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

19 Statement of compliance

The trial will be conducted in compliance with the approved protocol, the UK Regulations, EU GCP and the applicable regulatory requirement(s).

20 References

Methodology:
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3. US Department for Health and Human Services, Food and Drug Administration. Applying human factors and usability engineering to medical devices. Guidance for Industry and Food and Drug Administration staff. February 2016.
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