GE Healthcare

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Clinical Study Protocol:

U-TruSignal SpO_2 Testing in Neonates

(STUDY NO. 123.04-2017-GES-0002)

Version: 2.0; 01/Mar/2019

GE Healthcare

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Sponsor: General Electric Company, acting through its GE Healthcare Business
3000 N. Grandview Blvd
Waukesha, WI 53188

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GE Healthcare

Investigational Device/Product: U-TruSignal

Modality: GE Healthcare (GEHC) - - Monitoring Solutions

FOR QUALIFIED INVESTIGATORS, STUDY STAFF, AND THEIR ETHICS COMMITTEE(S) ONLY

CONFIDENTIALITY STATEMENT

Information in this RESEARCH STUDY PROTOCOL is for investigators, site personnel involved with the study, ethics committee(s), and/or their authorized representative(s) except as required to obtain consent from study participants or as otherwise required by law. Once signed, the terms of the protocol are binding for all parties.

The Sponsor and Investigator have approved this protocol version, and I confirm hereby to conduct the study according to the protocol and in accordance with applicable principles of the World Medical Association Declaration of Helsinki and Good Clinical Practice (GCP) guidelines as per ISO 14155:2011, any conditions of approval imposed by the reviewing Ethics Committee (EC) or governing regulatory body, and applicable laws and regulations. The Investigator should not deviate from this protocol except for emergency use. I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Local Principal Investigator at study site:

Investigator Signature	Date
Print Name	
Site Name, Department, Address	

Table of Contents

List of Figures and Tables

DOCUMENT AND VERSION CONTROL

This section records all changes made to the protocol for a specific study. In the table below, record every relevant change by indicating what changes were made.

Revision	Date	Revision Author	Comments/Changes
1.0	25/Apr/2017	Catherine Cadogan	Clinical Writer – This is the initial version.
2.0	01/Mar/2019	Catherine Cadogan	Clinical Writer – The purpose of this protocol amendment is to include the language required by the EU Data Protection Regulation 2016/679. Details of the changes can be found in Appendix D.

LIST OF ABBREVIATIONS AND TERMS

ADE	Adverse Device Effect
AE	Adverse Event
ALARP	As Low as Reasonably Practical
AMA	American Medical Association
ARMS	Accuracy Root Mean Square
CA	Competent Authority
CAPM	GE Clinical Affairs Project Manager
CCG	Case Report Form Completion Guidelines
CFR	Code of Federal Regulations
CHF	Clinical History File (synonymous with e-Trial Master File)
COHb	Carboxyhemoglobin
CRF	Case Report Form
DCF	Data Clarification Form
EC	Ethics Committee
EU	European Union
FDA	United States Food and Drug Administration
FCOHb	Fractional Carboxyhemoglobin
FMetHb	Fractional Methemoglobin
FO_2Hb	Fractional Oxyhemoglobin
GCP	Good Clinical Practice (see ISO 14155:2011) [1]
GE	General Electric
GEHC	General Electric Healthcare
Hb	Hemoglobin
ICF	Informed Consent Form
ISO	International Standards Organization
LDR	Legally Designated Representative
MetHb	Methemoglobin
MWS	GE MyWorkshop Internal Documentation System
NICU	Neonatal Intensive Care Unit
O_2Hb	Oxyhemoglobin
PI	Principal Investigator
PRT	Protocol
RHb	Deoxyhemoglobin
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SaO_2	Oxygen Saturation of Arterial Blood *(expressed as percentage)*

SpO_2	Peripheral Capillary Oxygen Saturation [also called as: pulse oximetry oxygen saturation [2] or an estimate of arterial oxygen saturation (SaO2)]
SPR	System Problem Report
tHb	Total Hemoglobin
U.S.	United States
USADE	Unexpected Serious Adverse Device Effect

STUDY SYNOPSIS

Sponsor:	General Electric Company, acting through its GE Healthcare Business
Research Type:	This is a clinical, open label, non-randomized, prospective research study.
Regulatory Status:	This is a pre-market research study of the following devices/products: *Pre-market*: U-TruSignal
Background and Rationale:	Pulse oximetry has the unique advantage of continuously monitoring the saturation of hemoglobin with oxygen; easily and noninvasively providing a measure of cardio-respiratory function.[3] It is the preferred method of oxygen monitoring in neonates.[2] At a neonatal intensive care unit (NICU), continuous health monitoring for the neonates provides crucial parameters for urgent diagnoses so that adequate medical treatment can be instituted.[4] The goal of SpO_2 monitoring for premature neonates is to adequately deliver oxygen to the tissue without causing the complications of oxygen toxicity. Often, the SpO_2 readings from neonates are labile and difficult to keep within a narrow range. The purpose of the study is to demonstrate proper function of the U-TruSignal device via clinical performance testing in a neonatal human subject population under standard clinical conditions. A study with human subjects will provide the needed clinical evidence for assessing the accuracy of the pulse oximeter as recommended by the United States Food and Drug Administration (FDA) Guidance Document (entitled: "Pulse Oximeters – Premarket Notification Submissions [510(k)s]: Guidance for Industry and Food and Drug Administration Staff").
Procedures/ Methods:	After providing consent, no preparation beyond the investigational site's standard of care is required before study procedures begin. At the start of the procedure, 1 to 2 sensors, upon the discretion of the Investigator, shall be applied to the subject. Record site/location of the sensors on the case report form. Allow readings to stabilize. After at least 10 minutes of data collection, collect arterial blood and analyze blood per hospital's standard procedure. Continue collection of data post blood draw for 2 minutes. Clinician shall monitor and record information as specified in this protocol and obtain results of arterial blood draw. The duration of the subject's participation in the study is dependent upon how long the arterial cannula is required for the subject. The period of data collection during the scheduled routine arterial blood draw (up to 3 independent arterial blood draws) is a minimum of 10 minutes and up to approximately 30 minutes from the application of the sensor to the subject. A maximum of 6 data pairs (3 data pairs per sensor) can be collected from each subject.

Objectives:	*Primary*:	To compare SpO_2 data from the U-TruSignal device to SaO2 values from CO-Oximeter analysis of simultaneously drawn arterial blood.
	Secondary:	To demonstrate U-TruSignal collects substantially continuous SpO2 measurements during a data collection interval, which is defined as the period in which SpO2 is collected.
	Safety:	To collect safety information, including type and number of AE's, SAEs, and device issues.
Endpoints:	*Performance*:	The primary endpoint will be Accuracy Root Mean Square (ARMS), comparing the accuracy of SpO2 values from the investigational device to SaO2 values from CO-Oximeter analysis of simultaneously drawn arterial blood. The secondary endpoint will be the percent of invalid data referred to as gaps per data collection interval.
	Safety:	Type and number of AEs, SAEs, and device issues.
Eligibility criteria:	*Inclusion criteria:* 1) Parents or legally designated representative (LDR) can understand and provide written informed consent; AND 2) Subjects are < 29 days old and requiring arterial blood samples per the site's standard of care. *Exclusion Criteria:* 1) Neonates with injuries, deformities or abnormalities may prevent proper application of the sensor; 2) Neonates with inadequate heart pump function affecting blood circulation caused by identified cardiac or cardiovascular conditions such as patent ductus arteriosus, persistent pulmonary hypertension, septal defects, or congenital heart disease; 3) Neonates with mean arterial blood pressure < 20mmHg; 4) Neonates with congenital diaphragmatic hernia; OR 5) Neonates under High frequency ventilation therapy.	
Sample size and Sites:	This study is intended to collect blood samples from neonates under normal clinical conditions. The minimum number of subjects is 17 subjects. Maximum total enrollment for the study is 140 subjects. Subjects will be enrolled at 2 sites.	
Study duration:	The study is expected to last 24 months.	

ADMINISTRATIVE STRUCTURE OF INVESTIGATION

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1. BACKGROUND AND JUSTIFICATION

Pulse oximetry arterial oxygen saturation (SpO_2) has become the "fifth vital sign" in the examination of every newborn and infant with respiratory system presentation. [2] Pulse oximetry has the unique advantage of continuously monitoring the saturation of hemoglobin with oxygen; easily and noninvasively providing a measure of cardio-respiratory function. [3] It is the preferred method of oxygen monitoring in neonates. [2]

In general, pulse oximeters use 2 wavelength absorption spectrophotometries to measure oxygen saturation. The wavelengths are selected to provide the best separation of absorbencies of oxyhemoglobin (O_2Hb) and deoxyhemoglobin (RHb) states. The ratio of the 2 absorbencies is used to calculate the oxygen saturation (SpO_2) value. The pulse oximeter can provide continuous non-invasive real time information, because an arterial sample of blood is not required to make the measurement.

At a NICU, continuous health monitoring for the neonates provides crucial parameters for urgent diagnoses so that adequate medical treatment can be instituted. [4] The goal of SpO_2 monitoring for neonates is to ensure adequate oxygen delivery to the tissue without causing oxygen toxicity. Often, the SpO_2 readings from neonates are labile and difficult to keep within a narrow range. The caregiver should aim to maintain the SpO_2 levels within the narrow range. [6]

The purpose of this study is to collect blood samples from neonates under normal clinical conditions to ensure proper function (clinical performance) with the U-TruSignal device per FDA Guidance Document: Pulse Oximeters – Premarket Notification Submissions [510(k)s]: Guidance for Industry and Food and Drug Administration Staff). [5] Testing will follow ISO 80601-2-61 Annex EE.4.2. [7] The study will include both the TruSignal AllFit Sensor and TruSignal Sensitive Sensor.

A study with human subjects will provide the needed clinical evidence for assessing the accuracy of the pulse oximeter as recommended by the FDA Guidance Document: Pulse Oximeters – Premarket Notification Submissions [510(k)s]: Guidance for Industry and Food and Drug Administration Staff). [5]

2. DEVICE/PRODUCT DESCRIPTION

2.1 Identity, Mechanism, and Function

Name: U-TruSignal

Modality/Type: GE Healthcare (GEHC) -- Monitoring Solutions

Manufacturer: GE Healthcare

Software version: The software version of the U-TruSignal is investigational and may be revised during the study

Regulatory Status: pre-market

Note: A record of number of devices issued, along with applicable identification numbers (e.g. serial/lot/batch) and components/accessories used in this study will be retained by the Sponsor as part of the clinical history file (CHF), as required by applicable laws and regulations.

The U-TruSignal functions primarily by measuring continuous non-invasive arterial oxygen saturation (SpO_2) and pulse rate monitoring. The U-TruSignal calculates the SpO_2 value and transmits the information to a patient monitor to display the calculated SpO_2 value. It is a smart cable device that consists of an over-molded circuit board, which includes the measurement electronics connectors for the SpO_2 sensor and the USB interconnect cable. The U-TruSignal is attached to the computer/medical PC for data collection by a dedicated USB cable. Patient isolation is built into the U-TruSignal circuit board.

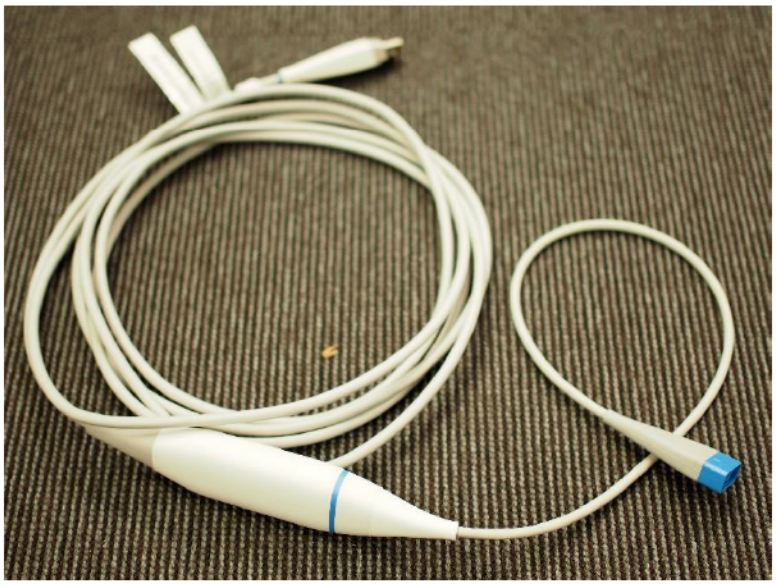
The study will collect complete data pairs from neonate subjects utilizing released sensors TruSignal AllFit Sensor (model #TS-AF-25 or TS-AF-10) and TruSignal Sensitive Skin Sensor (model # TS-SE-3)

with the U-TruSignal investigational device. The sensors will be attached to the patient non-invasively. The U-TruSignal investigational device is not in direct contact with the patient.

The research device, instructions for use, or packaging shall indicate that the research device is for use in a research investigation, in accordance with applicable regulations in the United States including applicable US FDA 21 CFR Part 812 for investigational devices, regulations in Europe under EN ISO 14155:2011, and other applicable laws and regulations. The investigational device will be exclusively used for research purposes.

The results of this study are intended for use in regulatory submission in the United States and Europe to obtain clearance for commercial use. Results may be used to help commercialize the product in other global regions in the future, at the discretion of the Sponsor.

Figure 1 – U-TruSignal Device



2.2 Intended Use

The investigational device is intended to be used for continuous monitoring and measuring of arterial oxygen saturation (SpO_2) and peripheral pulse rate by non-invasive pulse oximetry.

The sensors and accessories are biocompatible. TS-AF and TS-SE sensors that will be used in the study are cleared by the FDA for commercial use. The products can be traced through their respective (manufacturing) LOT numbers.

The procedures conducted in this study are intended for research purposes and are not intended as a substitute for required medical care. The study staff will be trained in the use of the devices and will be provided with the instructions for use.

2.3 Reference Standard

The reference standard for the SpO_2 accuracy as read by the test pulse oximetry system shall be traceable to SaO_2 values obtained from CO-Oximeter analysis of simultaneously drawn arterial blood.[7] The SpO_2 accuracy of the test pulse oximetry system is validated in comparison to "gold standard" measurements of blood SaO_2 by a CO-Oximeter.[7] To achieve this, paired observations of SpO_2 and SaO_2 values over the specified SpO_2 accuracy range (e.g. 70% to 100% SaO_2) of the test pulse oximeter system are compared.[7] The CO-Oximeter SaO_2 value may be based on a single CO-Oximeter reading. If

more than one CO-Oximeter is used, the pairwise comparisons are separately performed for each CO-Oximeter, and the data pairs are pooled together for the final accuracy assessment. [7]

2.4 Concomitant/Ancillary Administrations

2.4.1 Medications and Biologic Products

No medications or biologic products will be administered as part of study procedures.

2.4.2 Laboratory Tests and Sample Processing

Laboratory tests required for this clinical study will be performed according to the site's standard of care and will not be prescribed by the Sponsor.

2.5 Accountability

Accurate and adequate records will be maintained for all devices, from time of shipment to the sites until return or disposal of all devices issued by the Sponsor as part of this study, as required by applicable laws and regulations. The Principal Investigator will be ultimately responsible for the security and integrity of research devices at the investigational site during the study.

2.5.1 Issuance

The device and accessories will be provided by the Sponsor. Calibration/maintenance of study device/product(s) is not required.

2.5.2 Disposition

The device(s)/product(s) will be dispositioned after the study by returning the investigational device to the Sponsor or other contractual disposition, in accordance with applicable laws and regulations.

2.6 Anticipated Risks and Benefits

The product under study has undergone risk assessment, in accordance with International Standards Organization (ISO) 14971:2012, and risks are acceptable or mitigated to levels As Low As Reasonably Practical (ALARP).

The U-TruSignal is an investigational device similar to commercially released pulse oximeters regarding the subject-device interface. The circuit board design is similar to standard pulse oximeters regarding device safety and functional parts of the board. Therefore, the risks related to the signal detection system and accessories are the similar for the released SpO_2 measurement modules and accessories.

The risks of the U-TruSignal have been analyzed, mitigated, and verified by safety testing or labeling as recorded in the U-TruSignal instructions for use. Potential risks include failed isolation on the electrical board and excessive interface temperature. The risks are explained in the U-TruSignal instructions for use, which will be provided to the site.

The sensors TruSignal Allfit Sensor and TruSignal Sensitive Skin Sensor are FDA cleared and CE marked medical devices.

The risks of study participation are not expected to be greater than those of similar procedures routinely conducted in clinical practice. Post-trial care or follow-up is not required by this study.

Subjects are not expected to benefit directly from study participation. The results may benefit future patients by helping to better understand the continuous monitoring and measuring of SpO_2 and peripheral pulse rate.

2.6.1 Risk Category and Rationale

Under the United States FDA (USFDA) Guidance Document on Pulse Oximeters for Premarket Notification Submissions [510(k)], USFDA "believes pulse oximeters addressed by the guidance document are non-significant risk devices; therefore, the study would be subject to the abbreviated requirements of 21 CFR 812.2(b)." [5] Hence, it can be stated that the U-TruSignal device, accessories, and components, as used in this study, are not considered a significant risk device, per the USFDA 21 CFR §812.3(m) definition:

1) it is not intended as an implant;
2) is not purported or represented to be for a use in supporting or sustaining human life;
3) is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health;
4) and it does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

The application of risk management analysis to the U-TruSignal conforms to ISO 14971:2007 and EN ISO 14971:2012. For continued safe use of the U-TruSignal, the instructions in the User's Manual shall be followed.

2.6.2 Device/Product Classification and Rationale

The U-TruSignal and SpO_2 sensors are intended for use in the measurement of oxygen saturation (SpO2) by non-invasive pulse oximetry. The FDA has classified such devices as Class II.

The U-TruSignal conforms to the provisions of the Council Directive 93/42/EEC concerning medical devices amended by 2007/47/EC and fulfills the essential requirements of Annex I of this directive. The U-TruSignal is considered an active device, and are in Class IIb, per Classification Rule 10 of the Council Directive 93/42/EED Annex IX. Classification Rule 10 states: *"Active devices intended to allow direct diagnosis or monitoring of vital physiological process, unless they are specifically intended for monitoring of vital physiological parameters, where the nature of variations is such that it could result in immediate danger to the patient, for instance variations in cardiac performance, respiration, activity of CNS in which case they are in Class IIb."*

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Purpose of the Study

The purpose of the study is to demonstrate proper function of the U-TruSignal device via clinical performance testing in a neonatal human subject population under standard clinical conditions. For the purposes of this study, proper function will be defined by accuracy (i.e. ARMS value), substantially continuous measurement abilities, and safety profile.

3.1.1 Primary Objective

To compare SpO_2 data from the U-TruSignal device to SaO_2 values from CO-Oximeter analysis of simultaneously drawn arterial blood.

3.1.2 Secondary Objective

To demonstrate U-TruSignal collects substantially continuous SpO_2 measurements during a data collection interval, which is defined as the period in which SpO_2 is collected.

3.1.3 Safety Objective

To collect safety information, including type and number of AEs, SAEs, and device issues.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint will be Accuracy Root Mean Square (ARMS), comparing the accuracy of SpO_2 values from the investigational device to SaO_2 values from CO-Oximeter analysis of simultaneously drawn arterial blood.

3.2.2 Secondary Endpoint

The secondary endpoint will be the percent of invalid data, referred to as gaps, per data collection interval.

3.2.3 Safety Endpoints

Type and number of AEs, SAEs, and device issues.

3.3 Summary of Study Design

This is a pre-market, clinical, open label, prospective, non-randomized research study conducted at 2 sites.

4. STUDY DESIGN

4.1 Study Population

Subjects that will be enrolled are neonatal patients <29 days old requiring arterial blood draw as part of their routine care.

4.2 Number Subjects

This study is intended to collect blood samples from neonates under normal clinical conditions. The minimum number of subjects is 17 subjects. Maximum total enrollment for the study is 140 subjects.

4.3 Protection of Vulnerable Subjects

Vulnerable subjects are individuals whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate.

The Sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any Investigator(s), or other parties participating in, or contributing to, the clinical investigation.

All investigators shall avoid improper influence on, or inducement of, the subject, Sponsor, monitor, other Investigator(s), or other parties participating in, or contributing to, the clinical investigation.

The study activities cannot otherwise be performed without the use of vulnerable populations.

Neonates: Neonates will be subjects in this study. The purpose of this study involves meeting the health needs of these populations. These subjects are considered a vulnerable research population since neonates cannot provide valid informed consent to which their parent or LDR must provide written informed consent for their child's participation.

Studying subject populations as specified in the inclusion and exclusion criteria set forth in this protocol is necessary, because SpO_2 monitoring is a routine part of these population's clinical assessment. The

study staff will be present during all study procedures and no subject will be left alone during any part of the study procedure.

This research is approved by the EC prior to the start of the clinical study.

4.4 Eligibility Criteria

4.4.1 Inclusion Criteria

Subjects who meet all the following inclusion criteria may be included:

1) Parents or LDR can understand and provide written informed consent; AND
2) Subjects are < 29 days old and requiring arterial blood samples per the site's standard of care.

4.4.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will be excluded:

1) Neonates with injuries, deformities or abnormalities may prevent proper application of the sensor;
2) Neonates with inadequate heart pump function affecting blood circulation caused by identified cardiac or cardiovascular conditions such as patent ductus arteriosus, persistent pulmonary hypertension, septal defects, or congenital heart disease;
3) Neonates with mean arterial blood pressure < 20mmHg;
4) Neonates with congenital diaphragmatic hernia; OR
5) Neonates under High frequency ventilation therapy.

4.5 Recruiting and Screening

Subjects, who are neonates, will be recruited for potential enrollment in this study per the standard procedures of the investigational site, unless otherwise specified by the Sponsor in this study protocol. The parent(s) or LDR(s) of the neonate patient will be asked to volunteer their child to participate in this research study and provide written informed consent. All participation will be voluntary.

Subjects will be screened for enrollment in this study against the inclusion and exclusion criteria per the standard procedures of the investigational site.

Following recruitment, a subject will be considered enrolled (the point of enrollment) once the parent/LDR signs and dates the informed consent form (ICF). Once enrolled, the subject will be assigned a unique subject number, which will not contain information that could identify the subject (such as subject name or date of birth). The unique subject number will be used to label case report form (CRF) data for the subject throughout his/her participation in the study.

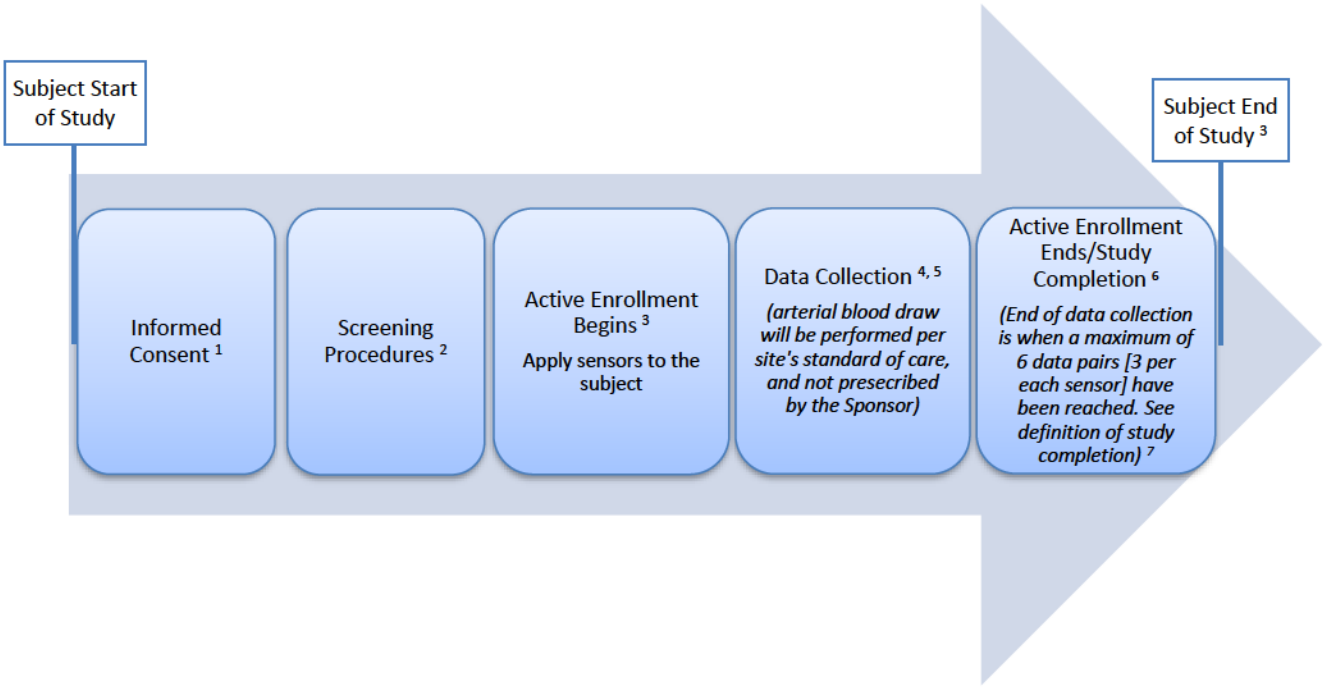
4.6 Criteria for Withdrawal/Discontinuation

The parent(s) or LDR(s) may withdraw their child from study participation at any time, for any reason. The Investigator may withdraw a subject at any time, for any reason. The reasons for withdrawal and discontinuation for any subject shall be recorded. These will be reported to the Sponsor. The EC should be notified per their notification of subject withdrawal policy.

5. STUDY PROCEDURES

5.1 Diagram of Procedures

Figure 2 – Diagram of Study Procedures



Notes:

1. *Subject is considered enrolled once the informed consent has been signed.*
2. *After the parent/LDR signed the informed consent form, subjects that did not completely fulfill the inclusion/exclusion criteria will be considered withdrawn.*
3. *Adverse Event monitoring and reporting begins when the subject's parent/LDR signed the informed consent form through study completion.*

   Study Completion or Subject's End of Study is defined as the last data collection as determined by the Investigator and/or study staff by recording the study completion date and time.
4. *The duration of the subject's participation in the study is dependent upon how long the arterial cannula is required for the subject. Data collection for a data pair (3 data pairs per sensor) is a minimum of 10 minutes and up to approximately 30 minutes from the application of the sensor to the subject.*
5. *Investigator or designee can determine when a longer data collection is needed.*
6. *Removal of the investigational device may or may not be the end of the study and the end of AE monitoring and reporting – see definition Study Completion/Subject's End of Study under Note#3 above.*
7. *Procedure may be repeated at the time of arterial blood draw to collect a maximum of 6 data pair (3 data pairs per sensor).*

5.2 Subject Preparation

Study staff will confirm that the subject is eligible and complies with applicable site requirements prior to starting study procedures.

After providing consent, no preparation beyond the investigational site's standard of care is required before study procedures.

5.3 Description of Study Procedures

The following are the steps to be performed:

1) To document the case, photographs of the position of the measurement sensors and other equipment may be taken at the request of the Sponsor at any point of the procedure, when necessary.

   Note: photographs are taken in a way that the subject cannot be identified from the pictures.

2) Apply sensor(s) to the subject as appropriate. No more than one SpO_2 sensor placed on the same limb, and no sensor placed close to blood draw site/IV cannulation (same limb). Record site of sensor(s) placed on the CRF.
3) Allow the clinical environment and readings to stabilize.
4) Start data collection using the data collection tool.
5) Collect data using the data collection tool for a minimum of 10 minutes prior to routine arterial blood draw, per the data collection tool. Record possible accidental annotations in CRF.

   Note: The arterial blood draw collected during this study will be performed according to the site's standard of care and will not be prescribed by the Sponsor.

6) When routine arterial blood draw is conducted, mark arterial blood draw time with data collection tool. The blood sample will be processed through hospital's standard procedure. Record possible accidental annotations in CRF.
7) After arterial blood draw, continue collecting data using the data collection tool for a minimum of 2 minutes. Record possible accidental annotations in CRF. Stop data collection.
8) Remove sensor(s) from the subject.
9) Monitor and record the following information using the data collection tool or recording on CRF during steps 4-7):
   a. clinical status notes; i.e., frequent apnea, hemodynamic instability, abnormal heart rhythm, or other status;
   b. environmental conditions such as changes in lightning conditions, ongoing care moving the neonate outside blood sampling, excessive clinical signs such as agitation, readjustment of a sensor; AND
   c. notes regarding data collection such as accidental annotations.
10) Obtain results of the arterial blood draw and record possible errors during standard procedure for blood sampling and analysis.
11) Repeat Steps 1-10 up to 3 times to obtain a maximum of 6 data pairs, 3 data pairs per sensor aiming to collect equal data for each sensor.

    Note: Alternate the sensors used; e.g.; if TS-AF was used first, then TS-SE should be used at the next data collection.

NOTE: *Study Completion or Subject's End of Study is defined as the last data collection determined by the Investigator and /or study staff by recording the study completion date and time.*

GE Healthcare engineering representatives may be present during study procedures, depending upon their need to observe the functioning of the investigational device (their need to observe will depend upon the study staff indicating there is an issue for the engineers to look at). These representatives will always be accompanied by study staff. These visits will be agreed upon and arranged by the Research Manager and the Investigator on a case-by-case basis.

5.4 Follow-up

No follow-up will be conducted. The subject will be followed for AEs from the time consent has been provided to study completion/end of study. (See definition of study completion.)

6. STUDY DATA COLLECTION AND ASSESSMENTS

6.1 Primary Assessment

The Investigator or designated study staff will perform the collection of SpO_2 and pulse rate, that will be recorded in the U-TruSignal Data Collector. Laboratory results from arterial blood draw will be collected from the hospital's medical records.

The following data will be collected on the CRF:

1) Demographics: date of birth, gender, length, and weight, skin tone (see Appendix C – Modified Fitzpatrick Scale);
2) U-TruSignal Serial Number, Sensor Type, LOT Number, and Attachment Location of the Sensor;
3) Notes regarding data collection e.g. incorrect annotation of data file or several data files;
4) Relevant information on the clinical status affecting hemodynamic stability such as frequent apnea, hemodynamic instability, abnormal heart rhythm;
5) Environmental conditions e.g. open bed, changing lightning conditions, ongoing care causing movements, readjustment of a sensor.

The laboratory results will include and to be collected from the hospital's medical record:

1) Co-Oximeter information,
2) Functional SaO_2 (%),
3) Fractional oxyhemoglobin (FO_2Hb) [%],
4) Fractional carboxyhemoglobin (FCOHb) [%],
5) Fractional methemoglobin (MetHb) [FMetHb] [%],
6) Total hemoglobin (tHb) (ctHb) [g/L]
7) Fetal hemoglobin (Hb) [g/L] (calculated), and
8) Fractional fetal hemoglobin [%].

6.2 Safety Assessments

The description, severity, and device relatedness of any AE or SAE during the study will be recorded. Subjects will, if necessary, be provided with emergency care. In the event of any device issues, the event will be recorded. Safety reporting will be conducted as described in this protocol.

7. QUALIFICATION AND TRAINING PLAN

7.1 Staff Qualifications

All members of the study staff participating in the conduct of the clinical investigation shall be qualified by education, training and/or experience to perform their tasks, and this shall be documented appropriately, as per ISO 14155:2011 for clinical studies.

7.2 Training Plan for the Protocol and Research Device/Product

Before starting the study, the study staff and hospital department staff will be trained on the clinical investigation requirements set forth in this study protocol according to the following requirements.

- Title of Training

- Training objectives
- Training logistics (who conducts training and training method)
- Target audience (who will be trained)
- Training content (including device operation and set-up, protocol review and understanding)Any personnel that will be involved in the study must receive protocol training prior to participating in the study. Additional training may be provided as needed.

Study staff directly operating or maintaining the research device will be trained based on the operator manual and/or qualified based on experience as qualified by the hospital/clinical site policy. A training log will be provided and maintained for the study.

The Principal Investigator will be ultimately responsible for execution of this study in accordance with the protocol and for device/product use in this study by members of the study staff.

8. SAFETY

8.1 Anticipated Adverse Events

Being in this study involves some foreseeable risks.

Pulse Oximetry Sensor placement involves positioning pulse oximetry sensors on the volunteer subject in the same manner used with released SpO_2 cables. The U-TruSignal investigational device is not in direct contact with the patient. The sensors that will be in contact with the subject are cleared for commercial use. The sensors may be warm to the touch. Under normal operating conditions (no fault conditions), the sensors are not expected to overheat. If the Investigator or delegate conducting the study senses the sensor is too warm or the subject is experiencing discomfort the sensor will be removed immediately and the area of concern will be massaged, and the sensor will be replaced at the discretion of the study staff, the sensor may be removed, and the study procedures discontinued at any time. Sensors may cause irritations to the skin in some subjects. The risk in the use of pulse oximetry sensors is considered minimal.

There is always a chance of unexpected risks. Throughout the study, the Sponsor will evaluate and update safety information in study documents.

8.2 Adverse Event Definitions

Adverse Event (AE): any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device [ISO 14155:2011 3.2]. This includes events related to the investigational device or the comparator and to the procedures involved. For users or other persons, this is restricted to events related to the investigational medical device.

Serious Adverse Event (SAE): an AE that led to death; led to a serious deterioration in the health of the subject, that either resulted in a life-threatening illness or injury, a permanent impairment of a body structure or a body function, or in-patient or prolonged hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function; or led to fetal distress, fetal death or a congenital abnormality or birth defect. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol without serious deterioration in health, is not considered a SAE [ISO 14155:2011 3.37].

Adverse Device Effect (ADE): an AE related to the use of an investigational medical device [ISO 14155:2011 3.1]. This includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This includes any event that is a result of a user error or intentional misuse of the investigational device [ISO 14155:2011 3.43].

Serious Adverse Device Effect (SADE): an ADE that has resulted in any of the consequences characteristic of a SAE [ISO 14155:2011 3.36].

Device deficiency: an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, such as malfunctions, use errors, and inadequate labeling [ISO 14155:2011 3.15].

Unanticipated serious adverse device effect (USADE): a SADE, which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report [ISO 14155:2011 3.42]. In the United States, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study documents, will be reported in accordance with 21 CFR §812.3 and applicable laws and regulations.

8.3 Documentation of Safety Events

All AEs, including all SAEs, are required to be collected, investigated, and documented during the study reporting period, as defined in the study procedure set forth in this protocol. Documentation will include:

- Description of Event
- Date of onset and resolution
- Severity (mild, moderate, or severe)
    - *Mild*: Symptom(s) barely noticeable to the subject or does not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
    - *Moderate*: Symptom(s) of a sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.
    - *Severe*: Symptom(s) of a sufficient severity to cause the subject severe discomfort. Treatment for symptom(s) may be given.
- Serious (yes/no)
- Causal relationship to investigational medical device? (not related, possibly related, or related)
    - *Not related*: The AE is reasonably expected to be related to (or caused by) a concurrent illness, effect of another device/drug or other cause, and is unlikely related to the investigational product.
    - *Possibly related*: The AE is reasonably expected to be related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product.
    - *Related*: There is a strong relationship to investigational product or recurs on re-challenge, and another etiology is unlikely or there is no other reasonable medical explanation for the event.
- Treatment given and/or action taken (procedure stopped, withdrawn from study, or no action)
- Anticipated (yes/no)

8.4 Reporting of Safety Events

The following events are to be reported to the Sponsor within 72 hours of the event occurrence and to the EC per their policy:

- All SAEs and USADEs
- All device issues that could possibly lead to an SAE

The following information is the Sponsor contact for SAEs and/or UADEs:

Helena Haukilehto, MD

Fax: +1 262-364-2544 (24 hours)
E-mail: SAE@ge.com

Additional follow-up information including the medical records of the subject may be requested by the Sponsor. In addition, safety information may be shared with regulatory agencies and other participating sites, as required by applicable law and regulation.

8.5 Device Deficiencies/Complaints

Device deficiencies related to the investigational device should be reported directly to the engineering team, after each case by the Investigator or study staff, who finishes the case. Device deficiencies related to the approved or cleared device should be reported to the study Sponsor.

Sponsor contact for device complaints:

Cynthia Hines-Sabol, *Clinical Affairs Project Manager*
Tel: +1 262-422-1306
E-mail: cynthia.A.hinessabol@ge.com

All device deficiencies will be collected, fully investigated, and documented in the source document and appropriate CRF during the study reporting period. The Principal Investigator is responsible for notifying the Sponsor if there is any device issue that could potentially lead to a SAE.

9. ETHICAL CONDUCT OF THE STUDY

The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki; the guidelines of GCP for medical devices, as set forth by ISO 14155:2011 and ISO 14971:2012; European Directive on medical devices 93/42/EEC for studies conducted in Europe; and applicable local regulatory authority's requirements of Finland – Valvira.

The study will be conducted and reported in accordance with applicable policies of the local EC and governing regulatory authorities in Finland and India (when India's law comes into effect).

If national or regional EC requirements are less strict than the requirements of GCP, such as ISO 14155:2011 for medical devices, the Sponsor shall apply the requirements of this International Standard to the greatest extent possible, irrespective of any lesser requirements, and shall record such efforts.

9.1 Ethics Committee

The responsible Principal Investigator at each site will ensure that approval from an appropriately constituted EC is attained for the clinical study prior to enrolling subjects, and Principal Investigator will ensure that documentation of approval is maintained for the duration of the study.

The Principal Investigator will ensure that the Sponsor is notified of any withdrawal of EC approval within 5 working days of such occurrence. If approval is terminated or suspended, the Principal Investigator will promptly notify the Sponsor and provide written explanation.

9.2 Regulatory Agencies and Competent Authority(ies)

The Sponsor will obtain approval from the local regulatory agency or competent authority before the start of the clinical trial, if necessary, per applicable local laws and regulations. Any additional requirements imposed by the EC or regulatory authority shall be followe d, if applicable. Documentation of notification will be maintained in the Site Regulatory Binder.

For clinical studies conducted in Finland, per the local regulatory agency or competent authority requirements the Sponsor will notify Valvira, the local regulatory agency or competent authority, before the start of the clinical trial, if necessary, per applicable local laws and regulations.

9.3 Management of Protocol Modifications and Amendments

Substantial amendments will only be implemented after approval of the EC.

9.4 Management of Protocol Deviations

A deviation is any instance(s) of failure to follow, intentionally or unintentionally, the requirements of the protocol. Under emergency circumstances, deviations from the protocol to protect the rights, safety, and well-being of human subjects may proceed without prior approval of the Sponsor and the EC. Such deviations shall be documented and reported to the Sponsor and the EC as soon as possible. Deviations will be reported as:

- **Critical Deviations:** Deviations that significantly affect the safety, efficacy, integrity, or conduct of the study. These deviations must be reported to the Sponsor no later than 5 working days from awareness of occurrence and reported to the EC per the deviation reporting policy.
- **Non-Critical Deviations:** Protocol deviations that do not significantly affect the safety, efficacy, integrity, or conduct of the trial. These deviations must be documented on the CRF Protocol Deviation page and will be reviewed by the study monitor.

Non-substantial modifications may be made during the normal course of device optimization, maintenance, and feasibility testing. Non-substantial modifications will be communicated to the CA as soon as possible, if applicable, and to the EC per their policy.

9.5 Participant Information and Informed Consent

The investigators will explain to each participant's parent(s) or LDR(s) the nature of the study, its purpose, the procedures involved, the expected duration of exposure to the investigational device, the potential risks and benefits, and any potential discomforts. Each participant's parent(s) or LDR(s) will be informed that participation in the study is voluntary, that he/she/they may withdraw his/her/their child from the study at any time, and that withdrawal of consent will not affect his/her/their child's subsequent medical assistance and treatment. The participant's parent(s) or LDR(s) must be informed that his/her/their child's medical records may be examined by authorized individuals other than their treating physician.

All participant's parent(s) or LDR(s) for the study will be provided an informed consent form, describing the study and providing sufficient information, to allow the participant's parent(s) or LDR(s): (i) to make an informed decision about his/her/their child's participation in the study, and (ii) to be fully aware of his/her rights under the applicable law. Informed consent documents will be subject to approval by the EC prior to enrolling subjects in the study.

The participant's parent(s) or LDR(s) should read and consider the statement before signing and dating the ICF and shall be given a copy of the signed document. The ICF must also be signed and dated by the Investigator (or his/her designee), and it shall be retained as part of the study records.

9.6 Early Termination of the Study

The Sponsor may terminate the study prematurely according to certain circumstances. Examples of such circumstances include ethical concerns, insufficient participant recruitment, participant safety concerns, alterations in accepted clinical practice that make the continuation of a clinical trial unwise, early evidence of benefit or harm of the research product, or for any other reason.

9.7 Incidental Finding

Incidental findings observed during the study conduct shall be processed under the purview of the Principal Investigator through the investigational site's standard of practice.

10. STATISTICAL METHODS

10.1 Statistical Hypothesis

Summary statistics will be used to summarize the data. No statistical hypothesis is being tested in this study.

10.2 Sample Size Determination

This study is to collect blood samples from neonates under normal clinical conditions. The minimum number of subjects is seventeen (17) subjects. Maximum total enrollment for the study is one hundred forty (140) subjects.

Per ISO 80601-2-61:2011, [7] at least 200 data pairs from at least 10 subjects is required for the adult desaturation test, with SaO_2 values distributed on 5 saturation plateaus spanning the range of 70-100%. Unlike the invasive controlled desaturation test on adults in a laboratory environment in which the SaO_2 can range from 70% to 100%, the SaO_2 collected in this study is expected to be around 90%. Since SaO_2 values in this study may be clustered in 1 plateau around 90%, a minimum of 50 data pairs is considered adequate to ensure proper function/clinical performance with neonates with U-TruSignal device. Up to 3 data pairs may be collected on an individual patient per sensor, patients with a minimum of one data pair will be included in the study. The TruSignal AllFit Sensor (model #TS-AF-25 or TS-AF-10) and TruSignal Sensitive Skin Sensor (model # TS-SE-3) will be used. The study is targeted to obtain 50 to 70 SpO_2/SaO_2 data pairs from 17 to 70 neonatal subjects per sensor.

10.3 Statistical Analysis

10.3.1 General Statistical Methods

The study data will be presented in tables, listings, and figures. Data will be summarized using descriptive statistics. The descriptive statistics for continuous variables will include mean, standard deviation, median, Q1 and Q3, minimum, maximum, and sample size. Categorical variables will be described with counts, percentages, and sample size. A 95% confidence interval may be presented, when necessary.

10.3.2 Analysis Set(s)

The study analysis will include all valid data collected from all participating subjects.

10.3.3 Analysis of Primary Endpoint

Data analysis for the data collection interval, which is defined as the 5 second period starting after a twelve (12) second technical delay from the time sampling occurs, will follow ISO80601-2-61, 2011, Annex EE and the FDA Guidance Document for Pulse Oximeters (FDA Guidance, March 4, 2013). Separate analysis will be performed for each sensor type.

The ARMS calculation is used as a means to define the SpO_2 Accuracy. Arms will be calculated as

$$Arms = \sqrt{\frac{\sum_{i=1}^{n}(DUT_i - \mathrm{Re}\, f_i)^2}{n}}$$, where

Ref_i = Reference CO-Oximeter Functional SaO_2 of data pair *i*

DUT_i = Device Under Test SpO_2 of data pair *i*

The difference between SpO_2 and SaO_2 will be summarized using mean, minimum and maximum. Number of subjects and number of data pairs will also be presented.

A least squares regression of SpO_2 on SaO_2 will be performed and results be presented with a regression plot and table.

Bland-Altman graphical plots, error (SpO_2 – SaO_2) versus average SaO_2 will be generated with mean, and upper 95% and lower 95% limits of agreement according to Section 3 of "Agreement Between Methods Of Measurement With Multiple Observations Per Individual" by Bland and Altman in 2007 Journal of Biopharmaceutical Statistics. Individual test subjects will be color coded in the Bland-Altman graphical plot.

Data listed below will be excluded from analysis:

- Data with SaO_2 < 70%, tHb < 10g/L, MetHb > 2%, COHb > 3%;
- Draws with values smaller than -0.5% in any of the Hb values;
- Artefacts/other external error sources indicated by clinical documentation or derived from the collected data around sampling including but not limited to:
    - changes in sensor fit;
    - excessive movement during draw;
    - low perfusion (mod% < 0.5%);
    - irregular plethysmographic waveform or artefacts in the waveform;
- Data with error conditions on CO-Oximeter analysis indicated by clinical documentation e.g. air bubbles in syringe, clots, violation of hospital's standard procedure;
- Data with error conditions on pulse oximeter;
- Unstable SpO_2 readings from the respective device under test:
    - SpO_2 max-min ≥ 4% in time window during 30 sec prior/after the blood sample;
    - SpO_2 max-min ≥ 8% in time window during 10 minutes prior to the blood sampling time;

A rationale will be provided for any data that is excluded from the data analysis.

10.3.4 Analysis of Secondary Endpoint

Invalid data will be characterized during the data collection interval, which is defined as the period in which SpO_2 is collected excluding annotated invalid data periods. Gaps in the data collection interval will be seen in the e-data file as invalid (negative number) as identified by GE engineering.

- Invalid data < 10%

10.3.5 Safety Analysis

Safety events will be presented as a listing, and frequency of instances will be calculated. This will be conducted for all subjects.

10.4 Handling of Missing Data

Analysis will be based on collected data, and no imputation will be done for missing data. The Investigator is obligated to provide written documentation of any missing data to the Sponsor and to provide clarification upon Sponsor request if possible.

10.5 Deviation(s) from the Original Statistical Plan

Any changes or deviations from the original statistical plan specified in this protocol will be described and justified in the statistical analysis plan (SAP) and study final report, per ISO 14155:2011.

11. QUALITY ASSURANCE AND CONTROL

11.1 Data Management

Data management processes for handling study data will be maintained by the Sponsor.

11.1.1 Completion of Case Report Forms (CRFs)

The data reported on the CRFs (eCRFs) shall be derived from source documents and be consistent with these source documents. Paper CRFs and/or electronic CRFs (eCRFs) will be used to collect data. The Sponsor will provide CRFs (eCRFs) and train study staff on completion of CRFs (eCRFs) using Good Documentation Practices (GDP). CRF Completion Guidelines (CCG) may be provided by the Sponsor to help facilitate training.

CRFs (eCRFs) are to be completed as information becomes available at the site. CRFs (eCRFs) should be signed by indicated parties, in indicated area(s), to certify the contents of the form. The Principal Investigator is ultimately responsible for ensuring completion of CRFs (eCRFs).

If discrepancies are discovered on paper CRFs during monitoring, the Sponsor's representative will ensure that the study staff makes necessary corrections directly to the paper CRF(s) prior to collection.

The original copies of paper CRF shall be sent to the Sponsor after the study monitor has completed data verification. Photo copies of the paper CRF shall be kept by the site along with the study documents. Upon receipt of the paper CRF by the Sponsor, the Sponsor will review the data. A Data Clarification Form (DCF) may be provided to the site to correct or clarify discrepancies.

If a site discovers discrepancies after paper CRF collection, the site may notify the Sponsor and request data modification.

In the event that any discrepancies are discovered on the eCRF, whether during monitoring or during data review by the study team, a query will be raised, and the site shall make the correction within the electronic database, noting the reason for change. Data will be considered clean once all queries are answered and closed.

If the Sponsor discovers discrepancies on eCRFs, a query will be raised, and necessary corrections will be made by the site. The reason for any changes will be noted. All queries will be resolved prior to study completion.

There will be electronic data collected by the U-TruSignal data collection tool to which only authorized personnel will have access. Data collected by the data collection tool will be fully de-identified; i.e., all personal identifying information has been removed and replaced by using the subject identification number assigned to the subject. Electronic data will be transferred to GEHC as indicated in the Data Management Plan. A copy of this electronic data shall be provided to the site to which the site will store with the subject's study documents.

11.1.2 Data Handling and Record Keeping

All documents and data shall be produced and maintained in a manner that assures control and traceability.

11.1.3 Source Data and Documents

Source data includes information in original records, certified copies of original records of clinical findings, observations, or other activities for the study. Source documents for each subject must be retained throughout the investigation, including printed or electronic documents containing source data. Elements should include:

- **Source data and documentation** relevant to data recorded for subject screening and CRF corroboration.
- **Subject records** containing the completed ICFs, CRFs, and electronic data copied from the data collection tool.
- **Regulatory binder** containing the protocol and any subsequent amendments, EC submissions and approvals, blank ICF(s), and site logs.
- **Reference manuals** containing Investigator responsibilities, Sponsor, AE/SAE and informed consent guidelines, applicable study aids and training materials, and operator's manuals.

The Principal Investigator or institution shall provide direct access to source data during and after the clinical investigation for monitoring, audits, EC review, and regulatory authority inspections.

11.1.4 Archiving

All study data must be archived for the period defined by local law after study termination or premature termination of the clinical trial. No source documents or study records will be destroyed without Sponsor notification and approval.

12. MONITORING PLAN

In collaboration with the site, the Sponsor will ensure proper monitoring of the study to confirm that all the research requirements are met. Monitoring visits will oversee the progress of a clinical investigation and ensure that it is conducted, recorded, and reported in accordance with the protocol, written procedures, GCP ISO 14155:2011, and the applicable regulatory requirements.

12.1 Confidentiality and Data Protection

The Investigator affirms and upholds the principle of the participant's right to privacy, and the Investigator shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing data in scientific journals.

Individual subject medical information obtained as a result of this study will be considered confidential, and disclosure to third parties will be prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers. For data verification purposes, authorized representatives of the Sponsor, a competent authority (CA), or an EC may require direct access to parts of the medical records relevant to the study, including subject medical history.

12.1.1 Storage of Images and Associated Health Data

Electronic data from the U-TruSignal Data Collector and associated data will be collected and disclosed to the Sponsor as part of this study. Fully de-identified data, which has had all personal identifying information removed, may be stored and used by the Sponsor indefinitely. The Sponsor and/or its authorized representatives may use any de-identified data collected in this study for future technology and engineering development, marketing purposes, education, regulatory submissions, publications, or other possible uses.

12.2 Publication Policy

The results of this study may be used in future publications. The conditions of publication are described in a separate contractual agreement.

REFERENCES

1. ISO. *Clinical investigation of medical devices for human subjects - Good Clinical Practice*: International Organization for Standardization; 2011. ISO 14155:2011(E).

2. Kugleman A, Wasserman Y, Mor F, Goldinov L, Geller Y, and Bader D. Reflectance Pulse Oximetry from Core Body in Neonates and Infants: Comparison to Arterial Blood Oxygen Saturation and to Transmission Pulse Oximetry. *Journal of Perinatology*. April 2004;24:366-371.

3. Kamat V. Pulse Oximetry. *Indian J. Anaesth*. August 2002;46(4):261-268.

4. Chen W, Ayoola I, Oetomo S, Feijs L. Non-invasive blood oxygen saturation monitoring for neonates using reflectance pulse oximeter. Paper presented at: 2010 Design, Automation & Test in Europe Conference & Exhibition, 2010; Dresden.

5. FDA -- U.S. Food and Drug Administration. *Guidance Documents (Medical Devices and Radiation-Emitting Products)*. March 4, 2013. https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm081352.pdf. Accessed May 11, 2016.

6. The Royal Children's Hospital Melbourne. *Royal Children's Hospital Melbourne Clinical Guidelines (Nursing)*. December 2012. http://www.rch.org.au/rchcpg/hospital_clinical_guideline_index/Oxygen_Saturation_SpO2_Level_Targeting_Premature_Neonates/. Accessed October 31, 2014.

7. ISO. *Medical electrical equipment--Part 2-61: Particular requirements for basic safety and essential performance of pulse oximeter equipment*: Internal Organization for Standardization; 2011. ISO 80601-2-61.

8. Fitzpatrick T. Soleil et peau. *J Med Esthet*. 1975;2(33034).

APPENDIX A – STUDY SCHEDULE

Table A.1 - Schedule of Study Procedures

Evaluation	Visits*	
	Screening (enrollment)	Study Procedure
Written Informed Consent	**X**	
Patient Demographics	**X**	
Inclusion criteria	**X**	
Exclusion criteria	**X**	
Blood draw		**X**

*Subjects will be followed for AE reporting purposes from the time the parent(s) or LDR(s) provided written consent to end of study procedures. There will be no follow-up after the completion of the study.

APPENDIX B – STUDY SITE AND INVESTIGATOR LIST

The following investigators at each study site will be responsible for the conduct of this study:

Investigator(s):[1]	**Rajiv Agarwal**, *MD* *Director & Senior Consultant Pediatrics and Neonatology* *MBBS (AIIIMS), Pediatrics (AIIMS)* *Principal Investigator* *Tel*: +91 80 7122 2360 *E-mail*: rajiv.aggarwal.dr@narayanahealth.org	**NH Narayana Multispecialty Hospital** **Unit of Narayana Health, Mazumdar Shaw Medical Center** *Address*: 258/A Bommasandra Industrial Area, Anekal Taluk, Hosur Road, Bangalore 560099 Karnaktaka
	Outi Tammela, *MD* *Principal Investigator* *Tel:* +358-3-311-66334 *E-mail:* outi.tammela@pshp.fi	**Tampere University Hospital (TAYS)** *Address*: Teiskontie 35 33520 Tampere, Finland

[1] The role of the ***Principal Investigator*** is to implement and manage the conduct of the investigation as well as ensure data integrity and the rights, safety, and well-being of humans involved in the study [ISO 14155:2011 9.1]. ***Co-Investigators*** share all responsibilities of the ***Principal Investigator***, and ***Sub-investigators*** share only those responsibilities designated by the ***Principal Investigator***.

APPENDIX C – MODIFIED FITZPATRICK SCALE [8]

Modified Fitzpatrick Scale [8] excluding the skin's sensitivity to the sun and only utilizing the color descriptions:

Type I	White; very fair; freckles; typical albino skin
Type II	White; fair
Type III	Beige, very common
Type IV	Beige with a brown tint; typical Mediterranean Caucasian skin
Type V	Dar brown/black

APPENDIX D - AMENDMENTS (PROTOCOL VERSION 1.0 TO 2.0)

A detailed amendment is provided for version 1.0 to version 2.0. Version 1.0 was the first version to receive EC approval and was active at the site.

Purpose of Amendment:

1) To extend the duration of the study.
2) To include the required language by the EU Data Protection Regulation 2016/679.
3) To replace the former Project Manager, Research Manager, and Biostatistician.
4) To make general typographical/formatting corrections, in accordance with current standard style guides, American Medical Association (AMA) style, and internal standards of the Sponsor.

These changes are not expected to increase subject or operator risk or to adversely impact the scientific integrity or conduct of the study.

In the table below, point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment from the previous version.

Item	Section	Revision or Clarification	Justification
1	Cover Page	*Changes to the Protocol Version number and date were changed throughout the protocol:* Version: 2.0~~1.0~~; 01/Mar/2019~~25/Apr/2017~~	This correction made indicate the next version number and date of the protocol amendment. This correction does not impact the study design or risk.
2	Cover page – Sponsor Contact	Cynthia Hines-Sabol~~Stephanie Karwodsky~~, Clinical Affairs Project Manager Tel: +1-262-422-1306~~+1 262 443 7008~~ E-mail: cynthia.A.hinessabol@ge.com ~~Stephanie.Karwodsky@ge.com~~	This change does not impact the study design or risk.
3	Principal Investigator – signature page	The Sponsor and Investigator have approved this protocol version, and I confirm hereby to conduct the study according to the protocol and in accordance with applicable principles of the World Medical Association Declaration of Helsinki and Good Clinical Practice (GCP) guidelines as per ISO 14155:2011, any conditions of approval imposed by the reviewing EC~~/IRB~~ or governing regulatory body, and applicable laws and regulations. The I~~i~~nvestigator should not deviate from this protocol except for emergency use. I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.	Administrative changes. The changes do not have an impact on the study design or risk.

<table>
<tr><td>4</td><td>Table of Contents</td><td>Updated the table of contents based on the changes made.</td><td>The change does not impact the study design or risk.</td></tr>
<tr><td>5</td><td>Document and Version Control</td><td>
<table>
<tr><th>Revision</th><th>Date</th><th>Revision Author</th><th>Comments/Changes</th></tr>
<tr><td>1.0</td><td>25/Apr/2017</td><td>Catherine Cadogan</td><td>Clinical Writer – This is the initial version.</td></tr>
<tr><td>2.0</td><td>01/Mar/2019</td><td>Catherine Cadogan</td><td>Clinical Writer – The purpose of this protocol amendment is to include the language required by the EU Data Protection Regulation 2016/679. Details of the changes can be found in Appendix D.</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>
</td><td>The addition of the revision does not impact the study design or risk.</td></tr>
<tr><td>6</td><td>List of Abbreviations and Terms</td><td>
ADE Adverse Device Effect
AE Adverse Event
~~ADE Adverse Device Effect~~
ALARP As Low as Reasonably Practical
AMA American Medical Association
ARMS Accuracy Root Mean Square
…
EC Ethics Committee
~~EC/IRB Institutional Review Board~~
ISO International Standards Organization
LDR Legally Designated Representative
…
SpO2 Peripheral Capillary Oxygen Saturation (also called as: pulse oximetry oxygen saturation 2 or an estimate of arterial oxygen saturation (SaO2)
…
U.S. United States
</td><td>The corrections made does not impact the study design or risk.</td></tr>
<tr><td>7</td><td>Synopsis – Research Type</td><td>This is a ~~Clinical~~clinical, open label, non-randomized, prospective research study.</td><td>The link for the field code was removed. This change does not impact the study design or risk.</td></tr>
<tr><td>8</td><td>Synopsis – Background and Rationale:</td><td>Correction made in the last paragraph:
A study with human subjects will provide the needed clinical evidence for assessing the accuracy of the pulse oximeter as recommended by the United States Food and Drug Administration (FDA) Guidance Document (entitled: “Pulse Oximeters – Premarket~~market~~ Notification Submissions</td><td>The changes made does not impact the study design or risk</td></tr>
</table>

		[~~50~~510(k)s]: Guidance for Industry and Food and Drug Administration Staff"~~.~~).	
9	Synopsis – Procedures/Methods:	After providing consent, no preparation beyond the investigational site's standard of care is required before study procedures begin. At the start of the procedure, ~~one~~ 1 to 2~~two~~ sensors, upon the discretion of the ~~I~~investigator, shall be applied to the subject. Record site/location of the sensors on the case report form. Allow readings to stabilize. After at least 10 minutes of data collection, collect arterial blood and analyze blood per hospital's standard procedure. Continue collection of data post blood draw for 2~~two~~ minutes. Clinician shall monitor and record information as specified in this protocol~~,~~ and obtain results of arterial blood draw. The duration of the subject's participation in the study is dependent upon how long the arterial cannula is required for the subject. The period of data collection during the scheduled routine arterial blood draw (up to 3 independent arterial blood draws) is a minimum of 10 minutes and up to approximately 30 minutes from the application of the sensor to the subject. A ~~and obtaining the~~ maximum of 6 data pairs (3 data pairs per sensor) can be collected from each subject.	Clarification was made on the duration of the subject's participation and the length of data collection as well as administrative changes. The changes made do not impact the study design or risk.
10	Synopsis – Objectives	Formatting changes made.	The change does not impact the study design or risk.
11	Synopsis – Endpoints	Formatting changes made.	The change does not impact the study design or risk
12	Synopsis – Eligibility Clear	Inclusion Criteria: 1) Parents or legally ~~authorized~~ designated representative (~~LAR~~LDR) can understand and provide written informed consent; AND 2) 2) Subjects are < 29 days old~~,~~ and requiring arterial blood samples per the site's standard of care.	The change does not impact the study design or risk.
13	Synopsis – Sample Size ad Sites:	This study is intended to collect blood samples from neonates under normal clinical conditions. The minimum number of subjects is ~~seventeen (~~17~~)~~ subjects. Maximum total enrollment for the study is ~~one hundred forty (~~140~~)~~ subjects. Subjects will be enrolled at 2~~two~~ sites.	The change does not impact the study design or risk.
14	Synopsis – Study duration:	The study is expected to last 24~~12~~ months.	The expected duration of the study was increased.

15	Administrative Structure of Investigation	Clinical Affairs Project Manager (Sponsor Contact: Cynthia Hines-Sabol ~~Stephanie Karwodsky~~ *Tel:* +1-262-422-1306 ~~+1262-443-7008~~ *E-mail:* Cynthia.A.hinessabol@ge.com ~~Stephanie.Karwodsky@ge.com~~ Research Manager: ~~Petra Peltola~~ Jaana Vedenjuoksu *Tel:* +358 ~~40-354-8482~~40-524-3886 *Email:* Jaana.Vedenjuoksu@ge.com ~~Petra.Peltola@ge.com~~ Biostatistician: ~~Shanggon Zhou~~ Bin Xing *Tel:* +262 ~~548-2906~~ 420-8926 *Email:* Bin.Xing@ge.com ~~Shanggon.zhou@ge.com~~	Changes made in Sponsor's personnel. The changes made do not impact the study design or risk.
16	Section 1 – Background and Justification	In general, pulse oximeters use 2~~two~~ wavelength absorption spectrophotometries to measure oxygen saturation. The wavelengths are selected to provide the best separation of absorbencies of oxy-hemoglobin (O2Hb) and deoxyhemoglobin~~-homeglobin~~ (RHb) states. The ratio of the 2~~two~~ absorbencies is used to calculate the oxygen saturation (SpO2) value. The pulse oximeter can provide continuous non-invasive real time information, because an arterial sample of blood is not required to make the measurement. At a NICU~~neonatal intensive care unit (NICU)~~, continuous health monitoring for the neonates provides crucial parameters for urgent diagnoses so that adequate medical treatment can be instituted. 4 The goal of SpO2 monitoring for neonates is to ensure adequate oxygen delivery to the tissue without causing oxygen toxicity. Often, the SpO2 readings from neonates are labile and difficult to keep within a narrow range. The caregiver should aim to maintain the SpO2 levels within the narrow range. 6 The purpose of this study is to collect blood samples from neonates under normal clinical conditions to ensure proper function (clinical performance) with the U-TruSignal device per FDA~~ood and Drug Administration (FDA)~~ Guidance Document: Pulse Oximeters – Pre-market~~market~~ Notification Submissions [510(k)s]: Guidance for Industry and Food and Drug Administration Staff). 5 Testing will follow ISO 80601-2-61 Annex EE.4.12. 7 The study will include both the TruSignal AllFit Sensor and TruSignal Sensitive Sensor.	Administrative changes. The changes made do not impact the study design or risk.

		A study with human subjects will provide the needed clinical evidence for assessing the accuracy of the pulse oximeter as recommended by the FDA~~ood and Drug Administration (FDA)~~ Guidance Document: Pulse Oximeters – Pre-market~~market~~ Notification Submissions [510(k)s]: Guidance for Industry and Food and Drug Administration Staff). 5	
17	Section 2.2. – Intended Use	The investigational device is intended to be used for continuous monitoring and measuring of arterial oxygen saturation (SpO2) and peripheral pulse rate by non-invasive~~invasive~~ pulse oximetry. The sensors and accessories are biocompatible. TS-AF and TS-SE sensors that will be used in the study are cleared by the FDA~~ood and Drug Administration (FDA)~~ for commercial use. The products can be traced through their respective (manufacturing) LOT numbers. The procedures conducted in this study are intended for research purposes and are not intended as a substitute for required medical care. The study staff will be trained in the use of the devices and will be provided with the instructions for use.	Administrative changes. The changes made do not impact the study design or risk.
18	Section 2.3 – Reference Standard	*Last sentence corrected:* If more than one CO-O~~e~~ximeter is used, the pairwise comparisons are separately performed for each CO-O~~e~~ximeter, and the data pairs are pooled together for the final accuracy assessment. 7	Administrative changes. The changes made do not impact the study design or risk.
19	Section 2.5 – Accountability	*Last sentence corrected:* The Principal Investigator will be ultimately responsible for the security and integrity of research devices at the investigational site during ~~the course of~~ the study.	Administrative changes. The changes made do not impact the study design or risk.
20	Section 2.6.1 – Risk Category and Rationale	*First sentence corrected:* Under the United States FDA~~ood and Drug Administration~~ (USFDA) Guidance Document on Pulse Oximeters for Premarket Notification Submissions [510(k)],	Administrative changes. The changes made do not impact the study design or risk.
21	Section 3.1 – Purpose of the Study	*Last sentence corrected:* For the purposes of this study, proper function will be defined by accuracy (i.e. ~~A$_{RMS}$~~ ARMS value), substantially continuous measurement abilities, and safety profile.	Administrative changes. The changes made do not impact the study design or risk.
22	Section 3.2.1 – Primary Endpoint	The primary endpoint will be Accuracy Root Mean Square (~~A$_{RMS}$~~ARMS), comparing the accuracy of SpO2 values from the investigational device to	Administrative changes. The changes made do not impact the study design or risk.

		SaO2 values from CO-Oximeter analysis of simultaneously drawn arterial blood.	
23	Section 3.3 – Summary of Study Design	This is a pre-market, clinical, open label, prospective, non-randomized research study conducted at 2~~two~~ sites.	Administrative changes. The changes made do not impact the study design or risk.
24	Section 4.2 – Number of Subjects	This study is intended to collect blood samples from neonates under normal clinical conditions. The minimum number of subjects is ~~seventeen (~~17~~)~~ subjects. Maximum total enrollment for the study is ~~one hundred forty (~~140~~)~~ subjects.	Administrative changes. The changes made do not impact the study design or risk.
25	Section 4.3 – Protection of Vulnerable Subjects	*Second to the last paragraphs were corrected:* The Sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any I~~i~~nvestigator(s), or other parties participating in, or contributing to, the clinical investigation. All investigators shall avoid improper influence on, or inducement of, the subject, Sponsor, monitor, other I~~i~~nvestigator(s), or other parties participating in, or contributing to, the clinical investigation. The study activities cannot otherwise be performed without the use of vulnerable populations. Neonates: Neonates will be subjects in this study. The purpose of this study involves meeting the health needs of these populations. These subjects are considered a vulnerable research population since neonates cannot provide valid informed consent to which their parent or L~~A~~DR~~legally authorized representative (LAR)~~ must provide written informed consent for their child's participation. Studying subject populations as specified in the inclusion and exclusion criteria set forth in this protocol is necessary, because SpO2 monitoring is a routine part of these population's clinical assessment. The study staff will be present during all study procedures and no subject will be left alone during any part of the study procedure. This research is approved by the ~~Ethics Committee (~~EC~~) and/or Institutional Review Board (IRB)~~ prior to the start of the clinical study.	Administrative changes. The changes made do not impact the study design or risk.
26	Section 4.4.1 – Inclusion Criteria	1) Parents or ~~legally authorized representative (LAR~~LDR~~)~~ can understand and provide written informed consent; AND 2) Subjects are < 29 days old~~,~~ and requiring arterial blood samples per the site's standard of care.	Administrative changes. The changes made do not impact the study design or risk.

27	Section 4.5 – Recruiting and Screening	Subjects, who are neonates, will be recruited for potential enrollment in this study per the standard procedures of the investigational site, unless otherwise specified by the Sponsor in this study protocol. The parent(s) or ~~LAR~~LDR(s) of the neonate patient will be asked to volunteer their child to participate in this research study and provide written informed consent. All participation will be voluntary. Subjects will be screened for enrollment in this study against the inclusion and exclusion criteria per the standard procedures of the investigational site. Following recruitment, a subject will be considered enrolled (the point of enrollment) once the parent/~~LAR~~LDR signs and dates the informed consent form (ICF). Once enrolled, the subject will be assigned a unique subject number, which will not contain information that could identify the subject (such as subject name or date of birth). The unique subject number will be used to label case report form (CRF) data for the subject throughout his/her participation in the study.	Administrative changes. The changes made do not impact the study design or risk.
28	Section 4.6 – Criteria for Withdrawal/Discontinuation	The parent(s) or ~~LAR~~LDR(s) may withdraw their child from study participation at any time, for any reason. The ~~i~~investigator may withdraw a subject at any time, for any reason. The reasons for withdrawal and discontinuation for any subject shall be recorded. These will be reported to the Sponsor. The EC/~~IRB~~ should be notified per their notification of subject withdrawal policy.	Administrative changes. The changes made do not impact the study design or risk.
29	Section 5.1 – Diagram of Procedures	*Notes under Figure 2—Diagram of Study Procedures corrected:* Notes: 1 Subject is considered enrolled once the informed consent has been signed. 2 After the parent/~~LAR~~LDR signed the informed consent form, subjects that did not completely fulfill the inclusion/exclusion criteria will be considered withdrawn. 3 Adverse Event monitoring and reporting begins when the subject's parent/~~LAR~~LDR signed the informed consent form through study completion. Study Completion or Subject's End of Study is defined as the last data collection as determined by the Iinvestigator and /or study staff by	Clarification was made on the duration of the subject's participation and the length of data collection as well as administrative changes. The changes made do not impact the study design or risk.

		recording the study completion date and time. 4 The ~~maximum~~ duration of the subject's participation in the study is dependent upon how long the arterial cannula is required for the subject. Data collection for a data pair (3 data pairs per sensor) is a minimum of 10 minutes and ~~approximately~~ up to approximately 30 minutes from the application of the sensor to the subject. 5 Investigator or designee can determine when a longer data collection is needed. 6 Removal of the investigational device may or may not be the end of the study and the end of AE monitoring and reporting – see definition Study Completion/Subject's End of Study under Note#3 above. 7 Procedure may be repeated at the time of arterial blood draw to collect a maximum of 6 data pair, (3 data pairs per sensor).	
30	Section 5.3 – Description of Study Procedures	a. To document the case, photographs of the position of the measurement sensors and other equipment may be taken at the request of the S~~s~~ponsor at any point of the procedure, when necessary. 7) After arterial blood draw, continue collecting data using the data collection tool for a minimum of 2 minutes. Record possible accidental annotations in CRF. Stop data collection. 9) Monitor and record the following information using the data collection tool or recording on CRF during steps 4-7): a. clinical status notes; i.e., frequent apnea, hemodynamic instability, abnormal heart rhythm, or other status; b. environmental conditions such as changes in lightning conditions, ongoing care moving the neonate outside blood sampling, excessive clinical signs such as agitation, readjustment of a sensor; AND c. notes regarding data collection such as accidental annotations~~-~~. **NOTE:** Study Completion or Subject's End of Study is defined as the last data collection determined by the I~~i~~nvestigator and /or study staff by recording the study completion date and time. GE Healthcare engineering representatives may be present during study procedures, depending upon	Administrative changes. The changes made do not impact the study design or risk.

		their need to observe the functioning of the investigational device (their need to observe will depend upon the study staff indicating there is an issue for the engineers to look at). These representatives will always be accompanied by study staff ~~at all times~~. These visits will be agreed upon and arranged by the Research Manager and the I~~i~~nvestigator on a case-by-case basis.	
31	Section 6.1 – Primary Assessment	The following data will be collected on the CRF~~case report form (CRF)~~: 1) Demographics: date of birth, gender, length, and weight, skin tone (see Appendix C – Modified Fitzpatrick Scale [8]); 2) U-TruSignal Serial Number, Sensor Type, LOT Number, and Attachment Location of the Sensor; 3) Notes regarding data collection e.g. incorrect annotation of data file or several data files; 4) Relevant information on the clinical status affecting hemodynamic stability such as frequent apnea, hemodynamic instability, abnormal heart rhythm; 5) Environmental conditions e.g. open bed, changing lightning conditions, ~~on going~~ongoing care causing movements, readjustment of a senso~~.~~r. The laboratory results will include and to be collected from the hospital's medical record: 1) Co-Ooximeter information, 2) Functional SaO2 (%), 3) Fractional oxyhemoglobin (FO2Hb) [%], 4) Fractional carboxyhemoglobin (FCOHb) [%], 5) Fractional methemoglobin (MetHb) [FMetHb] [%], 6) Total hemoglobin (tHb) (ctHb) [g/L~~ or g/dL~~], ~~and~~ 7) Fetal hemoglobin (Hb) [g/L~~ or g/dL~~] (~~, if available~~calculated),and~~.~~ ~~7)~~8) Fractional fetal hemoglobin [%].	Administrative changes. The changes made do not impact the study design or risk.
32	Section 7.1 – Staff Qualification	All members of the study staff participating in the conduct of the clinical investigation shall be qualified by education, training and/or experience to perform their tasks, and this shall be documented appropriately, as per ISO 14155:2011 for clinical studies.	Administrative changes. The changes made do not impact the study design or risk.
33	Section 8.1 – Anticipated Adverse Events	Pulse Oximetry Sensor placement involves positioning pulse oximetry sensors on the volunteer subject in the same manner used with released SpO2 cables. The U-~~-~~TruSignal investigational device is not in direct contact with the patient. The	

		sensors that will be in contact with the subject are cleared for commercial use. The sensors may be warm to the touch. Under normal operating conditions (no fault conditions), the sensors are not expected to overheat. If the Iinvestigator or delegate conducting the study senses the sensor is too warm or the subject is experiencing discomfort the sensor will be removed immediately and the area of concern will be massaged, and the sensor will be replaced at the discretion of the study staff, the sensor may be removed, and the study procedures discontinued at any time. Sensors may cause irritations to the skin in some subjects. The risk in the use of pulse oximetry sensors is considered minimal.	
34	Sections: 8.2 – Adverse Event Definitions 8.3 – Documentation of Saftey Events	*Throughout this section full-term words were replaced by its abbreviation because it has been defined in previous section.* ▪ "adverse event" was corrected to "AE" ▪ "adverse device effect" was corrected to "ADE" ▪ "serious adverse device effect" was corrected to "SADE" ▪ "serious adverse events (SAE)" was corrected to "SAEs"	Administrative changes. The changes made do not impact the study design or risk.
35	Section 8.4 – Reporting of Safety Events	The following events are to be reported to the Sponsor within 72 hours of the event occurrence and to the EC/~~IRB~~ per their policy: • All SAEs and USADEs • All device issues that could ~~possible~~ possibly lead to an SAE The following information is the Sponsor contact for SAEs and/or UADEs: Helena Haukilehto, MD Fax: +1- 262-364-2544 (24 hours) ~~800-888-3983~~ E-mail: SAE@ge.com Additional follow-up information including the medical records of the subject may be requested by the Sponsor. In addition, safety information may be shared with regulatory agencies and other participating sites, as required by applicable law and regulation.	Administrative changes and corrected the phone number to report any SAEs and/or UADEs. The changes made do not impact the study design or risk.
36	Section 8.5 – Device Deficiencies/Complaints	Device deficiencies related to the investigational device should be reported directly to the engineering team, after each case by the Iinvestigator or study staff, who finishes the case. Device deficiencies related to the approved or	Administrative changes. The changes made do not impact the study design or risk.

		cleared device should be reported to the study Sponsor. **Sponsor contact for device complaints:** Cynthia Hines-Sabol~~Stephanie Karwedsky~~, Clinical Affairs Project Manager Tel: +1 262-422-1306~~ +1 262 443 7008~~ E-mail: cynthia.A.hinessabol@ge.com ~~Stephanie.Karwedsky@ge.com~~ All device deficiencies will be collected, fully investigated, and documented in the source document and appropriate CRF~~case report form (CRF)~~ during the study reporting period. The Principal Investigator is responsible for notifying the Sponsor ~~in the event that~~if there is any device issue that could potentially lead to a SAE.	
37	Section 9 – Ethical Conduct of the Study	The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki; the guidelines of GCP~~ood Clinical Practice (GCP)~~ for medical devices, as set forth by ISO 14155:2011 and ISO 14971:2012; European Directive on medical devices 93/42/EEC for studies conducted in Europe; ~~applicable regulatory authority's requirements of the United States – USFDA 21 Code of Federal Regulations (CFR);~~ and applicable local regulatory authority's requirements of Finland – Valvira. The study will be conducted and reported in accordance with applicable policies of the local ~~Ethic~~Ethics Committee ~~Institutional Review Board~~ (EC~~/IRB~~) and governing regulatory authorities in Finland and India (when India's law comes into effect). If national or regional EC~~/IRB~~ requirements are less strict than the requirements of GCP, such as ISO 14155:2011 for medical devices, the Sponsor shall apply the requirements of this International Standard to the greatest extent possible, irrespective of any lesser requirements, and shall record such efforts.	Administrative changes and removed the reference to the USFDA 21 CFR since the study is conducted in Finland and India. The changes made do not impact the study design or risk. Reason for deletion of USFDA 21 CFR reference: The FDA Guidance on Acceptance of Clinical Data to Support Medical Device Applications and Submissions FAQs states: *"Under the new rule, FDA is requiring that data submitted from clinical investigations OUS intended to support an IDE, 510(k), De Novo, PMA, HDE, or PDP applications, be from investigations conducted in accordance with GDP, which includes review and approval by an IEC and informed consent from subjects. The GCP requirements in the final rule encompass both data quality and intertiy and ethical standards for device clinical investigations."*

38	Section 9.1 – Ethics Committee	The responsible Principal Investigator at each site will ensure that approval from an appropriately constituted EC~~/IRB~~ is attained for the clinical study prior to enrolling subjects, and Principal Investigator will ensure that documentation of approval is maintained for the duration of the study. The Principal Investigator will ensure that the Sponsor is notified of any withdrawal of EC~~/IRB~~ approval within 5 working days of such occurrence. If approval is terminated or suspended, the Principal Investigator will promptly notify the Sponsor and provide written explanation.	Administrative changes. The changes made do not impact the study design or risk.
39	Section 9.2 – Regulatory Agencies and Competent Authority(ies)	The Sponsor will obtain approval from the local regulatory agency or competent authority before the start of the clinical trial, if necessary, per applicable local laws and regulations. Any additional requirements imposed by the EC~~/IRB~~ or regulatory authority shall be followed, if applicable. Documentation of notification will be maintained in the Site Regulatory Binder.	Administrative changes. The changes made do not impact the study design or risk.
40	Section 9.3 – Management of Protocol Modifications and Amendments	Substantial amendments will only be implemented after approval of the EC~~/IRB~~.	Administrative changes. The changes made do not impact the study design or risk.
41	Section 9.4 – Management of Protocol Deviations	A deviation is any instance(s) of failure to follow, intentionally or unintentionally, the requirements of the protocol. Under emergency circumstances, deviations from the protocol to protect the rights, safety, and well-being~~being~~ of human subjects may proceed without prior approval of the Sponsor and the EC~~/IRB~~. Such deviations shall be documented and reported to the Sponsor and the EC~~/IRB~~ as soon as possible. Deviations will be reported as: • Critical Deviations: Deviations that significantly affect the safety, efficacy, integrity, or conduct of the study. These deviations must be reported to the Sponsor no later than 5 working days from awareness of occurrence and reported to the EC~~/IRB~~ per the deviation reporting policy. • Non-Critical Deviations: Protocol deviations that do not significantly affect the safety, efficacy, integrity, or conduct of the trial. These deviations must be documented on the CRF Protocol Deviation page and will be reviewed by the study monitor. Non-substantial modifications may be made during the normal course of device optimization, maintenance, and feasibility testing. Non-substantial	Administrative changes. The changes made do not impact the study design or risk.

		modifications will be communicated to the CA as soon as possible, if applicable, and to the EC~~/IRB~~ per their policy.	
42	Section 9.5 – Participant Information and Informed Consent	The investigators will explain to each participant's parent(s) or ~~LAR~~LDR(s) the nature of the study, its purpose, the procedures involved, the expected duration of exposure to the investigational device, the potential risks and benefits, and any potential discomforts. Each participant's parent(s) or ~~LAR~~LDR(s) will be informed that participation in the study is voluntary, that he/she/they may withdraw his/her/their child from the study at any time, and that withdrawal of consent will not affect his/her/their child's subsequent medical assistance and treatment. The participant's parent(s) or ~~LAR~~LDR(s) must be informed that his/her/their child's medical records may be examined by authorized individuals other than their treating physician. All participant's parent(s) or ~~LAR~~LDR(s) for the study will be provided an informed consent form, describing the study and providing sufficient information, to allow the participant's parent(s) or ~~LAR~~LDR(s): (i) to make an informed decision about his/her/their child's participation in the study, and (ii) to be fully aware of his/her rights under the applicable law. Informed consent documents will be subject to approval by the ~~Ethics Committee (~~EC~~)/Institutional Review Board (IRB)~~ prior to enrolling subjects in the study. The participant's parent(s) or ~~LAR~~LDR(s) should read and consider the statement before signing and dating the ICF~~,~~ and shall be given a copy of the signed document. The ICF must also be signed and dated by the i~~I~~nvestigator (or his/her designee), and it shall be retained as part of the study records.	Administrative changes. The changes made do not impact the study design or risk.
43	Section 9.7 – Incidental Findings	Incidental findings observed during the study conduct shall be processed under the purview of the Principal Investigator through the investigational site's standard of practice.	This section was added to communicate with the PI's and study staff's responsibility in handling incidental findings. This addition does not impact the study design or risk.
44	Section 10.3.3 – Analysis of Primary Endpoint	Data analysis for the data collection interval, which is defined as the 5~~five (5)~~ second period starting after a twelve (12) second technical delay from the time sampling occurs, will follow ISO80601-2-61, 2011, Annex EE and the FDA Guidance Document for Pulse Oximeters (FDA Guidance, March 4,	Administrative changes. The changes made do not impact the study design or risk.

		2013). Separate analysis will be performed for each sensor type. The ARMS~~-ccuracy Root Mean Square (ARMS)~~ calculation is used as a means to define the SpO2 Accuracy. Arms will be calculated as $Arms = \sqrt{\frac{\sum_{i=1}^{n}(DUT_i - \mathrm{Re}f_i)^2}{n}}$, where Refi = Reference CO-Oximeter Functional SaO2 of data pair i DUTi = Device Under Test SpO2 of data pair i The difference between SpO2 and SaO2 will be summarized using mean, minimum and maximum. Number of subjects and number of data pairs will also be presented. A least squares regression of SpO2 on SaO2 will be performed and results be presented with a regression plot and table. Bland-Altman graphical plots, error (SpO2 – SaO2) versus average SaO2 will be generated with mean, and upper 95% and lower 95% limits of agreement according to Section 3 of "Agreement Between Methods Of Measurement With Multiple Observations Per Individual" by Bland and Altman in 2007 Journal of Biopharmaceutical Statistics. Individual test subjects will be color coded in the Bland-Altman graphical plot. Data listed below will be excluded from analysis: ▪ Data with SaO2 < 70%, tHb < 10g/L, MetHb > 2%, COHb > 3%; ▪ Draws with values smaller than -0.5% in any of the Hb values; ▪ Artefacts/other external error sources indicated by clinical documentation or derived from the collected data around sampling including but not limited to: o changes in sensor fit; o excessive movement during draw; o low perfusion (mod% < 0.5%); o irregular plethysmographic waveform or artefacts in the waveform; ▪ Data with error conditions on CO-Oximeter analysis indicated by clinical documentation e.g. air bubbles in syringe, clots, violation of hospital's standard procedure; ▪ Data with error conditions on pulse oximeter; ▪ Unstable SpO2 readings from the respective device under test:	

		○ SpO2 max-min ≥ 4% in time window during 30 sec prior/after the blood sample; ○ SpO2 max-min ≥ 8% in time window during 10 minutes prior to the blood sampling time; A rationale will be provided for any data that is excluded from the data analysis.	
45	Section 10.4 – Handling of Missing Data	*Last sentence corrected:* The Iinvestigator is obligated to provide written documentation of any missing data to the Sponsor and to provide clarification upon Sponsor request if possible.	Administrative changes. The changes made do not impact the study design or risk.
46	Section 11.1.3 – Source Data and Documents	Source data includes information in original records, certified copies of original records of clinical findings, observations, or other activities for the study. Source documents for each subject must be retained throughout the investigation, including printed or electronic documents containing source data. Elements should include: • Source data and documentation relevant to data recorded for subject screening and CRF corroboration. • Subject records containing the completed ICFs, CRFs, and electronic data copied from the data collection tool. • Regulatory binder containing the protocol and any subsequent amendments, EC~~/IRB~~ submissions and approvals, blank ICF(s), and site logs. • Reference manuals containing Iinvestigator responsibilities, Sponsor, AE/SAE and informed consent guidelines, applicable study aids and training materials, and operator's manuals. The Principal Investigator or institution shall provide direct access to source data during and after the clinical investigation for monitoring, audits, EC~~/IRB~~ review, and regulatory authority inspections.	Administrative changes. The changes made do not impact the study design or risk.
47	Section 11.1.4 -- Archiving	All study data must be archived for the period defined by local law ~~a minimum of 3 years or according to the site's standard procedure,~~ after study termination or premature termination of the clinical trial. No source documents or study records will be destroyed without Sponsor notification and approval.	The period of archiving was changed to reflect the new Medical Device Regulation requirement. This change does not impact the study design or risk.
48	Section 12 – Monitoring Plan	In collaboration with the site, the Sponsor will ensure proper monitoring of the study to confirm that all the research requirements are met.	Administrative changes. The changes made do not

		Monitoring visits will oversee the progress of a clinical investigation and ensure that it is conducted, recorded, and reported in accordance with the protocol, written procedures, GCP~~ood Clinical Practice (GCP)~~ ISO 14155:2011, and the applicable regulatory requirements.	impact the study design or risk.
49	Section 12.1 – Confidentiality and Data Protection	The ~~I~~investigator affirms and upholds the principle of the participant's right to privacy, and the ~~I~~investigator shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing data in scientific journals. Individual subject medical information obtained as a result of this study will be considered confidential, and disclosure to third parties will be prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers. For data verification purposes, authorized representatives of the Sponsor, a competent authority (CA), or an ~~institutional review board (~~EC~~/IRB)~~ may require direct access to parts of the medical records relevant to the study, including subject medical history.	Administrative changes. The changes made do not impact the study design or risk.
50	Appendix A – Study Schedule	**Table A.1** - Schedule of Study Procedures **Visits*** / **Screening (enrollment)** / **Study Procedure** **Written Informed Consent**: X / **Patient Demographics**: X / **Inclusion criteria**: X / **Exclusion criteria**: X / **Blood draw**: / X *Subjects will be followed for AE reporting purposes from the time the parent(s) or ~~LAR~~LDR(s) provided written consent to end of study procedures. There will be no follow-up after the completion of the study.	Administrative change. The change made does not impact the study design or risk.

51	Appendix B – Study Site and Investigator List	Investigator(s): Rajiv Agarwal ~~Russel Hirsch~~, MD Director & Senior Consultant ~~Associate Professor of~~ Pediatrics and Neonatology MBBS (AIIIMS), Pediatrics (AIIMS) Principal Investigator Tel: +91 80 7122 2360 ~~1-515-636-7072~~ E-mail: ~~russel.hirsch@cchmc.org~~ rajiv.aggarwal.dr@narayanahealth.org NH Narayana Multispecialty Hospital Unit of Narayana Health, Mazumdar Shaw Medical Center ~~Cincinnati Children's Hospital Medical Center~~ Address: 258/A Bommasandra Industrial Area, Anekal Taluk, Hosur Road, Bangalore 560099 Karnaktaka ~~3333 Burnet Avenue Cincinnati, OH 45229~~	A different site was selected for the study. This change does not affect the study design or risk.