

INVESTIGATOR'S BROCHURE

SafeBoosC phase II - OxyPrem

Revision history

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2. ABOUT THIS DOCUMENT

This document is the 'Investigator's Brochure' as required by EN/ISO 14155 (Clinical investigation of medical devices for human subjects). It is to be distributed to all investigators of the study 'SafeBoosC'. The document rationalizes the need for a clinical investigation of NIRS in neonatology. A general description of the OxyPrem (Biomedical Optics Research Laboratory, 8091, Zurich, Switzerland), the INVOS 5100c (Covidien, Boulder, CO, USA), the FORE-SIGHT™ Cerebral Oximeter (CAS Medical Systems, Inc., Mansfield, MA, USA), and the NONIN EQUANOX 7600 (Plymouth, MN, USA) devices is given as well as the results of the risk analysis.

3. BACKGROUND

The content of this chapter is taken from Wolf and Greisen review (1).

3.1. General information about NIRS

Near-infrared spectroscopy (NIRS) is an emerging diagnostic tool for the neonatal brain. Although the technology is approximately 30 years old, recent advances in quantification and instrumentation and the availability of commercial instruments have increased the interest in NIRS in clinical medicine, although so far its use in neonates is restricted to research. From a clinical point of view, NIRS is being tested as a tool to identify pathologies and thus predict or eventually prevent adverse outcomes, i.e., cerebral palsy and other forms of neuro-psychological impairment. In general, two strategies of clinical use have been followed.

1. The measurement of cerebral autoregulation, blood volume, flow, and oxygenation. Here the future aim is to safeguard the brain by adjusting the blood and oxygen supply to the brain to adequate levels and to prevent brain lesions.
2. The assessment of brain activity. Here the aim is to develop functional tests to understand neonatal brain activity. In the future, such tests may enable early detection and prognosis of disabilities and may help to guide therapy.
3. The aim is to review the progress and state of NIRS instrumentation and their clinical application.

3.2. Medical background

Brain lesions occur relatively often in preterm infants. The etiology is still largely unknown. Approximately 25,000 infants are born extremely preterm, i.e. before 28 weeks of gestation. Since brain lesions are relatively common in this population and potentially cause permanent disabilities, prematurity constitutes a serious problem. About 25% of survivors live with cerebral palsy or low intelligence quotient. No screening test during the neonatal period has been shown to predict neurodevelopmental outcome with a reliability that is clinically satisfactory (2). Since prevention of preterm has been largely unsuccessful, it would be desirable to develop a reliable method to assess the oxygenation, haemoglobin concentration, and function of the preterm brain. In the future this may enable to detect and prevent conditions, which lead to brain lesions. Since the transport of critically ill neonates and adults is associated with a high risk, methods such as MRI and CT are often not applicable. Therefore one method of choice is near-infrared spectroscopy (NIRS), which is applicable at the bedside. NIRS is able to assess the oxygenation, haemoglobin concentration, and function of the brain non-invasively. In addition NIRS does not use ionizing radiation or contrast agents and thus is appreciated by patients, relatives and staff.

3.3. The application of NIRS in neonatology

Photometers provide continuous signals of O₂Hb and HHb concentration, potentially at a very fast rate, up to 100 Hz. The limitation is that measurements are relative, i.e. only available as changes from an arbitrary set-point. Whereas photometers may give qualitative information on changes in brain blood

volume, or on relative brain oxygenation, their usefulness is severely limited by the inability always to distinguish between a change in blood volume or in saturation (3). Therefore, while photometers have given and continue to provide important data for research, their use will not become a useful clinical method unless combined with other physiological parameters in innovative ways.

Using a NIRS photometer along with challenges, either by increased oxygen concentration in inspired air or by obstructing venous outflow, it is possible to obtain good quality data of cerebral blood volume, cerebral blood flow, and cerebro-venous saturation, as reviewed recently (4). Again, this approach has been useful for research and still is used, but is too cumbersome for clinical practice. In principle, this approach could be automated, but that has not been attempted. A problem is that hyperoxygenation as well as impedance of venous outflow from the brain may not be absolutely without risks.

Thus, tissue oximetry is the most promising NIRS method for clinical use. Tissue oximetry provides a ratio of O₂Hb to total Hb, rStO₂, regional tissue oxygen saturation of haemoglobin. In brief this is done by measuring the attenuation of the reflected light as a function of distance and make some reasonable assumptions above tissue homogeneity and propagation of light (5). This way the unknown scattering properties of the tissue become less important. However different approaches are used in different commercial instruments and two main problems with current technology are the low precision and the difference in absolute between different instruments (6). Nevertheless, much experience has been gathered in neonatology as well as in pediatric cardiology, and some technical improvements are possible. Furthermore, after FDA approval, commercial instruments are rapidly being put to clinical use, also in neonatology. Thus we will see a large volume of more or less well-planned clinical observations in the years to come.

In the following discussion, a few of the questions addressed in the existing literature on tissue oximetry in neonatology are reviewed with a focus on limitations and potentials. Severe hypoxic-ischemic encephalopathy is followed by cerebral hyperperfusion, as shown by Doppler ultrasound and Xenon-clearance (7,8). NIRS tissue oximetry has demonstrated that this event is in fact hyperperfusion, since rStO₂ is abnormally high, and that this hyperoxygenation carries the same poor prognosis as does the hyperperfusion (9). Prognosis, however, was determined only at the statistical level and was not feasible for individual infants.

Large studies with long-term follow-up are necessary to compute sensitivity and specificity for poor outcome. NIRS is not going to replace EEG for early prediction and selection for cooling or other brain protective treatment because cerebral hyperoxygenation is a consequence of the secondary energy failure that comes late. In comparison, the EEG depression is a consequence of the primary insult. A persistent arterial duct (PDA) is a frequent problem in very preterm infants. In spite of ever improving sonographic diagnosis of the duct and quantification of the shunt, the best management of this problem is still debatable. Cerebral tissue oximetry is one way of quantifying the systemic hypoperfusion resulting from excessive left-to-right shunting. Indeed, PDA has been associated with decreased cerebral saturation (10) and its closure with increased rStO₂ (11), although the opposite has also been found (12). This discrepancy is likely to represent different clinical severity at the time of surgical closure.

Extracorporeal membrane oxygenation is used relatively frequently in newborn infants, either to treat pulmonary failure following meconium aspiration, neonatal infection or congenital diaphragmatic hernia, or to treat circulatory failure before or after surgery for congenital heart malformation. Cannulation usually takes place during maximal distress, and is performed using the right-sided neck vessels. rStO₂ in the right frontal area fell in all of three patients following ligation of the right carotid artery during cannulation, whereas no change was seen over the left hemisphere (13). StO₂ reflected episodes of desaturation (14,15), and was recommended as clinical routine for extra safety in this high-risk treatment, as it has for bypass during cardiac surgery (16).

Finally, newborn infants also suffer from congenital heart disease, an area where tissue oximetry is particularly appealing because of the large deviations in oxygenation and the frequency of neurological deficits at follow-up. In general, the findings have been more substantial, compared with the results discussed above, and recently a clinical benefit in terms of less invasive treatment of infants with hypoplastic left heart syndrome monitored by tissue oximetry was shown by comparison with a historic group of controls (17)

3.4. Precision and bias of NIRS Tissue oximetry

Precision, which tells us how likely it is to receive the same value when a measurement is repeated, is necessary to trust an individual value. In-vitro precision of tissue oximetry is good. It is determined on optical phantoms and depends on optic and electronic limitations. This in-vitro precision is 1-2%. The problem is that in-vivo precision is not so good. It is assessed by the limits of agreement of the

Bland-Altman analysis (by the ability to come close to the comparison measurement at each measurement) (18) or by more conventional analysis of repeated measurements under stable conditions (repeatability, intraclass correlation coefficient). Neither approach is perfect; however, the following assumptions may be made: that a method with a low bias (good agreement of averages) also could be precise; that cerebral oxygenation is expected to be stable over time, since neither cerebral blood flow nor cerebral metabolic rate of oxygen is known to vary markedly spontaneously; and finally that cerebral oxygenation is expected to vary little from one brain region to another for the same reasons. In this light, it is remarkable that the limits of agreement in tissue oximetry are wide and the repeatability is poor, at least compared with pulse oximetry, another non-invasive method based on red/infrared light. Repeatability of pulse oximetry is 2-3%. For comparison, the standard deviation calculated from Bland-Altman analysis and the repeatability for NIRS oximetry is in the range of 5-8% (15,19-21). The problem appears to be associated with the replacement of sensors. Possibly the sensors are sensitive to small local heterogeneities of the optical properties of tissue (hair, blood vessels, subarachnoidal space, gyral folding) (22). For clinical application, a precision <3% would be desirable.

Different commercial instruments give different mean values of rStO₂ (23-25). This is most likely caused by different mathematical algorithms for converting the measured light attenuation at various wavelengths into corresponding concentration changes of the substances of interest, O₂Hb and Hb (26). However even within the same commercial instrument different types of sensors give different estimates of oxygenation in the same subject (27). Since no dedicated neonatal/paediatric sensor were available when NIRS first became commercially available most research with NIRS in infants has been made with sensors only approved for subjects > 40 kg. Later on dedicated sensors were developed and FDA-approved/CE-marked for use on neonates. However several studies have shown that these sensors have a positive bias compared to the adult sensors and estimates rStO₂ about 10 percentage points higher (27,28). Unpublished data suggest that this is the case with both INVOS and Fore-Sight neonatal sensors. Since no reference standard is available in preterm infants since the oxygen saturation of venous blood from the brain is impossible to measure reliably when the jugular vein is too small for cannulation evaluation of the values of rStO₂ from the different sensors/instruments has to be pure theoretical. Since the mathematical algorithms of the commercial instruments are well-kept secrets, we are left to judge the physiological reasonableness of the values of rStO₂. Studies where the neonatal sensors have been used in preterm infants have reported cerebral rStO₂ values about 80% (28-30). This corresponds to a venous saturation of 75% and an oxygen extraction fraction of 0.22, if the arterial saturation is 95% and the arterial:venous volume ratio is 25:75. This would normally be considered hyperperfusion. Preterm infants are generally considered to be in high risk of low systemic flow (31-33), thus it would be surprising if hyperperfusion would be the norm. Compared to values of cerebral oxygen extraction in adults about 0.35 (34), it altogether seems likely that mean rStO₂ of 80% are an overestimation.

4. RATIONAL FOR THE DESIGN OF THIS CLINICAL TEST OF NIRS CEREBRAL OXIMETRY

Cerebral NIRS oximetry is a potentially important monitoring modality for the possible benefit of preterm infant. The overall goal of SafeBoosC is to determine the benefits and harms of a treatment guideline based on cerebral NIRS oximetry in preterm infants and to collect the adverse reactions/events.

4.1. Rationale for use of INVOS Adult SomaSensors® as reference standard for mean values in neonates in the study

Although INVOS 5100c has the designated OxyAlert™ NIRSensors for use in infants below 5 kg the clinical testing of OxyPrem will use the Adult SomaSensors®. This is based on clinical data that suggests that the OxyAlert™ NIRSensors and the Pediatric SomaSensor give values that are about 10 percentage points higher than what found with the Adult SomaSensors® or other NIRS devices (27,29,35). In addition a large body of evidence from the group of Petra Lemmers and Frank Van Bel documents that the application of the Adult SomaSensor in this population is safe (10,20,36-38). Moreover data collected with the Adult SomaSensor indicates that a high rStO₂ could possibly predict poor outcome (39).

Normal ranges of rStO₂ of 55-85% has been determined from monitoring of almost 400 preterm infants by the group of Lemmers and Van Bel and represent the mean \pm 2 standard deviation. This implies that by using the OxyAlert™ NIRSensors or Pediatric SomaSensor it will be impossible to detect and monitor hyperoxygenation, since the +10 percentage point bias will result in values over 95% which as discussed previously are unlikely to be physiological.

5. STUDY DESIGN

5.1. Introduction

SafeBoosC phase II trial is a randomized trial that hypothesize that a dedicated treatment guideline based on threshold rStO₂ values of 55% and 85% will reduce the burden of hyper- and hypoxia by at least 50%.

The trial will include 150 infants born before 28 weeks of gestation. The primary outcome is burden of hyper- and hypoxia, i.e. the area below rStO₂ of 55% plus area above 85% in %hours. Secondary and exploratory outcomes include estimates of brain injury such as cerebral ultrasound, magnetic resonance imaging, amplitude integrated EEG, and three different blood biomarkers.

5.2. Limitations of the study, inclusion and exclusion criteria, and contraindications

Infants who are born before 28 weeks of gestation can be enrolled, if a decision to provide full life support has been made.

5.2.1. Inclusion and exclusion criteria

Inclusion criteria:

- Preterm infants (age less than 28 weeks)

Exclusion criteria:

- Decision not to provide life support

Number of randomisations: 150 (twins will randomised together and count as one)

5.2.2. Contraindications

There are no contraindications.

5.3. Recording and reporting of adverse device effects and device deficiencies

Adverse events are recorded and reported to the competent authority in all countries in which the trial is being conducted according to national guidelines, Directive 90/42/ECC, as amended by the Directive 2007/47/EC and the EU Commission guidelines on medical devices, Meddev 2.7/3 "Clinical investigations: serious adverse event reporting".

Adverse reactions (i.e. both expected and unexpected with a 'certain' or 'probable/likely' relation to the device) will be recorded and reported with the trial results and reported to the competent authorities.

Serious adverse reactions (i.e., both expected and unexpected related to the device and/or the treatment guideline will be recorded and analysed as a secondary outcome measure, but only those related to the device will be reported to the competent authority. Due to the nature of the population and the intervention, the near-incidents (SAE-NI) will not be recorded or reported.

6. DEVICE DESCRIPTIONS

6.1. OxyPrem

The Neonatal NIRS System for measuring cerebral tissue oxygen saturation (OxyPrem) provides the functionality to continuously measure cerebral StO₂ in neonates. OxyPrem includes the Neonatal NIRS Device (OxyPrem-Device) and the Control and Analysis Unit (OxyPrem-Host). The OxyPrem-Device consists of the mains-adapter to power the device and to charge the battery, the power-supply box containing the antenna for the wireless transmission of the measurement values and the sensor-head with the NIRS lightsources and detectors. The OxyPrem-Host is a personal computer (a notebook or subnotebook) with application specific software (OxyPrem-Soft), connected to the OxyPrem-Device via a standard communication interface (Bluetooth) making use of custom build communication protocol layers.

OxyPrem can be operated in two modes: mains-cable powered and battery supply. If the OxyPrem-Device is connected to the mains supply by a mains adapter, the electrical power for the sensor-head and the Bluetooth communication is provided by the mains adapter. If disconnected from the adapter, OxyPrem is powered by a battery, which is charged as long as OxyPrem is connected to the mains supply. The data transmission to the OxyPrem-Host is in both modes based on wireless communication (Bluetooth). Future devices may also use a galvanically isolated USB connection.

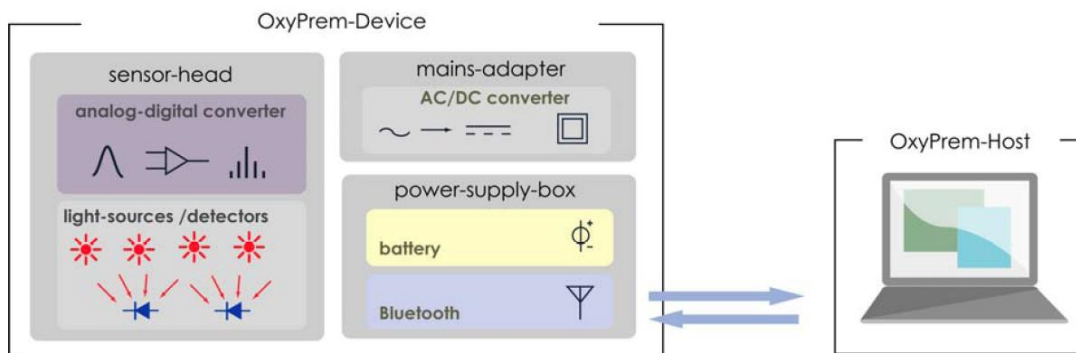


Image 1 – System block diagram. EU: electronics unit, SU: sensor unit, PS: power supply. EU, SU and PS may be fused into one casing or configured as separate units, interconnected by cables. Linkage between OxyPrem-Device and OxyPrem-Host may also be incorporated using a galvanically isolated USB-connection.

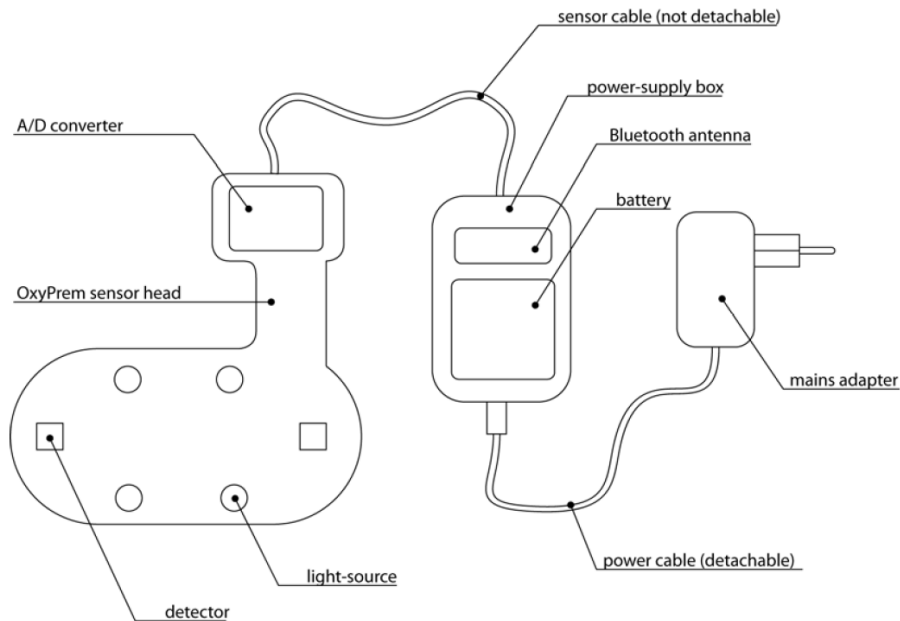


Image 2 – OxyPrem Device. The sensor cable may be detachable in some devices. Linkage between OxyPrem-Device and OxyPrem-Host may also be incorporated using a galvanically isolated USB-connection.

The regulatory classification of OxyPrem can be found in the operations manual.

A detailed description of the OxyPrem and its components including materials used and summary of relevant manufacturing processes and related validation processes can be found in the operations manual that should be available in close proximity to the device at any time.

6.1.1 Novel aspects of OxyPrem

OxyPrem features three major differences to conventional and commercially available NIRS devices:

- Firstly, it was specifically and from scratch designed exclusively to be used with preterm neonates in an intensive care situation. Mainly, this influences the design, more specifically the size, of the probe containing light sources and detectors. The designers of OxyPrem were very aware of the problems associated with the use of NIRS in (neonatal) clinical practice, e.g. those associated with the precision of the measurements (see above), and hence one may expect that OxyPrem will perform better and may be applied easier when used for preterm neonatal patients as compared to instrumentation that was designed without focusing on that patient group.
- Secondly, the device features a wireless transmission of the measurement data to the host computer which will facilitate handling of the device since no (fiber-optical) cables must be disinfected and the by far most bulky component of the system, the host computer, may be positioned in a range of up to 5 meters from the patient, which is a advantage the often space-constricted environment that is an intensive care unit.
- Thirdly, the power driving OxyPrem may be provided by battery, which allows continuing the NIRS monitoring uninterrupted even when the patient is transferred or moved (e.g. for examinations or care-taking).

6.1.2. Intended use

It will be applied as an in-vivo diagnostic device to acquire physiological information in order to answer questions of interest in basic and applied clinical research. These questions concern mainly the oxygenation and blood perfusion of tissue (cerebrum and muscular tissue) and the effect of neurological activity to the oxygen delivery and consumption in the brain.

Potentially, OxyPrem may help to investigate the following questions:

1. Can NIRS be used to assess the existence and/or severity of a cerebral haemorrhage or stroke, that both occur relatively often in the target population (infants of a gestational age less than 34 weeks during the first days and weeks of life)
2. Does NIRS provide the means to study neuronal development of preterm infants (either of the individual or as a population)?
3. Does the continuous NIRS monitoring of preterm infants provide information to improve the patient oxygen management (e.g. by adjusting ventilation parameters).

6.1.3. Mode and conditions of application

The OxyPrem sensor may be fixed with a self-adhesive single use bandage. The design of OxyPrem does not impose any limitation on the choice of the bandage except that it must allow a tight adhesion of the OxyPrem sensor to the patient's body surface. However, using a certified medical grade, single-use product is required by the manufacturer of OxyPrem, which he declares so in the OxyPrem manual. OxyPrem is primarily applied inside an incubator. OxyPrem is therefore designed to operate reliably and safely in an environment with air temperatures between 18°C and 42°C and air humidity between 50% and 95%.

6.1.4. Limits of application

Any implantation or insertion of the OxyPrem sensor, surgically or through orifices, as well as insertion into visceral cavities is neither intended nor permitted by the manufacturer.

Rationale: OxyPrem is not designed to meet the regulatory requirements imposed for invasive devices e.g. with respect to sterilizability or biocompatibility.

Any measurement results or other data acquired by OxyPrem must not be considered for decisions concerning patient treatment or care. Specifically, it will be forbidden to administer medication, change ventilation parameters or to alter artificial oxygen supply, either fully or partially based on the measurement values provided by OxyPrem. OxyPrem does not provide any life support or life sustaining functionality whatsoever.

Rationale: Accuracy, precision and reliability of OxyPrem are up to date unknown and hence patient health cannot in any way depend on the accurate, precise or reliable functioning of OxyPrem.

OxyPrem does not provide treatment to patients.

Rationale: OxyPrem is intended and designed to be a purely diagnostic device.

OxyPrem is not used for ex-vivo applications, pregnancy testing, or birth-control.

Rationale: OxyPrem is not intended or designed to perform any of said functionalities.

OxyPrem is not to be applied, prescribed or operated by personnel who are not instructed to use it safely.

Rationale: NIRS is, apart from pulseoxymetry, not a standard procedure in clinical care and its reliable and safe application must therefore be specifically trained.

OxyPrem must not be used in the presence of strong electro-magnetic RF fields as used in magnetic resonance imaging devices.

Rationale: Exposure to MRI RF fields will induce eddy-currents in the metallic parts of the OxyPrem sensor which leads to heat generation and thus potentially harm the patient. Also, the metallic parts of OxyPrem potentially cause severe MR image artefacts and hence could invalidate MRI findings.

OxyPrem must not be used in the presence of inflammable gases, specifically anaesthetic gases.

Rationale: OxyPrem was not specifically designed to operate under such conditions and hence doing so potentially bears uncontrolled risks.

6.1.5. Power supply

OxyPrem features two modes of operation: mains-cable mode (MCM) and battery supply mode (BSM). Most of the time (when the patient rests in the bed or incubator), power is provided by an AC/DC power converter (mains adapter). It connects to a 230 V / 50 Hz AC power outlet and generates a DC voltage of 5 V, which is provided to the OxyPrem power supply box by cable. If the patient has to be disconnected (i.e. for examinations or care-taking) the power supply is provided by a rechargeable battery located inside the power supply box.

BSM is an optional feature, i.e. OxyPrem may be issued without a battery supply. If that is the case, of course, OxyPrem ceases to work if disconnected from the 230 V AC supply. The mains adapter (mains part) including the cable connecting it to the power-supply box is provided by a third party manufacturer. The device is compliant with EN/ISO 60601, Class II (galvanic separation from mains voltage with both basic and supplementary insulation).

6.1.6. Used materials

The sensor, which is directly in contact with the patient's or subject's skin, is made of medical grade flexible silicone which is certified to fulfill the biocompatibility requirements as formulated in EN/ISO 10993.

6.1.7. Preclinical testing

A comparison between the OxyPrem, INVOS 5100c, NIRO 200 NX and NIRO 300 (Hamamatsu) on the adult forearm showed that OxyPrem had superior reproducibility with a within-standard deviation of 2.7% compared to the other devices 5-6% (21).

6.1.8. Clinical testing

The MCP II, an earlier version of the OxyPrem, had a reproducibility of 2.7% in mixed population of preterm infants (59).

6.1.9. Summary of risk assessment

A risk assessment according to EN/ISO 14971:2007 has been performed for the OxyPrem device. Since functional principle of OxyPrem is similar to existing NIRS spectroscopy devices used in every day clinical practice (pulse oximeters), and NIRS devices increasingly used in neonatal research the authors were able to identify potential risks based on their previous experience in clinical research. The aim of the study formulated by this clinical investigation plan is to assess the accuracy and precision of OxyPrem. The investigators are explicitly forbidden to use measurement values acquired by OxyPrem as a base for clinical decisions (such as the adjustment of ventilation parameters or the prescription of drugs). Hence the accuracy and precision of the measurement data acquired by OxyPrem is considered not being relevant for the safety of OxyPrem.

Six relevant sources of hazards were identified:

Hazard 1: The LED sources produce a certain amount of lost heat which could, localizedly, irritate or, in the worst case, burn the patient's skin. If the regulation mechanism for the intensity of the LED light sources, which is partially software-controlled, fails, the LED could produce excessive lost heat caused by high supply currents.

Hazard 2: Short circuiting the lithium-polymer battery or charging/discharging with a current above the permitted maximum could result in excessive heating of the rechargeable battery. This potentially leads to its destruction by causing a rupture in the casing of the battery and thus chemicals might be released which themselves could ignite if they get in contact with water or moisture.

Hazard 3: The Bluetooth radio frequency emissions may cause third-party medical devices such as ventilators, infusion pumps or monitoring equipment to malfunction, thus endangering the patient(s).

Hazard 4: Improper disinfection of the OxyPrem sensor casing may cause transmission of pathogens between patients.

Hazard 5: The OxyPrem sensor casing is in direct contact to the patient skin and may thus cause skin irritation, allergies or intoxication by diffusion of toxic compounds into the patient's body.

Hazard 6: Since OxyPrem is a medical electrical device (ME devices), patients may potentially suffer electrical shock if they are in contact with exposed and energized electrical conductors.

To ensure that OxyPrem can be applied safe for both the investigator and the patient the following measures of protection (MOP) are undertaken in the design of (MOP numbers correspond to hazard numbers):

MOP 1: In normal operation, the LED light source's power does not exceed the power used in standard pulse oximeters. Hence irritation of the skin is not to be expected. Fast acting fuses are installed in the LED current driver circuit, thus limiting the maximum LED supply current and with it the maximum power dissipation in case of regulation failure to a level which is inapt to cause skin irritation or burns by heating.

MOP 2: Only rechargeable batteries with pre-installed passive (i.e. independent of the remaining electronics) safety circuits are installed. Said safety circuits disconnect the battery when the threshold of maximum current (during either charging or discharging) is exceeded (first MOP). Secondly, the battery is held inside a flexible but ductile container that will insulate the battery from the surroundings in case of rupture to avoid release of battery chemicals and to protect the battery from moisture or liquid (second MOP).

MOP 3: So far, crosstalk between Bluetooth devices and other medical devices (electro-magnetic interference, EMI) has not been reported in the literature to our knowledge. On the contrary, setups to

provoke such interference deliberately could not produce evidence that such interference is to be expected. To minimize potential risk associated with electro-magnetic interference, only Bluetooth components that are compliant to EN 61000 (electro-magnetic compatibility) will be used for OxyPrem thus further limiting the danger of EMI.

MOP 4: The casing of OxyPrem sensor (i.e. all components potentially in contact with the patient) are made of silicone and are designed with respect to facilitate disinfection: the surface will be made as plain as possible and the silicone is de-aired in vacuum prior processing to avoid superficial air bubbles forming cracks or cavities which might allow pathogens to survive disinfection. The outline of the sensor avoids edges, notches and ducts for the same reason. Overall, the design will allow OxyPrem to be disinfected following standard procedures as applied for ultrasound transducers, stethoscopes or other multiple-use medical devices used in neonatology.

MOP 5: The silicone casing in contact with the patient is made of medical grade silicone validated and certified by a proper body to be compliant with EN/ISO 10993 (biocompatibility of medical devices).

This technical normative standard extensively covers the problem of biocompatibility and materials compliant with EN/ISO 10993 can be considered inapt to cause irritation, intoxication or allergies.

MOP 6: The mains adapter (mains part) including the cable connecting it to the OxyPrem sensor is provided by a third party manufacturer. The device will be compliant with EN/ISO 60601,

Class II (potential separation from mains voltage with both basic and supplementary insulation).

Hence, the danger of electrical shock caused by the mains supply is negligible.

The highest voltage present to supply OxyPrem is 8V DC (direct current). Although such a low DC voltage is considered inapt to cause significant electrical current flow in the patient, a silicone casing is implemented as a further measure of protection to insulate the patient from live parts.

After careful consideration, the manufacturer concludes that the risk for the patient and the investigator associated with the application of OxyPrem can be well controlled applying the measures of protection described above and that both the probability of occurrence and the severity of potential adverse effects are small. Furthermore, it is the conviction of the manufacturer that OxyPrem has the potential to serve as a valuable diagnostic medical device in neonatal clinical practice, especially providing means to achieve better control of neonatal oxygen management and hence concludes that the potential benefits of OxyPrem clearly outweigh its potential risks.

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