INVESTIGATOR'S BROCHURE

SafeBoosC phase II

Revision history

Version	Author	Date	Changes
1.0	Simon Hyttel-Sørensen	01.02.2012	Initial Version

1. TABLE OF CONTENT

2. ABOUT THIS DOCUMENT

This document is the 'Investistigator'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 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 tools 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 O_2Hb 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 O_2Hb to total Hb, $rStO_2$, 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 $rStO_2$ 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 $rStO_2$ (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. $rStO_2$ 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). StO_2 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 $rStO_2$ (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, O_2Hb 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 how shown that these sensors have a positive bias compared to the adult sensors and estimates $rStO_2$ 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 to small for cannulation evaluation of the values of $rStO_2$ 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 $rStO_2$. Studies where the neonatal sensors have been used in preterm infants have reported cerebral $rStO_2$ 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 $rStO_2$ 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 that 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 $rStO_2$ could possibly predict poor outcome (39).

Normal ranges of $rStO_2$ 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 ± 2 standard deviation. This implies that by using the OxyAlert™ NIRSensors or Pediatric SomaSensor it will be impossible to detect and monitor hyperoxygention, 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 $rStO_2$ 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 $rStO_2$ 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”.

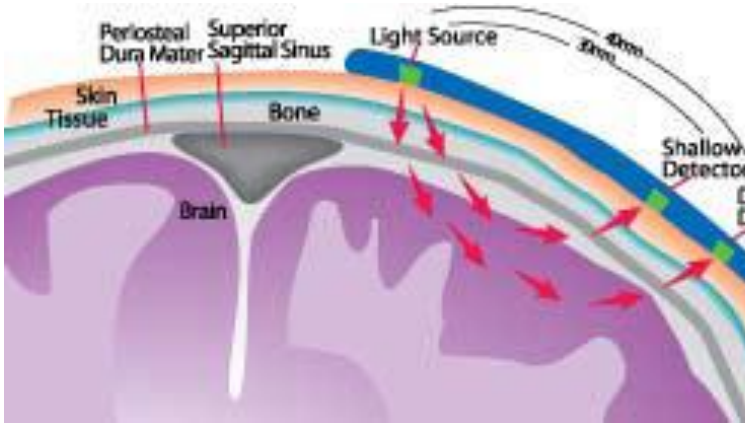
Adverse reactions (i.e. both expected and unexpected with a ‘certain’ or ‘probable/likely’ relation to the device) will be recorded and reported with the trial results and reported to the competent authorities.

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. INVOS 5100c

Between the Somanetics sensor and the brain or somatic tissue being monitored, there are several tissue layers with differing compositions and differing concentrations of blood.



By placing detectors at different distances from the light source, two depths of penetration are measured. Subtracting the shallow measurement from the deep minimizes superficial signal contamination, and emphasizes changes in tissue oxygen saturation beneath the sensor. This is called "depth resolution."

To reduce the interference of surface tissue on the oxygenation measurement, the INVOS® System uses two source-detector spacings: a near (shallow) spacing of 3 cm and a far (deep) spacing of 4 cm. Both sample about equally the shallow layers in the tissue volumes directly under the light sources and detectors, but the far spacing photons reach deeper. Subtracting the near signal (surface data from the skin and skull) from the far signal results in an oxygenation value specific to the deeper tissues under the sensor.

INDICATIONS:

The noninvasive INVOS Cerebral / Oximeter is intended for use as an adjunct trend monitor of regional hemoglobin oxygen saturation of blood in the brain in an individual. It is also intended for use as an adjunct trend monitor of haemoglobin oxygen saturation of blood in a region of skeletal muscle.

CONTRAINDICATIONS:
None.

Disposable OxyAlert™ NIRSensors (CNN) is intended for use in infants < 5 kg.

Disposable Paediatric SomaSensor® (SPFB) is intended for use in infants < 40 kg.

Disposable Adult SomaSensor® (SAFB-SM) is intended for use in adults > 40 kg.

The regulatory classification of INVOS 5100c can be found in the operations manual.

A detailed description of the INVOS 5100c 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.

6.1.2. Mode and conditions of application

The following instructions describe the correct application of the Adult SomaSensor on preterm infants and cannot replace the operations manual.

1. To ensure good contact, clean/degrease the skin using water. Ensure patient's skin is completely dry with a gauze pad.
2. Check that the SomaSensor is not defect. If it is, discharge it immediately and take a new.
3. Apply the adhesive side of the SomaSensor on a clean surface, e.g. the inside of the packaging repeatedly until the adhesive strength wears off.
4. Select sensor site on the head. Aim for a site with as little hair as possible, as this can introduce inaccurate readings. Do not place the sensor over sinus cavities, the superior sagittal sinus, subdural or epidural haemotomas or other anomalies such as arteriovenous malformations, as this may cause readings that are not reflective of brain tissue or no readings at all.
5. Insure intact skin surface.
6. Apply sensor to the head so that the light source is facing towards the skin The SomaSensor may be fixed with a self-adhesive single use bandage. The manufacturer of INVOS does not provide this bandage and the design of INVOS does not impose any limitation on the choice of the bandage except that it must allow a tight adhesion of the sensor the patient's body surface. However, using a certified medical grade, single-use product is required.
7. Secure the cable to a fixed object to avoid strain on the sensor to skin interface.

CAUTION : FOR EXTENDED MONITORING THE SENSOR SHOULD BE REPOSITIONED AT A DIFFERENT LOCATION EVERY 4 HOURS TO AVOID DAMAGE FROM HEAT.

CAUTION : TO AVOID PRESSURE SORES, KEEP THE EXTERNAL PRESSURE ON SENSOR TO A MINIMUM WHILE MAINTING SUFFICIENT SENSOR-SKIN CONTACT.

CAUTION : IF THE SENSOR IS DIFFICULT TO REMOVE, THE LOCAL PROTOCOL FOR PROTECTION OF THE INTEGRETY OF THE SKIN SHOULD BE FOLLOWED.

CAUTION: THE SENSOR IS NOT MRI COMPATIBLE.

6.1.3. Preclinical testing

The operations manual indicates an in vitro reproducibility within 1%. This is most likely data from test phantoms and represents the root mean square (RMS). In a porcine model of the $rStO_2$ was reasonably well correlated with mixed venous blood from the brain ($SjVO_2$) ($r = 0.74$, $p < 0.001$) during extracorporal membrane oxygenation (ECMO)(40).

6.1.4. Clinical testing

6.1.4.1. Validation
$rStO_2$ as measured by INVOS is a measure of tissue saturation and cannot be validated against a reference standard. Instead in has been compared to either mixed central venous blood from the superior vena cava (SvO_2), the mixed cerebral venous blood from the jugular bulb ($SjvO_2$), or against a calculated mixture of arterial and venous blood ($refStO_2 = 0.25SaO_2 + 0.75SjvO_2$).

During a wide range of conditions the $rStO_2$ has been shown to highly correlate with SvO_2 with correlation coefficient ranging from 0.4 to 0.9, but usually about 0.7 (41-47). The same correlation has been found with $SjvO_2$ with a mean correlation coefficient of 0.7 (42,43,48-51).

6.1.4.2. Relation to outcome
There is accumulating evidence that $rStO_2$ measured by INVOS has predictive value.

In adult surgery ROC analysis of minimal preoperative oxygen supplemented $rStO_2$ and 30-day mortality revealed an area under the curve (AUC) of 0.71 (95% CI, 0.68–0.73; $P < 0.0001$) and a cutoff value of ≤51% (sensitivity 41.5%, specificity 93.6%) in the total cohort 1178 patients undergoing cardiac surgery (52). Intraoperative cerebral desaturation has been shown to associated with an increased risk of cognitive decline (53,54) and increased length of hospital stay (54,55).

In infants undergoing surgery for congenital heart disease Psychomotor Development Index score (P=0.02) and brain hemosiderin (P=0.04) were significantly associated with rStO2 during the 60-minute period following cardiopulmonary bypass (56), while in another study infants with low preoperative $rStO_2$ tended have lower developmental quotient (57). In another cohort mean cerebral $rStO_2$ of less than 56% over the first 48 hours after surgery yielded a sensitivity of 75.0% and a specificity of 79.4% to predict those at risk for subsequent adverse events (58). In asphyxiated newborns a high $rStO_2$ at 24 hours predicts adverse outcome (9).

6.1.5. Summary of risk assessment
A risk assessment according to EN/ISO 14971:2007 has been performed for the INVOS device. INVOS 5100c has CE approval for use in newborn infants albeit with the OxyAlert™ NIRSensors. The risk analysis is thus an assessment of the possible additional risk of application of the Adult SomaSensor® (SAFB-SM) in the newborn infant.

Two relevant sources of hazards were identified:
Hazard 1: The LED sources produce a certain amount of lost heat that could irritate or, in the worst case, burn the patient's skin.
Hazard 2: The Adult SomaSensor® (SAFB-SM) sensor is in direct contact to the patient skin and the adhesive strength could cause damage to the skin when the sensor is removed.

To ensure that INVOS 5100c can be applied safely 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 oxymeters. The sensor is to be removed every fourth hour to avoid tissue damage.
MOP 2: Instructions to weaken the adhesive strength by applying the sensor on a clean surface repeatedly before application on an infant.

After careful consideration, the both investigators and sponsor conclude that the risk for the patient and the investigator associated with the application of INVOS 5100c with Adult SomaSensor® (SAFB-SM) 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 given the large previous experience with this specific sensor on neonates.

6.2. 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.

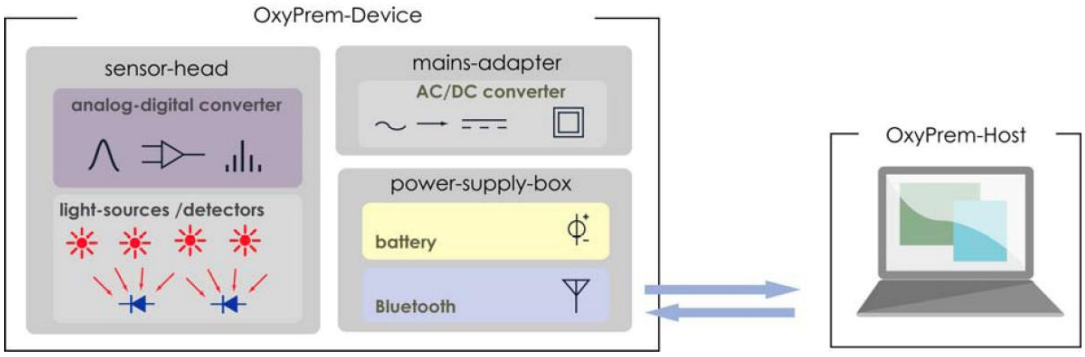


Image 1 – System block diagram. EU: electronics unit, SU: sensor unit, PS: power supply. EU, SU and PS may be fused into one casing or configured as separate units, interconnected by cables. Linkage between OxyPrem-Device and OxyPrem-Host may also be incorporated using a galvanically isolated USB-connection.

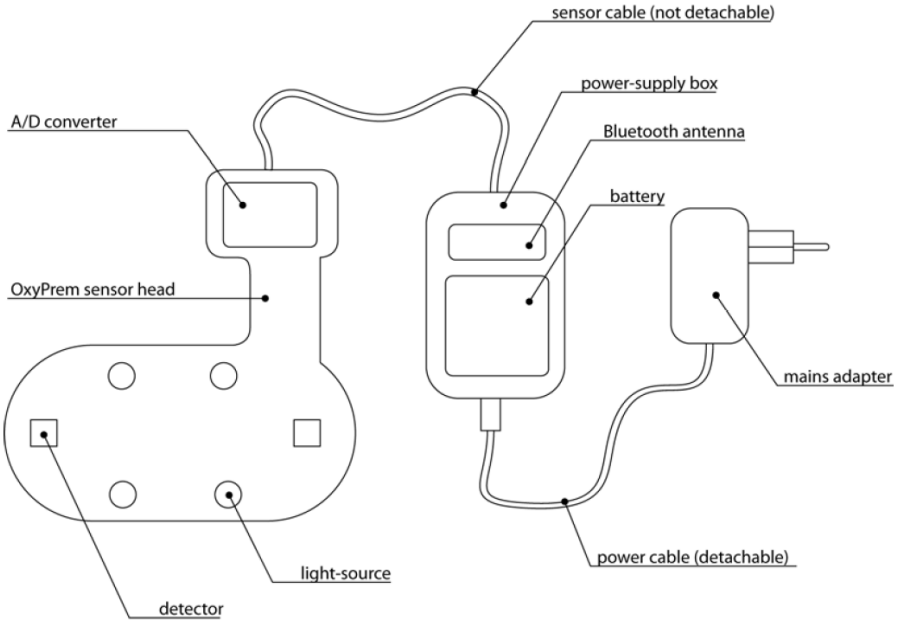


Image 2 – *OxyPrem Device. The sensor cable may be detachable in some devices. Linkage between OxyPrem-Device and OxyPrem-Host may also be incorporated using a galvanically isolated USB-connection.*

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.

6.2.1 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).

6.2.2. 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 manly 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 asses 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).

6.2.3. 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 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 safe in an environment with air temperatures between 18°C and 42°C and air humidity between 50% and 95%.

6.2.4. Limits of application

Any implantation or insertion of the OxyPrem sensor, surgically or trough 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 sterilizabilty 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 what so ever.

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.

6.2.5. Power supply

OyxPrem 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 VAC 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).

6.2.6. 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.

6.2.7. Preclinical testing

A comparison between the OxyPrem, INVOS 5100c, NIRO 200 NX and NIRO 300 (Hamamatzu) 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).

6.2.8. Clinical testing

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

6.2.9. 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 oxymeters), 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 oxymeters. 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 form 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 asapplied 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 a 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 OyxPrem 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.

6.3. FORE-SIGHT™ Cerebral Oximeter

The FORE-SIGHT™ Cerebral Oximeter system design incorporates several features for data accuracy.

- Advanced Optics - utilizes LASER-SIGHT™ technology for increased light source precision and data accuracy.
- Innovative, Patented Data Analysis Algorithm – accounts for optical characteristics of background tissue in determining cerebral tissue oxygen saturation values to minimize patient dependent variables.
- Novel Patient Sensor Design –minimizes interference from tissues outside the brain, when combined with our patented data analysis algorithm, resulting in exceptional measurement accuracy.

INDICATIONS:
The FORE-SIGHT™ Cerebral Oximeter provides clinicians with an absolute indication of cerebral tissue oxygen saturation. This absolute value, displayed on the monitor and updated every few seconds, gives clinicians an immediate, clear indication of a patient's cerebral oxygen saturation status.

CONTRAINDICATIONS:
None.

Large Sensor (Dual Sensor) is intended for use in patients > 40 kg.

Medium Sensor (Dual Sensor) is intended for use in patients 4-60 kg.

Small Non-Adhesive Sensor (Single Sensor) is intended for use in patients < 8 kg.

Small Sensor (Dual Sensor) is intended for use in patients < 8 kg.

The regulatory classification of INVOS 5100c can be found in the operations manual.

A detailed description of the FORE-SIGHT™ Cerebral Oximeter, 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.

6.3.2. Mode and conditions of application

The following instructions describe the correct application of the Large Sensor on preterm infants and cannot replace the operations manual.

1. To ensure good contact, clean/degrease the skin using water. Ensure patient's skin is completely dry with a gauze pad.
2. Check that the sensor is not defect. If it is, discharge it immediately and take a new.
3. Apply the adhesive side of the sensor on a clean surface, e.g. the inside of the packaging repeatedly until the adhesive strength wears off.
4. Select sensor site on the head. Aim for a site with as little hair as possible, as this can introduce inaccurate readings. Do not place the sensor over sinus cavities, the superior sagittal sinus, subdural or epidural haematomas or other anomalies such as arteriovenous malformations, as this may cause readings that are not reflective of brain tissue or no readings at all.
5. Insure intact skin surface.
6. Apply sensor to the head so that the light source is facing towards the skin. The Large Sensor may be fixed with a self-adhesive single use bandage. The manufacturer of Fore-Sight does not provide this bandage and the design of Fore-Sight does not impose any limitation on the choice of the bandage except that it must allow a tight adhesion of the sensor the patient's

body surface. However, using a certified medical grade, single-use product is required.
7. Secure the cable to a fixed object to avoid strain on the sensor to skin interface.

CAUTION : FOR EXTENDED MONITORING THE SENSOR SHOULD BE REPOSITIONED AT A DIFFERENT LOCATION EVERY 4 HOURS TO AVOID DAMAGE FROM HEAT.

CAUTION : TO AVOID PRESSURE SORES, KEEP THE EXTERNAL PRESSURE ON SENSOR TO A MINIMUM WHILE MAINTING SUFFICIENT SENSOR-SKIN CONTACT.

CAUTION : IF THE SENSOR IS DIFFICULT TO REMOVE, THE LOCAL PROTOCOL FOR PROTECTION OF THE INTEGRETY OF THE SKIN SHOULD BE FOLLOWED.

CAUTION: THE SENSOR IS NOT MRI COMPATIBLE.

6.3.3. Preclinical testing

There are no published preclinical data on the FORE-SIGHT™ Cerebral Oximeter. However the device is both FDA-approved and CE-marked for clinical use.

6.3.4. Clinical testing

6.3.4.1. Validation

Adult Subject Validation: Healthy adult volunteers were subjects for comparison using an internal jugular bulb catheter on the subject's right side and a radial arterial line on the left. Two sensors from the FORE-SIGHT Cerebral Oximeter monitor were placed bilaterally on the patient's forehead. Hypoxic mixtures of gas were delivered and data was collected in 5-minute intervals during periods of ascending and descending concentrations. At each data collection point, blood samples were drawn simultaneously from the jugular bulb and the radial arterial catheters and analyzed for hemoglobin oxygen saturation using a co-oximeter. The patient was monitored and the protocol stopped if SPO2 values from a pulse oximeter reached 70%. Cerebral Oximeter $rStO_2$ showed a strong correlation with the reference $rStO_2$ over the spectrum of values between 45 to 95%. The RSME = $\sqrt{(bias^2 + precision^2)}$ for the Cerebral Oximeter Monitor $rStO_2$ compared to reference $rStO_2$ derived from co-oximetry of arterial (SaO_2) and jugular bulb ($SjvO_2$) blood samples was - 3.70 %.

Infant & Neonate $rStO_2$**:** Using the FORE-SIGHT Small Sensor, the Cerebral Oximeter SctO2 showed strong agreement with the reference $rStO_2$ over the spectrum of values between 50 to 95%. The RSME for the Cerebral Oximeter Monitor $rStO_2$ compared to the reference $rStO_2$ derived from pulse oximetry measured arterial oxygen saturation SaO_2 and co-oximetry measured internal jugular vein venous oxygen saturation ($SjvO_2$) from blood samples was ± 4.77 %.

Compared to INVOS 5100c Adult SomaSensor: Two small studies compared the Large Sensor of FORE-SIGHT with INVOS 5100c Adult SomaSensor. Both found a bias less than 5 percentage point (24,25).

6.3.4.2. Relation to outcome

There is accumulating evidence that $rStO_2$ has predictive value. The following studies have been conducted with the INVOS 5100c that is equivalent to the FORE-SIGHT.

In adult surgery ROC analysis of minimal preoperative oxygen supplemented $rStO_2$ and 30-day mortality revealed an area under the curve (AUC) of 0.71 (95% CI, 0.68–0.73; $P < 0.0001$) and a cutoff value of ≤51% (sensitivity 41.5%, specificity 93.6%) in the total cohort 1178 patients undergoing cardiac surgery (52). Intraoperative cerebral desaturation has been shown to associated with an increased risk of cognitive decline (53,54) and increased length of hospital stay (54,55).

In infants undergoing surgery for congenital heart disease Psychomotor Development Index score (P=0.02) and brain hemosiderin (P=0.04) were significantly associated with rStO2 during the 60-minute period following cardiopulmonary bypass (56), while in another study infants with low preoperative $rStO_2$ tended have lower developmental quotient (57). In another cohort mean cerebral $rStO_2$ of less than 56% over the first 48 hours after surgery yielded a sensitivity of 75.0% and a

specificity of 79.4% to predict those at risk for subsequent adverse events (58). In asphyxiated newborns a high $rStO_2$ at 24 hours predicts adverse outcome (9).

6.3.5. Summary of risk assessment

A risk assessment according to EN/ISO 14971:2007 has been performed for the FORE-SIGHT™ Cerebral Oximeter device. It has CE approval for use in newborn infants albeit with the two Small Sensors. The risk analysis is thus an assessment of the possible additional risk of application of the Large Sensor in the newborn infant.

Two relevant sources of hazards were identified:
Hazard 1: The laser sources produce a certain amount of lost heat that could irritate or, in the worst case, burn the patient's skin.
Hazard 2: The Large Sensor is in direct contact to the patient skin and the adhesive strength could cause damage to the skin when the sensor is removed.

To ensure that Large Sensor can be applied safely 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: The laser system is designated as a Class 1 laser product by the FDA, i.e. a non-significant risk device. The laser light source's power does not exceed the power used in standard pulse oximeters. The sensor is to be removed every fourth hour to avoid tissue damage.
MOP 2: Instructions to weaken the adhesive strength by applying the sensor on a clean surface repeatedly before application on an infant.

After careful consideration, the both investigators and sponsor conclude that the risk for the patient and the investigator associated with the application of FORE-SIGHT™ Cerebral Oximeter 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 given the large previous experience with adult NIRS sensors on neonates.

6.3. NONIN EQUANOX 7600

NONIN EQUANOX Model 7600 4-Channel Regional Oximeter System with EQUANOX™ Technology and Bluetooth Wireless Technology and compatible sensors continuously monitor and record the mixed arterial/venous blood oxygen levels through non-invasive near-infrared spectroscopy sensors.

The system is comprised of three subsystems: sensor, patient oximetry device (pod) and 4-channel display unit. The sensor allows light absorption measurements at various wavelengths in the near-infrared spectrum. The sensor plug into the patient oximetry device, which controls the light emitted form the sensor LED and measures the light returning to the sensor photodiodes. From these measurements, the pod determines specific absorption values and calculates the mixed arterial/venous oxygen saturation values $rStO_2$. The pods then communicate the $rStO_2$ to the display unit.

The 4-channel display unit displays absolute real-time $rStO_2$ numeric data and trend lines. it is battery-backed, mains powered device equipped with audio and visual alarm indicators. Real-time data and playback output is accomplished through a Bluetooth transceiver module.

INDICATIONS:
NONIN EQUANOX Advance™ is intended for monitoring of absolute regional tissue oxygenation $rStO_2$. It should not be used as a stand-alone diagnostic test.

CONTRAINDICATIONS:
None.

Model 8004CA EQUANOX™ Advance is intended for absolute $rStO_2$ measurement in patients > 40 kg.

Model 8000CA EQUANOX™ Classic is intended for $rStO_2$ trend measurement in patients > 40 kg.

Model 8004CB EQUANOX™ Neonatal/Pediatric is intended for absolute $rStO_2$ measurement in patients < 40 kg.

The regulatory classification of NONIN EQUANOX 7600 can be found in the operations manual.

A detailed description of the NONIN EQUANOX 7600, 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.

6.3.2. Mode and conditions of application

The following instructions describe the correct application of the Model 8004CA EQUANOX™ Advance on preterm infants and cannot replace the operations manual.

1. To ensure good contact, clean/degrease the skin using water. Ensure patient's skin is completely dry with a gauze pad.
2. Check that the sensor is not defect. If it is, discharge it immediately and take a new.
3. Apply the adhesive side of the sensor on a clean surface, e.g. the inside of the packaging repeatedly until the adhesive strength wears off.
4. Select sensor site on the head. Aim for a site with as little hair as possible, as this can introduce inaccurate readings. Do not place the sensor over sinus cavities, the superior sagittal sinus, subdural or epidural haematomas or other anomalies such as arteriovenous malformations, as this may cause readings that are not reflective of brain tissue or no readings at all.
5. Insure intact skin surface.
6. Apply sensor to the head so that the light source is facing towards the skin. The Large Sensor may be fixed with a self-adhesive single use bandage. The manufacturer of Fore-Sight does not provide this bandage and the design of Fore-Sight does not impose any limitation on the choice of the bandage except that it must allow a tight adhesion of the sensor the patient's body surface. However, using a certified medical grade, single-use product is required.
7. Secure the cable to a fixed object to avoid strain on the sensor to skin interface.

CAUTION : FOR EXTENDED MONITORING THE SENSOR SHOULD BE REPOSITIONED AT A DIFFERENT LOCATION EVERY 4 HOURS TO AVOID DAMAGE FROM HEAT.

CAUTION : TO AVOID PRESSURE SORES, KEEP THE EXTERNAL PRESSURE ON SENSOR TO A MINIMUM WHILE MAINTING SUFFICIENT SENSOR-SKIN CONTACT.

CAUTION : IF THE SENSOR IS DIFFICULT TO REMOVE, THE LOCAL PROTOCOL FOR PROTECTION OF THE INTEGRETY OF THE SKIN SHOULD BE FOLLOWED.

CAUTION: THE SENSOR IS NOT MRI COMPATIBLE.

6.3.3. Preclinical testing

There are no published preclinical data on NONIN EQUANOX 7600. However the device is both FDA-approved and CE-marked for clinical use.

6.3.4. Clinical testing

6.3.4.1. Validation

Adult Subject Validation: In 18 adult healthy subjects the $rStO_2$ was highly correlated with the reference $rStO_2$ ($rStO_{2,ref} = 0.3xSpO_2 + 0.7xS_{jugularbulv}O_2$) through SpO_2 values of 70-100% . Bias was 0.13%, and limits of agreement were -7.27 to 7.53% (60). In 24 adult subjects the A_{RMS} (ISO 80601-2-61:2011) was 4.1% in a similar study with the Model 8004CA EQUANOX™ Advance (61). While in yet another study Model 8000CA EQUANOX™ Classic had a bias of 2.48% ± 8.12% and A_{rms} 8.47% and Model 8004CA EQUANOX™ Advance had a bias of 2.84% ± 6.27% and A_{rms} 6.86% (24).

Compared to INVOS 5100c Adult SomaSensor both Model 8000CA EQUANOX™ Classic and Model 8004CA EQUANOX™ Advance shoved mean values within 5 percentage (24).

6.3.4.2. Relation to outcome

There is accumulating evidence that $rStO_2$ has predictive value. The following studies have been conducted with the INVOS 5100c that is equivalent to the NONIN EQUANOX 7600.

In adult surgery ROC analysis of minimal preoperative oxygen supplemented $rStO_2$ and 30-day mortality revealed an area under the curve (AUC) of 0.71 (95% CI, 0.68–0.73; $P < 0.0001$) and a cutoff value of ≤51% (sensitivity 41.5%, specificity 93.6%) in the total cohort 1178 patients undergoing cardiac surgery (52). Intraoperative cerebral desaturation has been shown to associated with an increased risk of cognitive decline (53,54) and increased length of hospital stay (54,55).

In infants undergoing surgery for congenital heart disease Psychomotor Development Index score (P=0.02) and brain hemosiderin (P=0.04) were significantly associated with rStO2 during the 60-minute period following cardiopulmonary bypass (56), while in another study infants with low preoperative $rStO_2$ tended have lower developmental quotient (57). In another cohort mean cerebral $rStO_2$ of less than 56% over the first 48 hours after surgery yielded a sensitivity of 75.0% and a specificity of 79.4% to predict those at risk for subsequent adverse events (58). In asphyxiated newborns a high $rStO_2$ at 24 hours predicts adverse outcome (9).

6.3.5. Summary of risk assessment

A risk assessment according to EN/ISO 14971:2007 has been performed for the NONIN EQUANOX Model 7600 4-Channel Regional Oximeter System with EQUANOX™ Technology. It has CE approval for use in newborn infants albeit with the Model 8004CB EQUANOX™ Neonatal/Pediatric sensor. The risk analysis is thus an assessment of the possible additional risk of application of the Model 8004CA EQUANOX™ Advance in the newborn infant.

Two relevant sources of hazards were identified:
Hazard 1: The LED sources produce a certain amount of lost heat that could irritate or, in the worst case, burn the patient's skin.
Hazard 2: The Model 8004CA EQUANOX™ Advance is in direct contact to the patient skin and the adhesive strength could cause damage to the skin when the sensor is removed.

To ensure that Model 8004CA EQUANOX™ Advance can be applied safely 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: The laser system is designated as a Class 1 laser product by the FDA, i.e. a non-significant risk device. The laser light source's power does not exceed the power used in standard pulse oximeters. The sensor is to be removed every fourth hour to avoid tissue damage.
MOP 2: Instructions to weaken the adhesive strength by applying the sensor on a clean surface repeatedly before application on an infant.

After careful consideration, the both investigators and sponsor conclude that the risk for the patient and the investigator associated with the application of Model 8004CA EQUANOX™ Advance 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 given the large previous experience with adult NIRS sensors on neonates.

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