INVESTIGATOR'S BROCHURE

SafeBoosC phase II - INVOS 5100 C

Revision history

Version	Author	Date	Changes
1.0	Simon Hyttel-Sørensen	22.03.2012	Initial Version
1.1	Simon Hyttel-Sørensen	24.04.2012	List of applied standards included, changed in- and exclusion criteria.

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.

List of legal and technical standards relevant for this document
The following standards were considered relevant by the author(s) of this document. To the best knowledge of the authors, this document and the medical device described therein complies with the regulations and standards listed below.

EN/ISO 14971:2007, EN/ISO 14155:2011.

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:

- Neonates born more than 12 weeks preterm (gestational age up to 27 weeks and 6 days).
- Decision to conduct full life support.
- Possibility to place cerebral NIRS oximeter within 3 hours after birth.
- Obtained parental signed written informed consent.

Exclusion criteria:

- A clinical decision not to provide full life support.
- No possibility to place the cerebral NIRS oximeter within 3 hours after birth.
- Lack of parental signed written informed consent.

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 93/42/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”.

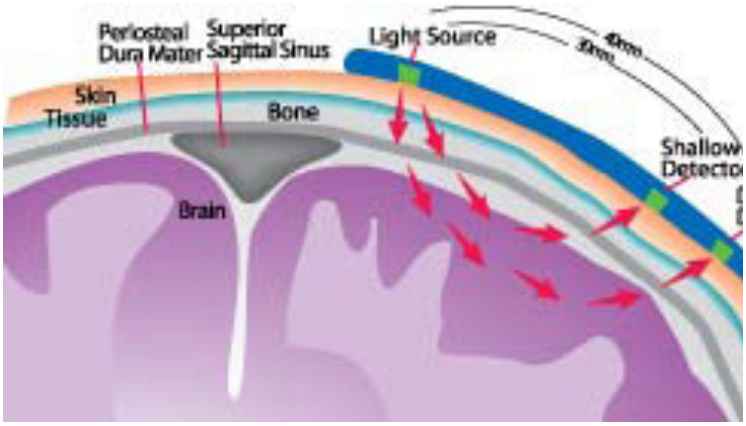
Adverse reactions (i.e. both expected and unexpected with a ‘certain’ or ‘probable/likely’ relation to the device) will be recorded and reported with the trial results and reported to the competent authorities.

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 5100 C

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.

6.1.1. 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.

6.1.2. 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).

6.1.3. Clinical testing

6.1.3.1. 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).

6.1.3.2. 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).

6.1.4. 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.

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