Medtronic

# Clinical Investigation Plan

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| **Clinical Investigation Plan/Study Title** | Validation of Next Generation INVOS NIRS Cerebral and Tissue Oximeter to Measure Cerebral and Somatic Tissue Oxygen Saturation in Healthy Volunteers |
| **Clinical Investigation Plan Identifier** | MDT16010MAVJB3 |
| **Study Product Name** | Next Generation INVOS |
| **Sponsor/Local Sponsor** | Covidien LP, a Medtronic company ("Medtronic")<br>MITG, Patient Monitoring & Recovery (PMR)<br>6135 Gunbarrel Avenue,<br>Boulder, CO 80301<br>U.S.A. |
| **Document Revision** | B |
| **Lead Principal Investigator(s)** | David MacLeod, FRCA<br>Human Pharmacology & Physiology Lab<br>Duke University Medical Center<br>Durham, NC 27710<br>U.S.A. |

**Confidentiality Statement**

# 1 Version History

| Version | Date | Summary of Changes | Author(s)/Title |
|---|---|---|---|
| A | 11 July 2016 | New Document | [redacted] |
| B | 15 MAR 2017 | Justification for sample size was added. Also, additional changes required by CIP template were included. Term and definition section was updated to add additional terms. The adverse event reporting requirements were clarified. Hypocapnic state was removed from the study protocol. | [redacted] |

# 2 Investigator Statement

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| **Study product Name** | Validation of Next Generation INVOS NIRS Cerebral and Tissue Oximeter to Measure Cerebral and Somatic Tissue Oxygen Saturation in Healthy Volunteers |
| **Sponsor** | Medtronic |
| **Clinical Investigation Plan Identifier** | MDT16010MAVJB3 |
| **Revision Number/Date** | B / 15 MAR 2017 |

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with the protocol and ethical principles that have their origin in the Declaration of Helsinki and will follow the United Stated Food and Drug Administration (FDA) regulations 21 CFR part 812.2(b) - Investigational Device Exemption Abbreviated Requirements and other national regulatory guidelines as appropriate. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.

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| **Investigator's Signature:** | |
| **Investigator's Name:** | |
| **Institution:** | |
| **Date:** | |

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# 3 Glossary

| *Term* | *Definition* |
|---|---|
| AE | Adverse Event. For definition, refer to Section 12. |
| A-Line | Arterial catheterization. A catheter inserted into the artery that allows measurement of Mean Arterial Pressure (MAP) and sampling of arterial blood gas samples. |
| $A_{RMS}$ | Arithmetic Root Mean Square |
| CBC | Complete Blood Count. |
| Capnograph | A device that measures the concentration of carbon dioxide from each inspired and expired breath. Gases are collected with non-invasive side stream from the inhaled and exhaled gases of the subject. Capnograph outputs numeric values and waveform of the fractioned concentration of $CO_2$ of each breath. |
| CBF | Cerebral Blood Flow. The volume of blood flowing through the brain per unit time. |
| CIP | Clinical Investigational Protocol |
| $CO_2$ | Carbon Dioxide. It can be measured with a capnograph. |
| COHb | Carboxyhemoglobin. Hemoglobin (Hb) with irreversibly bound carbon monoxide (CO). Carbon monoxide hinders the ability of Hb to deliver oxygen to the body. |
| CRF | Case Report Form. Forms where the clinical data are collected. eCRF is the electronic version of the CRF. |
| ECG | Electrocardiogram. A diagnostic tool that measures and records the electrical activity of the heart. |
| EDC | Electronic Data Capture. Electronic system where the study data are collected through the eCRF (Oracle Clinical). May also be referred to as RDC (Remote Data Capture). |
| eCRF | Electronic version of the CRF. |
| EMR | Electronic Medical Record. Digital version of a patient's medical record |

| *Term* | *Definition* |
|---|---|
| | within a single facility. |
| $EtCO_2$ | End-tidal Carbon Dioxide. The value of exhaled carbon dioxide displayed by the capnograph device. |
| FDA | Food and Drug Administration |
| fSO2 | Calculated Field Oxygen Saturation. It is calculated from a weighted average of arterial and jugular venous blood oxygen saturation measurements (based on assumption that cerebral tissue contains arterial and venous blood in a specific ratio.) |
| GCP | Good Clinical Practice. |
| Hb | Hemoglobin |
| HR | Heart Rate. Heart contractions per minute. |
| [redacted] | [redacted] |
| ICF | Informed Consent Form |
| IDE | Investigational Device Exemption |
| INVOS | In-Vivo Optical Spectroscopy. |
| IRB | Institutional Review Board. |
| ISF | Investigator Site File. (Also known as Regulatory binder.) |
| kg | Kilogram |
| MAP | Mean Arterial Pressure. The calculated mean pressure within an artery over a complete cycle of one heartbeat. The pressure exerted by circulating blood upon the walls of blood vessels. Measured invasively via arterial line. |
| MetHb | Methemoglobin. A compound formed from hemoglobin by oxidation. Methemoglobin cannot carry oxygen. |
| MITG | Minimally Invasive Therapies Group |
| NIBP | Non-Invasive Blood Pressure. Sphygmomanometer inflated cuff method |

| *Term* | *Definition* |
|---|---|
| NIRS | Near Infrared Spectroscopy. |
| Normocapnia/ Normocarbia | Subject specific state of normal carbon dioxide pressure, as measured at study start while breathing room air. |
| NPO | Null per os (refrain from eating or drinking for certain time). |
| PI | Principal Investigator. The person responsible for overseeing the study and assuring study completion in compliance of applicable regulations. |
| PMR | Patient Monitoring & Recovery |
| POC | Point of Care. It is when clinicians deliver healthcare products and services to patients at the time of care. |
| rSO2 | Regional hemoglobin oxygen saturation. Measured by a regional tissue oximeter (NIRS device). |
| RDC | Remote Data Capture |
| SADE | Serious Adverse Device Effect. For definition, refer to Section 12. |
| SAE | Serious Adverse Event. For definition, refer to Section 12. |
| SAFB-SM | INVOS sensor, Adult Somasensor. |
| SaO2 | Arterial oxygen saturation. The true hemoglobin oxygen saturation of arterial blood, measured by a co-oximeter from an arterial blood sample. |
| SpO2 | A non-invasive spectroscopic estimate of arterial oxygen saturation measured transcutaneously by a pulse oximeter. |
| SjvO2 | Jugular venous oxygen saturation. The true hemoglobin oxygen saturation of jugular venous blood, measured by a co-oximeter from a jugular vein blood sample. |
| SOP | Standard Operating Procedures. |
| SV | Stroke Volume. The volume of blood pumped from one ventricle of the heart with each beat. |
| UADE | Unanticipated Adverse Device Effect. For definition, refer to Section 12. |
| UCB | Upper confidence bound |
| USA | United State of America |

# 4 Synopsis

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|---|---|
| **Title** | Validation of Next Generation INVOS NIRS Cerebral and Tissue Oximeter to Measure Cerebral and Somatic Tissue Oxygen Saturation in Human Volunteers |
| **Clinical Study Type** | Interventional (premarket) |
| **Product Name** | An investigational next generation In-Vivo Optical Spectroscopy (INVOS) Near Infrared Spectroscopy (NIRS) system will be used in this study. The system includes production equivalent [redacted] System (investigational preamplifiers, monitor, and associated cables) in conjunction with Adult sensor [redacted]).<br><br>The investigation NIRS system is similar in function and application to a currently cleared and marketed NIRS system – the INVOS 5100C. The INVOS 5100C is intended for use as an adjunct a monitor of regional hemoglobin oxygen saturation of blood in the brain or in other tissue beneath the sensor. |
| **Sponsor** | Medtronic, MITG, PMR |
| **Indication under investigation** | **INVOS Indication for Use:**<br>The noninvasive INVOS Cerebral/Somatic Oximetry System is intended for use as an adjunct monitor of regional hemoglobin oxygen saturation of blood in the brain or in other tissue beneath the sensor. It is intended for use in individuals greater than 40 kilograms (kg).<br><br>**Sensor Indications for Use:**<br>The INVOS™ Adult rSO2 Sensor is indicated for single patient use when cerebral/somatic monitoring of site-specific regional oxygen saturation (rSO2) is required in patients weighing >40 kg. |
| **Investigation Purpose** | The purpose of the study is to provide data for validation of the next generation of the INVOS Oximeter. |
| **Product Status** | Investigational, Investigational Device Exemption (IDE) |
| **Primary Objective(s)** | The primary objective of the study is to validate that the production equivalent [redacted] System, in conjunction with Adult Sensors [redacted]), meets product requirements for cerebral accuracy, cerebral trending accuracy, and somatic trending. |
| **Study Design** | This is a prospective data collection, non-randomized, single center study to validate the accuracy of the [redacted] System in conjunction with |

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| | Adult Sensors ([redacted]). This is achieved by comparing INVOS collected cerebral tissue oxygen saturation with a calculated value derived from simultaneous arterial and jugular venous blood samples. Next generation INVOS $rSO_2$ trending performance will be compared to legacy INVOS $rSO_2$ on the somatic site.<br><br>Up to 50 healthy adult and transitional adolescent volunteers with a variety of skin pigmentation will be enrolled. The subjects will be distributed across both genders as equally as practical and a range of skin pigmentations, including at least [redacted] darkly pigmented subjects or at least [redacted] of the subject pool.<br><br>This study will be conducted in three phases: Enrollment Phase, Desaturation Phase, and Follow-up Phase. During Enrollment Phase, subjects will be screened and qualified subjects will be enrolled. After enrollment, during Desaturation Phase, ECG and pulse oximetry will be applied. Intravenous and radial artery catheters will be placed. The jugular venous bulb catheter will be placed in the right or left jugular venous bulb with ultrasound guidance, and its position will be confirmed with skull x-ray. Two investigational INVOS sensors will be placed bilaterally on the patient's forehead and other sensors will be placed on somatic sites.<br><br>The INVOS investigational device will be evaluated for a targeted range of 70-100% SpO2 levels. Hypoxic mixtures of gas are delivered and data are collected at approximately (~) 5-minute intervals during steady periods of increasing and decreasing oxygen concentration (for more details refer to *Section 10*).<br><br>At each INVOS data collection point, blood samples are drawn simultaneously from both jugular bulb and the radial arterial catheters and analyzed for hemoglobin oxygen saturation using a co-oximeter.<br><br>The subjects are monitored and the protocol is stopped if SpO2 values from a pulse oximeter reach 60%.<br><br>Subjects are followed up within 48 hours after the procedure. |
| **Sample Size** | The subject population will include up to a total of 50 subjects. |
| **Inclusion/Exclusion Criteria** | **Inclusion Criteria**<br><br>Each patient must meet the following criteria to be enrolled in the study:<br><br>1. Healthy, male or female subjects between the ages of 18 to ≤46 years;<br>2. Completion of a health screening for a medical history by a licensed physician, nurse practitioner, or physician assistant;<br>3. Minimum weight 40kg;<br>4. BMI within range 18.0 - 30.0. |

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| | **Exclusion Criteria**<br>Patients who meet any of the following criteria will be excluded from the study:<br>1. Prior or known allergies to lidocaine (or similar pharmacologic agents, e.g., Novocain) [self-reported];<br>2. Prior known severe allergies to medical grade adhesive/tape (Band-Aid) [self-reported];<br>3. Taking any medication other than birth control [self-reported];<br>4. Is currently participating in, or has recently participated in (discontinued within 30 days prior to the hypoxia procedure for this study) in an investigational drug, device, or biologic study [self-reported];<br>5. Has a negative Allen's Test to confirm non-patency of the collateral artery [clinical assessment by PI or delegate];<br>6. Has made a whole blood donation or has had at least 450 ml of blood drawn within 8 weeks prior to the study procedure [self-reported];<br>7. Is female with a positive pregnancy test [serum or urine], or is female and is unwilling to use effective birth control between the time of screening and study procedure or is breastfeeding;<br>8. Has anemia [lab values specific for gender];<br>9. Has a history of sickle cell trait or thalassemia [self-reported];<br>10. Has an abnormal hemoglobin electrophoresis test [lab measurement];<br>11. Has a positive urine cotinine test or urine drug screen or oral ethanol test [Point of Care (POC) testing];<br>12. Has a room air saturation less than 95% by pulse oximetry [measurement by PI or delegate];<br>13. Has a clinically significant abnormal ECG [assessment by PI or delegate];<br>14. Has a clinically significant abnormal pulmonary function test via spirometry [assessment by PI or delegate];<br>15. Has a COHb greater than 3%, or MetHb greater than 2% [measured by venous blood sample co-oximetry]; |
| **Study Procedures and Assessments** | Subjects will undergo medical screening including a medical history, physical examination, spirometry, electrocardiogram (ECG) and blood draw, Complete Blood Count (CBC), hemoglobin electrophoresis and venous co-oximetry [to measure carboxyhemoglobin (COHb) & methemoglobin (MetHb)]). A urine sample will be tested for the presence of cotinine (nicotine metabolite) to exclude smokers. Demographics, skin pigmentation intensity and baseline readings from |

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| | current INVOS 5100C will be recorded. All subjects will have urine drug screen and alcohol breathalyzer tests. Female subjects will also have a urine pregnancy test done. Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled. Jugular bulb and arterial catheters will be inserted for each subject. Jugular bulb catheter will be placed under ultrasound guidance. The study device (sensors) will be placed on subjects. Subjects will complete controlled desaturation (targeted range 70%-100%) sequences with arterial and jugular blood sample collections. Subjects will be followed up within 48 hours after desaturation phase. For more details on procedures, refer to *Section 10*. |
| **Safety Assessments** | Medtronic believes that this study is a "non-significant risk" (NSR) study. Subjects will be monitored for Adverse Events, Serious Adverse Events, and Device-Related Adverse Events as noted in Risks and Benefits of *Section 11.3*. |
| **Statistics** | The subject population will include up to a total of 50 subjects. The planned sample size was determined through a power-based analysis based on previously collected Jugular Bulb study data during the device development cycle, and will be documented in the Statistical Analysis Plan (SAP). The study size is pre-defined to enroll up to 50 subjects accounting for larger than anticipated screen failures and subject dropouts.<br><br>Sample size was initially estimated by bootstrapping the historical data collected from two Jugular Bulb clinical studies performed at Duke University. Results of bootstrapping data was compared for different study sizes, subject based to minimize the likelihood of a reported performance statistic greater than the product specification, taking into account repeated measurements per subject. [redacted]<br><br>Statistical analyses will be conducted by Medtronic or its designee as outlined in the Statistical Analysis Plan (SAP). Any changes in statistical methods will be detailed in the SAP.<br><br>Briefly, standard demographic information and baseline characteristics data will be summarized using descriptive statistics.<br><br>For safety assessments, adverse events (AEs) will be summarized using frequency counts and percentages. Descriptive statistics will be provided by severity and relationship.<br><br>Individual listings of adverse events, including event type, start date, duration, severity, and device-relatedness will be provided as appropriate. The safety analysis will be based on all patients participated in the study.<br><br>The effectiveness analysis will be based on all evaluable data from this study. A per protocol analysis will be performed based on all subjects who are compliant with the study protocol, i.e. who provide valid informed consents and do not experience any major protocol deviations |

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| | and completed desaturation phase.<br><br>INVOS rSO2 values will be compared to the calculated global field saturation of brain tissue (25% arterial saturation + 75% jugular venous saturation). The arithmetic root mean square ($A_{RMS}$), bias, and standard deviation will be calculated for both individual and pooled data.<br><br>Pearson linear correlation coefficient will present the strength of the linear correlation between fSO2 and rSO2. Bland-Altman analysis will assess agreement between rSO2 and fsO2 with multiple observations per individual. Any deviations from the original statistical plan will be justified and documented appropriately. |

# 5 Introduction

## 5.1 Background

Cerebral oximeters estimate continuous, non-invasive cerebral oxygenation, values using near-infrared spectroscopy (NIRS) technology. An oximeter setup consists of a single patient use sensor, preamplifiers, and a display unit. The oximeters can support up to four sensors. The sensors have an adhesive pad that can be placed on the forehead and a cable that connects the sensors to the preamplifier. The pad contains a light source and light detectors. [1] The light source emits light in the near infrared range (724 and 850 nm) that penetrates the skull and cerebrum, and the detector detects the light not absorbed during the light pathway through the skull and cerebrum. The preamplifier receives the light signal from the sensor and converts it to an electrical signal for future processing. The amount of oxygen present in the brain is a function of the difference between the amount of light emitted and collected by the sensor, which is projected by the percentage of oxygen displayed on the monitor screen as a number and a trend of changes in percentage oxygen.

The In-Vivo Optical Spectroscopy (INVOS) system is used non-invasively to continuously monitor regional hemoglobin oxygen saturation ($rSO_2$ index) of blood in the brain. The appropriate clinical testing to develop and advance the ability of the device to perform its intended function is considered to be a controlled desaturation in volunteer subjects. $rSO_2$ is a measure of the combination of arterial and venous blood oxygen in the brain. The study is designed to evaluate the ability of the next generation INVOS (NIRS) system to monitor $rSO_2$ in comparison against known reference methods, namely blood sample analysis by a co-oximeter. Since the majority of blood volume in the brain is venous blood, $rSO_2$ can be expected to change when there is a change in the relative balance between oxygen delivery and oxygen consumption. This clinical testing has been designed to evaluate the ability of INVOS to measure trends in $rSO_2$ during periods of controlled hypoxia and during periods of known hypercarbia. Such situations create a change in the availability of oxygen in the brain. Previous hypoxia studies [2, 3] have compared the $rSO_2$ as reported by the INVOS to the "field" saturation (fSO2) calculated from arterial and jugular venous blood oxygen saturation measurements, based on the assumption that cerebral tissue contains arterial and venous blood in a given ratio at different levels of arterial oxygen saturation and different levels of inspired $CO_2$. Increases or decreases in End-tidal Carbon Dioxide ($EtCO_2$) will create events that occur primarily in the brain. These increases or decreases can be created by changing inspired $CO_2$ levels to cause an increase in cerebral blood flow of approximately 3% for every 1 mmHg change in $EtCO_2$ without an associated change in the blood flow of the extra cerebral tissues. This will allow comparisons and challenges the algorithm at various levels of cerebral blood flow (CBF) [4]. Based on the assumption that cerebral tissue contains arterial and venous blood in, for example, a 1:3 ratio, $fSO_2$ is calculated as: $fSO_2 = (0.25 \text{ X } SaO_2) + (0.75 \text{ X } SjvO_2)$.

## 5.2 Purpose

The purpose of the study is to provide data for validation of the next generation INVOS. Monitored physiological parameter data will be collected and analyzed to support validation, and data may be used for additional product development lines within Medtronic as needed.

# 6 Objectives and Endpoints

## 6.1 Objectives

### 6.1.1 Primary Objective(s)

The primary objective of the study is to validate that the [redacted] System in conjunction with Adult Sensors [redacted] meet product requirements for cerebral accuracy, cerebral trending accuracy, and somatic trending.

[redacted]

# 7 Study Design

This is a prospective data collection, non-randomized, single center study to validate the accuracy of [redacted] System in conjunction with Adult Sensors [redacted]). This is achieved by comparing INVOS collected cerebral tissue oxygen saturation with a calculated value derived from simultaneous arterial and jugular venous blood samples.

Up to 50 healthy volunteers with a variety of skin pigmentation will be enrolled. The subjects will be distributed across both genders as equally as practical and a range of skin pigmentations, including at least [redacted] darkly pigmented subjects or [redacted] of the subject pool.

This study will be conducted in three phases: Enrollment Phase, Desaturation Phase, and Follow-up Phase (see *Figure 1 and Figure 2*). During Enrollment Phase, subjects will be screened and qualified subjects will be enrolled. After enrollment, during Desaturation Phase, ECG, and pulse oximetry will be applied. Intravenous and radial artery catheters will be placed. A jugular venous bulb catheter will be placed in either the right or left jugular venous bulb with ultrasound guidance, and its position will be confirmed with skull x-ray.

Two investigational INVOS sensors will be placed bilaterally on the patient's forehead and other sensors will be placed on somatic sites.

The INVOS investigational device will be evaluated for a targeted range of 70-100% SpO2 levels. Hypoxic mixtures of gas will be delivered and data are collected at approximately (~) 5-minute intervals during steady periods of increasing and decreasing oxygen concentration (for more details refer to *Section 10*).

At each INVOS data collection point, blood samples will be drawn simultaneously from both jugular bulb and the radial arterial catheters and analyzed for hemoglobin oxygen saturation using a co-oximeter.

The subjects will be continuously monitored and the protocol will be stopped if SpO2 values from a pulse oximeter reach 60%.

Subjects will be followed up within 48 hours after the procedure.

### 7.1 Duration

The study duration is anticipated to take approximately six hours to complete both the Enrollment and the Study Visits. The Enrollment Visit should take approximately 2 hours to complete and the Study Visit should take approximately 4 hours to complete per subject. Each subject will be contacted by phone within 48 hours of the study participation.

### 7.2 Rationale

The INVOS line of tissue oximeters is predominantly in clinical use due to its long presence in the market and a vast array of publications supporting its use. [5, 6] It is in the interest of the medical community to continue the development of enhanced tissue oximeters, with improved performance and a wider range of capabilities. To satisfy this interest, Medtronic is pursuing this study. The new INVOS system features investigational new sensors, monitors, preamplifiers, and associated cables. The study is designed to evaluate the ability of the next generation INVOS (NIRS) system to monitor rSO2 in comparison against known reference methods, namely blood sample analysis by a co-oximeter.

## 8 Product Description

### 8.1 General

An investigational NIRS system (next generation INVOS system) will be used in this study. The new INVOS system features investigational new sensors, monitors, preamplifiers, and associated cables.

The investigation NIRS system is similar in function and application to a currently cleared and marketed NIRS system –INVOS™ 5100C system. The INVOS™ 5100C system is an adjunct, a non-invasive real-time monitor of changes in regional oxygen saturation ($rSO_2$) of blood in the brain or other body tissues beneath the sensor in adults, pediatrics, infants, and neonates.

## 8.2 Packaging

The Sponsor is responsible for packaging and labeling of the device for shipment to the study site Device.

Research conducted for this study will utilize investigational devices and devices cleared through the 510(k) regulatory process. FDA cleared devices are being used within the FDA-cleared indications for use and do not require special labeling.

Investigational devices used for research on humans in the United States are provided under the Investigational Device Exemption regulation (full or abbreviated), meaning there are no regulatory approvals in place for marketing the device (e.g., 510(k)), but the device will be labeled with the following:

"CAUTION - Investigational Device. Limited by Federal (or the United States) Law to investigational use."[1]

It is the investigator's responsibility to ensure the appropriate labeling is visible and remains intact throughout the life of the study.

## 8.3 Intended Population

Healthy adult volunteers will be selected for this study. The investigational NIRS system will provide non-invasive real-time monitoring of changes in regional oxygen saturation ($rSO_2$) of blood in the brain or other body tissues beneath the sensor for effective oxygen monitoring in adults and transitional adolescents.

## 8.4 Equipment

### 8.4.1 Investigational New Generation INVOS

An investigational next generation INVOS (NIRS) system will be used in this study. The investigational next generation INVOS is a production equivalent [redacted] System consisting of an investigational monitor, investigational preamplifiers, and associated cables in conjunction with investigational adult sensors [redacted]).

#### 8.4.1.1 Investigational Adult Sensor [redacted]).

Investigational Adult Sensors [redacted] will have the same principles of operation as production sensors but have mechanical changes such as a different number of emitters / detectors, and/or different spacing. Investigational sensors have the same risk profile as the production sensors.

The Sensors are disposable transducers capable of producing and detecting optical data from the patient, converting that data into electrical signals and sending them to the INVOS System. They are applied to

[1] 21CFR812.5

the forehead or somatic region via self-contained, medical-grade patient adhesive. Electrical signals from the detectors are sent through the shielded cable to the INVOS System for processing.

#### 8.4.1.2 Investigational Preamplifiers

Investigational preamplifiers used in this study have the same principle of operation as the currently marketed INVOS 5100C preamplifiers. The sensors are connected to the preamplifiers. The preamplifier processes the optical signals and synchronizes operation to enable simultaneous data collection from multiple sensors.

#### 8.4.1.3 Investigational INVOS Monitor

Investigational monitor will be used as a display system.

[redacted]

### 8.4.2 INVOS 5100C System

The INVOS™ 5100C system (FDA cleared) will be used including monitor, preamplifier, and associated cables in conjunction with Adult Sensor SAFB-SM.

### 8.4.3 Other Study Materials (Sponsor)

Additional equipment such as Pulse Oximetery (SpO2 sensors and N600x monitors), and a co-oximeter machine may be provided by the sponsor to the study site (if needed).

The Data Collection tool is a data acquisition system (DAS) housed in a laptop connected to the INVOS systems and is used to harvest the raw data.

### 8.4.4 Other Study Materials (Site)

Standard site monitoring equipment will be used and applied to the subjects, such as pulse oximeter(s), electrocardiography (ECG), capnography (with EtCO2), heart rate (HR), and continuous blood pressure.

Arterial and jugular venous catheters will be used for arterial and jugular sampling, respectively.

Blood will be processed immediately after sampling with co-oximeter. All parameters will be monitored electronically and may be recorded.

## 8.5 Product Use

Complete instructions for using the INVOS systems and the DAS with data collection software will be communicated via the Instructions For Use (IFU) of the INVOS and the data collection instructions provided to the study at the Site Initiation Visit.

## 8.6 Product Training Requirements

Prior to investigation site activation or subsequent involvement in clinical study activities, Medtronic will provide clinical study training relevant and pertinent to the involvement of personnel conducting clinical study activities and investigator responsibilities.

As a minimum, Investigators and coordinators will be trained on their responsibilities, the Clinical Investigation Plan (CIP), Informed Consent process, the use of data acquisition systems, and any applicable local regulations prior to enrollment of their first subject. Study-specific training will be documented prior to investigation site activation.

The support and training of the site using the study product will be performed by employees of Medtronic.

## 8.7 Product Receipt and Tracking

The investigator or designee will maintain records of investigational and non-investigation product delivery to the study site e.g. device shipping forms.

## 8.8 Product Storage

The investigator will store the investigational product and any other devices, which are provided by the Sponsor for the sole purpose of conducting the study. The storage area should be locked/secure with access limited only to approved study staff. Devices should not be stored with standard clinical inventory.

## 8.9 Product Return

### 8.9.1 Return

The Investigator will return all Medtronic provided unused and used investigational and non-investigational equipment (e.g. monitors, pre-amplifiers, and etc.) and maintain documentation of return. All used investigational and non-investigational INVOS sensors will be returned to Medtronic. All other pulse oximeter (FDA cleared) sensors (e.g. Max-A) will be discarded per site's institutional requirements.

### 8.9.2 Recalls

Medtronic will immediately inform investigators to cease the use of the recalled product and will arrange for the return of the recalled devices.

## 8.10 Product Accountability

The investigator will record/track use of the investigational and non-investigational devices for each subject. The investigator/site staff is responsible for maintaining accurate records:

- Devices received (sponsor to investigator) will be tracked on device shipment form,
- All used investigational and non-investigational devices (investigator to subject) will be tracked on the study provided electronic Case Report Forms (eCRFs),
- Devices returned/discarded (investigator to sponsor) will be tracked on return forms.

The site monitor will verify accountability of the study devices during routine monitoring visits to the site.

# 9 Selection of Subjects

## 9.1 Study Population

Up to 50 healthy volunteers will be selected for this study. The subjects will be distributed across both genders as equally as practical and a range of skin pigmentations, including at least [redacted] darkly pigmented subjects or at least [redacted] of the subject pool.

## 9.2 Subject Enrollment

Subjects will be enrolled in the study once all eligibility requirements for the study have been met. Subjects who give informed consent for the protocol in order to undergo eligibility screening for will not be considered enrolled until the screening is completed as indicated in *Section 10* and they are determined to meet all eligibility criteria. Study enrollment will be accomplished by successful completion of the study inclusion /exclusion criteria and screening evaluation.

The Enrollment Phase Visit 1 and its results will stay effective for **60 days**.

## 9.3 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in the study:

1. Healthy, male or female subjects between the ages of 18 to 46 years;
2. Completion of a health screening for a medical history by a licensed physician, nurse practitioner, or physician assistant;
3. Minimum weight 40kg;
4. BMI within range 18.0 - 30.0.

## 9.4 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Prior or known allergies to lidocaine (or similar pharmacologic agents, e.g., Novocain) [self-reported];
2. Prior known severe allergies to medical grade adhesive/tape (Band-Aid) [self-reported];
3. Taking any medication other than birth control[self-reported];
4. Is currently participating in, or has recently participated in (discontinued within 30 days prior to the hypoxia procedure for this study) in an investigational drug, device, or biologic study [self-reported];
5. Has a negative Allen's Test to confirm non-patency of the collateral artery [clinical assessment by PI or delegate];
6. Has made a whole blood donation or has had at least 450 ml of blood drawn within 8 weeks prior to the study procedure [self-reported];

7. Is female with a positive pregnancy test [serum or urine], or is female and is unwilling to use effective birth control between the time of screening and study procedure or is breastfeeding;
8. Has anemia [lab values specific for gender];
9. Has a history of sickle cell trait or thalassemia [self-reported];
10. Has an abnormal hemoglobin electrophoresis test [lab measurement];
11. Has a positive urine cotinine test or urine drug screen or oral ethanol test;
12. Has a room air saturation less than 95% by pulse oximetry [measurement by PI or delegate]
13. Has a clinically significant abnormal EKG [assessment by PI or delegate];
14. Has a clinically significant abnormal pulmonary function test via spirometry [assessment by PI or delegate];
15. Has a COHb greater than 3%, or MetHb greater than 2% [measured by venous blood sample co-oximetry].

# 10 Study Procedures

The study consists of three phases: Enrollment Phase, Desaturation Phase, and Follow-up Phase (see *Figure 1 and Figure 2*). The associated activities of each phase will be completed during Visits 1 – 2 and Follow-up.

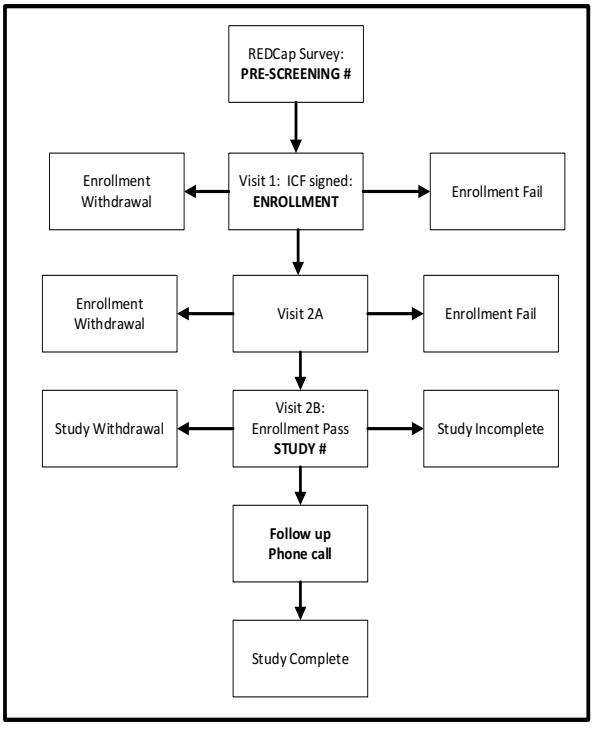



**Figure 1: Study Flow Diagram**

## 10.1 Schedule of Events

The Schedule of Events (Table 1) summarizes the intervals and data collection procedures. Clinical data will be entered electronically into secure systems (EDC, Oracle Clinical); Enrollment, Baseline Assessments, Adverse Events, Protocol Deviations, and Device Deficiencies will be collected through eCRF.

**Table 1: Schedule of Events**

| | Pre-Screening | Enrollment Phase | | Desaturation Phase | Follow-up Phase |
|---|---|---|---|---|---|
| | | Visit 1 | Visit 2A | Visit 2B | Phone call |
| Informed Consent [1] | | x | | | |
| Inclusion/exclusion | | x | x | | |
| Demographics | x | x | | | |
| Medical History | x | x | x | | |
| Physical Exam including vitals [2] | | x | | | |
| INVOS 5100C reading[3] | | x | | | |
| Pulmonary function test[4] | | x | | | |
| A single 12-lead ECG | | x | | | |
| Skin tone [5] | | x | | | |
| Blood pressure, Heart Rate [6] | | x | | x | |
| ASA physical status and Allen's Test | | x | | | |
| ROBD Mild Hypoxia Exposure | | x | | | |
| Jugular bulb and arterial catheters[7] | | | | x | |
| Two investigational sensors placed on the forehead [8] | | | | x | |
| Two (investigational and legacy) sensors placed on somatic sites [9] | | | | x | |
| Sensor placement images [10] | | | | x | |
| ECG monitoring | | | | x | |
| Breathe a gas mixture of $O_2/N_2/CO_2$ steps (#1-18) [11] | | | | x | |
| Study Blood Draws [12] | | | | x | |
| Adverse Event Assessment [13] | | x | x | x | x |
| Concomitant Medications | | x | x | x | x |
| **Laboratory Assessment [14]** | | | | | |
| CBC | | x | | | |
| Hemoglobin electrophoresis [15] | | x | | | |
| Venous co-oximetry [16] | | x | | | |
| Urine cotinine test | | x | x | | |
| Serum Pregnancy Test (Female) | | x | | | |
| Urine drug screen | | x | x | | |
| Alcohol breathalyzer (Oral Ethanol) tests | | | x | | |

| | Pre-Screening | Enrollment Phase | | Desaturation Phase | Follow-up Phase |
|---|---|---|---|---|---|
| | | Visit 1 | Visit 2A | Visit 2B | Phone call |
| Urine pregnancy test (Female) | | | x | | |
| Participant stipend [17] | | x | x | x | |
| **Follow up** | | | | | |
| Phone call within 48 hrs [18] | | | | | x |

1) Written informed consent must be obtained prior to any study-specific evaluations. After successful completion of the screening survey and survey review by study staff, qualified subjects will be invited to attend Visit 1 to complete the ICF.
2) Physical Exam will be performed during the enrollment phase, Visit 1. It will include subject's heart rate, sitting blood pressure, respiration, height, weight, and body mass index.
3) Baseline readings will be collected from the forehead with one or two sensors using the 510k cleared INVOS 5100C.
4) Pulmonary function test (PFT) assessment via spirometry.
5) Subject's Skin tone will be evaluated and recorded (e.g. light, medium, and dark) will be evaluated and recorded on provided study eCRFs.
6) Blood pressure (BP) and Heart rate (HR) will be recorded at enrollment visit 1. BP and HR continuously will be monitored during desaturation phase.
7) Jugular bulb and arterial catheters will be inserted for each subject. Jugular bulb catheter will be placed under ultrasound guidance and placement will be verified with a single lateral skull x-ray. The tip of the jugular catheter should be positioned cephalad to the inferior border of the first cervical vertebrae (C1) to minimize the risk of jugular venous blood mixing with extra-cranial effluent venous drain. Side and location of the catheters will be recorded in the study provided eCRFs.
8) Two investigational NIRS sensors will be placed on the forehead.
9) Two sensors (investigational and legacy) will be placed on somatic site (e.g. calf) of the subjects.
10) De-identified images may be taken on the locations before and after sensor application(s).
11) Each subject will complete a series of Desaturation Sequence steps (#1-18) with incremental reduction/increase of SpO2 to target ranges between 70-100%. Each subject will complete three Desaturation Sequences ([redacted] For more details, refer to *Section 10.5*.
12) The arterial ($SaO_2$) and venous ($SjvO_2$) blood draws will be repeated to target two paired samples per step. A total of [redacted] paired arterial and venous draws (pair = 1 jugular: 1 arterial) will be collected during the study. The jugular sample will be drawn approximately over a period of [redacted] seconds ([redacted]). For more details, refer to *Section 10.5*.
13) Information will be collected throughout the study with starting Visit 1, Enrollment Phase and through Follow-up Phase. Adverse Event assessment for the purposes of this study will cease

after follow-up phone call within 48 hours after desaturation visit. All Adverse Events, regardless of relatedness or outcome, must be reported. For more details, refer to *Section 12*.

14) The local laboratory will be used for all laboratory assessments.

15) Hemoglobin electrophoresis is used to identify variant and abnormal hemoglobin.

16) Venous co-oximetry to measure carboxyhemoglobin (COHb) and methemoglobin (MetH)

17) The subject will be paid [redacted].

18) Each subject will be contacted by phone within 48 hours of the study participation. Any AEs will be recorded.

Sponsor representatives may be available at the site as needed to assist with data acquisition systems.

## 10.2 Subject Screening

Prior to the Enrollment Phase, interested subjects will complete an online REDCap screening survey and have the opportunity to review the Informed Consent Forms (ICFs). After successful completion of the screening survey, the study staff will review the survey and qualified subjects will be invited to attend study Visit 1.

## 10.3 Subject Consent

Informed consent must be obtained before a subject is enrolled in the study and/or before any study-specific procedures are initiated. Well in advance of the consent discussion, the subject will receive electronic copies of the IRB approved Patient Information and Informed Consent Form (ICF) for personal review.

Prior to the Enrollment Phase, potential subjects will complete an online screening survey and have the opportunity to review the study ICFs. After successful completion of the screening survey, the study staff will review the survey and qualified subjects will be invited to attend study visit to complete the ICF. During the study visit, the Investigator or designee will inform the prospective subjects on the study procedures, the expected and unknown risks and possible benefits, and explain the consenting process and answer all subject questions and concerns. The subject interested in the study will be asked to sign and date the ICF.

The signed original informed consents will be maintained in the investigator's records, and an electronic or paper copy of each ICF will be given to the subject.

If the ICF is amended/updated throughout the life-cycle of the study, study subjects may be asked to re-consent by reviewing, signing, and personally dating the updated ICF. If the ICF is updated, subjects who are still receiving treatment will be re-consented at the direction of the IRB.

## 10.4 Enrollment Phase

Enrollment phase includes Visit 1 and Visit 2A (Figure 2).

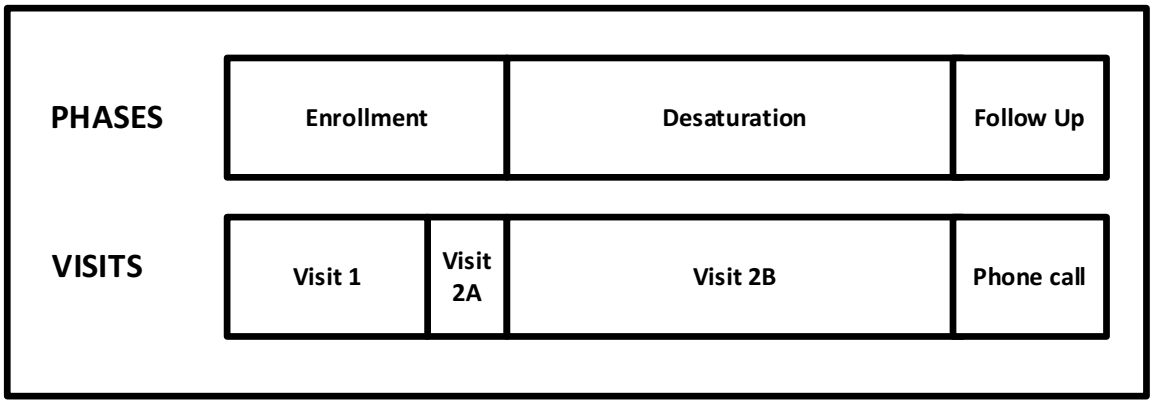



**Figure 2: Study Phase Diagram**

### 10.4.1 Visit 1

Once ICF is signed, the following will be performed:

- Demographics (gender, race, ethnicity);
- Skin tone will be evaluated and recorded (for example light, medium, and dark);
- Medical History including known allergies to lidocaine or medical adhesive;
- Concomitant Medications including the history of prescription and over the counter medication will be carefully noted and recorded. Medication name, indication for use, dose, frequency, route of administration start/stop date;
- Physical examination including an evaluation of general appearance, cardiovascular, respiratory musculoskeletal system, skin, neurologic function, and head, eyes, ears, nose and throat;
- Vital signs - height, weight, calculated body mass index (BMI) and temperature will be recorded at visit 1 only. Heart Rate, Systolic & Diastolic Blood Pressures, Respiratory Rate and Oxygen Saturation (SpO2) will be recorded at visit 1 and during the Desaturation Phase;
- The American Society of Anesthesiologist (ASA) physical status classification system is used to evaluate the degree of a patient's "sickness" or "physical state." Only subjects with ASA Physical status 1 will be enrolled;
- Pulmonary function test (PFT) assessment via spirometry and a single 12-lead ECG are to be completed at screening;
- Blood samples analyzed for:
    - CBC – (hemoglobin and red blood cell (RBC));
    - Serum human chorionic gonadotropin level for pregnancy in women of childbearing potential;
    - Hemoglobin electrophoresis is used to identify variant and abnormal hemoglobin;
    - Venous co-oximetry to measure carboxyhemoglobin (COHb) and methemoglobin (MetH);

- Urine sample will be tested for the presence of cotinine (nicotine metabolite) to exclude smokers;
- Urine drug screen will be performed to test for the presence of drugs such as opiates, benzodiazepines, marijuana, amphetamines, and barbiturates;
- Female subjects will have to attest to birth control methods between Visit 1 and Visit 2 A (desaturation phase);
- Allen's Test will be performed to confirm patency of the collateral artery. The following information will be evaluated Hand Dominance, Right Radial, Right Ulnar, Left Radial, Left Ulnar;
- Baseline readings ($rSO_2$) from current INVOS 5100C will be recorded from the forehead with one or two sensors (left and right);
- Gas and facemask test:
    - A clear plastic tight-fitting facemask connected to Reduced Oxygen Breathing Device [ROBD] (gas mixer) breathing circuit will be placed on the subject.
    - A pulse oximeter will be placed on subject's finger to monitor the oxygen saturation.
    - The subject will be asked to breathe 21% oxygen (room air) for 2 minutes followed by 15% oxygen for 2 minutes to determine the subject's suitability to breathe a mildly hypoxic gas mixture through a facemask.
- The **Enrollment Phase** Visit 1 and its results will stay effective for **60 days**.

### 10.4.2 Visit 2A (Study Day)

- On the study day, subjects will arrive at the clinical research unit with appropriate fluid and solid intake as directed by study staff.
- Any significant change in health status since Visit 1 will be recorded.
- Concomitant Medications: All subjects will have urine drug screen and alcohol breathalyzer (Oral Ethanol) tests done.
- Female subjects will also have a urine pregnancy test done.
- Inclusion and Exclusion Criteria will be reviewed.
- Enrollment Pass is based upon successful meeting all of inclusion and none of exclusion criteria during Visits 1 and 2A.

## 10.5 Desaturation Phase (Study Day)

### 10.5.1 Visit 2B (Study Day)

After Enrollment Pass is received, subjects will enter the Desaturation Phase:

- Jugular vein bulb and arterial catheters will be inserted for each subject. Jugular vein bulb catheter will be placed under ultrasound guidance and catheter tip placement will be verified with a single

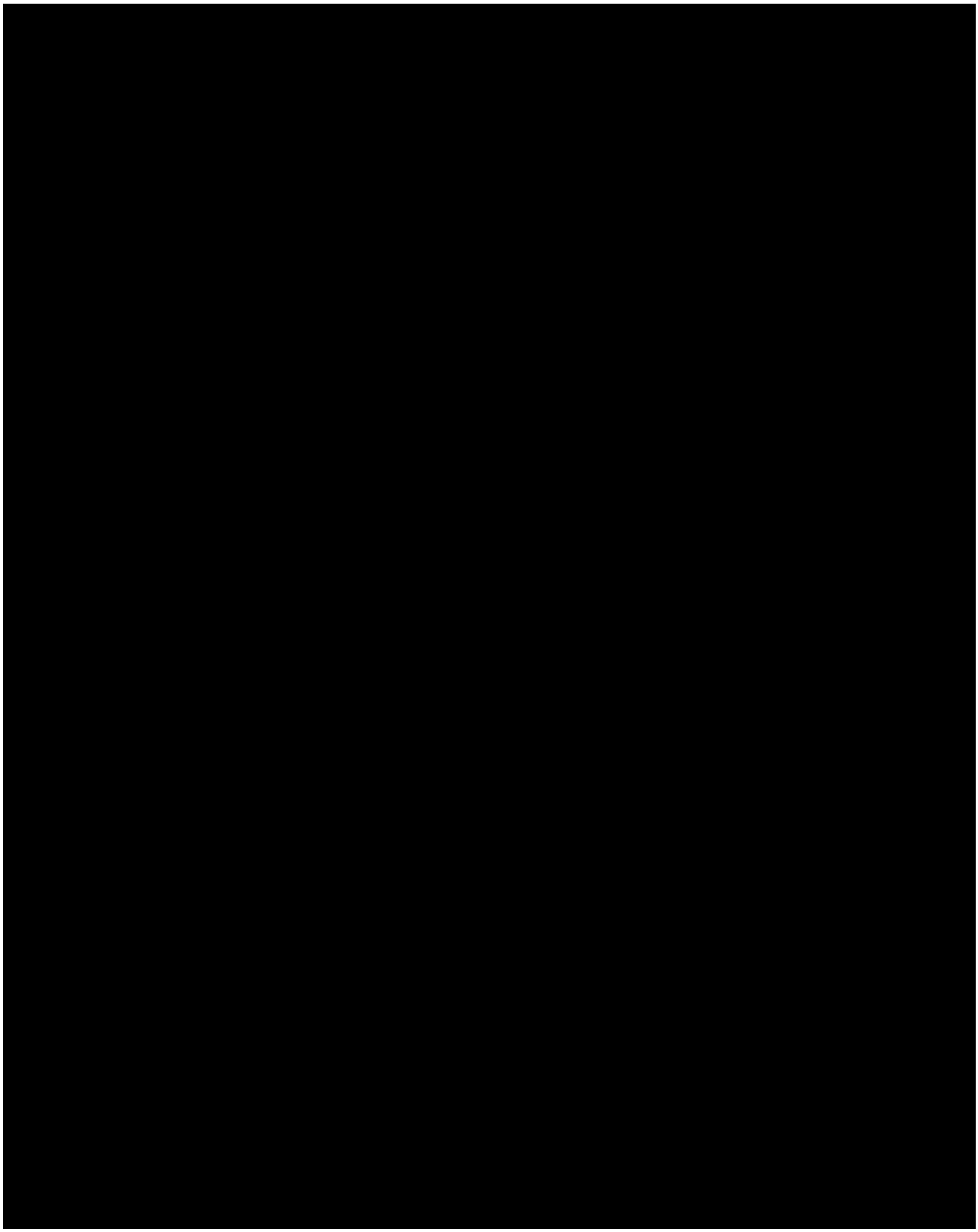
lateral skull x-ray. Ideally, the tip of the jugular catheter should be positioned cephalad to the inferior border of the first cervical vertebrae (C1) to minimize the risk of jugular venous blood mixing with extra-cranial effluent venous drain.

- Intravenous access will be established for maintenance hydration and drug administration (if needed).
- ECG electrodes will be placed on subject's chest, arms, and feet. Areas, where electrodes will be placed may be shaved as needed.
- Two or more pulse oximeters will be placed on fingers to monitor the amount of oxygen in the blood.
- A blood pressure cuff (ccNexfin) will be placed on one finger to measure the non-invasive blood pressure continuously.
- Two investigational (Adult sensor [redacted]) sensors will be placed bilaterally on the forehead. Forehead skin where sensors will be applied is cleaned. Sensors will be connected to investigational next generation INVOS system.
- Two sensors (investigation Adult sensor [redacted] and legacy SAFB-SM) will be placed on somatic sites (e.g. calf) of the subjects. Areas where sensors will be placed may be shaved as needed. Both sensors will be connected to [redacted] preamplifiers, which will be connected to investigational next generation and Legacy INVOS 5100C monitors.
- De-identified images may be taken on the locations before and after sensor application.
- Subjects will be asked to breathe a gas mixture of $O_2/N_2/CO_2$ with a tight fitting mask using a closed-looped gas delivery system or alternative method allowing the control of $CO_2$ blood levels at normocapnia (subject specific normal value of ~ 40 mmHg) and at different desired $CO_2$ levels. Each subject will complete a series of steps (#1-18) with incremental reduction/increase of $SpO_2$ to target ranges between 70-100%. Each subject will complete at least one of three Desaturation Sequences (Figure 3). Completion all three Sequences are desirable. Please refer to *Section 10.10*
- Each desaturation sequence step will last approximately 2 to 6 minutes. All three Desaturation Sequences are presented in Figure 3 below:
    - Sequence #1: steps # 1-8
    - Sequence #2: steps # 9-13
    - Sequence #3: steps # 14-18[redacted]
    - The first two desaturation sequences are conducted in subject specific normocapnia and the third desaturation sequence will be conducted under [redacted].
    - [redacted]
    - Modifications to the hypoxia sequence for patient safety will be left to the judgment of the Principal Investigator.

- Study Blood Draws:
  - At each plateau, after ~ [redacted] minutes wait time (stability period) and extended wait time ~ [redacted] minutes for return to room air and 100% oxygen saturation steps, two paired (simultaneously drawn) jugular bulb vein and arterial blood samples are drawn ([redacted] Draw waste or leader blood samples prior to the draw of paired blood samples may be used to ensure the accuracy of blood samples.
  - Co-oximetry is used to determine the jugular venous saturation ($SjvO_2$) and arterial saturation ($SaO_2$). Each blood sample will be analyzed multiple times or using multiple co-oximeter machines. Blood samples will be averaged to provide one $SjvO_2$ and one $SaO_2$ value for each paired draw at that plateau. Blood samples are analyzed in real-time and results from the co-oximeters will be stored electronically.
  - Co-oximetry raw data (co-oximeter blood oximetry results and the time of analysis) will be provided to Medtronic. [redacted]
  - The jugular sample will be drawn approximately over a period of [redacted] (targeting rate of [redacted].)
  - The arterial sample will be drawn at approximately the midpoint of the jugular bulb draw.
  - Each blood draw (either venous or arterial) is approximately 1.5 ml, totaling approximately [redacted] ml per paired sample (pair = 1 jugular plus 1 arterial).
  - With a target of two paired samples per plateau step, a total of [redacted] paired arterial and venous draws may be collected during the study. Total blood draw during the study is estimated to be [redacted] If less than the targeted [redacted] pairs of blood samples are collected, it will not be considered a protocol deviation.

**After the procedure**:

- The breathing circuit will be disconnected and the subject will be monitored by the clinical staff until normal baseline levels are attained.
- All equipment will be removed from the subject.
- A copy of the IRB-approved site's discharge instructions will be provided to the subject.



[redacted]

## 10.6 Follow-up Phase

### 10.6.1 Phone Call

Each subject will be contacted by phone within 48 hours after completion of desaturation phase to perform a safety assessment. The safety assessment will include asking the subject the following questions:

- Have you had any medical problems since your discharge from the clinical research unit?
- Have you taken any medications (either prescribed or self-medicated) since discharge from the clinical research unit?

For more details on AE, refer to *Section 12.*

## 10.7 Assessment of Safety

Safety analysis will be performed on all participants who will have the NIRS sensors placed on the forehead or any sensor placed on somatic sites. Methods and timing for assessing, recording, and analyzing safety parameters, including adverse events are described in *Section 12 and Section 14*.

## 10.8 Recording Data

### 10.8.1 Source Documents

The investigator will clearly mark the clinical records to indicate that the subject is enrolled in this clinical study.

Subject's medical record will be used as part of source documents. Source documents are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Adequate original records will be maintained for the study. Examples of these original documents and data records include: ICF, all events, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, device dispensing records, collected records, copies or transcriptions certified after verification as being accurate and complete, radiology files (ultrasounds, X-rays), informed consent form, and records kept at the laboratories and at medical-technical departments involved in the clinical trial.

In order to accurately collect all study data, worksheets/ forms may be developed for study specific data not found in the medical records and will be considered as the source document for these data points.

The device (investigational and non-investigational) use (disposition) for the individual subject during this trial will be recorded directly on the study provided eCRF page and will be considered as source data. The copy of device disposition eCRF page will be printed and left at the site as the source document.

### 10.8.2 Case Report Forms

The electronic Case Report Forms (eCRFs) will be utilized for participants enrolled in the study. The appropriate eCRF will be completed by the site within a target of 5 business days after each study examination. All data requested on the eCRF must be recorded or the entry will be queried.

The investigator must ensure accuracy, completeness, and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs, which are derived from source documents, such as patient medical records, must be consistent with the source documents or the discrepancies need to be justified in a documented rationale, signed and dated by the Principal Investigator (PI), to be filed in the subject file.

Training will be provided to site personnel on the use of data collection tools. The final version of eCRFs will be provided to the investigation sites when the investigational site has been declared ready for the study.

All clinical data generated in the study will be submitted to Medtronic for quality assurance review and statistical analysis. All eCRFs will be reviewed for completeness and evident errors. Questions or queries will be resolved by contact with the clinical sites.

Sponsor study personnel will review collected data and create data queries for missing data that impacts data analysis. Queries will be sent to the investigator or appropriate support staff for resolution.

## 10.9 Deviation Handling

### 10.9.1 Deviations

The investigator is required to conduct this study in accordance with the protocol, Good Clinical Practice (GCP), Institutional Review Board (IRB) requirements, and applicable regulations.

A study deviation is defined as an event when the investigator or site personnel did not conduct the study according to the protocol or the clinical trial agreement.

The investigator is required to obtain prior approval from the sponsor and IRB *before* initiating deviations from the study protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval will be documented in writing and maintained in the study investigator files.

Major deviations are defined as deviations with respect to:

- Patient informed consent procedure;
- Patient eligibility criteria;
- Study data collection and reporting;
- Serious Adverse Event /Serious Adverse Device Effect /Unanticipated Adverse Device Effect /Unanticipated Serious Adverse Device Effect reporting (*for reporting refer to Section 12*).

All deviations and reasons to deviate from the study protocol must be reported to the Sponsor as soon as a possible, but **no later than 5 working days** of the protocol deviation.

The Principal Investigator is responsible for reporting the protocol deviation in accordance with the policies and procedures established by the IRB.

### 10.9.2 Informed Consent

If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB **within 5 working days** after the use occurs.

The sponsor shall submit to FDA a copy of any report by an investigator of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.

## 10.10 Subject Withdrawal or Discontinuation

Subjects may withdraw from the study at any time and for any reason. If a subject officially withdraws from the study, the reason for withdrawal will be documented.

Possible reasons for withdrawn from the study are:

- Subject withdrew consent;
- Investigator withdrew subject from the study for medical reasons;
- Investigator withdrew subject from the study due to failure to maintain adequate compliance;
- Investigator withdrew subject from the study due to inclusion/exclusion criteria not met.
- Investigator withdrew subject from the study due to an inability to establish arterial and/or jugular lines.
- Investigator withdrew subject from the study due to the occurrence of slurred speech, confusion, somnolence, fainting, or other alteration of the mental status of the subject.

Following terms are used for withdrawal and completion:

- *Enrollment Withdrawal:* Removal from study prior to Desaturation Phase; initiated by either by subject, sponsor or PI (Visits 1 or 2A);
- *Study Withdrawal:* Removal from the study after Enrollment Pass;
- *Study Incomplete:* Completion of some study related activities by the subject in Visit 2B;
- *Study complete:* Completion of all study related activity by the subject in Visits 1 and 2, and Follow-up phone call. Desaturation Phase, Visit 2B, is considered complete if Sequence #1 or #2 are completed. Completion of all Sequences #1, #2, and #3 are desirable, but not considered incomplete, should subjects withdraw for any reason;
- *Lost to follow up:* Subjects lost to follow-up will be documented. The investigator should make every attempt to contact the subject to have the subject complete the follow-up phone call within 48 hours or to determine the occurrence/resolution of adverse events (if any).

# 11 Risks and Benefits

## 11.1 Potential Risks

Risks to participation are primarily physical. There are no social, economic, legal, long-term psychological or other risks that have been identified. Risks under this protocol relate to both study devices and study procedures. We believe that the risks from the device(s) are in keeping with the definition of non-significant risk devices (NSR) (See *Section 11.3*). Further, the devices in this study are non-invasive and the clinical protocol design is minimal risk to the subject. No treatment or treatment decisions will be made during the course of this study. Following is a list detailing potential risks from study devices and the clinical protocol.

### 11.1.1 Investigational Devices

#### 11.1.1.1 Sensors/ Preamplifiers/ Monitor

[redacted]

### 11.1.2 Clinical Protocol/ Procedural Risks

#### 11.1.2.1 Arterial and Jugular Bulb Catheters

Complications of jugular bulb catheter insertion/monitoring are uncommon and usually related to catheter insertion. Placement of an arterial or venous catheter is often uncomfortable, even with local anesthesia. The risks common to arterial and venous catheter placement are those associated with any vascular catheter. These include pain, bleeding, hematoma, infection, thrombosis and embolism. Complications with internal jugular bulb catheterization include carotid artery puncture, pneumothorax, nerve injury, infection, thrombosis [4] hemomediastinum, hydromediastinum, hydrothorax, and vessel perforation/damage and catheter embolism. The insertion complications will be reduced by inserting the catheter under ultrasound guidance. In the case of accidental arterial puncture, local pressure will be

applied to the site. Drawing of the venous sample will be done under careful slow draw to avoid collapsing of the jugular bulb structure.

Radial arterial cannulation is used often in appropriate patients during clinical care. Major complications rates are rare and <1%. [7] Complications of arterial catheters include trauma at the insertion site, catheter-related difficulties, bleeding, and hematomas. More severe complications, which occur less frequently include phlebitis, infection, sepsis, radial artery aneurysm, thrombosis, abscess formation, cellulitis, paralysis of the median nerve, air embolism, compartment syndrome, carpal tunnel syndrome, occlusion with local and distal ischemia and loss of hand. The use of an aseptic cannulation technique performed by clinicians who have extensive experience and the short duration of catheterization will minimize these risks. Subjects are counselled to avoid strenuous wrist activity after removal of the catheter to minimize for hematoma formation and bruising.

#### 11.1.2.2 Desaturation

Scientific literature suggests that hypoxia to 50% saturation and even lower, has been experienced or induced in healthy volunteers for short periods of time without serious adverse effects. [8-11] The risks of breathing increased levels of oxygen for short period of time has no associated risks. The risk of breathing decreased levels of oxygen in the study is minimal. The lower level of oxygenation attained are comparable to those attained at high altitude (up to about 17,000 feet), but are well within the tolerance of normal volunteers for short-term exposure. Subjects are counselled that they may discontinue breathing from the facemask or mouthpiece at any time they feel discomfort. The subjects "cardiorespiratory" parameters are monitored continuously during the study.

Controlled desaturation is part of a standard required for pulse oximetry validation.

In the event that any of the above mentioned risks should occur despite the intensive monitoring of subjects that takes place during the study, there is always a licensed board certified anesthesiologist present during the study.

#### 11.1.2.3 X-Ray

Skull x-ray is taken to confirm catheter tip position. X-rays are monitored and regulated to provide the minimum amount of radiation exposure needed to produce the image. The radiation exposure from this research is about 0.1 microsievert (mSv). [12] There is radiation that naturally occurs from space and from rocks in the soil. This natural radiation is greater at higher altitudes. The total amount of radiation is the same as a person would get from living in a high altitude city such as Denver for 4 weeks, or taking 8 airplane flights from New York to Los Angeles.

A possible health problem seen with radiation exposure is the development of cancer later in life. This extra cancer risk is higher at younger ages and for girls and women. The extra lifetime risk of dying of fatal cancer due to the radiation exposure from this research may range from about one in 70,000 to about one in 30,000. At such low radiation exposures, scientists disagree about the amount of risk. These estimates are very uncertain, and there may be no extra risk at all.

When compared this possible extra cancer risk to other risks (over a lifetime) that everyone is subject to in everyday life. For example, the chances of a person dying of cancer with no extra radiation exposure are about one in 4. The chances of dying in a car crash are about one in 82, and the chances of being killed by a car while crossing the street are about one in 730. [10]

#### 11.1.2.4 [redacted]

[redacted]

[redacted]

## 11.2 Potential Benefits

There are no medical benefits to the subjects who participate in this study. There is, however, the potential for benefiting future patients should this study enable the development of improved medical monitoring devices.

## 11.3 Risk-Benefit Rationale

[redacted]

[2] 21CFR812.2 (b)(1)(ii) and 21CFR812.3(m)

[3] Information Sheet Guidance For IRB, Clinical Investigators, and Sponsor. Significant Risk and Nonsignificant Risk Medical Device Studies/ January 2006/UMC126418

[redacted]

### 11.4 Factors that may Compromise the Study Outcome Data

The study outcome may be compromised by a misplaced or dislodged jugular vein catheter. To minimize this possibility, the catheter will be inserted by a clinician with experience of jugular venous catheter placement. Placement will be guided by ultrasonography and the position of the catheter tip will be confirmed by lateral skull x-ray.

[redacted]

## 12 Adverse Event Assessments

### 12.1 Definitions/Classifications

- **Adverse Events (AE):** Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.
- **Adverse Device Effect (ADE):** Adverse event related to the use of an investigational medical device.
- **Serious Adverse Event (SAE):** Adverse event that
    1) led to death,
    2) led to a serious deterioration in the health of the subject, that either resulted in
        a) Resulted in a life threatening illness or injury, or
        b) Resulted in a permanent impairment of a body structure or a body function, or
        c) In-patient or prolonged hospitalization, or
        d) Medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or
    3) led to fetal distress, fetal death or a congenital abnormality or birth defect

    Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.
- **Serious Adverse Device Effect (SADE):** Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
- **Unanticipated Adverse Device Effect (UADE):** Any serious adverse effect on health or safety or any life threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the CIP or

application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

- **Device Deficiency (DD):** Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

## 12.2 Recording and Reporting Adverse Events

**AE**

AE information will be collected throughout the study starting with Visit 1 Enrollment Phase and through Follow-up Phase.

Adverse Event assessment for the purposes of this study will cease after follow-up phone call **within 48 hours** after desaturation visit. All AEs considered at least possibly related to the study will be followed until resolved, stabilized, and/or returned to baseline.

All Adverse Events and Device Deficiency information will be collected throughout the study on the source, regardless of relatedness or outcome and will be reported to study sponsor **as soon as possible, but no later than 10 working days** after the investigator learns of the event.

Information reported on the eCRF will may include:

- A description of the event
- The date of event onset
- The relatedness of the event to the device
- Actions are taken as a result of the event
- The outcome of the event

**UADE/SADE/SAE**

The investigator must report any UADE/SADE/SAE to the sponsor and IRB **as soon as possible, but no later than 10 working days** after the investigator learns of the effect.

Medtronic will immediately conduct an evaluation of any UADE/SADE/SAE and report the results to reviewing IRB, all participating investigators, and to the FDA within **10 working days** of first receiving notice of the effect.

**DD/Product Complaint/Product Malfunction**

Complaints can be filed orally, in writing, or electronically by an employee of the Company, a user facility, a healthcare professional, a subject, or a subject representative.

All INVOS system failures, malfunctions, and product nonconformities will be documented on the appropriate eCRF and the device should be returned to Medtronic for analysis. Instructions for returning the investigational device will be provided to the study site.

In addition, potential complaints may be found throughout the clinical study data as reported on eCRFs. Additionally, potential complaints may be learned about in alternative fashions within source documents or in discussions with site staff.

Any complaint should be reported to the Medtronic research contact below **as soon as possible, but no later than 10 working days** after the investigator first learns of the effect**.** If an event occurs on late Friday evening, or if office is closed due to long holidays or for any other reasons, the event will be reported the following working day.

**Emergency Contact Information**

[redacted]

# 13 Data Review Committees

Not applicable.

# 14 Statistical Design and Methods

Statistical analyses will be conducted by Medtronic or its designee as outlined in the Statistical Analysis Plan (SAP). Any changes in statistical methods will be detailed in the SAP.

## 14.1 Sample Size Justification

The subject population will include up to a total of 50 subjects. The planned sample size was determined through a power-based analysis based on previously collected Jugular Bulb study data during the device development cycle, and will be documented in the Statistical Analysis Plan (SAP). The study size is pre-defined to enroll up to 50 subjects accounting for larger than anticipated screen failures and subject dropouts.

[redacted]

A priori statistical power analysis determined that a minimum of [redacted] subjects for normocapnia [redacted] study procedures is required to achieve at least [redacted] power at [redacted] to detect a difference to [redacted] $A_{RMS}$ success criterion for cerebral overall accuracy, and [redacted] $A_{RMS}$ for cerebral and somatic trending accuracy. The null hypothesis and expected accuracy were adjusted conservatively, and the sample size was increased to account for any unexpected inter and intra subject variability and performance of the final revision of the INVOS system.

Based on the study desaturation sequence profile it is required secondary to the minimum number of subjects, that a minimum number of paired blood draws for each study endpoint will be collected as defined below:

| [redacted] | [redacted] | [redacted] | [redacted] |
|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |

## 14.2 Statistical Analysis

Briefly, standard demographic information and baseline characteristics data will be summarized using descriptive statistics.

For safety assessments, adverse events (AEs) will be summarized using frequency counts and percentages. Descriptive statistics will be provided by severity and relationship.

Individual listings of adverse events, including event type, start date, duration, severity, and device-relatedness will be provided as appropriate. The safety analysis will be based on all patients participated in the study.

The effectiveness analysis will be based on all evaluable data from this study. A per protocol analysis will be performed based on all subjects who are compliant with the study protocol, i.e. who provide valid informed consents and participated in the desaturation phase.

INVOS rSO2 values will be compared to the calculated global field saturation of brain tissue (25% arterial saturation + 75% jugular venous saturation). The arithmetic root mean square ($A_{RMS}$), systemic bias, and standard deviation will be calculated for both individuals and pooled data.

Pearson linear correlation coefficient will present the strength of the linear correlation between fSO2 and rSO2. Bland-Altman analysis with limits of agreement will assess agreement between rSO2 and fsO2 with

multiple observations per individual. Any deviations from the original statistical plan will be justified and documented appropriately.

# 15 Ethics

## 15.1 Statement(s) of Compliance

The investigator is responsible for ensuring that the clinical study is conducted in accordance with:

- The CIP and to Standard Operating Procedures (SOPs),
- Food and Drug Administration (FDA) Good Clinical Practice (GCP) guidelines and regulatory requirement(s), including 21 CFR 812, 21 CFR 50, 21 CFR 56. FDA Financial Disclosure regulations, as well as International Conference on Harmonization (ICH) guidelines and any other regional/national requirements for clinical trials, as applicable.
- The clinical study will not begin until IRB and regulatory authority approvals/notification are received. Written IRB approval and any conditions of approval imposed by the IRB must be submitted to the sponsor.

## 15.2 IRB Approval

The clinical study will not begin until IRB approval notification is received. This protocol and an informed consent form and any other written information to be provided to the subjects and, if applicable will be approved initially and reviewed at least annually by an IRB constituted according to regulatory and institutional requirements. The IRB granting the initial approval shall be responsible for continuing review and approval of this study including the ICF. A copy of the IRB's dated approval will be retained in the study files or Investigator Site File. Any additional requirements imposed by the IRB or regulatory authority shall be followed, if appropriate.

### 15.2.1 Progress Reports

The sponsor shall submit progress reports to the IRB at least yearly.

### 15.2.2 Final Report

The sponsor shall submit a final report to the IRB within 6 months after termination or completion of the investigation.

### 15.2.3 Withdrawal of IRB Approval

The investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.

## 15.3 Subject Compensation

The study will incur no cost to the subject. Total of up to [redacted] per study compensation will be provided to subjects for their participation in the study.

### 15.4 Liability Insurance

The clinical study liability insurance coverage statement will be included in the Clinical Trial Agreement between Medtronic and the site.

## 16 Study Administration

### 16.1 Monitoring

Site monitoring visits will be performed by the Clinical Research Specialist (CRS) or other qualified sponsor staff per the monitoring plan to ensure:

- Overall compliance with the protocol, GCP, and the applicable regulations
- Accurate records are being maintained
- Accurate and complete study data are being reported (comparing CRF to source documents)
- Informed consent has been obtained for all study subjects
- Adverse events and protocol deviations are documented and reported.
- Investigational device accountability and disposition are accurately documented.

Monitoring visits will be conducted at the start, during, and at the closure of the clinical study in accordance with Medtronic internal SOPs and the Monitoring Plan. An interim monitoring visit may be combined with the closing monitoring visit.

The frequency of monitoring visits will occur based on subject enrollment, duration of the study, study compliance, site performance, site adherence to the protocol, findings from previous monitoring visits, and any suspected inconsistency in data that requires investigation. The monitoring visit frequency may be changed based on subject enrollment rates.

If problems are encountered with the quality of the collected data, the study will be halted for the period of time until the problem has been assessed and possible additional training or other actions have been completed to correct the problem. The evaluation of the data quality will be the responsibility of the Medtronic Clinical Affairs' personnel or designee.

The Investigator or authorized study personnel must be available at each monitoring visit. Access to the subject records and other source data must be provided to study CRAs, the sponsor, regulatory authorities, auditors, IRB members or inspectors.

Source data entered in the CRFs should be documented in the subject's clinical study records, i.e. study files that contain original information used for study data collection or adverse event reporting.

### 16.2 Data Management

Some data will be recorded via an electronic data capture (EDC) system, using electronic Case Report Forms (eCRFs).

The investigator must ensure accuracy, completeness, and timeliness of the data reported in the CRFs and in all other required reports. Data reported on the CRFs which are derived from source documents must be consistent with the source documents and discrepancies need to be justified in a documented rationale, signed and dated by the Investigator, and filed in the subject medical file.

Only authorized persons can complete eCRFs. eCRFs shall be signed by investigators (physicians only) as specified on the Delegated Tasks List included in the Investigator Site File.

The EDC system maintains an audit trail of entries, changes or corrections in eCRFs. If a person is only authorized to complete eCRFs or make changes to an already signed eCRF, the investigator shall re-sign this CRF.

All collected data will be reviewed for completeness, correctness and consistency. In the event of discrepant data, the CRS will request data clarification from the sites, which the sites will resolve electronically in the EDC system. The quality checks will be included in the eCRFs. Medtronic will perform oversight of the data management of this trial according to Medtronic SOPs that will be made available on request.

Medtronic will produce an EDC Study Specification document that describes the quality checking to be performed on the data. eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at Medtronic and records retention for the study data will be consistent with Medtronic SOPs.

It is expected that eCRFs will be completed within 5 business days from the performed visit or as soon as source documents are available, except for any adverse events and device deficiencies that require immediate reporting per *section 12* above and for Protocol Deviation requiring pre-approval.

A delayed completion of the eCRF will not be considered a Protocol Deviation.

INVOS raw data will be collected by data acquisition system (DAS). Additional raw data will be collected from the site's data acquisition systems (e.g. co-oximeters and LabChart). These data will be transferred to Medtronic for analysis directly.

## 16.3 Audits and Investigation Site Inspections

In addition to regular monitoring visits, Medtronic may conduct audits at participating investigation sites. The purpose of an audit is to verify the adequate performance of the clinical study related activities, independent of the employees involved in the clinical study. Regulatory authorities may also perform inspections at participating investigation sites. Any regulatory authority inspection announcements shall be forwarded immediately to Clinical Study Manager.

The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform clinical study related monitoring, audits, IRB review (if applicable), and regulatory inspections.

## 16.4 Direct Access to Source Data/Documents

The investigator and institution will permit study-related monitoring, audits, IRB/ review, and regulatory inspection(s) by providing direct access to applicable source data.

The Study monitors will perform ongoing study monitoring visits to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Raw data will not be monitored.

## 16.5 Confidentiality

All records and other information about subjects participating in this study will be treated as confidential. The identity of a subject will never be disclosed in the event that study data are published.

Subject confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique subject identification code will be assigned and used to allow identification of all data reported for each subject.

Regulatory authorities and IRB may also be granted direct access to the medical history records in order to comply with legal and regulatory requirements. Investigators are to instruct their staff in the methods and importance of maintaining subject confidentiality according to local and national regulations and institutional requirements.

## 16.6 CIP Amendments

The investigator will propose any appropriate modification(s) of the Clinical Investigation Plan or investigational device or investigational device use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic will submit any significant amendment to the Clinical Investigation Plan, including a justification for this amendment, to the appropriate regulatory authorities and to the investigators to obtain approval from their IRB.

Any amendment to the protocol requires written approval by the IRB prior to its implementation, unless there are overriding safety reasons. In some instances, an amendment may require a change to the ICF.

The Sponsor and Investigator will obtain the IRB approval concerning the revised ICF prior to implementation of the change. The Investigator understands that subjects must be consented using the most current IRB approved version of the ICF. If the ICF is updated, subjects who are still receiving treatment will be re-consented at the direction of the IRB.

## 16.7 Record Retention

Study related documents including all study related Source Documents (*Section 16.4*), CRFs, ICFs, Investigator Site File, Final study reports, etc. should be maintained on site for a minimum of 2 years after the completion or termination of the study. Prior to the destruction of the study related data, the investigator must notify the sponsor.

An investigator may withdraw from the responsibility to maintain records for the period required as indicated in the section above and transfer custody of the records to any other person who will accept responsibility. An investigator must notify sponsor immediately if records are being transferred.

Medtronic will notify FDA no later than 10 working days after the transfer occurs.

## 16.8 Publication and Use of Information

Publication/Presentation statement will be included in the Clinical Trial Agreement between Medtronic and the site.

### 16.9 Suspension or Early Termination

Early termination results when the study is closed prior to the end of the study. A study suspension is a temporary postponement of the study activities related to enrollment. Both are possible for the study.

If the study is terminated or suspended, no additional enrollment will be allowed unless otherwise informed by the sponsor. The current subjects will be followed according to the protocol.

If the study is terminated prematurely or suspended by the sponsor, the sponsor will promptly inform the investigators and regulatory authorities (if required) of the termination and the reason(s). IRB will also be promptly informed and provided with the reason(s) for termination or suspension by the sponsor or by the investigator. The investigator will promptly inform the patients and assure appropriate therapy and follow-up for the subject.

If the investigator (or IRB) terminates or suspends the investigation without prior agreement of the sponsor, the investigator will promptly inform the sponsor, the institution (if required) and the IRB, and provide a detailed written explanation of the termination or suspension. The sponsor will inform the regulatory authorities (if required).

In the case of early termination of the study, all study subjects should be followed until the resolution of any pending adverse event(s).

Medtronic reserves the right to discontinue the study at any time for administrative or other reasons. Written notice of study termination will be submitted to the investigator in advance of such termination. Termination of a specific site can occur because of, but not limited to, inadequate data collection, low subject enrollment, or non-compliance with the protocol or other research requirements.

## 17 References


1. Elser, H.E., D. Holditch-Davis, and D.H. Brandon, *Measurement of Cerebral Blood Flow and Cerebral Oxygenation.* Newborn & Infant Nursing Reviews, 2011. **11**(3): p. 153-159.
2. *510(k) K960614.*
3. Michael B. Kim, et al., *Estimation of jugular venous O2 saturation from cerebral oximetry or arterial O2 saturation during isocapnic hypoxia.* Journal of Clinical Monitoring and Computing, 2000. **16**(3): p. 191–199.
4. Schell, R.M. and D.J. Cole, *Cerebral Monitoring: Jugular Venous Oximetry.* Anesthesia & Analgesia, 2000. **90**(3): p. 559-566.
5. Casati, A., et al., *Continuous Monitoring of Cerebral Oxygen Saturation in Elderly Patients Undergoing Major Abdominal Surgery Minimizes Brain Exposure to Potential Hypoxia.* Anesthesia & Analgesia, 2005. **101**(3): p. 740-747.
6. Murkin, J.M., et al., *Monitoring Brain Oxygen Saturation During Coronary Bypass Surgery: A Randomized, Prospective Study.* Anesthesia & Analgesia, 2007. **104**(1): p. 51-58.
7. B, S., P. A, and P. UJ, *Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine.* Critical Care, 2002. **3**(6): p. 199–204.
8. Boye, S., et al., *Anesthesiological Management in a Non-accessible Environment Preparation of Volunteers for Investigations with Controlled Hypoxemia in a 3 Tesla Magnetic Field for Assessing*

*Cerebral Energy Metabolism*, in *IFMBE Proceedings* Olaf Dössel and W.C. Schlegel, Editors. 2009: Munich, Germany. p. 880-882.

9. H. Benoit, et al., *Accuracy of pulse oximetry during intense exercise under severe hypoxic conditions.* European Journal of Applied Physiology and Occupational Physiology, 1997. **76**(3): p. 260-263.
10. Mäntysaari, M., et al., *Unaltered Blood Coagulation and Platelet Function in Healthy Subjects Exposed to Acute Hypoxia.* Aviation, Space, and Environmental Medicine, 2011. **82**(7): p. 699-703.
11. Marla J. De Jong, et al., *Accuracy and precision of buccal pulse oximetry* Heart & Lung: The Journal of Acute and Critical Care, 2011. **40**(1): p. 31-40.
12. Society, A.N. *Radiation Dose Calculator*. 2016 [cited 2017 1/6/2017].