Near Infra-Red Spectrophotometry (NIRS)-Based Cerebral Oximetry Monitoring in Elderly Thoracic Surgical Patients Undergoing Single Lung Ventilation Procedures: A Single Center, Prospective, Randomized Controlled Pilot Study Assessing the Clinical Impact of NIRS-Guided Intervention

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STATEMENT OF CONFIDENTIALITY

the protocol author, Edwin G. Avery, IV, M.D., C.P.I., and will not be disclosed to others without the written authorization of the protocol author, except to the extent necessary to obtain informed consent from those persons who may be enrolled in this protocol.

1 PROTOCOL APPROVAL

Protocol Title:

NIRS-Based Cerebral Oximetry Monitoring in Elderly Thoracic Surgical Patients Undergoing Single Lung Ventilation Procedures: A Single Center, Prospective, Randomized Controlled Pilot Study Assessing the Clinical Impact of NIRS-Guided Intervention

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Philip Linden, M.D. Date

2 STUDY SYNOPSIS

Name of Sponsor: Investigator initiated – Philip Linden, M.D.

Name of Product: INVOS® 5100 Near Infra-Red Spectrophotometer (Covidien, Boulder, CO)

Title of Study: Near Infra-Red Spectrophotometry (NIRS)-Based Cerebral Oximetry Monitoring in Elderly Thoracic Surgical Patients Undergoing Single Lung Ventilation Procedures: A Single Center, Prospective, Randomized Controlled Pilot Study Assessing the Clinical Impact of NIRS-Guided Intervention

Study Center: University Hospitals Case Medical Center (UHCMC), Cleveland, OH – Case Western Reserve University School of Medicine (CWRUSOM)

Study Rationale
The use of bi-frontal, near infrared spectrophotometry (NIRS) based cerebral oximetry monitoring has been demonstrated to result in improved clinical outcomes in both general surgery patients and cardiac surgical patients using prospective, randomized controlled trial methodology. Elderly thoracic surgical patients undergoing procedures that involve single lung ventilation may also stand to benefit from the application of intraoperative and early postoperative NIRS cerebral oximetry monitoring. Cerebral oximetry has not been established as a standard of care monitoring modality in this patient population, thus permitting the application of randomized, controlled testing methodology to assess the potential impact of this monitoring modality upon these patients.

Hypothesis and Objectives:
The primary hypothesis in this pilot study of elderly thoracic surgical patients undergoing procedures involving single lung ventilation (SLV) is that there will be a measurable and significant clinical benefit (as assessed by a broad range of postoperative clinical outcome measures) to the subjects randomized to the intervention cohort (open bi-frontal NIRS based cerebral oximetry monitoring with a standardized intervention protocol) vs. the control cohort (blinded bi-frontal NIRS based cerebral oximetry monitoring).

The primary objective of this pilot study is to identify the most relevant clinical outcome variables which significantly diverge as a result of being randomized to the intervention cohort vs. the control cohort so that a larger, multicenter, prospective, randomized controlled clinical trial can be designed to further test the primary hypothesis as stated in the preceding section. The subsequent larger, multicenter trial will be conducted to definitively demonstrate the ability of INVOS® 5100 guided NIRS-based bi-frontal monitoring to improve clinical outcomes in this surgical patient group and potentially establish a new U.S. Food and Drug Administration cleared indication for this monitoring modality.

Secondary objectives of this pilot study include the following:

1) Assess the frequency of cerebral desaturations in both the intervention and control cohorts by examining both the total number of patients experiencing any cerebral desaturation as well as the total number of events among patients experiencing any cerebral desaturation (of at least 5% below

baseline and progressively larger desaturations). These analyses will be conducted on the entire study population as well as upon each cohort. The Area Under the Curve (AUC) analysis technique [incremental desaturation categories will be assessed based upon 5 to 50% decreases, measured in 5% increments, from established room air pre-incision baseline as well as oxygen supplemented preincision baseline as well as desaturations below absolute measured rSO_2 values] will be employed to conduct these analyses.

2) Assess the frequency of adverse clinical events and serious adverse events overall and in each cohort.

3) Perform a comprehensive assessment of the frequency and efficacy of predefined rSO_2 desaturation mitigation interventions and their collective ability to affect the observed cerebral oximetry values.

4) Assess the interventional cohort's preoperative demographics and collected covariates for association with the ease or difficulty of mitigating observed cerebral desaturation events.

Exploratory analyses will include performing all possible comparisons of the two groups based upon all collected perioperative variables to examine the potentially significant relationships between the collected clinical variables representing surrogates of organ perfusion/function and cerebral oximetry desaturations (AUC_{rSO2}). The following exploratory endpoints will be assessed:

- Logistic regression analysis to determine the most relevant AUC_{rSO2} desaturation value(s) associated with any detrimental clinical outcome(s) monitored in this study

- Logistic regression analysis to determine the most relevant AUC blood pressure values associated with any detrimental clinical outcome(s) monitored in this study

- Comparison of baseline rSO_2 values (room air and oxygen supplemented) to all collected clinical variables to assess for possibly significant associations

- Explore the potential impact of rSO_2 monitoring on changing the surgical conduct of the procedure

Methodology: Single center, prospective, randomized, controlled clinical pilot study

Number of Subjects: 100 subjects with balanced randomization (1:1) to control (blinded NIRS data) or intervention (open NIRS data) cohorts

Main Criteria for Inclusion: Elderly patients (> 65 years of age) scheduled for a thoracic surgical procedure at UHCMC that will involve SLV.

Duration of Treatment: Cerebral oximetry monitoring will begin with an assessment of both room air and oxygen supplemented bi-frontal baseline NIRS values and continue through the surgery to either PACU discharge or the initial 12 hours of post surgical ICU treatment. Mini Mental Status exam testing and Delirium testing with the Confusion Assessment Method will occur preoperatively and postoperatively through post-operative day (POD) #3 (or discharge if that occurs sooner than POD #3).

Enrolled subjects will be followed during the index hospitalization and will undergo a 30 day follow up telephone interview to assess their progress following hospital discharge.

Criteria for Evaluation:
A large number of intraoperative and postoperative clinical variables that include cerebral oximetry, pulse oximetry, blood pressure, a composite outcome measure and clinical variables representing organ function will be assessed with the primary endpoint being the determination of which clinical variables are improved, if any, as a result of being randomized to open NIRS data monitoring with a predefined desaturation intervention algorithm guideline. The Mini Mental Status exam and Confusion Assessment Method test will be used to determine if any measured clinical variables have an effect upon neuropsychological outcomes. The frequency and effectiveness of the various cerebral desaturation mitigating interventions will be assessed in the intervention cohort.

Additional Safety Observations:
The frequency and severity of adverse clinical events and serious adverse clinical events will be assessed to determine if the use of open NIRS data bi-frontal cerebral monitoring is associated with any significant change in the observation of such events.

Statistical Methods:
Preoperative demographics and clinical variables will be compared in the two groups to assess for significant differences using the independent t-test. Differences in the observed clinical data between groups will be determined with the Wilcoxon rank-sum test. Stepwise, forward, multivariable logistic regression analysis will be performed to assess for relationships between cerebral desaturations and any of the measured clinical variables with a p value < 0.05 being considered significant.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
AUC	Area Under the Curve
CAM	Confusion Assessment Method test
CI	Confidence Interval
CWRUSOM	Case Western Reserve University School of Medicine
GCP	Good Clinical Practices
H-LOS	Hospital Length of Stay
ICU	Intensive Care Unit
MMSE	Mini Mental Status Examination
MOMM	Major Organ Morbidity and Mortality
NIRS	Near Infra-Red Spectrophotometry
OR	Odds Ratio
POD	Post Operative Day
rSO_2	Regional Oxygen Saturation (frontal lobe)
SAE	Serious Adverse Event
SLV	Single Lung Ventilation
STS	Society of Thoracic Surgeons
UHCMC	University Hospitals Case Medical Center

5 Background and Rationale

5.1 Introduction

This protocol is a pilot study designed to assess the clinical impact of the intraoperative and immediate postoperative use of regional, near infra-red spectrophotometric (NIRS) monitoring using the INVOS® 5100 to assess bi-frontal cerebral oxygenation in elderly thoracic surgical patients undergoing procedures involving single lung ventilation (SLV). We seek to determine the impact of NIRS bi-frontal monitoring on any relevant clinical variables in the selected patient population in order to most efficiently design a multicenter, prospective, randomized controlled trial to definitively describe the potential clinical impact of this monitoring modality in the postoperative period.

This study will be conducted in compliance with Good Clinical Practices (GCP) including the Declaration of Helsinki and all applicable regulatory requirements.

5.2 Background

Cerebral oximetry monitoring has been in clinical use for over thirty years and has been commercially available to clinicians for over two decades. (Jobsis FF) The use of specific wavelengths of near infrared light along with an understanding of the Lambert-Beer Law permits determination of a regional, venous weighted saturation (75% venous : 25% arterial with the INVOS® device) of tissue beneath the sensor. Specifically, the device is measuring the percentage of oxygenated hemoglobin in blood vessels less than 100 microns in diameter (i.e. the exchange vessels including arterioles, capillaries and venules). (Avery EG) The venous weighted nature of the measurement allows for the determination of the oxygen balance within the interrogated tissue. For example, desaturated tissue will have lower regional saturation values as a result of decreased oxygen delivery and/or increased oxygen extraction.

5.3 Clinical Studies

Since this technology was made commercially available to practitioners several clinical studies including prospective, randomized controlled trials, both prospective and retrospective observational studies as well as a number of case reports have been published that support the use of NIRS-based cerebral and somatic tissue oximetry in surgical and critically ill patients. These clinical studies have been conducted in diverse groups of surgical patients which have demonstrated clinically beneficial outcomes for subjects who were monitored with this technology along with the implementation of standardized interventional algorithms designed to mitigate any observed desaturations. Among the patient groups that have been studied are general, vascular, adult cardiac, pediatric cardiac, adult thoracic surgical and neurocritical care patients. (Casati A et al, Murkin JM et al, Slater JP et al, Kasman N et al, Tang L et al) The use of these devices has been associated with improved clinical outcomes (decreased intensive care unit (ICU) and hospital length of stay (LOS), decreased stroke, decreased incidence of well accepted composite endpoints [i.e. the Society of Thoracic Surgery (STS) Major Organ Morbidity and Mortality (MOMM) composite endpoint that includes death, stroke, renal dialysis, surgical re-exploration, prolonged ventilation and mediastinitis] as well as decreased incidence of neurocognitive dysfunction) in observational studies as well as in prospective, randomized controlled trials which suggests more than an associative relationship between the use of NIRS cerebral monitoring and these improved outcomes.

Active testing of this technology over the past decade has brought forth the concept that by placing the sensors over the frontal lobe cerebral tissue and actively working to reverse the observed desaturations clinicians are very likely protecting the oxygen balance in all of the body's vital organs by using the brain as an index organ of adequate perfusion and oxygenation. (Grocott HP) Indeed, the improved clinical outcomes that have been published in the peer reviewed literature suggest a diffuse effect of generalized organ protection (e.g., decreased hospital LOS, decreased ICU LOS, decreased STS MOMM). It appears that despite the regional nature of the small amount of tissue that is monitored (i.e. 15 mm^3 of frontal lobe cortical gray matter) that this highly metabolically active cerebral tissue may be the most desirable tissue to assess and use as an index organ for providing adequate oxygen balance in the rest of the body.

Clinicians caring for perioperative cardiac surgical patients (e.g., cardiac anesthesiologists, cardiac surgeons and perfusionists) were early adopters of this technology related to the compromised cardiovascular status inherent to their patient population and the complex nature of the surgical procedures they perform (e.g., extracorporeal circulation and deep hypothermic circulatory arrest).

Study Rationale

There are presently two prospective, randomized controlled trials which strongly support the notion that these devices improve perioperative clinical outcomes in surgical patients as well as a large number of observational studies which strengthen the association of the use these devices to improved outcomes. (Murkin JM et al, Cassati A et al, Goldman S et al, Heringlake M et al, Schoen J et al) However, there is only one published observational study performed to date involving the use of NIRS-based regional cerebral oximetry of thoracic surgical patients undergoing SLV. That study only assessed the association of NIRS-based cerebral oximetry to postoperative neurocognitive dysfunction and did find a positive relationship between observed cerebral oximetry data and postoperative cognitive dysfunction (i.e. 29% of patients had significantly decreased Mini Mental Status Exam scores at 3 hours postoperatively and a ↓rSO_2 <65% for even just 5 minutes was associated with ↑OR 2.03 [95% CI: 0.74 – 5.59]) for developing early neurocognitive dysfunction. (Tang L)

Elderly thoracic surgical patients undergoing SLV related procedures were not included in any of the prospective randomized controlled trials and only the single, small observational study referenced above assessing postoperative neurocognitive dysfunction exists to test the hypothesis that NIRS based bifrontal cerebral monitoring has the potential to affect any clinical outcome in this subpopulation of surgical patients. Further, NIRS based bi-frontal cerebral monitoring is not accepted as a standard of care in thoracic surgical patients which permits the employment of randomized, controlled testing methodology in this patient population.

The establishment of cause and effect in clinical medicine is largely dictated by the conduct of multicenter, prospective, randomized controlled trials. This pilot study is intended to define the optimal clinical endpoints and statistical design needed to establish the potential benefits of NIRS based bi-frontal regional cerebral oximetry monitoring in elderly thoracic surgical patients undergoing procedures involving SLV.

This pilot study involves the collection not only of cerebral oximetry data but also of blood pressure and pulse oximetry data as well as a number of clinically relevant outcome measures that can reflect the adequacy of organ protection during the intraoperative and immediate postoperative period. Having serial

blood pressure and pulse oximetry data will allow for any possible correlations that exist between these standard physiologic parameters and the observed clinical outcomes to be assessed as it has been previously established that blood pressure control is associated with clinical outcomes in cardiac surgical patients (Weir M et al). Further, by collecting this data it will be possible to quantify the relative strength of any potential correlations of these standard physiologic parameters as well as cerebral oximetry data to the observed clinical outcomes potentially permitting a direct comparison of how useful optimizing these parameters may be in the postoperative period. Finally, we will potentially be able to establish the effect of blood pressure variability on observed cerebral oxygen balance in a real time clinical environment which could reveal that commonly used perioperative blood pressure goals alone are inadequate measures to optimally protect vital organs in our study population. A series of clinical experiments assessing cerebral autoregulation has recently been published by Dr. C. Hogue's group which strongly suggests that by using conventional medical approaches clinicians may do a poor job of predicting the lower limits of cerebral autoregulation and providing adequate cerebral blood flow in patients with advanced cardiovascular disease undergoing procedures involving the use of cardiopulmonary bypass. (Joshi B et al.) Our study has the ability to help solidify Dr. Hogue's findings which suggest that widely accepted discretionary blood pressure goals (e.g. maintaining mean arterial pressure within 20% of the preoperatively observed values) may not be adequate for optimal cerebral protection.

6 TRIAL OBJECTIVES AND PURPOSE

6.1 Primary Hypothesis

The primary hypothesis in this pilot study of elderly thoracic surgical patients undergoing procedures involving SLV is that there will be a measurable and significant clinical benefit (as assessed by a broad range of postoperative clinical outcome measures) to the subjects randomized to the intervention cohort (open bi-frontal NIRS based cerebral oximetry monitoring with a standardized intervention protocol) vs. the control cohort (blinded bi-frontal NIRS based cerebral oximetry monitoring).

6.2 Primary Objective

The primary objective of this pilot study is to identify the most relevant clinical outcome variables which significantly diverge as a result of being randomized to the intervention cohort vs. the control cohort so that a larger, multicenter, prospective, randomized controlled clinical trial can be designed to further test the primary hypothesis as stated in the preceding section. The subsequent larger, multicenter trial will be conducted to definitively demonstrate the ability of INVOS® 5100 guided NIRS-based bi-frontal monitoring to improve clinical outcomes in this surgical patient group and potentially establish a new U.S. Food and Drug Administration cleared indication for this monitoring modality.

6.3 Secondary Objectives

Secondary objectives of this pilot study include the following:

1) Assess the frequency of cerebral desaturations in both the intervention and control cohorts by examining both the total number of patients experiencing any cerebral desaturation as well as the total number of events among patients experiencing any cerebral desaturation (of at least 5% below baseline and progressively larger desaturations). These analyses will be conducted on the entire study population as well as upon each cohort. The Area Under the Curve (AUC) analysis

technique [incremental desaturation categories will be assessed based upon 5 to 50% decreases, measured in 5% increments, from established room air baseline as well as oxygen supplemented pre-incision baselines as well as desaturations below absolute measured rSO_2 values] will be employed to conduct these analyses.

2) Assess the frequency of adverse clinical events and serious adverse events overall and in each cohort.

3) Perform a comprehensive assessment of the frequency and efficacy of predefined rSO_2 desaturation mitigation interventions and their collective ability to affect the observed cerebral oximetry values.

4) Assess the interventional cohort's preoperative demographics and collected covariates for association with the ease or difficulty of mitigating observed cerebral desaturation events.

6.4 Exploratory Objectives

Exploratory objectives will include performing all possible comparisons of the two groups based upon all collected perioperative variables to examine the potentially significant relationships between the collected clinical variables representing surrogates of organ perfusion/function and cerebral oximetry desaturations (AUC_{rSO2}). The following exploratory endpoints will be assessed:

- Logistic regression analysis to determine the most relevant AUC_{rSO2} desaturation value(s) associated with any detrimental clinical outcome(s) monitored in this study

- Logistic regression analysis to determine the most relevant AUC blood pressure values associated with any detrimental clinical outcome(s) monitored in this study

- Comparison of baseline rSO_2 values (room air and oxygen supplemented) to all collected clinical variables to assess for possibly significant associations

7 STUDY DESIGN

7.1 Study Design

This study is a single center (University Hospitals Case Medical Center), prospective, randomized, controlled pilot study of elderly thoracic surgical patients undergoing procedures involving the use of SLV. A total of 100 eligible subjects will be randomized in a balanced fashion (1:1) to either the control cohort that will have electronically blinded bi-frontal cerebral oximetry monitoring or the intervention cohort that will have open bi-frontal cerebral oximetry monitoring with a predefined intervention protocol for observed desaturations of greater than 20% of established oxygen supplemented baseline values (see Appendix C). Both the control and intervention groups will have baseline NIRS data obtained in an unblinded fashion. The study will be divided into four separate periods that include screening, baseline acquisition, intraoperative and immediate postoperative and the postoperative follow up period.

7.2 Study Periods

7.2.1 Screening Period

Assessing patient's suitability for enrollment based upon defined inclusion and exclusion criteria. The informed consent process and enrollment will occur during this period after which preoperative demographics and study defined covariates will be recorded.

7.2.2 Baseline Acquisition Period

Following randomization using an envelope randomization technique to either the control or intervention cohort enrolled subjects will undergo baseline testing with the MMSE and CAM assessment tools. Subsequently all subjects will have acquisition of bifrontal NIRS cerebral oximetric readings on both room air and with 100% oxygen supplementation. The control group and the intervention group will have open NIRS baseline data collection. This will allow all enrolled subjects to demonstrate that a set of baseline rSO_2 values can be obtained and thus reduce the probability of unreadable outliers (i.e. subjects with anomalously located frontal sinuses) being studied in the control group. The baseline acquisition will occur in the operating room just prior to anesthesia induction.

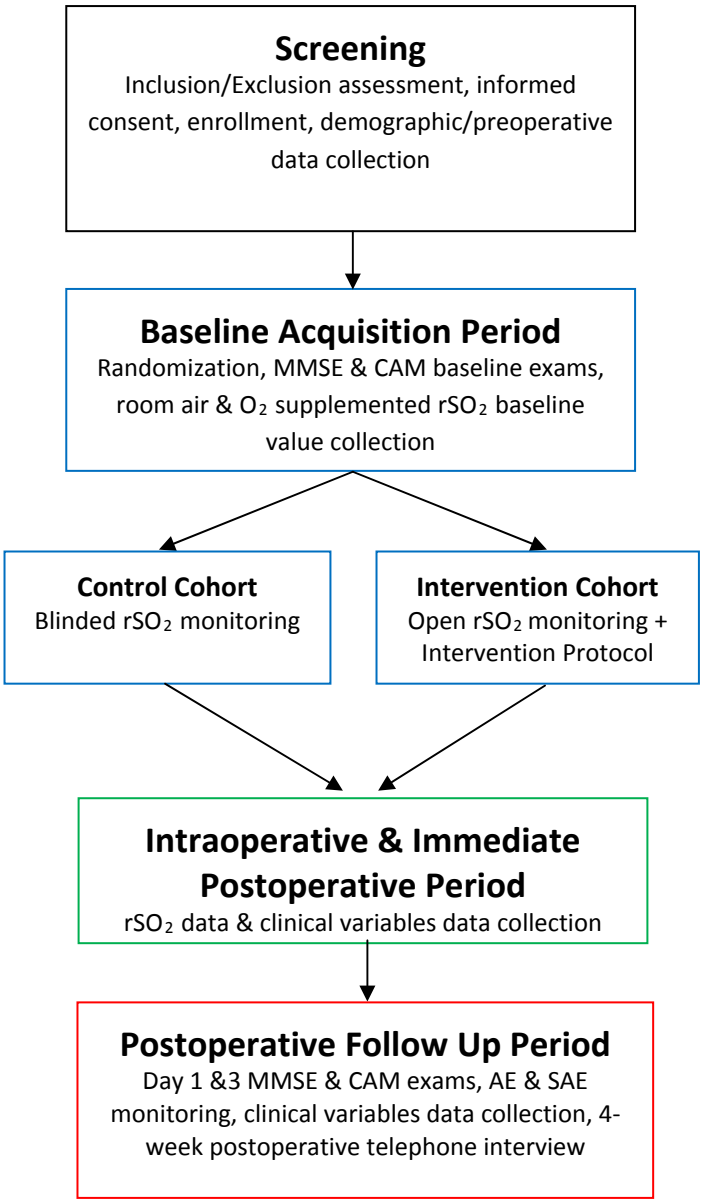
7.2.3 Intraoperative and Immediate Postoperative Period

The intraoperative period will occur immediately following completion of the Baseline Acquisition Period. Subjects randomized to the control group will be induced into general anesthesia with electronically blinded rSO_2 monitoring while those randomized to the intervention cohort will undergo open rSO_2 monitoring with the application of a standardized interventional protocol (Appendix D) for any observed significant cerebral desaturations. Significant cerebral desaturations are defined as any desaturation $\geq$ 10% of established room air baseline values for each individual subject. This period will continue through the end of the surgical procedure to PACU discharge or if the subject goes to the ICU through the first 12 hours of ICU admission.

7.2.4 Postoperative Follow Up Period

The postoperative follow up period will continue from PACU or ICU discharge until the patient telephone interview 4 weeks after the surgical procedure. The active elements of the study protocol which involve direct subject interaction during this period include a postoperative day 1 and 3 MMSE and CAM delirium assessments as well as the 4 week post-procedure follow up telephone interview to assess the patient's general state of health following surgery including a query of any need for hospital readmission.

Schematic Diagram of Trial Design


Screening
Inclusion/Exclusion assessment, informed consent, enrollment, demographic/preoperative data collection
Baseline Acquisition Period
Randomization, MMSE & CAM baseline exams, room air & O_2 supplemented rSO_2 baseline value collection
Control Cohort
Blinded rSO_2 monitoring
Intervention Cohort
Open rSO_2 monitoring + Intervention Protocol
Intraoperative & Immediate Postoperative Period
rSO_2 data & clinical variables data collection
Postoperative Follow Up Period
Day 1 &3 MMSE & CAM exams, AE & SAE monitoring, clinical variables data collection, 4-week postoperative telephone interview

7.4 Study Variables

7.4.1 Primary Endpoints

The relationship between the observed cerebral oximetry data and a number of predefined intraoperative and postoperative clinical variables will serve as the primary endpoints of this trial. The clinical variables will include the following intraoperative and postoperative (PACU or initial 12 hours of the ICU stay) parameters:

7.4.1.1 Intraoperative:

- Area under the curve of cumulative rSO_2 desaturations (AUC_{rSO2}) of progressive categorical degrees that will include the following:
    - < 5% of established room air baseline and oxygen supplemented baseline ○ < 10% of established room air baseline and oxygen supplemented baseline ○ < 15% of established room air baseline and oxygen supplemented baseline ○ < 20% of established room air baseline and oxygen supplemented baseline ○ < 25% of established room air baseline and oxygen supplemented baseline ○ < 30% of established room air baseline and oxygen supplemented baseline ○ < 35% of established room air baseline and oxygen supplemented baseline ○ < 40% of established room air baseline and oxygen supplemented baseline ○ < 60% of absolute measured value (if baseline > 60%) ○ < 55% of absolute measured value (if baseline > 55%) ○ < 50% of absolute measured value (if baseline > 50%) ○ < 45% of absolute measured value (if baseline > 45%) ○ < 40% of absolute measured value ○ < 35% of absolute measured value

- < 30% of absolute measured value - < 25% of absolute measured value - < 20% of absolute measured value

- Area under the curve for cumulative, high and low intraoperative values outside of preestablished, individualized patient blood pressure goals based upon preoperatively observed blood pressure values as well as values clinically accepted to provide adequate organ perfusion. This analysis will be performed for systolic, diastolic and mean arterial pressures ($AUC_{SBP\text{-}hi}$, $AUC_{SBP\text{-}low}$, $AUC_{SBP\text{-}cum}$, $AUC_{DBP\text{-}hi}$, $AUC_{DBP\text{-}low}$, $AUC_{DBP\text{-}cum}$, $AUC_{MAP\text{-}hi}$, $AUC_{MAP\text{-}low}$, $AUC_{MAP\text{-}cum}$). All intraoperative pressure data will be collected with either invasive arterial catheterization [Q30 secs] or non-invasive blood pressure monitoring [Q3 min] as determined by the attending anesthesiologist caring for the subject.

- Area under the curve of intraoperative progressive categorical pulse oximetry (SpO_2) desaturations (AUC_{SpO2}) including the following:

  - AUC_{SpO2} < 95% regardless of intraoperative FiO2 values - AUC_{SpO2} < 90% regardless of intraoperative FiO2 values - AUC_{SpO2} < 85% regardless of intraoperative FiO2 values - AUC_{SpO2} < 80% regardless of intraoperative FiO2 values - AUC_{SpO2} < 75% regardless of intraoperative FiO2 values - AUC_{SpO2} < 70% regardless of intraoperative FiO2 values

- Use of any intraoperative, intravenous vasopressor and/or inotropic agent (as assessed by amount of time in minutes on any IV drug support regardless of dose and assessed by total dose of drug to delivered to patient)

- Intraoperative urine output in any patient with an indwelling foley catheter as assessed by mLs urine/kg/hr for total time in operating room

- Need for intraoperative red blood cell transfusion (as assessed by number of RBC units transfused)

- Observed desaturation prompted change in surgical procedure (e.g., the surgery was paused to inflate the collapsed lung to improve systemic tissue oxygenation) - Occurrence of any intraoperative stroke or transient ischemic attack (as assessed by documented clinical neurological assessment or cerebral imaging study) - Any

observed intraoperative myocardial ischemia or infarction (as assessed by intraoperative ECG changes and/or myocardial biomarkers (i.e. troponin increase)

- Area under the curve of any observed intraoperative hyperglycemia (AUC_{Glu} > 110 mg/dL) in patients with a documented history of either type I or II diabetes mellitus
- Any occurrence of intraoperative atrial fibrillation (capturing duration of atrial fibrillation and whether treatment was required)
- Total time spent in operating room
- Total amount of narcotic administered in the operating room
- Total volume of crystalloid administered in the operating room
- Total volume of colloid administered in the operating room
- Anti-emetic medications administered in the operating room
- Surgical procedure performed
- Time on single lung ventilation

Intraoperative Use of epidural catheter

7.4.1.2 Postoperative:

- Area under the curve of rSO_2 desaturations (AUC_{rSO2}) of progressive categorical degrees that will include the following:
    - < 5% of established room air baseline and oxygen supplemented baseline
    - < 10% of established room air baseline and oxygen supplemented baseline
    - < 15% of established room air baseline and oxygen supplemented baseline
    - < 20% of established room air baseline and oxygen supplemented baseline
    - < 25% of established room air baseline and oxygen supplemented baseline
    - < 30% of established room air baseline and oxygen supplemented

baseline ○ < 35% of established room air baseline and oxygen

supplemented baseline ○ < 40% of established room air

baseline and oxygen supplemented baseline ○ < 60% of

absolute measured value (if baseline > 60%) ○ < 55% of

absolute measured value (if baseline > 55%) ○ < 50% of

absolute measured value (if baseline > 50%) ○ < 45% of

absolute measured value (if baseline > 45%) ○ < 40% of

absolute measured value ○ < 35% of absolute measured value

○ < 30% of absolute measured value

○ < 25% of absolute measured value ○ < 20% of absolute

measured value

- Area under the curve for cumulative, high and low postoperative values outside of preestablished, individualized patient blood pressure goals based upon preoperatively observed blood pressure values as well as values clinically accepted to provide adequate organ perfusion. This analysis will be performed for systolic, diastolic and mean arterial pressures ($AUC_{SBP\text{-}hi}$, $AUC_{SBP\text{-}low}$, $AUC_{SBP\text{-}cum}$, $AUC_{DBP\text{-}hi}$, $AUC_{DBP\text{-}low}$, $AUC_{DBP\text{-}cum}$, $AUC_{MAP\text{-}hi}$, $AUC_{MAP\text{-}low}$, $AUC_{MAP\text{-}cum}$). All postoperative blood pressure data will be collected with either invasive arterial catheterization [Q30 secs] or non-invasive blood pressure monitoring [Q15 min] as determined by the attending anesthesiologist caring for the subject in the PACU.

- Area under the curve of postoperative progressive categorical pulse oximetry (SpO_2) desaturations (AUC_{SpO2}) including the following:

  - AUC_{SpO2} < 95% regardless of intraoperative FiO2 values ○

  AUC_{SpO2} < 90% regardless of intraoperative FiO2 values ○

  AUC_{SpO2} < 85% regardless of intraoperative FiO2 values ○

  AUC_{SpO2} < 80% regardless of intraoperative FiO2 values ○

- AUC_{SpO2} < 75% regardless of intraoperative FiO2 values ○
- AUC_{SpO2} < 70% regardless of intraoperative FiO2 values

- Time from procedure completion to arrival in the post anesthesia care unit (PACU) or ICU
- Temperature upon PACU/ICU arrival
- Aldrete score upon PACU/ICU arrival and at 30 & 60 (or at discharge) min post-PACU arrival (See Appendix A)
- Any occurrence of immediate postoperative atrial fibrillation
- Any myocardial ischemia in the immediate postoperative period
- Any need for allogeneic RBC transfusion in the immediate postoperative period
- Any observed stroke or TIA in the immediate postoperative period
- Time to clinical readiness for PACU discharge as assessed by established institutional discharge criteria (see Appendix B)
- Frequency and severity of nausea and vomiting observed in the PACU and/or ICU as assessed by an accepted postoperative nausea and vomiting scale
- ICU length of stay (ICU-LOS) [anticipated to be at least 10-20 evaluable subjects for this parameter if 100 patients are enrolled] which will be defined as time to clinical readiness for ICU discharge as assessed by the clinical team caring for the patient
- Postoperative mechanical ventilation time if still intubated and admitted to the ICU following the surgical procedure
- Use of any immediate postoperative, intravenous vasopressor and/or inotropic agent (as assessed by amount of time in minutes on any IV drug support regardless of dose and assessed by total dose of drug to delivered to patient)
- Immediate postoperative urine output in any patient with an indwelling foley catheter as assessed by mLs urine/kg/hr for total time in operating room
- Hospital length of stay (H-LOS)
- Need for skilled nursing facility/rehabilitation hospital admission upon discharge from index hospitalization
- Length of time spent in a skilled nursing facility/rehabilitation hospital upon discharge from index hospitalization if a relevant data point for each subject

- Need for hospital readmission for any reason within 30 days of surgical procedure
- Observed change from preoperative baseline Mini-mental Status Examination (MMSE) score (including postoperative day #1 and postoperative day #3 or discharge scores)
- Presence/absence of postoperative delirium (as assessed by the CAM Delirium assessment tool results obtained preoperatively and postoperatively upon PACU discharge, Day#1 and 3 [or hospital discharge])

- Change in baseline renal function (as assessed by ΔGFR from baseline compared to inhospital nadir postoperative GFR estimated by the Cockroft-Galt method, Δpreoperative serum creatinine obtained within 6 weeks of surgical procedure to nadir postoperative value and any new need for any form of renal replacement therapy)

- Postoperative use of epidural catheter

- Documented return of bowel function time (as assessed by time to first bowel movement following surgical procedure)

- Need for postoperative (any time from transfer from OR to discharge) red blood cell transfusion (as assessed by number of RBC units transfused)
- Occurrence of any postoperative (any time from transfer from OR to discharge) stroke or transient ischemic attack (as assessed by documented clinical neurological assessment or cerebral imaging study)

- Any observed postoperative (any time from transfer from OR to discharge) myocardial ischemia or infarction (as assessed by physical examination, intraoperative ECG changes and/or myocardial biomarkers [i.e. troponin increase])

- Postoperative (any time from transfer from OR to discharge) occurrence of any form infectious complication up to POD 30

- Postoperative time to wean from supplemental oxygen

- Postoperative (any time from transfer from OR to discharge) composite endpoint that includes any subject with at least one of the following: new onset atrial fibrillation, ≥Grade 2 PONV, HLOS≥4.5 days, PACU LOS≥2 hours, any infectious complication, death, stroke, myocardial infarction, greater 0.5 mg/dL increase in creatinine or new need for renal dialysis, postoperative need for intravenous inotropes or vasoactive medications

8 STUDY DEVICE

8.1 Device Description

The INVOS® 5100C is a 2 wavelength, diffuse reflectance spectroscopy system employing near

infrared light to estimate the percentage of hemoglobin saturated with oxygen in tissue underneath the sensor. This is similar to the noninvasive technology widely used in pulse oximeters to monitor oxygen saturated hemoglobin percentage in arterial blood.
An adhesive sensor containing a light source and 2 photodiodes is applied to the skin over the tissue of interest and the returning light is analyzed for hemoglobin and deoxyhemoglobin light absorption. Absorption signals from the photodiode closer to the light source are subtracted from those from the farther photodiode where the returning photons penetrate more deeply in the tissue. This suppresses absorption events originating in the outer layers of tissue that are common to both photodiodes, including the effects of skin pigmentation and subcutaneous tissues.
The INVOS® 5100C tissue oximeter is a multichannel monitor with continuous recording and display of readings of regional tissue hemoglobin oxygen saturation from 4 separate sensors simultaneously. The monitor is connected to 2 preamplifiers, each of which in turn supports 2 sensors. It has USB connectivity for dynamic data capture, storage and transfer as well as a digital output port.

8.2 Indications for Use

The noninvasive INVOS® 5100C is intended for use as a monitor which provides accurate, immediate feedback of regional hemoglobin oxygen saturation of blood in the brain or in other tissue beneath the sensor. It is intended for use in any individual at risk for reduced-flow or noflow ischemic states. The prospective clinical value of data from the INVOS® System has not been demonstrated in disease states. The INVOS® System should not be used as the sole basis for diagnosis or therapy.

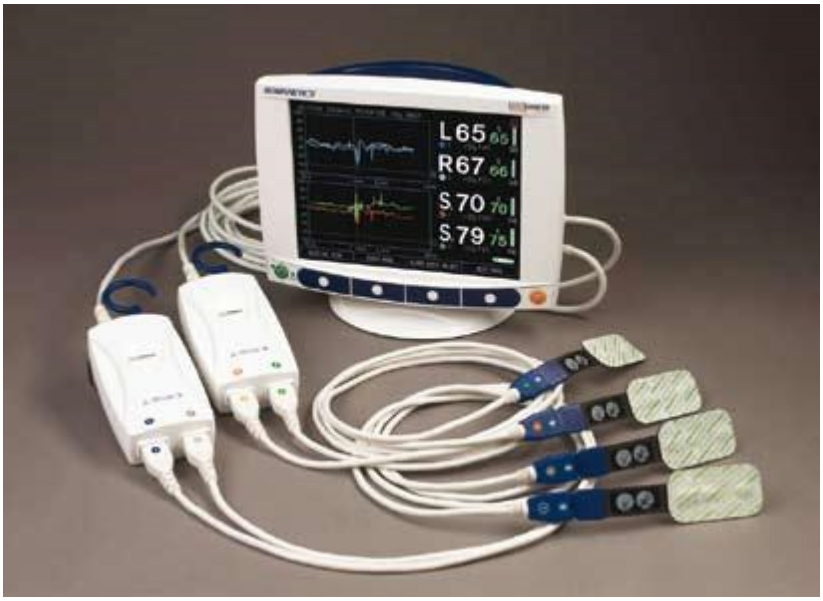
8.3 Food and Drug Administration Status

510K cleared (#K080769) April 2009

8.4 Technological Characteristics

The INVOS® 5100C is an in vivo optical spectrometer using two wavelengths(730 and 810 nm) of near infrared light that is projected into any tissue beneath the sensor. A portion of the emitted light is reflected back to one of two fixed distance photodiodes (30 and 40 mm from the LED light source). Returning light signals are processed with a technique known as spatial resolution which permits removal of the majority of saturation data obtained in the more superficial scalp tissue and thus the final reading is thought to reflect primarily a venous weighted saturation (75% venous to 25% arterial) of hemoglobin below the sensor pads. The data processing occurs in the device preamplifier and is then sent to the display module for graphic display and storage. Device data can be directly transferred to a collection system via a serial cable or can be downloaded to a USB memory stick and further processed for analysis with an Excel® macros. The device has the capacity to simultaneously monitor, display and store 4 separate sets of monitoring data.

8.5 Device Image



8.6 Device Modification

The subjects randomized to the control group will be monitored with a modified device following the acquisition of the baseline NIRS data. The modification involves electronic blinding of the data via an adjustment made to the device by the manufacturer that prevents the active display of the current data and graphic trends on the display console. However, the modified device will still electronically store the acquired NIRS data for later analysis. The use of this modified version of the device will help to reduce investigator bias that might be introduced if a blinder were affixed to the display console.

9 SUBJECT SELECTION

9.1 Study Population

A total of 100 evaluable subjects will be enrolled into this protocol. Patients at least 65 years of age who are scheduled to undergo non-emergent, thoracic surgical procedures planned to involve the use of single lung ventilation will be evaluated in this study.

9.1.1 Inclusion Criteria:

1. Any male or female patient ≥ 65 years of age and able to provide informed consent (or consent may be provided by a legally authorized representative) who is scheduled for a thoracic surgical procedure that is expected to involve the use of intraoperative single lung ventilation (SLV)

2. Able to adequately complete a baseline mini-mental status examination (MMSE)

3. Able to complete a baseline confusion assessment method (CAM) examination

4. Able to obtain bi-frontal baseline rSO_2 values prior to induction of anesthesia

9.1.2 Exclusion criteria:

1. Any patient who has participated in a clinical study of an investigational drug or device in the past 30 days

2. Any patient who the principal investigator feels at any time or for any reason should not participate in this clinical study

3. Withdrawal of informed consent for any reason

9.2 Withdrawal Criteria

All patients have the right to withdraw any point during the trial without prejudice. The investigator can discontinue any subject at any time if medically necessary. If the ability to monitor the cerebral oximetry is data is lost during the conduct of the study for a significant period of time that precludes useful data analysis then the subject will be withdrawn by the principal investigator.

10 TREATMENT OF SUBJECTS

10.1 Study Device

The study device, INVOS® 5100C, is described in Section 8. Enrolled subjects will be randomized in a balanced fashion (1:1) to either the control group (blinded cerebral oximetry monitoring intraoperatively and in the immediate postoperative period) or to the intervention group (open cerebral oximetry monitoring with the use of a standardized intervention protocol for observed desaturations greater than 20%).

10.2 Control Group

The control group will have both room air and oxygen supplemented baselines obtained in an antecedent fashion to establish that they can produce reliable bilateral cerebral oximetry readings. Because it is known that the device may not be able to produce a valid reading in some individuals with pigmented skin or aberrantly located frontal sinuses this step is necessary to insure that all subjects in the control group will produce useful NIRS data. Once the baseline values have been recorded the cerebral oximetry will be monitored in an electronically blinded manner. Specifically, the device will capture data but neither the current values nor the trend will be displayed on the device's display console. The use of this modified version of the device will help to reduce investigator bias that might be introduced if a blinder were affixed to the display console. The baseline values will be obtained prior to the induction of general anesthesia.

10.3 Intervention Group

The intervention group will have baseline NIRS values obtained in a manner analogous to the control group. Following recording of the baseline values the subjects will be induced into general anesthesia and the clinicians as well as an IRB registered research assistant will be able to openly monitor the NIRS data. Upon observed cerebral desaturations greater than 20% of the oxygen supplemented baseline on either frontal hemisphere the research assistant will inform the anesthesia clinician that a significant cerebral desaturation is occurring and requires treatment. At this point a standardized interventional protocol will be followed that is detailed in Appendix C. The clinicians caring for the subject will have the ability to override the study intervention algorithm based upon the patient's physical condition at the time.

The intervention protocol for observed desaturations >20% will involve insuring that the subject's head vessels are not kinked or obstructed, increasing the mean arterial pressure via an intravenous fluid bolus or administration of a vasoconstrictor (i.e. henylephrine or ephedrine) as deemed appropriate by the anesthesia clinician caring for the subject, normalizing $PaCO_2$ to a value between 40 to 50 mmHg, or alternatively normalizing end tidal CO_2 to a value of 35 to 45 mmHg. Subsequent interventions may include increasing the FiO_2, especially if the SpO_2 is below 98% or administering an intravenous inotropic agent if a low flow state is suspected. Administration of an inotrope will occur as judged by the clinician caring for the subject. Finally, in cases where the subject's hematocrit is known or suspected to critically low transfusion of allogeneic blood will be considered. The decision to transfuse allogeneic blood will be made by the anesthesia and surgery clinicians caring for the subject.

11 PROTOCOL ASSESSMENTS AND PROCEDURES

The Schedule of Assessments which details the sequence of assessments and procedures is presented in Table 1. Note that as described in Section 7.2 there are four separate periods that this study is divided into that include the following: screening, baseline , intraoperative and immediate postoperative and postoperative follow up.

Table 1: Schedule of Assessments

	Screening	Baseline Acquisition	Intraoperative and Immediate Postoperative	Postoperative Follow Up
Study Assessment				
Review of inclusion/exclusion criteria	**X**			
Informed consent	**X**			
Demographics	**X**			
Medical history	**X**			
Randomization		**X**		
MMSE & CAM testing		**X**		**X**
Serum creatinine	**X**			**X**
Obtain baseline room air and O_2 supplemented rSO_2		**X**		
Continuous rSO_2, SpO_2, blood pressure data collection			**X**	
Employ rSO_2 desaturation algorithm (intervention group only)			**X**	
Continuous intra/immediate post-operative clinical variable collection			**X**	
PACU and ICU clinical variable collection			**X**	
Postoperative clinical variable collection			**X**	**X**
Adverse and Serious Adverse Event Monitoring		**X**	**X**	**X**
Telephone interview				**X**

11.1 Protocol Assessments and Procedures – Screening Period

11.1.1 General Screening Period Description

Screening of potential subjects will occur prior to the planned surgical procedure to allow individuals time to consider their participation. Subjects will be screened from the daily Mather Operating Room printed schedule. Subjects scheduled to undergo surgical procedures that appear to meet the primary inclusion criteria will be approached for additional screening in the Mather Preoperative Area. An IRB registered investigator or nurse coordinator will approach the patient if they are willing to consider listening to a brief description of the study. Patients who verbally agree to learn more about the study will then have a discussion with the IRB registered study investigator or nurse coordinator which includes the details of the study explained in clear and concise language. During this conversation the voluntary nature of any individual's participation will be clearly communicated. Additionally, the discussion will include a description of what the patient's participation will entail, including the voluntary nature of their participation, their ability to withdraw at any time, the confidential nature of their participation, the procedures that will occur among study participants, the information that will be collected from participants and all of the risks and benefits associated with their participation in the trial. Additionally, the study staff will explain to the patient how their hospital care may be different if they choose to participate in the study, including the fact that they will be randomized to either the control group or the intervention group with a 50% chance of being assigned to either group. The implications of being assigned to either group will be discussed.

11.1.2 Informed Consent

Patients will also be given the opportunity to ask questions of the study investigator or nurse coordinator and express their personal concerns about what their participation may entail. If the patient wishes to participate then the study investigator will then review the study consent form in a page-by-page manner to insure that they understand all aspects of what their participation will include. At this point additional time to personally review the consent form document will be given to each potential subject. Following this, potential participants will then be given another opportunity to ask questions and once all of them have been satisfactorily addressed the subject and the study investigator will sign, time and date the consent form. A copy of the consent will be placed in the patient's chart and given to the patient's family/escort or will be secured and given to the patient after their surgical procedure.

11.1.3 Preoperative Variables Collected

Following finalization of informed consent the patient's chart will be reviewed to ensure that they are appropriate for participation based upon the study's inclusion and exclusion criteria.

Additionally, the patient's records will be reviewed and key demographics and clinical variables will be collected using a standardized data collection tool. 11.1.3.1 Demographics and clinical variables collected

Age	+/- Recent MI
Gender	+/- CHF
Race	+/- DM Type II (insulin)
Height	+/- DM Type II (non-insulin)
Weight	+/- Renal Insufficiency
BMI	+/- COPD
Serum creatinine	+/- OSA
Hemoglobin	+/- Dementia
LVEF	+/- Alcohol use
+/- Vascular disease	+/- Tobacco use
+/- Stroke/TIA	+/- Illicit drug use
+/- CAD	

11.2 Protocol Assessments and Procedures – Baseline Acquisition Period

11.2.1 General Baseline Acquisition Period Description

During the baseline acquisition period each subject will be randomized and then the neurocognitive baseline exams will be obtained. Additionally, the baseline rSO_2 data will be collected.

11.2.2 Randomization

Next, each subject will be randomized in a balanced fashion (1:1) to either the control group or the intervention group. Randomization will occur through the use of a blinded envelope technique at which time each subject will acquire a unique study identifier for their study records.

11.2.3 MMSE and CAM Baseline Exams Performed

The mini-mental status examination and the confusion assessment method examination will be performed upon each subject to establish baseline performance prior to entering the operating room for their surgical procedure. A trained study investigator will conduct these two exams.

11.2.4 Baseline rSO_2 Data Acquisition

Once in the operating room the patient will have standard monitors applied as well as bilateral rSO_2 sensor pads to the glabrous skin of the forehead just above the eyebrow line. The application of the pads will be preceded by swabbing the skin with an alcohol pad and applying both mastisol and clear tape to promote pad adhesion throughout the collection of NIRS data.

11.2.4.1 Room Air Baseline rSO_2

Once the pads are in place approximately one minute will elapse to insure that a reliable NIRS signal is obtained and that it is producing stable values bilaterally while they are in the supine position just prior to the preoxygenation period of anesthesia induction. Both the left and right baseline values will then be recorded. The time of this event will be recorded on the study data collection tool.

11.2.4.2 Oxygen Supplemented Baseline rSO_2

Once that subject has been breathing 100% oxygen for a full two minutes as assessed by the research assistant's timer the oxygen supplemented rSO_2 baselines will be recorded when the NIRS data is stable bilaterally. The time of this event will be recorded on the study data collection tool. 11.2.4.3 Blinding of Control Group

After recording the two sets of baseline rSO_2 data the subjects that have been randomized to the control group will have their rSO_2 data electronically blinded via activation of a device modification that will have been previously performed by the device manufacturer.

11.3 Protocol Assessments and Procedures – Intraoperative and Immediate Postoperative Period

11.3.1 General Intraoperative and Immediate Postoperative Period Description

During this period a host of clinical variables will be collected on each subject that will serve as the primary endpoints of this pilot study.

11.3.2 Serial rSO_2, SpO_2 and Blood Pressure Data Collection

Anesthesia induction will be accompanied by continuous electronic acquisition of the rSO_2, SpO_2 and MAP data. PICIS will be used to collect blood pressure data as well as rSO_2 data in individuals randomized to the intervention group. The INVOS devices will also be collecting the rSO_2 data in both groups of subjects for download at a later time. Note that the time on the oximeter will be synchronized with the time on the PICIS Anesthesia Computer prior to the collection of any NIRS or hemodynamic data.

11.3.3 Intraoperative and Immediate Postoperative Clinical Variable Data Collection

11.3.3.1 Intraoperative Clinical Variables Collected

Vasopressor use
Inotrope use
Amount of narcotic administered
Time on single lung ventilation

Urine output
Myocardial ischemia
Stroke or TIA
Hyperglycemia $AUC_{Glu} > 110$
Atrial fibrillation
Use of epidural catheter
Surgical procedure
Time spent in operating room
Anti-emetic medication administered
Total crystalloid administered
Total colloid administered
Total transfused allogeneic RBCs
rSO_2 prompted change in surgery

11.3.3.2 Immediate Postoperative Clinical Variables Collected

Vasopressor use
Inotrope use
Urine output
Myocardial ischemia
Stroke or TIA
Hyperglycemia $AUC_{Glu} > 110$
Atrial fibrillation
Time spent in PACU/ICU
Amount of narcotic administered
Antiemetic medication administered
Total crystalloid administered
Total colloid administered
Temperature on arrival
Aldrete score (arrival, 30 & 60 min)
PONV Severity
Time to PACU d/c readiness
Time on mechanical ventilation

11.4 Protocol Assessments and Procedures – Postoperative Follow Up Period

11.4.1 General Description Postoperative Follow Up Period

During this period each subject will undergo repeat neuropsychological testing and a host of postoperative clinical variables will be collected prior to their discharge from the hospital. Additionally, this period includes a 4 week postoperative follow up telephone interview with each subject.

11.4.2 Postoperative Day 1 and 3 MMSE and CAM Assessments

The MMSE and the CAM assessment will be repeated on each subject on postoperative days 1 and 3.

11.4.3 Postoperative Clinical Variables Collected

11.4.3.1 Postoperative Clinical Variables Collected

ICU-LOS
Hospital-LOS
Atrial fibrillation
SNF or Rehab transfer on d/c

Time spent in SNF/Rehab
Need for hospital readmission
Change in baseline renal function
Return of bowel function time
Postoperative stroke or TIA
Postoperative myocardial ischemia
Postoperative RBC transfusion
Any postoperative infection
Postoperative composite endpoint

11.4.4 Postoperative 4 Week Telephone Interview

At 4 weeks (+/- 5 days) from the day of the surgical procedure a study team member will make a telephone call to the subject with the goal of assessing overall well being, if there was any need for hospital readmission or emergency ward visit, and if applicable how many days the subject remained in a skilled nursing facility or rehabilitation hospital.

12 TRIAL SAFETY

12.1 Expert Clinician Unbiased Trial Safety Assessment

This trial will not employ a data safety monitoring board as three clinical trials with a similar design, sicker patients and larger (n) values have been previously conducted using the same cerebral oximetry device without evidence of safety concerns. (Ref Casati, Murkin, Slater) Instead, there will be two planned interim assessments of the collected adverse event data that will be reviewed by a clinical expert in the care of thoracic surgical patients as well as in clinical trial design and execution. Professor Manuel L. Fontes, M.D. of the Department of Anesthesiology at Duke University School of Medicine will perform a review of collected adverse event data after enrollment of 25 subjects and 50 subjects. If Dr. Fontes has concerns additional analyses will be performed on the collected clinical data to determine in any real safety issues exist for the subjects participating in this trial. Dr. Fontes will provide a report to detail his conclusions and recommendations based upon the data he reviews. This data will be shared with the UHCMC IRB.

13 ADVERSE EVENTS

13.1 DEFINITIONS

13.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product or procedure and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal lab finding), symptom or disease temporarily associated with the use of a medicinal product or procedure, whether or not considered related to this treatment.

Planned hospital admissions and/or surgical operations for an illness or disease that existed before the drug or procedure was given to the subject or the subject was randomized in a clinical study are not to be considered AEs.

The severity of an AE and the relationship to study drug will be assessed by the investigator. The investigator will ensure that any patient experiencing an AE receives appropriate medical support until the event resolves.

13.1.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that:

- results in death,
- is life threatening, i.e., the subject was,, in the opinion of the investigator, at immediate risk of death from the event as it occurred (It does not include an event that, had it occurred in a more severe form, might have caused death),
- results in a persistent or significant disability/incapacity, is
- a congenital anomaly/birth defect, or
- is another medically significant event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

A distinction should be drawn between serious and severe AEs. Severity is an estimate or measure of the intensity of an AE, while the criteria for serious AEs are indications of adverse subject outcomes for regulatory reporting purposes. A severe AE need not necessarily be considered serious and a serious AE need not be considered severe.

13.2 PROCEDURES FOR ADVERSE EVENT RECORDING

An AE report will be created for each observed event and keep with the study records. Both co-PIs will review and sign all generated AE reports. At the time the AE is reported the causality relationship to the study procedures will be determined by the co-PIs. The AE reports will be reviewed by an external, unbiased expert at defined intervals as described in Section 12.1.

Additionally, all observed SAEs will prompt the creation of a report which will be handled in a similar manner to that described for any observed AE. All SAE reports will be completed within 24-48 hours of learning of their occurrence. The SAE reports will also be shared with the IRB once they are completed.

14 PROTOCOL DEVIATIONS

This trial will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well being of the subject requires immediate intervention, based on the judgment of the investigator. In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee will report the deviation to the UHCMC IRB in a timely manner (i.e. within approximately one business week from learning of the deviation). The UHCMC IRB will be informed of all protocol changes by the principle investigator in accordance with established procedure. No deviations of any type will be made without complying with all the UHCMC IRB established procedures.

15 STATISTICAL PLAN

All collected data in the case report form will be transferred into a customized electronic database upon completion of the study for the purpose of facilitating statistical analysis.

Preoperative demographics and clinical variables will be compared in the two groups to assess for significant differences using the independent t-test. Differences in the observed clinical data between groups will be determined with the Wilcoxon rank-sum test. Stepwise, forward, multivariable logistic regression analysis will be performed to assess for relationships between cerebral desaturations and any of the measured clinical variables with a p value < 0.05 being considered significant.

16 RECORDS RETENTION

Study records will be retained for a period of at least five years following completion of this clinical study and, if applicable for at least two years after a new indication application is submitted to the US FDA based on this data. All records will be kept in limited access areas of UHCMC in locked offices or will be transferred to secure file storage facilities. All electronic data will be kept on UHCMC password protected computer hard drives that are located in locked office space.

17 ETHICS AND RESPONSIBILITY

This study will be conducted in compliance with the protocol, with US FDA regulations, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, Declaration of Helsinki and with the UHCMC IRB procedures.

17.1 INFORMED CONSENT

Written informed consent will be obtained from all patients (or their guardian or legally authorized representative) before any study-related procedures (including any pre-treatment procedures) are performed. The investigator(s) has both the ethical and legal responsibility to ensure that each patient being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent form, which shall be approved by the

UHCMC IRB. Each informed consent shall include the elements required by FDA regulations in 21 CFR Part 50 and ICH, Part E6, Section 4.8.

Once the appropriate essential information has been provided to the patient and fully explained by the investigators (or qualified designee) and it is felt that the patient understands the implications of participating , the patient and the investigator (or designee) shall sign the IRB-approved written informed consent form. The patient shall be given a copy of the signed informed consent, a second copy will be placed in the subject's medical records, and the original shall be kept in the site's regulatory file or the patient's medical record.

17.2 INSTITUTIONAL REVIEW BOARD

This protocol and the written informed consent shall be submitted to the UHCMC IRB. Notification in writing of approval must come from the UHCMC IRB to the principal investigators as a letter. The investigator will submit continuing review reports to the UHCMC IRB when applicable per regulations. The UHCMC IRB will be notified in writing of the interruption or completion of the study by the principal investigator. The principal investigator will maintain accurate and complete set of all written correspondence to and received from the UHCMC IRB.

18 CONFIDENTIALITY

All information generated in this study will be considered highly confidential and will not be disclosed to any persons not directly concerned with the study without written prior permission. However, authorized regulatory officials will be allowed full access to the records. Only the subjects initials and a unique subject identification number that will be documented in the source records and the CRF will be used to identify patients as study subjects.

19 REFERENCES

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