GE Healthcare

Clinical Study Protocol:

Multi-site Anesthesia randomized controlled STudy of End tidal control (Et Control) compared to conventional anesthesia Results (MASTER-Anesthesia Trial)

(STUDY NO.123.07-2015-GES-0002)

Version: 6.0; 02/Nov/2016

Sponsor: General Electric Company, acting through its GE Healthcare Business
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Investigational Device/Product: Et Control feature of the Aisys CS² Anesthesia Machine **Modality:** Life Care Solutions (LCS) -- Anesthesia and Respiratory Care

FOR QUALIFIED INVESTIGATORS, STUDY STAFF, AND THEIR ETHICS COMMITTEE(S) ONLY

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The Sponsor, Statistician, and Investigator have approved this protocol version, and I confirm hereby to conduct the study according to the protocol and in accordance with applicable principles of the World Medical Association Declaration of Helsinki and Good Clinical Practice (GCP) guidelines as per ISO 14155:2011, any conditions of approval imposed by the reviewing EC or governing regulatory body, and applicable laws and regulations. The investigator should not deviate from this protocol except for emergency use. I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Principal Investigator at study site:

Investigator Signature

Date

Print Name

Site Name, Department, Address

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DOCUMENT AND VERSION CONTROL

This section records all changes made to the protocol for a specific study. In the table below, record each and every relevant change by indicating what changes were made.

Revision	Date *(DD/Mmm/YYYY)*	Revision Author	Comments/Changes
1.0	02/Jun/2016	Catherine Cadogan	Clinical Writer – Initial study protocol for the MASTER Pivotal Study.
2.0	15/Aug/2016	Catherine Cadogan	Clinical Writer – Protocol Amendment – See Appendix 5 for details of changes made.
3.0	15/Sep/2016	Catherine Cadogan	Clinical Writer – Protocol Amendment – See Appendix 6 for details of changes made.
4.0	22/Sep/2016	Catherine Cadogan	Clinical Writer – Protocol Amendment – See Appendix 7 for details of changes made.
5.0	21/Oct/2016	Catherine Cadogan	Clinical Writer – Protocol Amendment – See Appendix 8 for details of changes made as clarification/administrative change.
6.0	02/Nov/2016	Catherine Cadogan	Clinical Writer – Protocol Amendment – See Appendix 9 for details of changes made as clarification/administrative change.

LIST OF ABBREVIATIONS

%vol	Percent concentration in volume
AA	Anesthetic Agent
ABS	Advanced Breathing System
AE	Adverse Event
ADE	Adverse Device Effect
ALARP	As low as reasonably practicable
ASA	American Society of Anesthesiologists
BP	Blood pressure
BPM	Beats Per Minute
CAPM	Clinical Affairs Project Manager
CHF	Clinical History File (synonymous with e-Trial Master File)
CO_2	Carbon Dioxide
eCRF	Electronic Case Report Form
CRM	CARESCAPE™ Respiratory Module
CRNA	Clinical Register Nurse Anesthetist
DBP	Diastolic Blood Pressure
DCF	Data Clarification Form
Des	Desflurane
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
EMR	Electronic Medical Record
EtAA	End tidal Anesthetic concentration
$EtCO_2$	End tidal carbon dioxide concentration
EtO_2	End tidal oxygen concentration
FDA	Food and Drug Administration
FG	Fresh Gas
FGF	Fresh Gas Flow
FGFR	Fresh Gas Flow Rate
FGM	Fresh Gas Module
FiAA	Fractional inspired anesthetic agent concentration
FiO_2	Fractional inspired oxygen concentration
GEHC	General Electric Healthcare

GE-Lung	Gas Exchange lung simulator
HFA	High flow anesthesia
HR	Heart rate
ICF	Informed Consent Form
ICU	Intensive Care Unit
IRB	Institutional Review Board
Iso	Isoflurane
ITT	Intent-To-Treat
LCS	Life Care Solutions
LFA	Low flow anesthesia
LMA	Laryngeal Mask Airway
MAC	Minimum Alveolar Concentration
MRI	Magnetic Resonance Imaging
MV	Minute ventilation
MWS	GE MyWorkshop Internal Documentation System
N_2O	Nitrous Oxide
NIBP	Non-Invasive Blood Pressure
O_2	Oxygen
OR	Operating Room
PACU	Post Anesthesia Care Unit
PEEP	Positive End Expiratory Pressure
PI	Principal Investigator
PRT	Protocol
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SBP	Systolic Blood Pressure
Sev	Sevoflurane
SID	Subject Identification Designation
SpO_2	Peripheral Capillary Oxygen Saturation
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

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STUDY SYNOPSIS

Sponsor:	General Electric Company, acting through its GE Healthcare Business
Research Type:	This is a Clinical, single blind, randomized, prospective research study.
Regulatory Status:	This is a pre-market research study of the following devices/products: *Pre-market:* End tidal Control (Et Control) feature of the Aisys CS² Anesthesia Machine
Background and Rationale:	The Et Control option added to the Aisys CS² enables general inhalation anesthesia to be set according to the anesthesia clinician's prescribed end-tidal concentration values. In conventional practice, clinicians adjust the anesthetic agent delivery by altering the concentration setting of the vaporizer. Output of the anesthetic agent is delivered to the patient via a fresh gas line and a breathing system. The purpose of this pivotal study is to demonstrate that End tidal Control (Et Control) performance is non-inferior to conventional anesthesia practice in an adult surgery population by comparing the performance of the Et Control Arm (investigational arm) to the Control Arm (fresh gas mode).
Procedures/ Methods:	Eligible subjects will be randomized into either the "investigational Et Control Arm" (Et Control Arm) or "Control Arm." Randomization will be stratified based on Investigator, subject's pre-existing hypertension status, and subject's ASA status. Randomization sequences will be assigned using the IVRS or IWRS system. Subjects will be considered enrolled after providing written informed consent. In the Et Control Arm, the clinician will use the legally marketed Aisys CS² anesthesia machine with the Et Control option and fresh gas module (FGM). While in the Control Arm, the clinician will use the legally marketed Aisys CS² without the Et Control feature. On the basis of the clinician's judgment for the patient's well-being, the clinician will perform the adjustments to the anesthesia machine settings, discontinuation of the use of the Et Control option, and changes to treatment. In the Control Arm, the clinician will use their conventional means to adjust the vaporizer and mixer, and monitor the patient gas concentrations. On the basis of normal clinical practice, all dosage decisions will be made by the clinician. The Aisys CS² will collect electronic data during the anesthesia case. Heart rate, blood pressure and saturation pulse oxygen (SpO2) will be collected from the departmental electronic medical record. Concomitant medications, vasoactive medications, intravenous agents used to facilitate and prior to intubation, and assessment of adverse events will also be collected throughout the study.

Objectives:	*Primary:* The primary objective is to demonstrate that End tidal Control (Et Control) achieves and maintains the concentration of end tidal anesthesia agent (EtAA) and the concentration of end tidal oxygen (EtO_2) in a manner that is non-inferior to conventional anesthesia practice by a margin of 5% in an adult surgery population. *Secondary:* The secondary objectives are to: (1) To gather additional functional and safety data in clinical use of the investigational Et Control option. (2) To gather data on the amount of inhaled anesthetic agent and gas used in the Et Control Arm versus the Control Arm. (3) To obtain data on the number and frequency of user interactions with the Aisys CS² user interface in the Et Control Arm versus the Control Arm. (4) To collect time to discharge from the operating room (OR), which is measured from the time of end of surgery *(often defined as procedure end time, last stitch, or placement of last bandage)* to time of last breath.
Endpoints:	*Performance:* (1) Percent duration without large deviation of EtAA: Percent duration of EtAA concentration during steady state maintained within the acceptable limit, which is defined as the greater of 5% of the steady state inhaled anesthetic agent concentration and 0.6% v/v for Desflurane (Des), 0.2% v/v for Sevoflurane (Sev), or 0.1% v/v for Isoflurane (Iso). The percent duration is the weighted average of all steady states for a subject, using the duration of steady state as the weight. (2) Percent duration without large deviation of EtO_2: Percent duration of EtO_2 concentration during steady state maintained within the acceptable limit, which is defined as 5% v/v. This definition is similar to that of the EtAA, except that the acceptable limit is set as 5% v/v. *Efficacy:* a. Response time: time to reach 90% of the desired change in EtAA and EtO_2 steady state mean concentration b. Settling time: time to achieve the desired EtAA and EtO_2 steady state mean concentration c. Overshoot amount of the desired EtAA and EtO_2 from steady state mean concentration d. Accuracy of Et Control in maintaining EtAA and EtO_2 control between user set target and settling end tidal concentrations – For Et Control only. The accuracy measures include percent difference relative to the user set target and percent duration over the steady status with percent difference greater than 5%, 10%, ad 15% of the user set target. *Safety:*

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	a. Adverse events will be observed and recorded, the number of events will be counted, and comparison between groups will be performed.	
Hypothesis/Analysis	The hypotheses for the primary endpoints are: H0: $\mu_{et} - \mu_{con} < -5\%$ vs H1: $\mu_{et} - \mu_{con} \geq -5\%$ for both EtAA and EtO_2, where μ_{et} is the average percent duration of Et Control with EtAA and EtO_2 maintained within the acceptable range, and μ_{con} is the average percent duration of control device with EtAA and EtO_2 maintained within the acceptable range. Data collected will be presented using summary tables, data listings, and graphs. Study endpoints and parameters will be summarized using descriptive statistics. Descriptive statistics for continuous variables will include mean, standard deviation, median, Q1 and Q3, minimum, maximum, and sample size. For comparison between arms (or against null values), categorical variables will be tested using appropriate contingency table analyses, and continuous variables will be tested using Student's t- test or non-parametric methods. P-values will be presented to 3 decimal places, and p-values less than 0.001 will be presented as '<0.001.' No imputation will be performed for missing data. The analysis of the primary endpoints will consist of: • the analysis on ITT population based on the algorithm determined end-tidal concentration (scenario 1) and clinician's recorded set target end-tidal concentration (scenario 2); AND • patients of different ASA status.	
Eligibility criteria:	**Inclusion criteria:** (1) Male or female 18 years old or greater. (2) Scheduled to undergo general inhaled anesthesia that can be safely exposed to 100% oxygen for up to 2 minutes during general anesthesia. (3) Expected to have airway secured with laryngeal mask airway (LMA) or endotracheal tube. (4) Undergoing a surgical procedure that is anticipated by the investigator to take greater than or equal to 1 hour (operative time measured from induction to cessation of general inhalation anesthetic). (5) American Society of Anesthesiologists (ASA) status classification system I through III: a. ASA Physical Status 1 = a normal healthy patient	**Exclusion criteria:** (1) Have emergency medical condition requiring surgery. (2) Are female subjects, who are pregnant or lactating. (3) Any subject undergoing cardiac bypass surgery. (4) Any subject undergoing open chest surgery. ***NOTE:*** *Exclusions 1 and 2 is established for ethical reasons. Exclusion criteria 3 and 4 are to avoid long gaps of data collection and transitions on and off the anesthesia machine during surgical case. None of these exclusions are due to limitations of the device.*

	b. ASA Physical Status 2 = a patient with mild systemic disease c. ASA Physical Status 3 = a patient with severe systemic disease (6) Undergoing intravenous induction. (7) Ability to provide written informed consent. ***NOTE:*** *The inclusion criterion related to the length of the surgical procedure is not related to any clinical, medical, or safety risk. Length of use or procedure length is not clinically relevant to the use of the Et Control option or Aisys CS² anesthesia machine. This is solely to help ensure that sufficient amounts of data are collected related to the use of the Et Control option during the study to maximize the clinical value of each subject enrolled.*	
Sample size and Sites:	A total of 248 subjects will be enrolled in the study with approximately 124 subjects enrolled in each arm: Et Control Arm and Control Arm. A minimum of 15 subject cases is the target enrollment for each of the 3 anesthesia agents (Desflurane, Sevoflurane, and Isoflurane) per arm *(only one inhalation anesthetic agent may be used for each enrolled subject in the study arm).* The study will be conducted at 4 hospitals (investigational sites) located within the United States. Each investigational site is to enroll a minimum of 30 to a maximum of 80 subjects with approximately 1:1 ratio for subject in the Et Control Arm and Control Arm.	
Study duration:	The study is expected to last approximately 24 months.	

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ADMINISTRATIVE STRUCTURE OF INVESTIGATION

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1. BACKGROUND AND JUSTIFICATION

1.1 Background

1.1.1 Literature Review

The Et Control option added to the Aisys CS² enables general inhalation anesthesia to be set according to the anesthesia clinician's prescribed end-tidal concentration values. (Clinician is defined as specialty clinician trained in the administration of anesthesia care including anesthesiologist, residents, fellows, certified registered nurse anesthetist [CRNA], or certified anesthesia assistant.) This literature review describes current general anesthesia practice to set and maintain anesthesia gas concentrations, and the state and clinical experiences of target end-tidal anesthesia technologies.

1.1.2 Principles of Minimum Alveolar Concentration

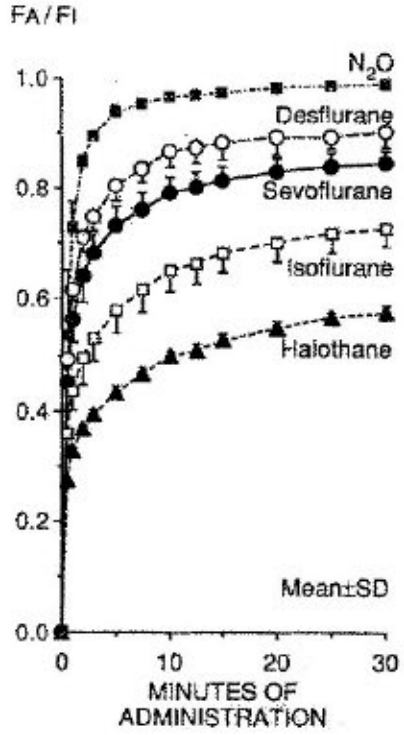


Figure 1-1: Yasuda [1] Anesthesia Analgesia 1991

Minimum Alveolar Concentration (MAC) is used to compare the potency of inhaled anesthetic vapors. [2] Inhaled anesthetic agents (isoflurane, [3] desflurane, [4] and sevoflurane [5]) are dosed according to MAC that is measured by the end-tidal concentrations.[1] In volunteer subjects ventilated in a non-rebreathing system, Yasuda [1] showed that after 30 minutes there remains

a difference between the alveolar and inspired anesthetic concentrations. The differences were illustrated by the FA/FI ratio of the alveolar (measured as the expired concentration) to the inspired concentrations of less than 1. For desflurane, sevoflurane and isoflurane these ratios were 0.91, 0.85, and 0.73. These differences are related to rate of patient uptake and distribution of anesthetic agent and its solubility.

1.1.3 Current Anesthesia Practice

In conventional anesthesia practice, clinicians adjust the anesthetic agent delivery by altering the concentration setting of the vaporizer. Output of the anesthetic agent is delivered to the patient via a fresh gas line and a breathing system. In high flow anesthesia (HFA) where the fresh gas flow (FGF) is above minute ventilation (typically 5 to 6 l/min for adults), the Aisys CS² breathing system operates similarly to a non-rebreathing system, see Figure 1-2. The fresh gas (from the mixer and vaporizer output) supplies all the inspired gases. As in Yasuda's [1] finding, a concentration difference can occur between the vaporizer output and the target expired anesthetic concentrations. To compensate this difference, the vaporizer setting must be adjusted to align the target and measured expired concentration for the desired dose concentration to be delivered to the patient.

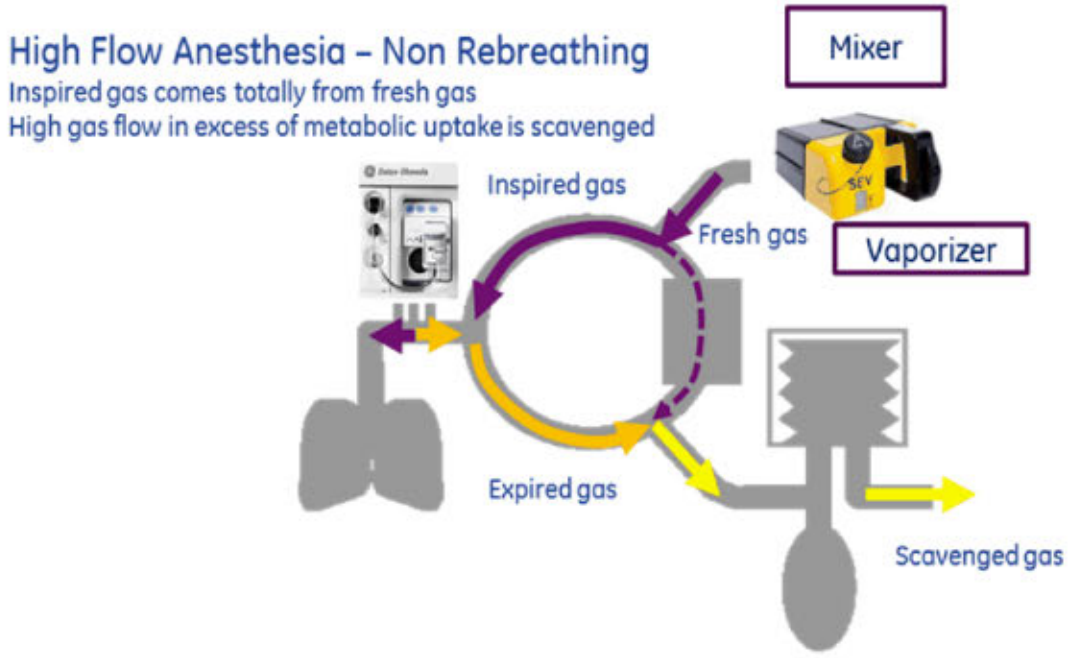


Figure 1-2: High Flow Anesthesia – Non-rebreathing

In low flow anesthesia (LFA) practice where the FGF is lower than the patient minute ventilation, expired patient gases are recirculated. After carbon dioxide is removed, these

recirculated gases combine with the fresh gas to form the patient inspired gases, see Figure 1-3. This recirculated patient gas mixes and dilutes the vaporizer anesthetic output concentration, and adds another layer of difference and uncertainty between the set vaporizer anesthetic output concentration and the MAC dosage prescribed for the patient. This decoupling increases as the fresh gas flow rate (FGFR) is decreased relative to the patient minute ventilation. More so than in HFA, the vaporizer setting must be adjusted frequently to align the measured end tidal anesthetic concentration to achieve the prescribed concentration dosage. At lower FGF and greater dilution by the recirculated gases, the challenge for the clinician is to achieve and maintain the patient's prescribed drug dosage.

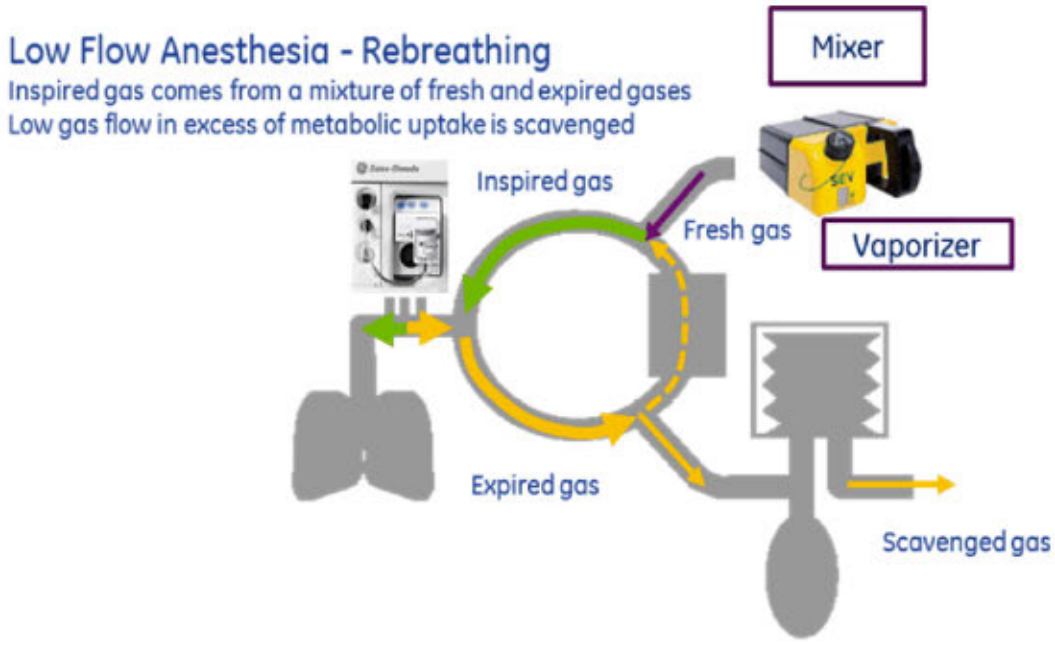


Figure 1-3: Low Flow Anesthesia – Rebreathing system

1.1.4 Approaches to End Tidal Concentration Measurement

Research devices that successfully delivered volatile anesthetics via end-tidal target anesthetic concentrations were reported as early as 1975. [6-12] Sieber et al. [12] reported in a study of 22 ASA I-III patients with elective surgery that end-tidal isoflurane concentrations can be executed more accurately and stably using an end-tidal targeted anesthesia system than conventional practice. Commercial (non-US) anesthesia machines with settable end-tidal agent targets were reviewed by Nathan et al, [13] Suzuki et al,[14] Lartat-Jacob et al,[15] and Struys et al [16] Lortat-Jacob et al[15] reported that clinicians successfully used settable target

anesthetic concentration to administer anesthesia with comparable duration of desired anesthesia responses as compared to setting gas mixer and vaporizer output directly. Furthermore, gas and vapor usage, and machine setting interactions were reduced.

	End Tidal Target setting	Conventional LFA 1 L/min
% duration Systolic BP 90; ref +15	89%	91%
% duration BIS [40 – 60]	82%	79%
Time to extubation (min)	5.2 +/- 2.8	6 +/- 3.0
Setting adjustments/hr	6.7 +/- 2.5	15.2 +/- 11.6

Lortat-Jacob et al[16] Anaesthesia. At 1 l/min FGFR clinicians used more than twice the number of machine interactions to set and maintain target concentrations for comparable responses.

In vitro comparison of an end-tidal target and a conventional anesthesia machine, Struys et al[16] concluded that a combination of the fastest time course and lowest consumption of sevoflurane and desflurane could be found using direct target of end-tidal anesthetic concentration.

1.1.5 Application of Et Control

The principle of Et Control technology is based upon well established and well published principles of anesthesia. The Et Control option allows clinicians to deliver inhaled anesthesia in a wide range of FGFR, from high to low levels. Early research and reviews of other non-US commercial anesthesia systems suggest that clinicians can successfully use end-tidal target gas concentrations to administer inhaled general anesthesia, and adjust according to individual patient response the prescribed end tidal dose concentration obtained in conventional practice by setting the mixer and vaporizer output. The technical task of the machines to achieve and maintain the prescribed target dose of end-tidal concentrations did not alter the clinician's control to manage the patient's anesthesia response. With target end-tidal concentration, the decision and control of the anesthesia treatment remains with the clinician.

1.2 Pre-Clinical (bench and animal) Trials and Previous Clinical (human) Experience

The investigational Et Control option was tested with the Gas Exchange Lung simulator (GE-Lung or GEL) that simulates selectable, wide, and repeatable range of lung mechanics and gas exchange (oxygen, nitrogen, carbon dioxide, nitrous oxide, anesthetic agent) behaviors of human breathing. The GE-Lung serves as a surrogate to test, refine and verify that the end-tidal target concentration algorithm performs according to the specified product requirements. These tests included measurements of step response and settling times, command overshoots, accuracy, and steady state deviations as described in IEC 60601-1-10. The final test results are documented in the GE document management system and project

files. These systematic simulator tests complement experiences in animal and human trials and help demonstrate that the Et Control option meets the specified requirements.

1.2.1 Pre-clinical Studies

Two animal studies were conducted at Kiel University in Germany during the final design and verification phase of the algorithm development. These studies tested the performance of the algorithm, usability of the system in various failure modes and misuse scenarios, and the overall function of the system during anesthesia. A survey/questionnaire captured the subjective experiences of the clinician.

The following is a summary of results:

(1) Preliminary animal trial – 2 pigs

While the algorithm met the specified performance requirements, issues related to the timing of the fresh gas sample check and transition to fall back or exit to conventional anesthesia modes were identified. Clinicians expressed concern with the visual clarity of the operational gas delivery mode. These issues were corrected prior to the final animal trial.

(2) Final animal trial - 5 pigs

In the final test, the Et Control option performed within the performance specifications. Anomalies discovered were tracked, reviewed, and corrected based on the risk management procedures for the Et Control option. The Et Control algorithm was further tuned to refine the performance response and further minimize oscillation and deviations from the set targets.

In the survey questionnaire regarding usability and subjective assessments, overall, the participants responded favorably to the Et Control option including the usability design, performance to achieve set targets, and management of various events tested. Participants commented that the Et Control option appeared to provide an improved workflow by helping with the stability of target agent concentrations, and reducing distractions during the case.

Experiences and improvement opportunities that originated from these animal trials were analyzed and necessary corrections were implemented prior to the human study (conducted outside of USA).

1.2.2 Human Studies (non-US)

Premarket (outside of USA) clinical investigations were performed at 2 European sites (Kiel University Hospital, Germany and University Hospital Helsinki, Finland) *[Clinical Investigational Plan entitled: "Aisys™ Carestation anesthesia machine (Aisys) Et Control Clinical Investigation using electronic control of fresh gas and agent provided by Aisys to achieve user set targets for end-tidal agent (EtAA) and oxygen (EtO_2), GE Healthcare/Datex-Ohmeda, Inc, 2009]*. These were

two separate studies with two separate reported results; however, a summary of the results was combined as follows. Inhalation anesthesia of 12 male and 28 female subjects was managed using the investigational Et Control option by 10 anesthesia clinicians. Summaries of the findings were:

- All clinicians were able to use Aisys with end tidal concentration targets to anesthetize all their subjects without unexpected clinician or Aisys initiated termination.
- During use, the vast majority (75%) of subject's blood pressure and heart rate were managed within 25% of the values at the start. In accordance with the protocol, the few exceptions were determined by the clinician not to be related to Et Control.
- During use, the vast majority (95%) of the subject's oxygen saturations were managed above 90%. In accordance with the protocol, the few exceptions were determined by the clinician not to be related to Et Control.

During the trial, the performance of the Et Control option response to clinician set target end tidal anesthetic and oxygen concentrations were within the product specifications. No unexpected subject adverse events were attributed to, or considered related to Et Control. The average measured performance and permissible specification limits are as follows:

Table 1-1 – Average Measured Performance and Permissible Specification Limits

Parameters	Average Measured		Permissible specification Limits
	Kiel	Helsinki	
EtAA Response (s)	78	59	< 240
EtAA Settling Time (s)	125	111	< 600
EtAA Overshoot (% of limit)	14	14	< (0.2 MAC, or 30% of setting)
EtAA Steady State Deviation (% of limit)	18	21	< | +/- 0.15 MAC |
EtO_2 Response (s)	142	138	< 600
EtO_2 Settling Time (s)	208	228	< 900
EtO_2 target overshoot (% of limit)	12	15	< (5% vol, or 20% of setting)
EtO_2 Steady State Deviation (% of limit)	29	24	< | +/- 3% vol, or 5% of setting |

At all times, the measured end tidal anesthetic concentrations did not exceed 4.8, and 14.4 % volume for sevoflurane and desflurane (or approximately 2.4 MAC), and the measured end tidal oxygen concentrations did not fall below the specified limit. The results of this study confirmed that the Et Control option met the performance and safety requirements of the study.

1.2.3 Human Studies – under U.S. FDA 21 CFR Part 812–Investigational Device Exemption (IDE)

A feasibility clinical study with human subjects was performed from 24/Feb/2014 to 30/Sep/2014 under the U.S. Food and Drug Administration (FDA) 21 Code of Federal Regulation (CFR) Part 812—Investigational Device Exemption (IDE) *(Study Title: Single Site, Randomized, Controlled Feasibility Study with and without Smartflow for Routine Anesthesia [Smartflow™ Feasibility], Study No. 123.01-2013-GES-0001, FDA IDE No. G120300)*. The purpose of this feasibility study was to collect and analyze safety and efficacy data on the investigational Et Control (formerly called as Smartflow) option to support the design of this pivotal clinical study. In this feasibility study, the Et Control option was used with the Aisys Anesthesia System, which was intended to provide general inhalation anesthesia and volume or pressure control ventilation support. There is no difference between Smartflow and Et Control (only a name change).

There were two arms in the study – Et Control (Smartflow) Arm (Aisys with Et Control) and the Control Arm (Aisys without Et Control). The study was conducted at University of Iowa Hospital and Clinics in Iowa City, Iowa, USA, and had a total of 28 evaluable subjects – 15 subjects in the Et Control Arm (6 females and 9 males) and 13 subjects in the Control Arm (9 females and 4 males). Results from the 28 evaluable subjects related to safety and efficacy were reported according to adverse events, Et Control performance, and comparison between the Et Control Arm and the Control Arm. Clinicians experiences in using the Et Control option were also reported.

There were no serious adverse events or deaths reported. Nine adverse events of hypotension were reported (6 were reported from the Et Control (Smartflow) Arm and 3 from the Control Arm). All events were anticipated and were considered hypotension. All events were determined by the clinician to likely not be related to the device or Et Control. All events were treated with medication, and resolved without sequalae.

Results showed evidence that Et Control (Smartflow) was able to successfully maintain and adjust settings in response to clinician selections, within a performance range equivalent to or potentially better than the Control Arm. Results also indicated that Et Control may reduce the duration of large deviations from the intended steady state settings.

The Et Control option performed as expected, delivering consistent and accurate EtAA and EtO_2 levels as set by the clinician. On average, the Et Control option exhibited a quicker response with a faster settling time while achieving a comparable overshoot amount. Additionally, the study showed that Et Control was able to maintain the desired steady state concentration better than seen in the Control Arm. The Et Control option exhibited a percent duration of large deviation of 3.9% ± 7.92 versus the Control result of 11.3% ± 18.02. Large deviation was defined as the difference between the measured end tidal concentration and the steady state concentration (target concentration) being the greater of 5% of the steady

state concentration or 0.1% v/v for Isoflurane, 0.2% v/v for Sevoflurane, and 0.6% v/v for Desflurane.

On the basis of the usability of Et Control, results showed that the number of setting interactions over the entire case between the Et Control Arm and the Control Arm was comparable; 26 ± 8.7 and 26 ± 12.6, respectively. The number of setting interactions made in the Et Control Arm was between 12 and 47; while, the number of setting interactions in the Control Arm was between 12 and 61. Overall, the user feedback collected in a questionnaire showed that the clinicians favored the Et Control option, because as a whole it was rated as being easier to use.

In summary, the feasibility study did not present any new evidence of risks or concerns related to the Et Control feature and provided additional indications that anesthesia cases with Et Control can be completed safely and successfully with at least equivalent performance.

1.2.4 Global non-US Post Market Experience

The optional Et Control feature was released for sale in Europe in 2010. Today, the Et Control feature is in use with the Aisys and Aisys CS² anesthesia systems. The Aisys CS² anesthesia system was released in 2013, and is the successor of the Aisys anesthesia system. There are no differences in the Et Control algorithm between the two systems. In addition to control via hard keys and a scroll wheel as in Aisys, the Aisys CS² added a touchscreen display.

Since the release of the Et Control option, more than 7758 Aisys or Aisys CS² systems have been upgraded or sold with the Et Control option for use in general inhalation anesthesia. It has been released for sale in approximately 100 countries, including Canada, UK, Netherlands, Sweden, Germany, Italy, France, Spain, and Australia.

GE Healthcare is not aware of any serious issues surrounding the feature, which continues to have a low complaint rate. With an estimate of more than 4 million cases since the commercial launch over the course of 6 years (assuming one Et Control case per day per machine for 250 OR [operating room] days per year), there has been only one reportable event involving the feature because of the clinician forgetting to set an EtAA concentration value. A user error such as this is inherent to any device, and could occur outside of Et Control as well.

1.3 Device Risk Analysis

In accordance with the GE Healthcare Risk Management procedure and ISO 14971:2012, a comprehensive risk assessment has been completed both for the cleared Aisys CS² 10.0 (K132530) as well as for the addition of the Et Control option (software and a gas multiplexing "Fresh Gas Module" (FGM) hardware) to Aisys CS². This Risk Assessment includes the

identification of risks and hazardous situations, the estimation and evaluation of risk, and the methods to control or mitigate the risks, along with the effectiveness of the risk controls.

1.3.1 Risks

For the Aisys CS² with 10.0 software, cleared under K132530 (without Et Control), following the completion of a comprehensive risk assessment and control analysis, the cross-functional team identified a total of 11 hazard categories and their potential hazard events and causes. These risks were mitigated or controlled to acceptable levels or to As Low As Reasonably Practicable (ALARP) in accordance with the procedure. This risk assessment was reviewed under K132530.

The Aisys CS² Anesthesia System with the Et Control option does not involve any new intended uses or clinical applications for the practice of anesthesia, or modifications to the practice of anesthesia. Analysis of incorporating the Et Control option resulted in the addition of several potential failure modes (causes of hazards) within 4 of the 11 hazard categories already identified for the cleared Aisys CS². While Et Control introduces some new potential causes of failures or hazards, the Et Control option does not introduce any new types of hazards or harms to the subject.

The Aisys CS² with the Et Control option continues to deliver anesthetics using the same agents/drugs, the same route of delivery (inhaled), the same vaporization, the same ventilation engine and breathing system, as well as the same modes and parameters of use, such as the mixer and vaporizer setting ranges. There is no change in what is delivered to the subject. The Et Control option does not provide dosing guidance, or alter the drug dosage as prescribed by the clinician trained in the administration of general anesthesia. The Et Control option is only helping to maintain the EtAA and EtO_2 concentrations that are selected by the clinician; therefore, no new types of hazards would be introduced.

The same hazards associated with potential over or under-delivery of anesthetic agent and oxygen are present both with Aisys CS² and Aisys CS² with Et Control. Similarly, inadequate fresh gas flow to replenish the gas volume in the bellows to deliver tidal breaths is also present in both the commercial Aisys CS² and Aisys CS² with Et Control. Environmental hazards such as fires at high oxygen concentrations or workplace anesthetic agent pollution also remain consistent.

While there are no new types of hazards or harms that are introduced to the subject, there are several additional failure modes or potential sources of the hazards that have been considered and appropriately mitigated in accordance with the GE Risk Management procedure. Some of the primary potential failure modes/causes of hazards related to Et Control include:

- Inaccurate end-tidal concentrations caused by an out of calibration respiratory gas monitor or inward ambient gas leak into the fresh gas sample line,

- Inaccurate end-tidal concentration caused by a leak in the patient gas sample line,
- Inaccurate end-tidal concentration caused by hardware failures,
- Unstable, biased, and oscillating end-tidal concentration,
- No patient breath detected due to a disconnected breathing hose or patient sample line.

The design mitigations in place that mitigate the potential hazard causes to acceptable levels or as low as reasonably practicable include:

- Pre-use Et Control system check
- Integrity (leak and obstruction) of sample and fresh gas line checks
- Periodic accuracy checks of the respiratory gas measurement with fresh gas module
- Supervisory software monitors the status of the anesthesia system for fault conditions, and the accuracy of the mixer, vaporizer and respiratory gas monitor.
- If issues are detected, the system triggers responses that include:
    a. For failure events that are not recoverable by the clinician or system configurations that are inappropriate for Et Control operation – Et Control notifies the user and exits to the conventional Aisys CS² fresh gas mode.
    b. For failure events that are recoverable by the clinician – Et Control notifies the clinician and maintains a steady state with the mixer O_2 and vaporizer output concentrations maintained at the targets previously set by the clinician. Normal Et Control operations resume when the fault condition is resolved.
- The clinician's ability to exit Et Control mode at any time and return to conventional Aisys CS² delivery modes

As described above, Et Control is an optional software/hardware feature that uses the same Aisys CS² hardware (mixers, vaporization, breathing system and ventilator) and the same range of gas and vaporizer output to deliver the same dose levels of anesthetic gas concentrations to the subjects as selected by the clinician in the conventional Aisys CS² fresh gas mode, and in accordance with the drug labeling. The Et Control option does not provide dosing guidance, or in any way alter the drug dosage as prescribed by the clinician. The Et Control option does not introduce any new types of hazards or harms to the subject.

With the mitigations in place, the use of Aisys CS² with Et Control is expected to provide an equivalent safety/risk profile and Et Control does not introduce significant additional hazards to the subject.

1.3.2 Potential Benefits

In addition to the equivalent level of risk anticipated, the use of the Et Control option has the potential to improve the clinical workflow for the clinician during a procedure and potentially present some additional safety mitigations.

Several potential benefits for the clinician and subject have been considered and are discussed below.

The Et Control option is designed to help simplify the workflow for the clinician during an anesthetic case. Et Control may help minimize the number and frequency of clinician interactions with the Aisys CS² user interface needed to target and maintain a desired anesthetic agent concentration and flow range for the subject. This can potentially allow the clinician to dedicate greater attention to the subject. During an anesthesia case, the clinician must monitor, manage, and control a multitude of complex parameters, constantly assessing the changing status of the patient and making adjustments to optimize care and maintain safety. This includes, among many things, analyzing and compensating for differences between the targeted and the delivered agent and oxygen concentrations. Et Control was designed with a thorough understanding of this complexity and the human factors involved. [18, 19]

Et Control allows the clinician to directly set the appropriate EtAA and EtO_2 for the subject based on his or her clinical judgment and the dosing detailed in the drug package insert. The drug labeling describes dosing guidance in terms of minimum alveolar concentration or MAC (based on EtAA), and Et Control was designed to further enhance the clinician's ability to directly target to the desired levels. With direct setting of end tidal targets and constant monitoring of the subject's end tidal levels, Et Control has the potential to improve the accuracy of, reduce deviation from, and responsiveness to achieve intended gas-mixture delivery to the subject, potentially reducing inadvertent over or under-shoot or setting errors. This can also help simplify the delivery and maintenance of desired concentrations throughout the broad range of total flows currently used in clinical practice, from 0.5 liters per minute (lpm) up to 6 lpm.

It is also possible that by streamlining the workflow and helping the clinician maintain the desired targeted levels of EtAA and EtO_2 at their chosen flow ranges, the clinician may reduce the amount of excess agent that is expelled into the environment (not used by the subject). This may help reduce the impact of excess emissions on the environment. [19]

By setting a minimum floor on the EtO_2 setting, Et Control is also designed to help prevent delivery of gas mixtures that could result in an end-tidal oxygen concentration less than 25%; thus, providing a secondary hypoxic mixture guard of the Et O_2 in addition to the standard primary fresh gas hypoxic mixture guard that prevents fresh gas mixtures from dropping below 21% O_2.

1.3.3 Conclusion

In summary, the Aisys CS² with Et Control presents an equivalent risk profile to the currently marketed Aisys CS² device, with several potential benefits in terms of workflow and human factors design, and additional safety mitigations. The risk/benefit assessment for this feature has resulted in the determination that the potential benefits outweigh the risks.

2. RESEARCH DEVICE

2.1 Identification and Description of Research Device

The proposed research study will be of the investigational Et Control option. This feature will be added to a legally marketed device, the Aisys CS² anesthesia machine [K132530].

2.1.1 Description of GE Datex-Ohmeda Aisys CS² Anesthesia System – legally marketed device:

The Aisys CS² anesthesia system is scalable, flexible, and functionally integrated featuring GE's advanced design, ventilation, respiratory monitoring, and breathing system. Module bays allow for the physical integration of legacy Datex-Ohmeda patient monitors and supports mounting of other GE Healthcare monitors. Optionally, the open architecture design supports mounting of non-Datex-Ohmeda patient monitors, record keeping, and connections to the hospital information system. The INview movable display arm helps keep the anesthetist's focus on the patient by offering control of gas delivery, anesthetic agent, and ventilation parameters.

This anesthesia system is designed for mixing and delivering inhalation anesthetics, Air, O_2, and N_2O.

This anesthesia system uses SmartVent ventilation technology offering Volume Control Ventilation with a tidal volume compensation and electronic PEEP. [redacted]

The GE Datex-Ohmeda Aisys CS² Anesthesia System, cleared under K132530, is intended to provide general inhalation anesthesia and ventilatory support to a wide range of patients (neonatal, pediatric, and adult). The device is intended for volume or pressure control ventilation. The Aisys CS² is not suitable for use in a magnetic resonance imaging (MRI) environment. It is to be used only by medical professionals who are trained and qualified in the administration of general anesthesia.

Although the GE Datex-Ohmeda Aisys CS² Anesthesia System has been cleared under K132530, this device becomes investigational when used in this study because of the investigational Et Control Option.

The version of Aisys CS² software that will be used in the study is Software Revision 10.X.

The GE Datex-Ohmeda Aisys CS² Anesthesia System is the modified version of the GE Datex-Ohmeda Aisys Anesthesia System cleared under K110213. The modified version uses the

touch screen technology, new software, new name, and was deemed substantially equivalent to the legally marketed predicate device by the Food and Drug Administration, and the device.

2.1.2 Description of the Investigational Et Control Option:

The investigational Et Control feature is an optional gas delivery mode. The Et Control option allows the clinician to set the target end tidal O_2 (EtO_2) and target end tidal anesthetic agent (EtAA) values based on his or her clinical judgment, the patient's physiological response, and the appropriate drug labeling identical to conventional practice. The system monitors the EtO_2 and EtAA measured values and adjusts the gas composition and total flow to maintain the target concentrations that the clinician has set (dose). The Et Control feature does not provide dosing guidance, or alter the set dose that is prescribed and entered by the clinician.

A patient airway (for example, endotracheal tube or laryngeal mask airway) must be in place and sealed while using Et Control mode. Et Control mode cannot be used with a mask or nasal airway.

The system must have a supply of oxygen and balance gas to enter Et Control mode. Et Control cannot be used with halothane, enflurane, non-circle circuit, and during cardiac bypass, Alternate O_2, or Air only modes. It is recommended that Et Control mode not be used during cases that have disturbances to the lungs such as during open chest surgery.

Et Control consists of hardware and software. The hardware required to enable the Et Control software is a gas multiplexing "Fresh Gas Module" (FGM) [redacted]

[redacted]

Et Control, when enabled, projects information onto several areas of the user interface including the waveform, quick keys, split screens, and trends menu. When not enabled, this information is absent and not visible to the user.

The Et Control software algorithm is a workflow simplification tool that allows the user to adjust the Aisys CS² vaporizer and gas mixer settings by inputting the desired EtAA and EtO_2 based on his or her clinical judgment, the patient's physiological response, and in accordance

with drug dosing detailed within the drug package insert. During anesthesia, the users can switch between Et Control and operate in the conventional Fresh Gas mode to input the mixer and vaporizer settings at any time. As such, enabling the Et Control option will not limit the ability to perform anesthesia conventionally with the Aisys CS².

The Et Control software algorithm follows these steps:

1. The clinician prescribes and sets the dose target EtAA and EtO_2 values for the patient based on his or her clinical judgment, the patient's physiological response, and drug dosing detailed within the drug package insert.
2. The respiratory gas monitor measures current EtAA and EtO_2 values at every breath.
3. Et Control compares the measured (current) values to the target values set by the clinician.
4. Et Control adjusts the mixer and vaporizer output accordingly to help achieve and maintain the target concentrations set by the clinician.
5. Every 3 minutes, the system samples the fresh gas as a safety check.

During operation, the Et Control software algorithm performs a vital safety check by periodically (every 3 minutes) [redacted].

The Et Control feature is indicated for adult patients, 18 years of age and older. For use of the optional Et Control feature, the patient's nominal measured breath rate must be between 8 and 35 breaths/minute and the patient must be able to safely be exposed to 100% oxygen for up to 2 minutes. The optional Et Control feature is only available using Isoflurane, Desflurane, and Sevoflurane. Et Control can be used with Air or N_2O as balance gases. Et Control cannot be used during a switch in inhaled agents. In these situations, the clinician is forced out of Et Control during the agent switch over period and is not allowed back into Et control until the previous drug concentration is less than 0.25 minimum alveolar concentration (MAC)[1] (approximately 1.5 %v/v Desflurane, 0.53 %v/v Sevoflurane, or 0.29 %v/v Isoflurane) and is therefore washed out of the system.

2.1.3 Additional Information Regarding the Investigational Device

2.1.3.1 Manufacturer:

Datex-Ohmeda Inc.

[1] Agent specific %v/v values representing 1 MAC are based on the agent specific product labeling for the following representative age groups: Desflurane 6.0 %v/v age 45, Sevoflurane 2.1 %v/v age 40, Isoflurane 1.15 %v/v age 44 +/- 7.

2.1.3.2 Legally marketed device:

- Software version: 10.X
- Datex-Ohmeda respiratory gas module: M-CAIOVX, M-CAIOV, M-CAIO, E-CAIOVX, E-CAIOV, or E-CAIO

2.1.3.3 Investigational device:

- Model: Aisys CS²
- Software version: 10.X with Et Control Option;
- With Fresh Gas Module (FGM) hardware

2.1.4 Traceability of the Investigational Device:

Each investigational Et Control option kit (including installation instructions, user reference manual, and hardware) is serialized.

In addition, unique serialized investigation warning labels will be affixed to the Aisys CS² each time the investigational Et Control option is enabled for the study subject and removed when the Et Control option is disabled. These activities along with the serialized investigation warning labels and the serial number of the legally marketed Aisys CS² will be recorded along with the subject ID in the Device Accountability Checklist/Log.

2.1.5 Intended Use of the Marketed Aisys CS² Device:

The GE Datex-Ohmeda Aisys CS² Anesthesia System is intended to provide general inhalation anesthesia and ventilatory support to a wide range of patients (neonatal, pediatric, and adult). The device is intended for volume or pressure control ventilation. The Aisys CS² is not suitable for use in an MRI environment.

2.1.6 Indications for Use of the Investigational Device:

The investigational Et Control option is designed to support clinicians in maintaining the targeted end tidal oxygen and end tidal anesthetic agent concentrations that the clinician sets during an anesthetic procedure by making multiple, limited adjustments to the fresh gas composition and total flow. The Et Control option is indicated for adult patients, 18 years of age and older.

2.1.7 Description of Materials that May Come into Contact with Tissues or Body Fluids:

The investigational Et Control option consists of a fresh gas module (FGM) inserted onto the Aisys CS², to periodically multiplex the fresh gases to the gases being sampled by the respiratory gas monitor. Gases sampled by the respiratory gas monitor are evacuated. The FGM modules for the investigational Et Control option does not contact the patient, tissues or body fluid as sample gas is not returned to the breathing system. No new materials are

introduced that are in contact with the patient. The gas pathway materials of the Aisys CS² device remain unchanged as cleared in K132530.

2.1.8 Summary of Training and Experience Required to Operate the Investigational Device:

Clinicians that participate in the clinical trial have proficiency in the delivery of general anesthesia and prior operational experience with the legally marketed Aisys or Aisys CS². The description of the legally marketed device is found in the Aisys CS² User's Reference Manual Software Revision 10.X, #2067226-001. The URM will be provided to all clinicians who participate in the trial.

Training in the use of the Et Control option is described in Section 7.2, Training Plan for Research Device. Et Control instructions for use are included in Aisys CS² Et Control Option Addendum Software Revision 10.X URM #2070086-001 that has been revised to include the Investigational User label on each page. This document will be provided to all clinicians involved in the study.

2.1.9 Device Import/Export Requirements:

No investigational devices will be imported into the US or exported out of the US. All research sites will be located in the US.

2.2 Regulatory Status

The Aisys CS² anesthesia device, upon which the investigational Et Control option will operate, is a legally marketed device under K132530.

The Datex-Ohmeda respiratory gas modules (M-CAIOVX, M-CAIOV, M-CAIO, E-CAIOVX, E-CAIOV or E-CAIO) are legally marketed devices under K001814, K051092. The Fresh Gas Module (FGM) hardware is investigational.

The investigational Et Control option is pre-market with an Investigational Device Exemption (IDE) required for clinical trials in the US.

2.3 Risk Category/Rationale

The investigational Et Control option is an optional feature of a life support system and is therefore a significant risk device.

2.4 Device Classification and Rationale

The legally marketed Aisys CS² anesthesia machine is an anesthesia system classified as a Class II medical device in 21 CFR 868.5160. The product code is BSZ.

Aisys CS², with the investigational Et Control option, remains a Class II medical device with the same classification.

The legally marketed Datex-Ohmeda respiratory gas modules (M-CAIOVX, M-CAIOV, M-CAIO, E-CAIOVX, E-CAIOV or E-CAIO) are classified as Class II gas analyzers under 21 CFR 868.1400 or 868.1720 with primary product codes of CCK or CCL respectively.

2.5 Device/Product Issuance and Replacement

2.5.1 Device Issuance and Replacement – Site -Owned Equipment

For an enrolled subject in the Et Control Arm, the Et Control software feature will be activated by a trained site technician, the Fresh Gas Module will be attached, and Et Control investigational labeling will be attached. When these actions are completed, the site's Aisys CS² is classified as an investigational device, and may not be used on a subject, who is not enrolled in the clinical trial.

Upon completion of anesthesia case in the Et Control Arm, the trained site technician will deactivate the Et Control feature, uninstall the hardware, verify that the Aisys CS² is reversed to its cleared device state, and finally remove and affix the investigational labels onto the Device Accountability Checklist/Log. These actions confirm that the site's Aisys CS² is no longer an investigational device; and may be used for a clinical patient, who is not enrolled in the research study.

For an enrolled subject in the Control Arm, the Et Control option will not be activated; the anesthesia case is conducted using a site Aisys CS² device cleared to be used for a clinical patient.

Upon completion of each research subject's surgery, a trained site technician will retrieve the electronic Aisys CS² data log.

It is anticipated that the transition from a non-investigational device to an investigational device and back again to a non-investigational device will take place more than once each day during the enrollment period. Tracking of these transitions and documenting the correct configuration for each research subject will be the responsibility of investigator or designee. The investigational device accountability checklist/log, which will be maintained by the investigator or designee, will provide a duplicate tracking mechanism to ensure accuracy and control of the use of the investigational device.

2.5.2 Maintenance and Storage

The investigational devices shall be clearly labeled per 21CFR 812.5: ***CAUTION-Investigational device. Limited by Federal law to investigational use.*** The investigational Et Control option, consisting of the FGM, will be located in a secured location at the investigational site under the supervision of the Principal Investigator.

The Sponsor may provide the Aisys CS2 device(s) to the participating investigational site for use in this clinical study, if not available. The site-owned Aisys CS² may be provided with airway gas module, if not available.

2.6 Disposition of the Device (including software version) and related materials (e.g. accessories, supplies, consumables)

The investigational Et Control option, consisting of the FGM, will be removed and returned to the Sponsor upon completion of the study. The legally marketed device, Aisys CS² anesthesia machine, which is owned by the investigational site, will remain as property of the site. If the site is provided an Aisys CS² anesthesia machine it may be returned to the Sponsor upon completion of the study.

3. OBJECTIVES OF RESEARCH STUDY

3.1 Purpose of the Study

The purpose of this pivotal study is to:

(1) demonstrate that End tidal Control (Et Control) performance is non-inferior to conventional anesthesia practice in an adult surgery population, AND
(2) support a marketing application in the U.S. for clearance of this feature.

3.2 General Design of Study (Descriptive Hypothesis)

This clinical study has been designed to compare the performance of the Et Control Arm (investigational arm) to the Control Arm (fresh gas mode). This is to demonstrate that the performance of the Et Control is non-inferior to the conventional anesthesia practice in an adult surgical population. A total of 248 subjects scheduled to undergo general anesthesia will be enrolled in the study. Subjects will be randomized to either the Et Control Arm or the Control Arm at a 1:1 ratio. Stratified randomization will be used based on Investigator, subject's pre-existing hypertension status, and subject's ASA status.

3.3 Study Objectives

3.3.1 Primary Objective:

The primary objective is to demonstrate that End-tidal Control (Et Control) achieves and maintains the concentration of end-tidal anesthesia agent (EtAA) and the concentration of end-tidal oxygen (EtO_2) in a manner that is non-inferior to conventional anesthesia practice by a margin of 5% in an adult surgery population.

The hypotheses for the primary endpoints are:

$H0: \mu_{et} - \mu_{con} < -5\%$ vs $H1: \mu_{et} - \mu_{con} \geq -5\%$

for both EtAA and EtO_2, where μ_{et} is the average percent duration of Et Control with EtAA and EtO_2 maintained within the acceptable range, and μ_{con} is the average percent duration of control device with EtAA and EtO_2 maintained within the acceptable range.

3.3.2 Secondary Objective:

The secondary objectives are to:

(1) gather additional functional and safety data in clinical use of the investigational Et Control option.

(2) gather data on the amount of inhaled anesthetic agent and gas used in the Et Control Arm versus the Control Arm.

The hypothesis for the anesthetic agent usage is:

$$H0: \mu et - \mu con = 0 \text{ vs } H1: \mu et - \mu con \neq 0$$

where μ_{et} is the average normalized anesthetic agent usage of the Et Control arm, and μ_{con} is the average normalized anesthetic agent usage of the control arm.

(3) obtain data on the number and frequency of user interactions with the Aisys CS² user interface in the Et Control Arm versus the Control Arm.

The hypothesis for the user setting interaction for the duration from induction to the end of anesthesia is:

$$H0: \mu et = \mu con \text{ vs } H1: \mu et \neq \mu con$$

where μ_{et} is the median of user setting interaction of the Et Control arm, and μ_{con} is the median of user setting interaction of the control arm.

(4) collect time to discharge from the operating room (OR), which is measured from the time of end of surgery *(often defined as procedure end time, last stitch, or placement of last bandage)* to time of last breath.

3.4 Study Endpoints

3.4.1 Primary Endpoint:

(1) Percent duration without large deviation of EtAA:

Percent duration of EtAA concentration during steady state maintained within the acceptable limit, which is defined as the greater of 5% of the steady state inhaled anesthetic agent concentration and 0.6% v/v for Desflurane (Des), 0.2% v/v for Sevoflurane (Sev), or 0.1% v/v for Isoflurane (Iso). The percent duration is the weighted average of all steady states for a subject, using the duration of steady state as the weight. It is expressed as:

$$PercentDuration = \frac{\sum_i \sum_j t_{ij} I_{ij}}{\sum_j T_j} \times 100\%$$ where t_{ij} is the i^{th} duration of EtAA concentration maintained within the acceptable limit during the j^{th} steady state, and T_j is the total duration of the j^{th} steady state. I_{ij} is an indicator for whether EtAA is maintained within the acceptable limit of i^{th} duration in j^{th} steady state, which is

$$I = \begin{cases} 1 & \begin{array}{l} if \quad Desflurane \quad and \quad \Delta EtAA \le \max(0.6\%, \ 5\% X \ steady \ state \ EtAA) \\ if \quad Sevoflurane \quad and \quad \Delta EtAA \le \max(0.2\%, \ 5\% X \ steady \ state \ EtAA) \\ if \quad Isoflurane \quad and \quad \Delta EtAA \le \max(0.1\%, \ 5\% X \ steady \ state \ EtAA) \end{array} \\ 0 & otherwise \end{cases}$$

ΔEtAA is the absolute difference between measured EtAA concentrations and steady state EtAA concentration.

(2) Percent duration without large deviation of EtO_2:

Percent duration of EtO_2 concentration during steady state maintained within the acceptable limit, which is defined as 5% v/v. This definition is similar to that of the EtAA, except that the acceptable limit is set as 5% v/v.

NOTE: *The steady state concentration is based on extraction algorithm for both Et Control and Control arms as well as based on the clinician's recorded target values for the Control Arm and the set target values for the Et Control Arm.*

These two primary endpoints, along with the secondary efficacy endpoints (response time, setting time, overshoot amount), are chosen to assess the capability of Et Control in achieving and maintaining the end tidal concentration of anesthetic agent and oxygen.

This study is designed to demonstrate that Et Control is non-inferior to the control device in maintaining end tidal anesthetic agent (EtAA) and end tidal oxygen (EtO_2) concentrations by a margin of 5%.

The hypotheses for the primary endpoints are:

H0: $\mu_{et} - \mu_{con} < -5\%$ vs H1: $\mu_{et} - \mu_{con} \ge -5\%$

for both EtAA and EtO_2, where μ_{et} is the average percent duration of Et Control with EtAA and EtO_2 maintained within the acceptable range, and μ_{con} is the average percent duration of control device with EtAA and EtO_2 maintained within the acceptable range.

3.4.2 Secondary Endpoint:

(1) Efficacy

a. Response time: time to reach 90% of the desired change in EtAA and EtO_2 steady state mean concentration

b. Settling time: time to achieve the desired EtAA and EtO_2 steady state mean concentration
c. Overshoot amount of the desired EtAA and EtO_2 from steady state mean concentration
d. Accuracy of Et Control in maintaining EtAA and EtO_2 control between user set target and steady state end tidal concentrations – For Et Control only. The accuracy measures include percent difference relative to the user set target and percent duration over the steady status with percent difference greater than 5%, 10%, and 15% of the user set target.

NOTE: *The response time, settling time, and overshoot amount data extraction will be done in two scenarios: 1) using the algorithmic determination of desired end-tidal concentration of anesthetic agent and oxygen for both arms (see Appendix 2), and 2) using the clinicians recorded target values of anesthetic agent and oxygen for the Control Arm and using the set target values for the Et Control arm.*

(2) Safety
a. Adverse events (see definition under Section 10.2—Adverse Event Definitions) will be observed and recorded, the number of events will be counted, and comparison between groups will be performed.

3.4.3 Other Endpoints:

(1) Usage of inhaled anesthetic agent;
(2) Number of user interactions; AND
(3) Time to discharge from the operating room (OR) (measured from the end of surgery *[often defined as the procedure end time, last stitch, or placement of last bandage]* to time of last breath).

4. DESIGN OF RESEARCH STUDY

4.1 Type of Research Study

This is a prospective, multi-site, single-blind, randomized, controlled clinical study of the investigational Et Control feature of the Aisys CS² Anesthesia Machine.

4.2 Controls and Minimization of Bias

All reasonable attempts will be made to control and minimize bias during this study, including the following:

- Consecutive enrollment of subjects will be employed to limit selection bias.

- Subjects will be randomized in a single-blind method to either the Et Control Arm or the Control Arm.
- Subjects will be blinded to their assignment; however, given the nature of the use of the investigational Et Control option during a case, the clinicians and Investigators cannot be blinded to the subject groups.
- Quotas or stratification criteria will be employed to ensure equitable distributions of patients and thus reduce spectrum bias.
- Multiple sites will be used to provide a broader cross-section of the population of patients and clinical practices, and thus reduce spectrum bias

5. STUDY SUBJECTS

5.1 Number of Subjects

A total of 248 Subjects will be enrolled in the study, with approximately 124 subjects enrolled in each arm: Et Control Arm and Control Arm. A minimum of 15 subject cases is the target enrollment for each of the 3 anesthesia agents (Desflurane, Sevoflurane, and Isoflurane) per arm *(only one inhalation anesthetic agent may be used for each enrolled subject in the study arm).*

The study will be conducted at 4 hospitals (investigational sites) located within the United States. Each investigational site is to enroll a minimum of 30 to a maximum of 80 subjects with approximately 1:1 ratio for subject in the Et Control Arm and Control Arm.

Each Investigator will be performing a minimum of five (5) cases for each arm (Et Control and Control). In situations where the Investigator is unable to complete a minimum of 5 cases in each arm, a Sponsor exception may be obtained. Subjects will be randomized to the Et Control Arm or the Control Arm, and randomization will be stratified based on Investigator, subject's pre-existing hypertension status, and subject's ASA status.

5.2 Subject Population

Adult male and female subjects, 18 years or older, who are scheduled to undergo general inhaled anesthesia will be invited to voluntarily participate in this study.

5.3 Protection of Vulnerable Subjects

This study does not examine any groups of subjects that are considered to be vulnerable subjects; i.e. pregnant women/fetuses, neonates, children or minor subjects, employees/faculty, cognitively impaired, and prisoners.

5.4 Inclusion Criteria

Subjects, who meet all of the following inclusion criteria, may be included:

2. Male or female 18 years old or greater
3. Scheduled to undergo general inhaled anesthesia that can be safely exposed to 100% oxygen for up to 2 minutes during general anesthesia
4. Expected to have airway secured with laryngeal mask airway (LMA) or endotracheal tube
5. Undergoing a surgical procedure that is anticipated by the investigator to take greater than or equal to 1 hour (operative time measured from induction to cessation of general inhalation anesthetic)
6. Meets one of the American Society of Anesthesiologists (ASA) status classification system I through III:
    a. ASA Physical Status 1 = a normal healthy patient
    b. ASA Physical Status 2 = a patient with mild systemic disease
    c. ASA Physical Status 3 = a patient with severe systemic disease
7. Undergoing intravenous induction
8. Able to provide written informed consent

NOTE: *The inclusion criterion related to the length of the surgical procedure is not related to any clinical, medical, or safety risk. Length of use or procedure length is not clinically relevant to the use of the Et Control option or Aisys CS² anesthesia machine. This is solely to help ensure that sufficient amounts of data are collected related to the use of the Et Control option during the study to maximize the clinical value of each subject enrolled.*

5.5 Exclusion Criteria

Subjects, who meet any of the following exclusion criteria, will be excluded:

1. Have emergency medical condition requiring surgery
2. Are female subjects, who are pregnant or lactating
3. Any subject undergoing cardiac bypass surgery
4. Any subject undergoing open chest surgery

NOTE: *Exclusions 1 and 2 is established for ethical reasons. Exclusion criteria 3 and 4 are is to avoid long gaps of data collection and transitions on and off the anesthesia machine during surgical case. None of these exclusions are due to limitations of the device.*

5.6 Screening and Recruiting Subjects for Enrollment

Enrollment in the study will begin after the IDE has been approved by the FDA and the investigational site identified has received Institutional Review Board (IRB) approval.

5.6.1 Recruitment/Consent Process

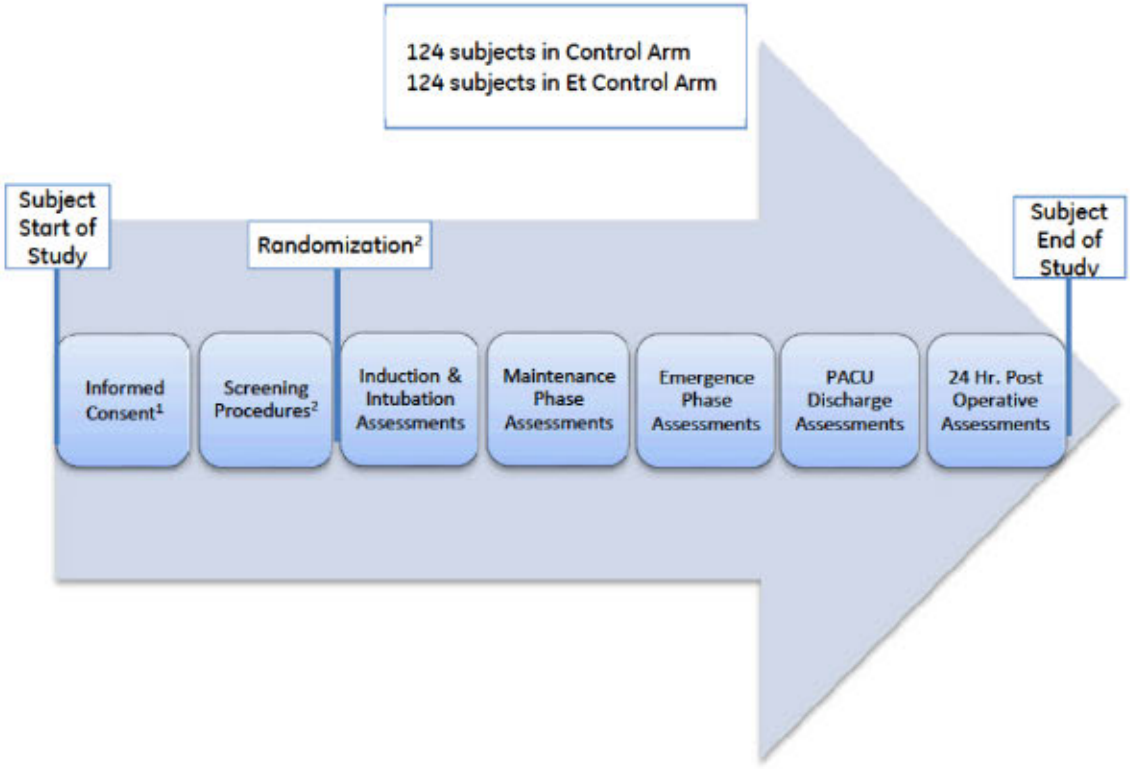
Subjects will be recruited for potential enrollment in this study according to the standard procedures of the investigational site, unless otherwise specified by the Sponsor in this study protocol. Subjects will be asked to volunteer to participate in this research study.

The subject or authorized representative will be informed of the requirements of the study as well as the potential risks and benefits. They will be required to read and indicate understanding of the IRB and Sponsor-approved Informed Consent document/HIPAA Authorization. The subject will be given the opportunity to ask questions. Upon provision of written informed consent, screening procedures begin, and subject is randomized into the study.

Following enrollment, a subject will be considered enrolled (the point of enrollment) once he/she signs and dates the informed consent form (ICF). Once enrolled, the subject will be assigned a unique subject number, which will not contain information that could identify the subject (such as subject name or date of birth). The unique subject number will be used to label electronic case report forms (eCRFs) data as well as data collected in by the Aisys CS2 for the subject throughout his/her participation in the study.

5.6.2 Screening

Figure 5-1 – Diagram of Study Procedures



Notes:
1. Subject is considered enrolled once written informed consent has been obtained. Screening procedures begins once informed consent has been obtained.
2. Screening procedures and randomization must occur within 24 hours prior to Induction and Intubation.

Upon provision of written informed consent, subjects will be screened for enrollment in this study against the inclusion and exclusion criteria; according to the standard procedures of the investigational site, unless otherwise specified by the Sponsor in this study protocol. Screening procedures and randomization must occur within 24 hours prior to induction and intubation.

6. PROCEDURES FOR RESEARCH STUDY

6.1 Randomization and Enrollment

Subjects will be randomized at a ratio of 1:1 to either the "Investigational Et Control Arm" or the "Control Arm." Stratified randomization will be used based on Investigator, subject's pre-existing hypertension status, and subject's ASA status. Randomization sequences will be

assigned through the IVRS/IWRS system. Subjects will be considered enrolled after providing written informed consent.

The following devices will be employed for each arm of the study:

- **Investigational Et Control Arm:** legally marketed Aisys CS² anesthesia machine with investigational Et Control option
- **Control Arm:** legally marketed Aisys CS² anesthesia machine without the investigational Et Control option

6.1.1 Investigational Et Control Arm

The subjects assigned to this group are induced and their airway secured based on each investigator's conventional intravenous induction and intubation practice. Machine log data are collected when the investigator initiates the start of anesthesia case on the Aisys CS².

The investigator will initiate Et Control after the airway is secured (intubation) and mechanical ventilation is initiated. Machine log data is collected when the investigator initiates the start of anesthesia case on the Aisys CS². Adjustments to the anesthesia machine settings, discontinuation of use of the investigational Et Control option, and changes to treatment are based upon clinician judgment for the wellbeing of the subject. This protocol does not in any way instruct the clinician to make any dosage changes or adjustments for study purposes. All dosage decisions are based on their normal clinical practice.

Aisys CS² machine log data collection will end when an "end case" is confirmed on the Aisys CS² at the end of the anesthesia case. Evaluable Aisys CS² data ends when the patient is finally disconnected from the Aisys CS² breathing system.

The clinician must continuously monitor measured inspired and end tidal oxygen and anesthetic concentrations to assess individual responses and compare to the target concentrations.

The clinician must maintain adequate ventilation to deliver appropriate oxygen and anesthetic agent to the patient. Et Control does not adjust ventilator parameters.

6.1.2 Control Arm

The subjects assigned to this group are induced and their airway secured based on each investigator's conventional intravenous induction and intubation practice. Machine log data is collected when the investigator initiates the start of anesthesia case on the Aisys CS².

The investigator will use their conventional means to adjust the vaporizer and mixer, and monitor the patient gas concentrations with the legally marketed Aisys CS² anesthesia machine without the investigational Et Control feature. Machine log data collection will end, when an "end case" is confirmed on the Aisys CS² at the end of the anesthesia case.

Evaluable data ends, when the patient is finally disconnected from the Aisys CS² breathing system.

6.2 Study Procedures

6.2.1 Induction and Intubation Phase

For purposes of this study, induction/intubation phase starts when the Aisys CS² machine records FiO_2 >80% (pre-oxygenation) with end tidal CO_2 breaths detected. During this phase, the subjects from both study groups receive the standard of care from their attending clinicians. This phase ends once maintenance phase begins, the subject is intubated (LMA or endotracheal) and when mechanical ventilation is turned on.

6.2.2 Maintenance Phase

The maintenance phase will start when mechanical ventilation is turned on and remains on for 10 breaths. Once the clinician starts mechanically ventilating the subject, he/she will initiate the Et Control option or will continue to provide the standard of care depending on the randomization assignment of the subject.

NOTE: *Et Control is intended to be used continuously up to and through the emergence phase, and until the subject is disconnected from the breathing circuit.*

6.2.3 Emergence Phase

This phase starts once the clinician stops administering anesthetic agent and the fresh gas flow rate is > 4 l/min for 5 breaths to begin washing out the inhaled anesthetic agent from the patient in preparation for the subject to regain consciousness. When no additional breaths are detected by the Aisys CS², then the patient is disconnected from the anesthesia machine. This phase ends when the subject is finally disconnected from Aisys CS² anesthesia machine.

6.2.4 Post Anesthesia Care Unit (PACU) Discharge

While the subject is in post anesthesia care unit (PACU), assessment of adverse events and collection of vital signs and other pertinent information (see Section 6.3 for data collection) shall be performed.

Note: Collection of vital signs at PACU Discharge will be the last vital signs taken at the time patient meets criteria to discharge from PACU.

6.2.5 Twenty-four (24) hours post PACU discharge

The Investigator or the designated study staff (designee) shall assess the intraoperative awareness of the subject (from induction to emergence). The Investigator or designee shall assess any adverse events that occurred, if any.

6.2.6 User Survey

The Investigator will complete a User Survey Questionnaire, after completing each subject case. The survey captures the usability of Et Control to help assess the learning curve associated with the device and training provided.

6.3 Data Collection for Treatment and Control

6.3.1 Preoperative Data Collection

The following information will be collected after the subject provided his/her consent:

1. **Demographics:** subject's age, gender (the biological sex of the subject), ethnicity, race
2. **Medical History:** review of major body systems (e.g. cardiovascular, respiratory, neurological, etc.) – diagnosis or condition, date of onset, and resolution
3. **Surgical History:** collect description of surgeries, surgery date, and adverse reaction to anesthesia
4. **Concomitant Medications:** review of current concomitant medications (e.g. antihypertensive drugs, diabetes medications,) within 2-weeks prior to surgery (include medications the patient have taken and what have been withheld) as reported by the patient during the pre-operative screening process
5. **Baseline Vitals:** height, weight, body mass index (BMI), heart rate, blood pressure (systolic/diastolic/MAP), and peripheral capillary oxygen saturation (SpO_2)
6. **Physical Examination:** cardiovascular, pulmonary, neurological systems, and ASA physical status will be assessed and documented
7. **Laboratory Assessments:** females of childbearing potential will have a serum or urine pregnancy test done (prior to randomization) to determine eligibility

8. **Current Surgery:** provide the type of scheduled surgical procedure the subject will undergo

6.3.2 Operative Procedure Data Collection (Induction/Intubation, Maintenance, and Emergence)

The following information will be collected from each subject case.

- Collect the following data from the departmental electronic medical record (EMR) from induction through emergence phase:

  NOTE: *Collection of vital signs shall be made at a minimum of every 2.5 minutes for the first 2 hours of each case, and at a minimum of every 5 minutes thereafter through the emergence phase. If the subject becomes unstable, the clinician shall revert to collecting the vital signs at a minimum of every 2.5 minutes, and shall record the reason for change in the collection of vital signs and any adverse events that may occur. Once the subject returns to a stable state, the clinician shall collect the vital signs at a minimum of every 5 minutes.*

  1. Heart Rate
  2. Blood Pressure (systolic and diastolic)
  3. Mean Arterial Pressure (MAP)
  4. Peripheral Capillary Oxygen Saturation (SpO_2)

- Record the following data on the eCRFs throughout the study:

  1. Concomitant Medications: Intravenous medications [name, dose, time administered, time stopped, and rate (if applicable); including intravenous anesthetic agents used prior to intubation] administered from pre-OP through emergence phase
  2. Vasoactive medications: (e.g., Ephedrine, Epinephrine, Dopamine Norepinephrine, Phenylephrine, etc.) including name, dose and unit, rate, time administered, time stopped, and reason for dose (prophylactic, hypotension, anesthetic overdose, hypovolemia, depressed cardiac output, depressed systemic vascular resistance, dose decrease or other) – administered from induction to emergence phase
  3. Anesthetic agents used prior to intubation *(Note: Record inhaled and intravenous anesthetic agent used prior to intubation. Intravenous anesthetic agent should be recorded in the Intravenous Medication During Study eCRF.)*
  4. Time of induction
  5. Time of intubation
  6. Operative positioning *(record the primary operating position)*
  7. Incision time

8. Estimated blood loss
9. End time of surgery *(often defined as the procedure end time, last stitch, or placement of the last bandage)*
10. Time subject is moved from the operating room (OR)
11. Assessment of adverse events – throughout the study

- Electronic data collection by the Aisys CS² machine log:
    1. If Et Control was activated, the time of activation will be recorded
    2. EtO_2, $EtCO_2$, EtAA, FiAA and FiO_2 (this data will be collected breath to breath)
    3. Anesthesia machine settings, alarms and events
- Calculation of the data collected from the Aisys CS² machine log
    1. Time of last breath (point of last breath from the data collection)
    2. Anesthetic agent usage

6.3.3 Post Anesthesia Care Unit (PACU) Data Collection

Prior to the subject's discharge from PACU *(defined as the time patient meets criteria for discharge from PACU)*, the following data will need to be collected on the electronic case report form:

1. Assessment of adverse events
2. Time of collection of vital signs *(this will be the last set of vital signs taken at the time patient meets criteria to discharge from PACU)*
3. Heart Rate
4. Blood Pressure (systolic and diastolic)
5. Mean Arterial Pressure (MAP)
6. Peripheral Capillary Oxygen Saturation (SpO_2)
7. Intravenous medications [name, dose, time/duration, and rate (if applicable)] administered from emergence through PACU discharge *(defined as the time patient meets criteria to discharge from PACU)*
8. Length of time in the PACU
9. Time of admission to ICU or general ward.

6.3.4 Twenty-four (24) hours Post PACU Data Collection

Collect the following information 24-hours (±8 hours) post PACU discharge *(defined as the time patient meets criteria to discharge from PACU)* for subjects that completed the study and those that were withdrawn or discontinued from study participation *during* the study procedure.

1. Assessment of adverse events
2. Assess intraoperative awareness

Intraoperative awareness shall be completed by the site study staff (from Induction to Emergence). The following are the questions to ask the patient:

- Perception:
  a. Did the patient hear the surgeon(s) talk during the surgery?
  b. Did the patient smell the skin or muscle burn during the surgery?
  c. Did the patient see the surrounding environment and clinician(s) in the OR during the surgery?
  d. Did the patient feel pain during the surgery?
- Motion:
  a. Did the patient feel he/she wanted to move his/her body but could not move?
- Mental:
  a. Did the patient understand what was going on during the surgery?
  b. Did the patient feel scared or anxious during the surgery?

6.3.5 User Survey Questionnaire

Collect the following information, after each subject case:

1. History of Use of the Et Control feature – provide the number of anesthesia cases performed (including the study case).
2. Rate the use of Et Control feature in achieving the intended target concentration compared to the conventional practice. Provide reason.

   1 = Et Control is much more difficult to use than Conventional
   2 = Et Control is more difficult to use than Conventional
   3 = Et Control is the same as the Conventional
   4 = Et Control is easier to use than Conventional
   5 = Et Control is much easier to use than Conventional
3. Assistance completing any of the following tasks. Provide type of assistance received, if any.
   a. start Et Control with/without assistance
   b. stop Et Control with/without assistance
   c. adjust Et Control user settings with/without assistance
   d. react to and understand Et control related alarms
4. Managing emergence using Et Control is easier than conventional mode. Explain.

   5 = strongly agree
   4 = agree
   3 = neutral
   2 = disagree
   1 = strongly disagree

5. When the clinician used the Et control feature in the study case, did the clinician treat the case subject with the same target end tidal concentrations as he/she would try to achieve indirectly in conventional practice by adjusting the mixer and vaporizer settings?
    a. Use the same target end tidal anesthesia concentration – yes/no; if no, provide reason.
    b. Use the same target end tidal oxygen concentration – yes/no; if no provide reason.
6. Was the outcome of this anesthesia case satisfactory – yes/no? If no, provide reason.

6.3.6 Stopping/Discontinuation of Et Control:

If for any reason the clinician needs to stop or discontinue the Et Control function during the maintenance phase, the following data will have to be recorded on the eCRF:

1. Reason for deactivation
2. Time of deactivation
3. Did the deactivation solve the clinical issue?

6.4 Withdrawal and Discontinuation Criteria

The subject may withdraw from study participation at any time, for any reason without consequence. The Investigator may withdraw a subject at any time for any reason. The reasons for withdrawal and discontinuation for any subject shall be recorded. These will be reported to the Sponsor and assessed for significance. The IRB should be notified per their notification of subject withdrawal policy.

7. QUALIFICATION AND TRAINING PLAN

7.1 Staff Qualification

All members of the study staff participating in the conduct of the Clinical investigation shall be qualified by education, training, and/or experience to perform their tasks; and this shall be documented appropriately, as per US FDA 21 CFR 812.43, Guidance for Industry—Investigator Responsibility—Protecting the Rights, Safety, and Welfare of Study Subjects and ISO 14155:2011 5.1, 8.2.1.

7.2 Training Plan for Research Device

Each clinician will be provided with the following documentation for training purposes:

- Aisys CS² 10.X user's manual URM #2067226-001
- Aisys CS² Et Control Option user's reference manual addendum URM #2070086-001

All clinicians will be trained prior to start of the study based on the above-mentioned documents that will be provided. Topics will include:

- Overview of the Aisys CS² anesthesia machine
- Principles of end tidal gas concentrations over a wide range of total flows
- Introduction and training on the use of Et Control
- Review of safety and labeling as defined in the user reference manual for Aisys CS² 10.X and the Et Control user reference manual addendum.
- System and feature limitations of Et Control

Completion of training by all device users will be recorded in the site training log. A copy of the site training log will be kept in the Site Regulatory Binder.

Site staff that will be performing the Et Control software enabling/disabling during the study enrollment period, will undergo training in person. Topics will include:

- Regulatory considerations for investigational device tracking: investigational device accountability
- Review of the Aisys CS²
- Installation and uninstallation of the fresh gas module
- Activation and deactivation of Et Control software feature
- Aisys CS² machine preuse check
- Aisys CS² Logs (breath and service logs)
- Documentation of investigational device usage

Completion of training by all site staff will be recorded in site training log.

7.3 Training Plan for Protocol

Site research personnel (including investigators, device users, study coordinators, and other appropriate personnel such as OR nurses) will be trained on the clinical investigation requirements set forth in this study protocol according to the following requirements:

- Title of training
- Training objectives
- Training logistics (who conducts training and training method)
- Target audience (who will be trained)
- Training content including device operation (as noted above), protocol review, and understanding

Training records shall be completed by all site study staff, and shall be maintained in the site's Regulatory Document Binder. A copy of the training record shall be provided to the Sponsor.

The Principal Investigator will be ultimately responsible for evaluation of this study in accordance with the protocol and for device used in this study by members of the study staff.

8. DATA ANALYSIS AND STATISTICS

8.1 Statistical Analysis Methods

8.1.1 Sample Size Determination

This study is intended to demonstrate that Et Control is non-inferior to the control device in maintaining end tidal anesthetic agent (EtAA) and end tidal oxygen (EtO_2) concentrations.

The primary efficacy endpoint is the weighted average per subject of percent duration of EtAA and EtO_2 concentrations maintained within the acceptable range for a subject. The acceptable range is specific for each steady state. For EtAA, the acceptable range is defined as +/- the larger of 5% of the steady state concentration or *0.1% v/v for Iso, 0.2% v/v for Sev, 0.6% v/v for Des*; and for EtO_2, it is +/- 5% v/v. The duration of each steady state will be used as the weight when calculating the weighted average. For EtAA,

$$PercentDuration = \frac{\sum_i \sum_j t_{ij} I_{ij}}{\sum_j T_j} \times 100\%$$ where t_{ij} is the i^{th} duration of EtAA concentration

maintained within the acceptable limit during the j^{th} steady state, and T_j is the total duration of the j^{th} steady state. I_{ij} is an indicator for whether EtAA is maintained within the acceptable limit of i^{th} duration in j^{th} steady state, which is

$$I = \begin{cases} 1 & \begin{array}{lllll} if & Desflurane & and & \Delta EtAA \le & \max(0.6\%,\ 5\% X\ steady\ state\ EtAA) \\ if & Sevoflurane & and & \Delta EtAA \le & \max(0.2\%,\ 5\% X\ steady\ state\ EtAA) \\ if & Isoflurane & and & \Delta EtAA \le & \max(0.1\%,\ 5\% X\ steady\ state\ EtAA) \end{array} \\ 0 & otherwise \end{cases}$$

ΔEtAA is the absolute difference between measured EtAA concentrations and steady state EtAA concentration.

Similar definition is used for EtO_2 except that acceptable limit is set as 5% v/v.

From the results of the feasibility study, the average percent duration of EtAA and EtO_2 concentrations that exceeded the defined acceptable range for the Control Arm was about 13% and about 18%, respectively. In this study, the non-inferiority margin is set at 5% for both EtAA and EtO_2, which is about 1/3 of the performance of the Control Arm, i.e., Et Control will be considered non-inferior to the control device if its performance is no worse than that of the control device by more than 5%.

So the hypotheses on the primary endpoints are:

H0: $\mu_{et} - \mu_{con} < -5\%$ vs H1: $\mu_{et} - \mu_{con} \ge -5\%$

for both EtAA and EtO_2, where μ_{et} is the percent duration of Et Control with EtAA and EtO_2 maintained within the acceptable range, and μ_{con} is the percent duration of control device with EtAA and EtO_2 maintained within the acceptable range.

Both null hypotheses have to be rejected for EtAA and EtO_2 to conclude non-inferiority. So the alpha is set at 0.025 one-sided with no need for multiplicity adjustment, but the power for each hypothesis is set at 0.95 to have an overall power of 0.9 for the study. And the larger sample size calculated for EtAA and EtO_2 will be the size of the study.

The results from the feasibility study on the weighted average of percent duration with EtAA and EtO_2 maintained within the acceptable range is listed below. The difference between Et Control and control device is assumed to be 50% less than what was observed, and the larger standard deviation observed is used in sample size calculation using the 2-sample t-test method.

Table 8-1 – Sample Size Calculation

Endpoint	Control device	EtControl (observed)	EtControl (expected)	Sample size per arm with 15% drop out	Sample size of the study
EtAA	87±16	94±16	90±16	124	248
EtO_2	81±19	98±19	89±19	68	136

So, on the basis of the above, the study will enroll approximately 248 subjects.

Superiority will be tested with no need for multiplicity adjustment, if non-inferiority is concluded. Superiority will be claimed for Et Control if EtAA is superior than the control, and EtO_2 is non-inferior to the control. The significance level will be at 0.025 one-sided.

8.1.2 Statistical Methods Overview

Data collected in this study will be presented using summary tables, data listings and graphs. Study endpoints and parameters will be summarized using descriptive statistics.

The descriptive statistics for continuous variables will include mean, standard deviation, median, Q1 and Q3, minimum, maximum, and sample size. Categorical variables will be described with counts, percentages, and sample size.

For comparison (between arms or against null values), categorical variables will be tested using appropriate contingency table analyses (exact or chi-square approximations), and continuous variables will be tested using Student's t-test or non-parametric methods, depending on variable distribution. P-values will be presented to three decimal places and p-values less than .001 will be presented as '<.001.'

Subjects using different anesthetic agents will be pooled for analysis per the arm they are randomized. Separate analysis may be performed by anesthetic agent when pooling data across anesthetic agents is not appropriate.

No imputation will be performed for missing data unless specified otherwise.

A data extraction algorithm is used to identify periods of end tidal concentration measurement stability following setting changes (i.e. Steady States) during a case, as well as to measure response times, settling times, and overshoot amounts from these steady states in order to compare across arms. The extraction algorithm is not part of the statistical analysis, but provides the above-mentioned endpoints. (See Appendix 2 – Extraction algorithm for more information on the extraction algorithm.)

There will be two scenarios in defining a step change and steady state when performing the data extraction: *1) using the data extraction algorithm to determine the desired end-tidal concentrations of anesthetic agent and oxygen for both arms* (See Appendix 2 – Extraction algorithm for more information on the extraction algorithm); *2) using the clinicians recorded end tidal target values of anesthetic agent and oxygen for the Control arm, and the set target value for the Et Control arm.*

Hypothesis tests will be performed on the following endpoints in the order they are listed: the primary endpoints, ie, percent duration with EtAA and EtO2 maintained within the acceptable range; agent usage; user setting interaction; and time to OR discharge. The sequential approach will be used to control the overall type I error. The next hypothesis and thereafter will not be tested unless the prior null hypothesis is rejected.

8.1.2.1 Analysis Sets

The study analysis sets include the intent-to-treat (ITT) population, evaluable population, per-protocol population, and safety population; and are defined as follows:

- Intent-to-treat (ITT) Population includes all randomized subjects.
- Evaluable Population includes all randomized subjects with at least 45 minutes of inhalation anesthesia data collected during the procedure.
- Per-Protocol Population includes all subjects in evaluable population without critical protocol deviation.
- Safety Population includes all randomized subjects, who underwent anesthesia using the investigational device or the control device.

8.1.3 Analysis of Primary Endpoints

Separate analysis of primary endpoints will be performed on the basis of the extracted data for the following scenarios: *1.) using the algorithm to determine the desired end-tidal concentrations of anesthetic agent and oxygen for both arms; and 2) using the clinicians*

recorded target values of anesthetic agent and oxygen for the Control Arm and using the set target values for the Et Control Arm.

Analysis of primary endpoints will be based on ITT population, evaluable population, and per protocol population. The conclusion will be based on the ITT population.

For EtAA and EtO_2 respectively, percent duration with EtAA and EtO_2 maintained within the acceptable range will be calculated for each steady state. And the per subject weighted average of the percent duration will be calculated for each subject using the duration of each steady state as the weight.

Using t-test, comparison of the weighted average percent duration between the Et Control and control device will be performed by calculating the difference and its 95% 2-sided confidence interval between the two arms. Non-inferiority will be concluded if the lower limit of the 95% confidence interval is ≥ -5% for both EtAA and EtO_2, and superiority will be concluded if the lower limit of the 95% confidence interval is > 0 for EtAA and the lower limit of the 95% confidence interval is ≥ -5% for EtO_2.

The primary analysis for the primary endpoints consists of the analysis on ITT population based on the algorithm determined end-tidal concentration (scenario 1) and clinician's recorded set target end-tidal concentration (scenario 2). This primary analysis will also be performed for patients of different ASA status.

8.1.4 Analysis of Secondary Endpoints

8.1.4.1 Performance Statistics

For response time, settling time and overshoot amount (% to steady state mean for anesthetic agent, and v/v for O_2), analysis will be on the basis of each steady state. The arithmetic average of all steady states will be calculated and be compared between the Et Control Arm and the Control Arm using t-test. Subjects with at least 1 overshoot amount greater than 10%, 20%, or 30% of steady state concentration will be counted and compared between the two arms using Fisher exact test.

For average deviation (% to steady state mean for anesthetic agent, and v/v for O_2) and half width of 95% CI of deviation, analysis will be on the basis of each subject. The weighted average using the duration of steady state duration as the weight for a subject will be calculated and compared between the Et Control and Control Arms using t-test. For the maximum deviation (% to steady state mean for anesthetic agent, and v/v for O_2), the maximum of all steady states for a subject is taken for analysis, and the maximum deviation be compared between Et Control and Control arms using nonparametric Wilcoxon rank sum method.

The analysis of above performance statistics will be performed by different ASA status.

8.1.4.2 Agent Usage

The agent usage will be compared between the two arms separately for each agent for the duration from induction to end of anesthesia. Usage of anesthetic agents will be normalized so that usage of different anesthetic agents can be pooled in analysis. It is intended to make claims on saving of anesthetic agent usage. The normalized anesthetic agent usage will be compared using t-test at two-sided alpha 0.05 between the Et Control Arm and Control Arm only if non-inferiority is concluded on primary endpoints; thus, no multiplicity adjustment is needed using the fixed sequence approach. The hypothesis to be tested on anesthetic agent usage is:

$$H0: \mu_{et} - \mu_{con} = 0 \text{ vs } H1: \mu_{et} - \mu_{con} \neq 0$$

where μ_{et} is the average normalized anesthetic agent usage of the Et Control arm, and μ_{con} is the average normalized anesthetic agent usage of the control arm.

Agent usage will also be analyzed for each agent.

Additional analysis on agent usage will be performed for the first 10 minutes after induction.

8.1.4.3 User Setting Interaction

User setting interaction will be counted for the first 10 minutes following induction, and for the duration from induction to the end of anesthesia. The analysis may be performed for other time periods. Comparison between arms will be performed using non-parametric Wilcoxon rank sum method.

It is intended to make claims on user setting interaction for the duration from induction to the end of anesthesia, only when non-inferiority is concluded on primary endpoints and saving of anesthetic agent usage is concluded. So no multiplicity adjustment on alpha is needed. The hypothesis to be tested on user setting interaction for the duration from induction to the end of anesthesia is:

$$H0: \mu_{et} = \mu_{con} \text{ vs } H1: \mu_{et} \neq \mu_{con}$$

where μ_{et} is the median of user setting interaction of the Et Control arm, and μ_{con} is the median of user setting interaction of the control arm. Statistical significance will be declared if the Wilcoxon rank-sum test 2-sided p-value is less than 0.05.

8.1.4.4 Time to Operating Room (OR) Discharge

Time to operating room (OR) discharge will be measured from end of surgery *(often defined as procedure end time, last stitch, or placement of last bandage)* to OR discharge (time of last breath, patient being disconnected from the anesthesia machine).

Hypothesis test on time to OR discharge will be performed only when non-inferiority is concluded on primary endpoints, saving on anesthetic agent usage and user setting

interactions are concluded. So no multiplicity adjustment on alpha is needed. The hypothesis to be tested on time to OR discharge is:

$$H0: \mu_{et} = \mu_{con} \text{ vs } H1: \mu_{et} \neq \mu_{con}$$

where μ_{et} is the average time to OR discharge of the Et Control arm, and μ_{con} is the average time to OR discharge of the control arm. Statistical significance will be declared if the student t-test 2-sided p-value is less than 0.05.

8.1.5 Et Control Accuracy

To assess the accuracy of Et Control in maintaining the target EtAA and EtO_2 concentrations for each steady state, both mean absolute difference and mean percent difference between measured Et concentrations of AA and the setting values will be calculated, and the mean differences will be summarized for all steady states using descriptive statistics and 95% confidence intervals for each anesthetic agent and overall. The same accuracy analysis will be performed for EtO_2. The mean differences will also be plotted against the setting values to assess consistency across the concentration range for each anesthetic agent. Percent of time duration in a steady state will also be assessed; when the percent difference exceeds 5%, 10%, and 15% of the setting values.

8.1.6 User Feedback

User survey and practice data on the effectiveness of training material and the ease to learn how to use Et Control will be summarized using descriptive statistics for the all subjects from each site.

8.1.7 Analysis of Adverse Events

Adverse events will be observed and recorded. Percent of subjects with AEs will be calculated, and comparisons between groups will be performed using Fisher exact test. Number of AEs and AE event rate will also be analyzed using non-parametric Wilcoxon method.

Analysis will be performed for a subset of adverse events of vital sign abnormalities including non-invasive blood pressure (NIBP), SpO2, and heart rate.

In addition, analysis of adverse events will be performed for each subset of patients defined by the pre-existing hypertension *(defined as a patient treated for hypertension)* status and ASA status.

8.1.8 Analysis of Vasoactive Medication Use

When vasoactive medication is used during the anesthesia procedure, the medication name, reason for use, amount used, duration of use will be recorded. Usage of vasoactive medication will be analyzed for the Et Control and the Control Arms in terms of types of vasoactive medication used, reason for use, number of subjects and total dose. The

vasoactive medication use will be analyzed by ASA status and by preexisting hypertension status. Comparison for categorical variables will be performed using Fisher exact test and comparison for numerical variables will be performed using Wilcoxon rank-sum method.

8.1.9 Other Analysis

Delivered EtAA and EtO_2 concentrations will be summarized by anesthetic agent and overall for both arms to demonstrate the comparability in anesthesia practice.

Delivered EtAA and EtO_2 concentrations and their deviations to set values for the duration of +/- 10 minutes of an AE will be summarized for both arms.

Oxygen (O_2) usage from induction to the end of surgery will be summarized and compared between the two study arms using t-test.

Post-anesthesia discharge time will be summarized and compared between the two study arms using t-test. Post- anesthesia discharge time is defined as OR discharge (patient disconnected from the anesthesia machine) to discharge time from the PACU *(defined as the time patient meets criteria to discharge from PACU).*

8.2 Interim Analysis

No interim analysis is planned for this study. A Data Safety Monitoring Board (DSMB) will be utilized for this study to monitor subject safety.

8.3 Handling of Missing Data

In general, data analysis will be performed on the basis of all available data.

For missing values of primary endpoints, multiple imputations will be performed and sensitivity analysis will be conducted for primary endpoints. The multiple imputation will be performed with SAS PROC MI, using the regression method for monotone missing pattern, with the covariates treatment arm, clinician, anesthetic agent, and subject ASA status as the independent variables. A total of 5 imputed data sets will be generated and analysis of primary endpoints will be performed on each imputed data set. PROC MIANALYZE will be used to summarize the results from imputed data sets.

Clinician recorded end tidal target values are considered missing, when a recorded target is not available for a setting adjustment resulting in a significant change in end tidal measurements. If the change in end tidal measurement results in more than 5% v/v O_2, 0.9% v/v DES, 0.31% v/v SEV, or 0.15% v/v ISO from the previous end tidal measurement over a period of 2 minutes, then the recorded target data is considered missing. This portion of the data is not used for the purpose of the analysis with the clinician recorded target values.

8.4 Pass/Fail Criteria of the Study

Successfully meeting the non-inferiority test for both EtAA and EtO_2 in the primary endpoints fulfills the pass criteria of the study.

9. DEVIATIONS

9.1 Management of Protocol Deviations

Deviations to the protocol may occur when necessary to protect the life or physical well-being of a subject. Except in an emergency, prior approval by the Sponsor is required for changes in, or planned deviations from this protocol. If these changes affect the scientific integrity or the safety and welfare of the subject, prior IRB approval is also required. Planned Protocol Deviation documentation must be filed in the Site Study Regulatory Binder.

There are two types of unplanned protocol deviations, critical deviations and non-critical deviations. All deviations must be documented and reported, the criticality of the deviation will determine the reporting path.

Critical Deviations: Deviations that significantly affect the safety, efficacy, integrity or conduct of the study. These deviations must be reported to the Sponsor no later than 5 working days from awareness of occurrence and reported to the IRB per the deviation reporting policy.

If an Investigator uses the investigational device without obtaining informed consent, the Investigator shall consider this a critical deviation and report the event to the Sponsor and the IRB within 5 working days of the occurrence.

The Sponsor shall inform the FDA within five (5) working days of the use of the investigational device without obtaining informed consent.

The critical deviation(s) will be reported via the electronic case report form. A copy will be submitted to the study Sponsor via fax, e-mail, or courier and the original will remain on site where it will be reviewed by the study monitor.

Non-Critical Deviations: Protocol deviations that do not significantly affect the safety, efficacy, integrity or conduct of the trial. These deviations must be documented on the Electronic Case Report Form Protocol Deviation page and will be reviewed by the study monitor.

10. COMPLAINT HANDLING AND ADVERSE EVENT REPORTING

10.1 Foreseeable Adverse Events and Device Effects

Being in this study involves some foreseeable risks. The following are some of the foreseeable adverse events related to general anesthesia that can be observed in both the control and investigational group: nausea, vomiting, hypoxemia, hypercapnia, emergence delay, agitation, hypertension, hypotension, postoperative pulmonary infection, intraoperative cardiac arrhythmias, myocardial ischemia, myocardial infarction, cardiac arrest, stroke, pulmonary embolism, intraoperative awareness, hypoventilation, hyperventilation, volutrauma, and barotrauma. The previous events can lead to death.

The following are foreseeable adverse events related to the use of the investigational Et Control option (this excludes surgical procedure related events and drug related events). Although each one of these events could occur through a failure specific to Et Control, these events are not exclusive to Et Control and can also occur with Aisys CS² operating in the conventional fresh gas mode as indicated above.

Table 10-1 – Anticipated Adverse Events and Device Effects

Event	Machine Failure	General Anesthesia	Aisys CS²	Et Control
Hypoxia	Insufficient oxygen delivery	x	x	x
	Incorrect oxygen concentration of fresh gas flow	x	x	x
	Insufficient ventilation	x	x	x
Hyperoxia	Excessive oxygen delivery	x	x	x
Cardiac Arrest	Incorrect anesthetic agent delivery	x	x	x
Intra-operative Awareness	Insufficient AA delivery	x	x	x
Hypertension	Insufficient anesthetic agent delivery	x	x	x
Hypotension	Excessive anesthetic agent delivery	x	x	x
Airway Fire	Electro-cautery in airway with high O_2	x	x	x

Adverse event assessment will be conducted from the time the subject provided consent to the end of the subject's participation in the study.

There is always a chance of unexpected risks. Throughout the study, the Sponsor will evaluate and update safety information in study documents.

10.2 Adverse Event Definitions

Adverse Event (AE): As defined by EN ISO 14155-2011: 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.

NOTE: *This definition includes events related to the investigational medical device or the comparator. This definition includes events related to the procedures involved.*

Given the frequency at which physiological changes occur during the course of general anesthesia, the following definitions for changes in blood pressure, heart rate, and oxygenation will be used to determine adverse event reporting. If any of the parameters reach the below thresholds they shall be reported to the Sponsor as adverse events.

(1) ***Non-Invasive Blood pressure (NIBP):*** defined as having the systolic blood pressure (SBP) reading < 70 mmHg or > 160 mmHg or mean arterial pressure (MAP) of < 55 mmHg or > 120 mmHg for > 5 minutes.
(2) ***Peripheral Capillary Oxygen Saturation (SpO_2):*** defined as having a value less than 90% for more than 5 minutes.
(3) ***Heart rate:*** defined as the heart rate < 45bpm or > 110bpm for more than 5 minutes.

Additional adverse events related to physiological changes can be reported at the clinician's discretion.

Serious Adverse Event (SAE): As defined by EN ISO 14155–2011: an adverse event that

a. led to death;
b. led to a serious deterioration in the health of the subject, that either resulted in:
   (1) a life-threatening illness or injury, or
   (2) a permanent impairment of a body structure or a body function, or
   (3) in-patient or prolonged hospitalization, or
   (4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function;
c. 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 Clinical Investigation Plan (clinical protocol), without serious deterioration in health, is not considered a serious adverse event.*

Anticipated Adverse Device Effect: Any adverse event and/or reaction, the specificity or severity of which is consistent with the IRB approved informed consent, protocol, investigator brochure, or product labeling.

Unanticipated adverse device effect (UADE): As defined by 21 CFR 812.3: means 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 investigational plan 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.

Adverse Device Effect (ADE): An adverse event related to the use of an investigational medical device [ISO 14155:2011 3.1]. This includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This includes any event that is a result of a user error or intentional misuse of the investigational device [ISO 14155:2011 3.43].

Serious Adverse Device Effect (SADE): An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event [ISO 14155:2011 3.36].

Device deficiency: An inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, such as malfunctions, use errors, and inadequate labelling [ISO 14155:2011 3.15].

Unanticipated serious adverse device effect (USADE): A serious adverse device effect, which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report [ISO 14155:2011 3.42]. In the United States, 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 study documents, will be reported in accordance with 21 CFR 812.3 and applicable laws and regulations.

10.3 Management of Adverse Event Reporting

Any adverse events (AEs) and serious adverse events (SAEs) will be recorded in the subject's study record and the Electronic Adverse Event Case Report Form. The following information should be obtained:

- Description of Adverse Event
- Onset date
- Onset time
- Relationship to device/study as assessed by the investigator (not related, possibly related, probably related)
    - Not related: The adverse event is reasonably expected to be related to (or caused by) a concurrent illness, effect of another device/drug or other cause, and is unlikely related to the investigational product
    - Possibly related: The adverse event is reasonably expected to be related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product
    - Probably related: There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely, or there is no other reasonable medical explanation for the event.
        - Related to device, specify: Investigational or Non-Investigational

- Caused by machine failure (yes/no); if yes, indicated type of machine failure

- Relationship to anesthetic agent *(yes/no) if yes, provide route of administration of anesthesia*
  - Inhaled anesthetic agent
  - Intravenous anesthetic agent
- Relationship to Surgical Procedure (not related, possibly related [describe], probably related [describe])
- Resolution – record date and time of resolution
- Anticipated, Serious, or Unanticipated (yes/no)
  - If Serious Adverse Event or Unanticipated Adverse Device Effect, record date of reporting to Sponsor and IRB.
  - If Serious Adverse Event, record one of the following:
    - Death and date of death
    - Life threatening
    - Significant Disability
    - Hospitalization
    - Congenital anomaly
    - Other, explain
- Outcome – indicate as follows:
  - Ongoing
  - Resolved without sequelae – describe outcome
  - Resolved with sequelae
- Severity (mild, moderate, severe)
  - **Mild**: Symptom(s) barely noticeable to the subject or does not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
  - **Moderate**: Symptom(s) of a sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.
  - **Severe**: Symptom(s) of a sufficient severity to cause the subject severe discomfort. Treatment for symptom(s) may be given.
- Treatment given and/or action taken (procedure stopped, withdrawn from study, no action, unanticipated ICU admission)

Adverse events will be reported to the local IRB per their policy.

NOTE: *Adverse events related to NIBP, SpO2, and Heart rate will be reported according to the definition outlined in Section 10.2 – Adverse Event Definitions.*

10.4 Management of Serious Adverse Event and Unanticipated Adverse Device Effect Reporting

All SAEs and/or UADEs will be documented as above and reported in writing to the Sponsor within 72 hours of knowledge of the event. The Investigator shall submit the Adverse Event eCRF and GEHC_GQP_10.07.005_F002 Site Notification and Assessment of Serious and Unexpected Adverse Events (DOC0910335) with redacted supporting documentation to SAE mailbox. If the event resulted in the death of a subject, the event shall also be reported via telephone to the Sponsor within 24 hours of knowledge of the event. SAEs will be reported to the local IRB per their policy.

UADEs shall be reported by the investigator to the IRB as soon as possible but no later than 10 working days per 21 CFR 812.140(a)(1). GE Healthcare, as study Sponsor, shall investigate and report any UADEs to FDA, all participating principal investigators and IRBs within 10 working days from receiving notice of the UADE from the Investigator per 21 CFR 812.150(b)(1).

Sponsor contact for SAEs and/or UADEs:

Medical Monitor: [redacted]
Fax: 800-888-3983
E-mail: SAE@ge.com

If additional information (i.e.; outcome of event, date event resolved, additional treatments) is required to submit a follow-up report, the Investigator shall update the AE eCRF and resubmit to the Sponsor's Clinical Affairs. The Investigator shall submit the follow-up SAE and/or UADE report to the local IRB per their policy.

10.5 Follow-up and Use of Collected Data of Subjects with Reported Event

Subjects with reported event (AE, SAE, ADE, SADE, UADE, or USADE) shall be followed until the resolution of the event. The Investigator shall submit a follow-up report as indicated in the above-mentioned section.

If an event occurred during the study procedure and the subject was withdrawn or discontinued as deemed necessary by the Investigator, any data collected up to the resolution of the event may be used by the Sponsor for the assessment of the event.

10.6 Management of Device Complaints

Any complaints regarding the operation of the device or software or any malfunctions are to be reported to the Sponsor Clinical Affairs Project Manager (CAPM).

Sponsor contact for device complaints:

[redacted]

E-mail: mary.t.duggan@ge.com

11. EARLY TERMINATION OR SUSPENSION

11.1 Early Termination of Subjects

Early termination of a subject is defined as any situation in which the clinician determines they no longer want to continue with the case, or the clinician may choose to discontinue the Et Control mode during a case. The following objective criteria are utilized to determine when it is appropriate to terminate the subject's participation in the study; additionally, to terminate the Et Control in the investigational arm:

- Mean arterial pressure of less than 55 mmHg that is sustained for greater than 10 minutes; OR
- SpO_2 less than 90% that is sustained for greater than 10 minutes; OR
- With respect to device performance, the Et Control device is not meeting the expected performance requirements such that:
  - Measured EtO2% is less than 21% for 5 min;
    OR
  - Measured ETAA% at steady state deviates from the set EtAA% by more than the following:
    - Desflurane +/- 2.0 % for 5 min
    - Sevoflurane +/- 0.6 % for 5 min
    - Isoflurane +/- 0.3 % for 5 min
- An unrecoverable failure that prevents the use of Et control *(Unrecoverable failure is defined as the inability to use Et Control mode because of unrecoverable device malfunction)*

The reason for early termination will be recorded on the Electronic Case Report Form.

If the Et Control system detects any issues or fault conditions during the case (such as leaks or accuracy issues), the Et Control program may temporarily transition to fall back mode or enter fresh gas mode until the clinician is able to address and resolve the issue. *This is not considered early termination.* This is a design element to help mitigate potential safety risks and correct failure modes.

Cases in which there are brief periods of use outside of Et Control based on the algorithm self-exiting will continue to be analyzed as part of the Et Control Arm.

11.2 Criteria for Early Termination or Suspension of the Study

The Sponsor has established a criterion for stopping/pausing enrollment in this study:

- Three (3) subjects in the Et Control Arm of the study have a serious adverse event (SAE) or an unanticipated adverse device effect (UADE) at any point in the study.

If this criterion is met, the enrollment in the study will be paused (placed on hold) and the study sites, IRB, and FDA will be notified. An IDE Supplement may be submitted to FDA to discuss resuming enrollment.

In addition to the above, the DSMB may make recommendations to terminate the study or enrollment for other observed safety concerns on the basis of their clinical judgment. The Sponsor is responsible for final decision regarding early termination of the study based on DSMB recommendations.

Also, the study may be terminated early if the Sponsor determines that unanticipated adverse event(s) presents an unreasonable risk to subjects or for any other reason as Sponsor determines to be appropriate.

Termination shall occur no later than 5 working days after the Sponsor makes the determination and no later than 15 working days after Sponsor first received notice of the effect.

The Sponsor will promptly notify the Investigators of any determination to terminate the study outside of the protocol timeframe. The Sponsor will provide each Investigator with written guidelines/instructions on termination processes and timelines.

The Investigator is responsible for reporting the early termination to their local IRB.

11.3 Follow-up and Use of Collected Data of Subjects Withdrawn/Discontinued

A 24-hour follow-up will be conducted for subjects that were withdrawn or were discontinued from study participation during the study procedure. Assessment of adverse events and intraoperative awareness shall be collected *[see Section 6.3.4—Twenty-four (24) hour Follow-up Post PACU data collection]*, and shall utilize the Electronic Adverse Events and Intra-Operative Awareness Questionnaire electronic case report forms (eCRFs). No additional follow-up will be conducted for subjects that withdrew or were withdrawn from study participation prior to study procedure.

Any data collected during the participation of the subject or prior to withdrawal will still be included in the study results and provided to the Sponsor.

12. INSTITUTIONAL REVIEW BOARD (IRB) AND REGULATORY FILINGS

12.1 Regulatory Authority Approval Requirements

This study will be conducted in the U.S. and will comply with the Medical Device Good Clinical Practice regulations promulgated pursuant to the Food, Drug, and Cosmetic Act, including 21 CFR Parts 11, 50, 54, 56, and 812. The regulatory authority which governs this clinical trial is the U.S. Food and Drug Administration. Significant risk device clinical investigations require

prior FDA approval of an Investigational Device Exemption and approval by participating Institutional Review Boards.

12.2 Institutional Review Board Approval Requirements

This study is to be submitted to the IRB applicable for each of the study sites for review and approval prior to enrolling subjects. The Investigator is responsible for keeping approval current and maintaining appropriate correspondence and reports.

Copies of all IRB applications, approval letters, Informed Consent Forms (ICF) and other correspondence are to be sent to the Sponsor, with originals kept in the Site Study Regulatory Binder.

12.3 Withdrawal of IRB Approval

The Investigator is to notify the Sponsor of any withdrawal of IRB approval within 5 working days of such occurrence. If the IRB terminates or suspends its approval of the Study, the Investigator will promptly notify Sponsor and provide a detailed written explanation of the termination or suspension. Upon receipt, the Sponsor will provide written guidelines/instructions on subject withdrawal/termination processes and timelines.

12.4 Management of Protocol Revisions/Amendments

All changes and updates to this protocol will be initiated by the GE Healthcare study team. The team will also determine the impact to the study and other study documents.

Any protocol amendments and/or study document revisions will be submitted to the Institutional Review Board and the U.S. FDA as IDE supplements for approval as required.

Site training will be documented and filed in the site's Study Regulatory Binder and in the Clinical History file along with the protocol amendment and/or study document revisions, as well as IRB submission(s) and approval(s).

12.5 Informed Consent and Privacy Requirements

Informed consent will be obtained from all subjects prior to participation in the study, per the determination of the IRB. The IRB shall formally approve the study's Informed Consent Form (ICF).

Informed consent will be documented in the source record of each subject. The Investigator or designee will consent the subject per regulatory guidelines which include the subject has ample time to review the ICF and have all questions answered to their satisfaction; the subject may take the ICF home to review with family members or others prior to agreeing to participate in the study; upon agreeing to participate in the study, the subject signs and dates the document while initialing any indicated lines; the person who consented the subject signs and dates the document; the Investigator signs and dates the document.

The subject will be given a copy of the signed informed consent form and the original will be retained with study files.

The subject will also be given information explaining his/her protection and rights under the Health Insurance Portability and Accountability Act (HIPAA) requirements.

12.6 Investigator Progress and Final Report

The Principal Investigator shall submit progress reports to the Sponsor and reviewing IRB annually at a minimum. The investigator shall submit a final report within three months after termination or completion of the investigation to the Sponsor and the reviewing IRB.

12.7 Sponsor Reporting

12.7.1 FDA Withdrawal

The Sponsor shall notify all reviewing IRBs and investigators of any withdrawal of FDA approval within five (5) working days.

12.7.2 Investigator List

The Sponsor shall submit to FDA at 6-month intervals, after initial IDE approval, a current list of the names and addresses of all participating investigators.

12.7.3 Progress Reports

The Sponsor shall submit progress reports to the FDA and all IRBs at least annually.

12.7.4 Final Report

The Sponsor shall notify FDA within 30 working days of the completion or termination of the investigation. The Sponsor shall submit a final report to FDA, IRBs and participating investigators within 6-months of completion or termination of the investigation.

13. DATA SAFETY MONITORING BOARD

A Data Safety Monitoring Board (DSMB) will be utilized for this study to provide additional assurance of subject safety.

The DSMB shall consist of three (3) members. The members shall be composed of two (2) clinicians with clinical expertise in anesthesia, and one (1) biostatistician knowledgeable in statistical methods for clinical trials and sequential analysis of clinical trial data.

Members of the DSMB shall have relevant experience in clinical trials, and do not have scientific, financial, personal, or other conflicts of interest related to the conduct of this

clinical trial. The chairperson of the DSMB should have prior experience serving or chairing a DSMB.

The DSMB shall hold meetings at regular intervals or ad hoc, as needed, and will be detailed in the DSMB Charter. The DSMB may make recommendations on the basis of the following established enrollment stopping/pausing criteria *(also noted in Section 11.2—Criteria for Early Termination or Suspension of the Study)* to ensure subject safety:

- If three (3) subjects in the Et Control Arm of the study have a Serious Adverse Event (SAE or an Unanticipated Adverse Device Effect (UADE) at any point in the study.
- At the discretion of the DSMB, any determination that the safety data indicates the study is not safe to continue.
- If the Sponsor is notified of two early subject terminations *(Section 11.1)* or the study stopping criteria *(Section 11.2)* is met, the Sponsor will notify all study sites to pause enrollment and the DSMB shall convene an ad hoc meeting to determine if the terminations were device related safety issues.

The Sponsor's medical monitor shall review the DSMB's findings and determination, and make the decision, if necessary, to stop the study to ensure subject safety.

14. DATA AND QUALITY MANAGEMENT

14.1 Management of Data

Data management processes for handling study data will be maintained by the Sponsor.

Upon enrollment, all subjects will be assigned a subject number and a randomization code. Electronic Case report forms (eCRFs) will use subject numbers only and will not include subject names or other identifiable personal information.

The Sponsor and/or its authorized representatives may use data collected in this study for future technology development, marketing purposes, publications, or other possible uses. Specifically, any data obtained in this study may be used as part of a regulatory submission.

The approved Data Management Plan (DMP) will be located in the study's Clinical History File (CHF) maintained by the Sponsor.

14.2 Subject De-identification

Data will be collected from subjects enrolled in this study and entered into eCRFs provided by GE Healthcare (GEHC). Data collected will be labeled with a de-identified Subject Identification Designation (SID), which consists of the Site number and subject number. eCRFs will not contain any identifiable personal information.

The clinical trial site will maintain a Subject Identification Log, which is a list of all subjects who are enrolled in the study, along with their address and medical record number in the

event that they must be contacted in the future. *The Sponsor will not take a copy of the Subject Identification Log.*

14.3 Completion of Electronic Case Report Forms (eCRFs)

Subject data will be recorded in source documents such as the subject's medical record or study-specific worksheets. Data will then be entered into eCRFs by site personnel. The eCRFs will be reviewed by the Sponsor's designated clinical monitor and then transmitted by the monitor to the Contract Research Organization's (CRO) electronic database. All data entered into the eCRF should be verifiable with source documents unless the eCRF is the source itself. The data collected from the Aisys CS² anesthesia machine and from the EMR will be saved onto CD/DVD or USB drives and transferred to the (CRO) to store the raw data for later evaluation.

To ensure the quality and integrity of the data, it is the responsibility of the Principal Investigator or designee to enter data into the eCRFs for each enrolled subject in a timely manner. GEHC will provide eCRFs and will train study staff on data entry using Good Documentation Practices (GDP). eCRF completion guidelines may be provided by the Sponsor to help facilitate training. eCRFs will be completed as information becomes available.

During the course of monitoring, if any errors or omissions are found, they shall be brought to the attention of the site designee, who shall make the corrections, as appropriate on the eCRFs. In the event of an eCRF audit or data review once the eCRFs have been completed, a data query will be generated and the error, omissions or clarifications will be corrected on the associated eCRF.

The Principal Investigator or a Sub-Investigator will electronically sign and date the indicated places on the eCRF. This signature will indicate that a thorough inspection of the data has been made and will thereby certify the contents of the form.

14.4 Data Handling and Record Keeping

All documents and data shall be produced and maintained in a manner that assures control and traceability.

14.5 Record Retention at the Site

All records pertaining to the conduct of the study, including source data, eCRFs, electronic data ICFs, IRB correspondence, and other study documentation must be retained at the site for inspection at any time by the Sponsor's authorized Study Monitor or designee or regulatory agency; i.e., US Food and Drug Administration (USFDA). These records will be maintained by the site for a minimum of 2 years, per US FDA 21 CFR Part 812.140(d), or a maximum of 3+ years, according to the Sponsors policies; after the investigation termination date or after the date the records are no longer required for purposes of supporting a

premarket approval application or notice of completion of a product development protocol. Elements should include the following:

- **Source data and documentation:** relevant to data recorded for subject screening and eCRF corroboration (i.e., information in original records, certified copies of original records of clinical findings, observations, or other activities for the study)
- **Subject Files**: containing the eCRF worksheets and completed patient eCRFs
- **Regulatory Binder**: containing the protocol and amendments, IRB submissions and approvals, blank and signed/dated ICF(s), and site study logs
- **Reference Manuals**: containing the protocol, responsibilities of the Investigator, Sponsor, AE/SAE and informed consent guidelines, applicable study aids (training material, device screen shots), and central supplier instructions

The Principal Investigator or institution shall provide direct access to source data during and after the clinical investigation for monitoring, audits, IRB review, and regulatory authority inspections.

The Principal Investigator is responsible for storing all study related records until notified by GE Healthcare that they can be destroyed. No source documents or study records will be destroyed without GE Healthcare notification and approval. If records are shipped to an off-site location due to space concerns, GE Healthcare must be notified of the change of location.

15. MONITORING PLAN

15.1 Brief Description

In collaboration with the site, the Sponsor will ensure proper monitoring of the study to confirm that all the clinical requirements are met. There will be a minimum one monitoring visit made to each participating site after enrollment commences. Monitoring visits will ensure adherence to the protocol, completion of informed consents, IRB review of the study, maintenance of records, primary outcomes review and review of the eCRFs and source documentation for accuracy and completeness.

Other monitoring visits will be determined by GE Healthcare study team on an as needed basis. Remote data collection and monitoring may be completed on a pre-determined schedule.

During monitoring, the Sponsor will conduct 100% source data verification on all data collection on the eCRFs. Source data verification will not be completed on data collected electronically from the anesthesia machine or electronic medical records, including heart rate, blood pressure, SpO_2, Et Control performance parameters (EtO_2%, EtAA%), anesthesia machine settings (device log, anesthetic agent usage, user setting interactions), measured parameters, and alarms.

At the Close-out Visit, the monitor will collect all original documents contained in the site's Study Regulatory Binder. All study documents will be filed in the Clinical History File (CHF). Copies will remain in the binder at the site.

15.2 Confidentiality and Data Protection

The investigator affirms and upholds the principle of the participant's right to privacy, and the investigator shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing data in scientific journals.

Individual subject medical information obtained as a result of this study will be considered confidential, and disclosure to third parties will be prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers. For data verification purposes, authorized representatives of the Sponsor, a competent authority (CA), or an ethics committee (EC) may require direct access to parts of the medical records relevant to the study, including subject medical history.

15.2.1 Storage of Collected Data and Associated Health Data

Electronic case report forms (eCRFs), electronic data collected by the Aisys CS² Anesthesia Machine, and associated data will be collected and disclosed to the Sponsor as part of this study. Fully de-identified data, which has had all personal identification information of the subject removed, may be stored and used by the Sponsor indefinitely. The Sponsor and/or its authorized representatives may use any de-identified data collected in this study for future technology and engineering development, marketing purposes, education, regulatory submissions, publications, or other possible uses.

15.3 Reference to Approved Monitoring Plan

The approved monitoring plan will be located in the study's CHF maintained by the Sponsor.

16. PUBLICATION POLICY

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the Sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study Sponsor. Any investigator involved with this study is obligated to provide the Sponsor with complete test results, data derived from the study, and additional clarification, upon Sponsor request.

Data obtained from this study may be used for submission to peer reviewed publications that are consistent with study contracts with prior permission from GE Healthcare. Data may also be used for marketing purposes.

17. REFERENCES

1. Yasuda N, Lockhart S, Eger II E, et al. Comparison of Kinetics of Sevoflurane and Isoflurane in Humans. *Anesth Analg*. March 1991;72(3):316-324.

2. Quasha A, Eger II E, Tinker J. Determination and Applications of MAC. *Anesthesiology*. 1980;53(4):315-334.

3. Corporation BH. Forane (isoflurane, USP) prescricribing information

4. Corporation BH. Suprane (desflurane, USP) prescribing information

5. Corporation BH. Sevoflurane prescribing information

6. Westenskow D, Zbinden A, Thomson D, B K. Control of end-tidal halothane concentration. Part A: Anaesthesia breathing system and feedback control of gas deliver. *Br J Anaesth*. May 1986;58(5):555-562.

7. Zbinden A, Frei F, Westenskow D, Thomson D. Control of end-tidal halothane concentration. Part B: Verification in dogs. *Br J Anaesth*. May 1996;58(5):563-71.

8. Ritchie R, Ernst E, Pale B, Pearson J, et.al. Closed-Loop Control of an Anesthesia Delivery System: Development and Animal Testing. *IEEE Transaction on Biomedical Engineering*. June 1987;34(6):437-443.

9. Ritchie R, Pearson J, Ernst E, BL P. Clinical experience with automatically controlled closed-circuit anesthesia delivery. *IEEE EMBS 1990 Twelfth Annual International Conference*. Nov 1980;34(6):437.

10. Vishnoi, et.al. Adaptive control of close-circuit anesthesia. *IEEE Trans BME*;38(1):39.

11. Kokkila J. *Control of End-Tidal Gases in Anaesthesia using Fuzzy control Algorithms*: Helsinki University of Technology; 2007. MsC Thesis.

12. Sieber T, et.al. Model-based automatic feedback control versus human control of end-tidal isoflurane concentration using low-flow anaesthesia. *BJA*. 2000;85(6):18-25.

13. Nathan N, et.al. Physioflex™ a target-control self-regulating closed-circuit inhalation anesthesia regulator. *Ann Fr Anesth Reanim*. 1997;16(5):534-540.

14. Suzuki B, et.al. Evaluation of the Physioflex™ closed-circuit anaesthesia machine. *EJA*. 2000;17(6):359-363.

15. Lortat-Jacob B, et.al. Assessing the clinical or pharmaco-economical benefit of target controlled desflurane deliver in surgical patients using the Zeus® anaesthesia machine. *Anaesthesia.* 2009;64:1229.

16. Struys M, et.al. Time course of inhaled anesthetic drug delivery using a new multifunctional closed-circuit anaesthesia ventilator. In vitro comparison with a classical anaesthesia machine. *BJA.* 2005;94(3):306-17.

17. Garufi G, Turchet F, Zanei A, Lucangelo U. Risk of Hypoxic Gas Mixture in Low Flow Anaesthesia: End-tidal Versus Manually Controlled Anaesthesia. Paper presented at: 5th International Meeting - Dialogues on aneaesthesia and intensive care, 2011; Napoli.

18. *Medtech innovation briefing: End-tidal Control software for use with Aisys closed circuit anaesthesia systems for automated gas control during general anaesthesia.* London: National Institute for Health and Care Excellence (NICE); 2014. ISBN: 978-1-4731-0753-3.

19. *End-tidal Control.* Giles, Buckinghamshire: GE Healthcare; 2014.

18. GLOSSARY OF TERMS

Air	Medical Air
Adverse Device Effect (ADE)	An adverse event related to the use of an investigational medical device [ISO 14155:2011 3.1]. This includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This includes any event that is a result of a user error or intentional misuse of the investigational device [ISO 14155:2011 3.43].
Adverse Event (AE)	As defined by EN ISO 14155-2011: 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.
Anticipated Adverse Device Effect	Any adverse event and/or reaction, the specificity or severity of which is consistent with the IRB approved informed consent, protocol, investigator brochure, or product labeling.
Balance gas	Remaining carrier gases other than oxygen delivered to the patient
Circle rebreathing system	An anesthesia breathing system with a gas reservoir that allows patient gases to be rebreathed after the expired carbon dioxide is removed.
Clinician	Specialty clinician trained in the administration of anesthesia care, including anesthesiologists, residents, fellows, CRNA, or certified anesthesia assistant.
Closed circuit anesthesia	Functional mode of circle breathing system with fresh gas flow equal to patient gas uptake
Device deficiency	An inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, such as malfunctions, use errors, and inadequate labelling [ISO 14155:2011 3.15].
Early termination of a subject	Any situation in which the clinician determines they no longer want to continue with the case, or the clinician may choose to discontinue the Et Control mode during a case.
End tidal Concentration	Gas concentration at the end of expiration
End of surgery	Often defined as the procedure end time, last stitch, or placement of the last bandage
Et Control (called Smartflow in feasibility study)	A mode of adjusting the mixer and vaporizer delivery based set target of end-tidal anesthetic agent and oxygen concentrations
Evaluable Population	This analysis set includes all randomized subjects with at least 45 minutes of inhalational anesthesia data collected during the study procedure.
Fresh gas	Combined gases from the mixer and vaporizer
Gender	Biological sex of the subject.
Heart rate	Defined as the heart rate < 45bpm or > 110bpm for more than 5 minutes.

High flow anesthesia	Anesthesia delivery with fresh gas flow above minute ventilation typically above 5 liters per min
Hypoventilation	Inadequate ventilation delivered to the patient
Hypoxia	Insufficient oxygen delivered to the patient defined as for SpO_2, for data collected every five minutes any single incidence of SpO_2 readings less than 90%.
Induction Time	Start: Aisys CS² recording F_iO_2 > 80% (pre-oxygenation) with end-tidal CO_2 breaths detected. End: When the subject is intubated (LMA or endotracheal) and when mechanical ventilation is turned on.
Intent-to-treat Population	This analysis sets includes all randomized subjects.
Low flow anesthesia	Anesthesia delivery with fresh gas flow of about 1 to 3 liter per min
Mechanical ventilation	Ventilation delivered by an anesthesia ventilator
Medium flow anesthesia	Anesthesia delivery with fresh gas flow of about 3 to 5 liter per min
Minimal flow anesthesia	Anesthesia delivery with fresh gas flow of about 0.5 to 1 liter per min
Minimum Alveolar Concentration	A concept used to compare the potency of anesthetic vapor. It is defined as the concentration of the vapor in the lungs that is needed to prevent movement (motor response) in 50% of subjects in response to surgical (pain) stimulus
Minute ventilation	Patient volume ventilation per minute
Mixer	A device used to control the flow of oxygen mixed with air or nitrous oxide
Non-Invasive Blood pressure (NIBP)	Defined as having the systolic blood pressure (SBP) reading < 75 mmHg or > 160 mmHg or mean arterial pressure (MAP) of < 55 mmHg or > 120 mmHg for > 5 minutes.
Non rebreathing system	A breathing system where the patient inspired gases is totally supplied by the gas mixer and the vaporizer.
OR discharge	Patient disconnected from the anesthesia machine
Peripheral Capillary Oxygen Saturation (SpO_2)	Defined as having a value less than 90% for more than 5 minutes.
Per Protocol Population	This analysis set includes all subjects in the evaluable population without critical protocol deviation.
Post-anesthesia discharge time	From the OR discharge to discharge time from the PACU *(the time patient meets criteria to discharge from PACU).*
Predicted Total Lung Capacity	An estimated lung capacity based on sex and height
Pre-existing Hypertension	Patient that has been treated for hypertension
Rebreathing system	A breathing system where expired patient gases are allowed to recirculate and rebreathed. Rebreathed gases mix with the gases supplied by the mixer and vaporizer to form the inspired patient gases.
Safety Population	This analysis set includes all randomized subject, who underwent

	anesthesia using the investigational device or the control device.
Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event [ISO 14155:2011 3.36].
Serious Adverse Event (SAE)	As defined by EN ISO 14155 – 2011: an adverse event that a. led to death; b. led to a serious deterioration in the health of the subject, that either resulted in: (1) a life-threatening illness or injury, or (2) a permanent impairment of a body structure or a body function, or (3) in-patient or prolonged hospitalization, or (4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function; c. led to fetal distress, fetal death or a congenital abnormality or birth defect.
Time of last breath from the anesthesia machine	Point of last breath from the data collection
Unanticipated adverse device effect (UADE)	As defined by 21 CFR 812.3: means 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 investigational plan 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.
Unanticipated serious adverse device effect (USADE)	A serious adverse device effect, which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report [ISO 14155:2011 3.42]. In the United States, 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 study documents, will be reported in accordance with 21 CFR 812.3 and applicable laws and regulations.
Unrecoverable failure	The inability to use Et Control mode because of unrecoverable device malfunction
Vaporizer	A device used to vaporize and meter the concentration output of volatile anesthetics added to the mixer gases.

APPENDIX 1 – ASA PHYSICAL STATUS CLASSIFICATION SYSTEM*

ASA Physical Status 1 - A normal healthy patient
ASA Physical Status 2 - A patient with mild systemic disease
ASA Physical Status 3 - A patient with severe systemic disease
ASA Physical Status 4 - A patient with severe systemic disease that is a constant threat to life
ASA Physical Status 5 - A moribund patient who is not expected to survive without the operation
ASA Physical Status 6 - A declared brain-dead patient whose organs are being removed for donor purposes

* These definitions appear in each annual edition of the ASA Relative Value Guide

APPENDIX 2 – EXTRACTION ALGORITHM

A high level description of the extraction algorithm is provided below. The extraction algorithm is common to both operational modes (Et Control and Control) for the derivation of user desired end-tidal concentrations for anesthetic agent or oxygen. In additional to derived user desired end-tidal concentrations with the algorithm, the clinicians also record desired end-tidal concentration values during the case. The extraction algorithm analyzes the end tidal oxygen performance separately from the end-tidal anesthetic agent performance.

Although this extraction algorithm provides an objective comparison between Et Control and Control group, it cannot be used as an engineering analysis of the Et Control controller. The biggest reason for this is described in Step 4 (below). Instead of analyzing all of the Et Control set target end-tidal values directly, smaller setting changes are combined and treated as one step change. This combination of setting changes leads to a more conservative assessment of Et Control.

The extraction algorithm steps are as follows:

1) Identify all device setting changes. The device setting changes in the Fresh Gas control mode are the total mixer flow, mixer oxygen concentration and vaporizer concentration settings. Any mixer and vaporizer setting changes are interpreted as a user attempt to alter the patient end tidal agent or oxygen concentration. In the Et Control mode, patient end tidal concentration is targeted directly by adjusting the set end tidal agent and oxygen concentration. Et Control commands the changes to the mixer and vaporizer to alter the patient end tidal concentrations.

2) Determine whether a device setting change is 'Significant' in magnitude. The criteria for significance is whether the subsequent measured response 2 minutes following the device setting change causes a 0.9 %v/v, 0.31 %v/v or 0.17 %v/v change for Desflurane, Sevoflurane or Isoflurane, respectively, or 5 %v/v for oxygen.

3) Identify all periods of end tidal concentration measurement stability, following setting changes (i.e. Steady States). A stable period for agent is defined as all points where the rate of change of measured EtAA is less than 0.2 %v/v per minute and persists for a period of 2 minutes. A stable period for oxygen is defined as all points where the rate of change of the measured EtO2 is less than 1.5 %v/v per minute and persists for a period of one minute.

4) Determine the desired end tidal concentration by averaging all EtAA or EtO2 points once stability is reached until the next significant setting change. Non-significant changes are ignored and treated as part of the current step change/steady state.

5) For all significant changes which reach a stable concentration, compute the efficacy performance statistics (Response Time, Command Overshoot, Settling Time, Steady State Mean and Standard Deviation).

    a. Response Time for agent is defined as the smaller of either the time to reach 90% of the change between the initial EtAA and the desired end tidal concentration or the

time to get to within 0.9 %v/v, 0.31 %v/v or 0.17 %/v for DES, SEV or ISO, respectively, of the desired end tidal concentration.

b. Response Time for oxygen is defined as the smaller of either the time to reach 90% of the change between the initial EtO2 and the desired end tidal concentration or the time to get to within 5 %v/v of the desired end tidal concentration.

c. Command Overshoot is defined as the maximum value beyond the desired end tidal concentration from the start of the step change until the Settling Time.

d. Settling Time for agent is determined by looking backwards from the stable concentration to the time where the agent is within 0.9 %v/v, 0.31 %v/v and 0.17 %v/v for DES, SEV and ISO, respectively, of the desired end tidal concentration.

e. Settling Time for oxygen is determined by looking backwards from the stable concentration to the time where the oxygen is within 5 %v/v of the desired end tidal concentration.

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APPENDIX 3 – STUDY SCHEDULE OF PROCEDURES

STUDY ACTIVITY	SCREENING	RANDOMIZATION	INDUCTION AND INTUBATION PHASE	MAINTENANCE PHASE	EMERGENCE PHASE	PACU DISCHARGE	24 HR POST OPERATIVE [4]
	Data Collection						
Informed Consent[1]	•						
Inclusion/Exclusion Assessment	•						
Randomization		•					
Demographics	•						
Medical History	•						
Surgical History	•						
Concomitant Medications	•						
Current Surgery	•						
Physical Examination	•						
Laboratory Assessment • pregnancy test, if applicable	•						
Height / Weight / BMI	•						
Heart Rate [3]	•		•	•	•	•	
Blood Pressure (systolic and diastolic) [3]	•		•	•	•	•	
Mean Arterial Pressure (MAP)	•		•	•	•	•	
SpO_2 [3]	•		•	•	•	•	
Concomitant Medication (intravenous)			•	•	•	•	
Vasoactive Medication			•	•	•		
Inhalation Agent used prior to Intubation			•				
Time of Induction			•				
Time of Intubation			•				
Incision Time			•				
Et Control Initiation				•[2]			
Operative Positioning			•				
Airway Pressure			•	•	•		
Tidal Volume			•	•	•		

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STUDY ACTIVITY	SCREENING	RANDOMIZATION	INDUCTION AND INTUBATION PHASE	MAINTENANCE PHASE	EMERGENCE PHASE	PACU DISCHARGE	24 HR POST OPERATIVE [4]
	Data Collection						
EtO_2			•	•	•		
$EtCO_2$			•	•	•		
EtAA			•	•	•		
F_iAA			•	•	•		
F_iO_2			•	•	•		
Adverse Event Assessment [5]	•	•	•	•	•	•	•
End Time of Surgery					•		
Estimated Blood Loss					•		
Time subject is moved from the operating room					•		
Length of time in recovery room						•	
Time of admission to ICU or general ward						•	
Assess for intraoperative awareness							•
User Survey [6]					•		

1 Informed consent must occur prior to any screening activities.

2 Only applicable to investigational arm (Et Control).

3 These parameters will be collected from the electronic medical records (EMR).

4 There will be no follow-up visit after the 24-hour Post-Operative period.

5 Adverse Event Assessment will be performed from the time the subject provided consent to the end of study participation.

6 User survey to be completed after the emergence phase for each case.

APPENDIX 4 – STUDY SITE AND INVESTIGATOR LIST

The following investigators at each study site will be responsible for the conduct of this study:

Investigator(s):[1]	**Edmund Jooste, MD** *Principal Investigator* *Tel:* [redacted]	**Duke University** *Address:* 2301 Erwin Road Durham, NC 27710
	Matthew A. Klopman, MD, *Principal Investigator* *Tel:* [redacted]	[redacted] 1364 Clifton Road NE Atlanta, GA 30322
	David Ramsingh, MD, *Principal Investigator* *Tel:* [redacted]	**Loma Linda University** *Address:* 11234 Anderson Street MC-2532-D Loma Linda, CA 92354
	Melinda Seering, MD *Principal Investigator* *Tel:* [redacted]	**University of Iowa Healthcare** *Address:* 200 Hawkins Drive Iowa City, IA 52242

[1] The role of the ***Principal Investigator*** is to implement and manage the conduct of the investigation as well as ensure data integrity and the rights, safety, and well-being of humans involved in the study [ISO 14155:2011 9.1]. ***Co-Investigators*** share all responsibilities of the ***Principal Investigator***, and ***Sub-investigators*** share only those responsibilities designated by the ***Principal Investigator***.

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APPENDIX 5 - AMENDMENTS (PROTOCOL VERSION 1.0 TO 2.0)

A detailed amendment is provided for version 1.0 to version 2.0. Version 1.0 was the first version submitted to the U.S. Food and Drug Administration (US FDA) for the Investigational Device Exemption (IDE) submission, and was not provided to the investigational sites for IRB approval.

Purpose of Amendment:

1) To make changes as requested by the US FDA, per FDA IDE deficiencies and disapproval letter dated 14/Jul/2016, per IDE #G160132.
2) Sponsor administrative changes.
3) To make general typographical/formatting corrections, in accordance with current standard style guides, American Medical Association (AMA) style, and internal standards of the Sponsor.

These changes are not expected to increase subject or operator risk or to adversely impact the scientific integrity or conduct of the study.

In the table below, point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment from the previous version.

Item	Section	Revision or Clarification	Justification
1	Cover Page	Version: 2.0~~1.0~~, 15/Aug/2016~~02/Jun/2016~~ Sponsor Contact: [redacted], BSc, Clinical Affairs Project Manager Tel: [redacted] E-mail: [redacted]	This is a clarification that does not impact the study design or risk. This is a clarification that does not impact the study design or risk.
2	Footer	Ver: 2.0~~1.0~~, 15/Aug/2016~~02/Jun/2016~~	This is a clarification that does not impact the study design or risk.
3	Table of Contents	*Updated table of contents to:* 1) included new sections: ▪ 10.5—Follow-up and Use of Data Collected of Subjects with Reported Event ▪ 11.3—Follow-up and Use of Collected Data of Subjects Withdrawn/Discontinued ▪ Appendix 5—Amendments (Protocol Version 1.0 to 2.0)	This is a clarification that does not impact the study design or risk.

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<table>
<tr><th>Item</th><th>Section</th><th>Revision or Clarification</th><th>Justification</th></tr>
<tr><td></td><td></td><td>2) sections moved:
"Early Termination of Subjects" from 6.5 to 11..1
"Withdrawal of IRB Approval" from 11.2 to 12.3</td><td></td></tr>
<tr><td>4</td><td>List of Figures and Tables</td><td>Updated list of figures and tables</td><td>This is a clarification that does not impact the study design or risk.</td></tr>
<tr><td>5</td><td>Document and Version Control</td><td><table><tr><th>Revision</th><th>Date (DD/Mmm/YYYY)</th><th>Revision Author</th><th>Comments/Changes</th></tr><tr><td>1.0</td><td>02/Jun/2016</td><td>Catherine Cadogan</td><td>Clinical Writer – Initial study protocol for the MASTER Pivotal Study.</td></tr><tr><td>2.0</td><td>15/Aug/2016</td><td>Catherine Cadogan</td><td>Clinical Writer – Protocol Amendment – See Appendix 5 for details of changes made.</td></tr></table></td><td>This is a clarification that does not impact the study design or risk.</td></tr>
<tr><td>6</td><td>List of Abbreviations</td><td>ADE Adverse Device Effect
eCRF Electronic Case Report Forms
ITT Intent-To-Treat
SADE Serious Adverse Device Effect
USADE Unanticipated Serious Adverse Device Effect</td><td>This is a clarification that is in consistent with word(s) used within the protocol, and does not impact the study design or risk.</td></tr>
<tr><td>7</td><td>Study Synopsis</td><td>Under Hypothesis/Analysis—last paragraph:
~~Efficacy analysis will be based on available data only from evaluable subjects with at least 45 minutes of inhaled anesthesia data collected during the procedure.~~The analysis of the primary endpoints will consist of:
the analysis on ITT population based on the algorithm determined end-tidal concentration (scenario 1) and clinician's recorded set target end-tidal concentration (scenario 2); AND
patients of different ASA status.</td><td>This correction is in response to Question #4 of the interactive questions, FDA email dated 8/Jul/2016 for IDE #G160132.</td></tr>
<tr><td>8</td><td>Administrative Structure</td><td>Under Clinical Affairs Project Manager (Sponsor Contact): [redacted]; telephone</td><td>This is a clarification that does not impact the</td></tr>
</table>

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Item	Section	Revision or Clarification	Justification
	of Investigation	*number was corrected:* [redacted] *Corrected Biostatistician's name:* [redacted] *Under the rows – Medical Monitor and Biostatistician:* **GEHC** ~~(or include other affiliation)~~	study design or risk.
9	Section 1.1.1—Literature Review	*On the 2nd sentence:* (Clinician is defined as specialty clinician trained in the administration of anesthesia care including anesthesiologist, residents, fellows, certified registered nurse anesthetist [CRNA], or certified anesthesia assistant.)	This is a clarification that is in consistent with the definition in the Glossary of Terms, and does not impact the study design or risk.
10	Section 1.3.1—Risks	*Under the 3rd paragraph, 3rd sentence:* The Et Control option does not provide dosing guidance, or alter the drug dosage as prescribed by the ~~anesthesiologist/~~clinician trained in the administration of general anesthesia ~~(clinician)~~.	This is a clarification that is in consistent with word(s) used within the protocol, and does not impact the study design or risk.
11	Section 2.1.2—Description of the Investigational Et Control Option	*Under the 1st paragraph, last sentence:* The Et Control feature does not provide dosing guidance, or alter the set dose that is prescribed and entered by the ~~anesthesiologist~~ clinician.	This is a clarification that is in consistent with word(s) used within the protocol, and does not impact the study design or risk.
12	Section 2.1.3.2—Legally marketed device	*First bullet removed and 3rd bullet corrected:* • ~~Model: Aisys CS2~~ • ~~With~~ Datex-Ohmeda respiratory gas module: M-CAIOVX, M-CAIOV, M-CAIO, E-CAIOVX, E-CAIOV, or E-CAIO	Administrative change.
13	Section 3.4.1—Primary Endpoint	*In the note under item #(2):* **NOTE:** The steady state concentration is based on extraction algorithm for both Et Control and Control arms as well as based on the ~~anesthesiologist's~~ clinician's recorded ~~set~~ target values for the Control Arm and the set target	This is a clarification in wording that is in consistent with describing scenarios for data analysis as used within the protocol, and does not impact the study design or risk.

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		values for the Et Control Arm.	
14	Section 3.4.2—Secondary Endpoint	*In the note under item #(1) d:* **NOTE:** The response time, settling time, and overshoot amount data extraction will be done in two scenarios: 1) using the algorithmic determination of desired end-tidal concentration of anesthetic agent and oxygen for both arms (see Appendix 2), and 2) using the ~~anesthesiologists~~clinicians recorded target values of anesthetic agent and oxygen for the Control Arm and the using ~~the~~ set target values for the Et Control arm.	This is a clarification that is in consistent with word(s) used within the protocol, and does not impact the study design or risk.
15	Section 3.4.3—Other Endpoints	(1) Usage of inhaled anesthetic agent~~ and fresh gas~~; (2) Number of user interactions; AND (3) Time to discharge from the operating room (OR) (measured from the end of surgery [last stitch] to time of last breath).	This clarification was made on the basis of the device claim, and does not impact the study design or risk.
16	Section 5.6.1—Recruitment/Consent Process	*Under the last paragraph, last sentence:* The unique subject number will be used to label electronic case report forms (eCRFs) data as well as data collected in by the Aisys CS2 for the subject throughout his/her participation in the study.	The correction was made to be consistent with the type of data collection system that will be used in the study, and does not impact the study design or risk.
17	*Throughout the protocol*	*The following word or acronym were corrected and can be found in Sections 6.3.2, 6.3.3, 6.3.6, 9.1, 10.3, 10.4, 11.1, 11.3, 15.1, 15.2.1:* Case Report forms – was corrected to Electronic Case Report Forms CRFs – was corrected to eCRFs	The correction was made to be consistent with the type of data collection system that will be used in the study, and does not impact the study design or risk.
18	Section 6.3.1—Preoperative Data Collection	*Under #3—Surgical History:* ~~obtain during the pre-operative screening –~~ collect description of surgeries, surgery date, ~~type of anesthesia,~~ and adverse reaction to anesthesia~~ and resolution~~	This is a clarification that removes redundancy and insignificant data, and does not impact the study design or risk.
		Under #5—Baseline Vitals: height, weight, body mass index (BMI), heart rate, blood pressure (systolic ~~and~~ /diastolic/MAP), and peripheral capillary oxygen saturation (SpO2)	The added information is in consistent with the data collected in the Operative Procedure, and does not impact the study design or risk.

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Item	Section	Revision or Clarification	Justification
		Under #5—Baseline Vitals: ~~*Note: Baseline blood pressure collection shall be performed between screening and induction.*~~	This is a clarification to remove redundant information and does not impact the study design or risk.
19	Section 6.3.2—Operative Procedure Data Collection (Induction/Intubation, Maintenance, and Emergence)	*Under the 1st bullet:* • Collect the following data from the departmental electronic medical record (EMR) from induction through emergence phase~~—at a minimum of 5-minute interval~~: **NOTE:** Collection of vital signs shall be made at a minimum of every 2.5 minutes for the first 2 hours of each case, and at a minimum of every 5 minutes thereafter through the emergence phase. If the subject becomes unstable, the clinician shall revert to collecting the vital signs at a minimum of every 2.5 minutes, and shall record the reason for change in the collection of vital signs and any adverse events that may occur. Once the subject returns to a stable state, the clinician shall collect the vital signs at a minimum of every 5 minutes.	This correction is in response to Question #2of the IDE deficiencies and disapproval letter dated 14/Jul/2016 from the FDA for IDE #G160132.
		Under the 2nd bullet, item #2, 4 and 5: 2. Vasoactive medications: (e.g., Ephedrine, Epinephrine, Dopamine Norepinephrine, Phenylephrine, etc.) including name, dose and unit, rate, time administered, time stopped, and reason for dose (~~standard of care~~prophylactic, hypotension, anesthetic overdose, hypovolemia, depressed cardiac output, depressed systemic vascular resistance, dose decrease or other) – administered from induction to emergence phase	This is a clarification of data collection and in response to Question #4 under the section "Additional Recommendations and Considerations—Study Design Considerations" of the IDE deficiencies and disapproval letter dated 14/Jul/2016 from the FDA for IDE #G160132.
		Under the 2nd bullet, item #4 and 5: 4. Time of induction 5. Time of intubation 9. End time of surgery (often defined as the last stitch or placement of the last bandage)	This is a clarification that includes data collected on the electronic case report form, and does not impact the design of the study design or risk.
20	Section 6.3.4—Twenty-four (24) hours Post PACU Data Collection	*First sentence:* Collect the following information 24-hours post PACU discharge for subjects that completed the study and those that were withdrawn or discontinued from study participation *during* the study procedure.	The is a clarification that conforms to Section 11.3 of the protocol, and does not impact the study design or risk.
21	Section 6.4—Withdrawal	*The following paragraph was moved to a new section 11.3—Follow-up and Use of*	This is a clarification that consolidates relevant

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Item	Section	Revision or Clarification	Justification
	and Discontinuation Criteria	*Collected Data of Subjects Withdrawn/Discontinued.* ~~A 24-hour follow-up will be conducted for subjects that were withdrawn or were discontinued from study participation during the study procedure. No additional follow-up will be conducted for subjects that withdrew or were withdrawn from study participation prior to study procedure. Any data collected during the participation of the subject or prior to withdrawal will still be included in the study results and provided to the Sponsor.~~	information and does not impact the study design or risk.
22	~~Section 6.5 Early Termination of Subjects~~	*This section was moved to Section 11 as 11.1—Early Termination of Subjects.* ~~Early termination of a subject is defined as any situation in which the clinician determines they no longer want to continue with the case, or the clinician may choose to discontinue the Et Control mode during a case. The following objective criteria are utilized to determine when it is appropriate to terminate the subject's participation in the study; additionally, to terminate the Et Control in the investigational arm:~~ ~~• Mean arterial pressure of less than 55 mmHg that is sustained for greater than 10 minutes; OR~~ ~~• SpO2 less than 90% that is sustained for greater than 10 minutes; OR~~ ~~• With respect to device performance, the Et Control device is not meeting the expected performance requirements such that:~~ ~~• Measured EtO2% is less than 21% for 5 min;~~ ~~• OR~~ ~~• Measured ETAA% at steady state deviates from the set EtAA% by more than the following:~~ ~~• Desflurane +/- 2.0 % for 5 min~~ ~~• Sevoflurane +/- 0.6 % for 5 min~~ ~~• Isoflurane +/- 0.3 % for 5 min~~ ~~• At least two device auto exits of Et Control because of unrecoverable failure (inability to use Et Control mode because of unrecoverable device malfunction)~~ ~~The reason for early termination will be recorded on a Case Report Form.~~ ~~If the Et Control system detects any issues or fault conditions during the case (such as leaks or accuracy issues), the Et Control program may temporarily transition to fall back mode until the clinician is able to address and resolve the issue. This is not considered auto exit or early termination. This is a design element to help mitigate potential safety risks and correct failure modes.~~	This is a clarification that consolidates relevant information and does not impact the study design or risk.

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		~~Cases in which there are brief periods of use outside of Et Control based on the algorithm self-exiting will continue to be analyzed as part of the Et Control Arm.~~	
23	Section 7.2—Training Plan for Research Device	*The following heading was deleted:* ~~7.2.1 Device User Training~~	This clarification simplifies Section 7 and does not impact the study design or risk.
		In the 1st sentence of 1st paragraph: Each clinician ~~(anesthesiologist or CRNA)~~ will be provided with the following documentation for training purposes: *Under the 2nd paragraph, 4th bullet:* • Review of safety and labeling as defined in the user reference manual for Aisys CS2 10.X and the Et Control user reference manual addendum~~:~~	Administrative change
		Under 2nd paragraph, 1st sentence: All clinicians will ~~undergo~~ be ~~device~~ train~~ed~~ing prior to start of the study based on the above-mentioned documents that will be provided. *The following heading was deleted:* ~~7.2.2 Site Technical Training~~	This clarification simplifies Section 7 and does not impact the study design or risk.
		Under the 4th paragraph, 2nd to the last bullet: • Activation and deactivation of Et Control software feature~~.~~ • Aisys CS2 machine preuse check~~.~~ • ~~-~~Aisys CS2 Logs (breath and service logs)	Administrative change
24	Section 7.3—Training Plan for Protocol	*The following heading was deleted:* ~~7.3.1.1 Investigator Site Training~~ *Under the 1st paragraph:* Site research personnel (including investigators, device users, study coordinators, and other appropriate personnel such as OR nurses) will ~~receive training~~be trained on the clinical investigation requirements set forth in this study protocol, according to the following ~~topics~~requirements: • Title of training	This clarification removes duplicate information and simplifies Section 7, and does not impact the study design or risk.

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		• Training objectives • Training logistics (who conducts training and training method) • Target audience (who will be trained) • Training content including device operation (as noted above), protocol review, and understanding ~~• Overview of Good Clinical Practices~~ ~~• Responsibilities of the Investigator~~ ~~• Clinical trial protocol~~ ~~o Objectives of the study~~ ~~o Study procedures~~ ~~o Adverse event and serious adverse event reporting~~ ~~• Case report form completion~~ ~~• Study Regulatory Binder maintenance~~ ~~• Data management, incl. query resolution/data clarification form (DCF)~~ ~~• Monitoring visit expectations~~ ~~• Foreign country commercial experience with Et Control~~ ~~The Study Monitor(s) will complete training on the following topics:~~ ~~• Clinical trial protocol~~ ~~o Objectives of the study~~ ~~o Study procedures~~ ~~o Adverse event and serious adverse event reporting~~ ~~• Aisys CS2 Logs and how to review the data for protocol compliance~~ ~~• Case report form completion~~ ~~Data management, including query resolution/DCF~~	
		Added the following last paragraph: The Principal Investigator will be ultimately responsible for evaluation of this study in accordance with the protocol and for device used in this study by members of the study staff.	This added information conforms to US FDA 21 CFR part 812, ISO 14155:2011, and ICH E6; and does not impact the study design or risk.
25	Section 8.1.2—Statistical	*Under the 2nd paragraph, last sentence:* Categorical variables will be described with counts, percentages, and sample size.	Administrative change

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	Methods Overview	*Paragraphs 6 and 7 were deleted:* ~~Efficacy analysis will be based on available data only from evaluable subjects with at least 45 minutes of inhalational anesthesia data collected during the procedure.~~ ~~Evaluable subjects without critical protocol deviations constitute the per-protocol population.~~	This is a clarification that corresponds to the response to Questions #2 under the section "Additional Recommendations and Considerations—Study Design Considerations" of the IDE deficiencies and disapproval letter dated 14/Jul/2016 from the FDA for IDE #G160132.
		Under 9th paragraph: There will be two scenarios in defining a step change and steady state when performing the data extraction: 1) using the data extraction algorithm to determine the desired end-tidal concentrations of anesthetic agent and oxygen for both arms (See Appendix 2 – Extraction algorithm for more information on the extraction algorithm.); 2) using the ~~anesthesiologists~~ clinicians recorded end tidal target values of anesthetic agent and oxygen for the Control arm, and the set target value for the Et Control arm.	This is a clarification that is in consistent with word(s) used within the protocol, and does not impact the study design or risk.
26	Section 8.1.3—Analysis of Primary Endpoints	*Under 1st paragraph:* Separate analysis of primary endpoints will be performed on the basis of the extracted data for the following scenarios: 1.) using the algorithm to determine the desired end-tidal concentrations of anesthetic agent and oxygen for both arms; and 2) using the ~~anesthesiologists~~ clinicians recorded target values of anesthetic agent and oxygen for the Control Arm and using the set target values for the Et Control Arm.	This is a clarification that is in consistent with word(s) used within the protocol, and does not impact the study design or risk.
		Under the 2nd paragraph: Analysis of primary endpoints will be based on ITT population, evaluable population, and per protocol population. The conclusion will be based on the ITT population.	This correction is in response to interactive questions from FDA.
		Under the 5th paragraph: The primary analysis for the primary endpoints consists of the analysis on ~~evaluable~~ ITT ~~subjects~~ population based on ~~extracted data using~~ the algorithm~~e~~ determined~~ation of desired~~ end-tidal concentration (scenario 1) and clinician's recorded set target end-tidal concentration (scenario 2) ~~is considered the primary analysis for the primary endpoints. And t~~This primary analysis will also be performed for patients of different ASA status.	This correction is in response to Questions #2 under the section "Additional Recommendations and Considerations—Study Design Considerations" of the IDE deficiencies and disapproval letter dated 14/Jul/2016 from the FDA for IDE #G160132.

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27	Section 8.1.4.1—Performance Statistics	*Under the 1st paragraph – 1st sentence:* For response time, settling time and overshoot amount (% to steady state mean for anesthetic agent, and ~~vol%~~v/v for O2), analysis will be on the basis of each steady state. *Under the 2nd paragraph:* For average deviation (% to steady state mean for anesthetic agent, and ~~vol%~~v/v for O2) and half width of 95% CI of deviation, analysis will be on the basis of each subject. The weighted average using the duration of steady state duration as the weight for a subject will be calculated and compared between the Et Control and Control Arms using t-test. For the maximum deviation (% to steady state mean for anesthetic agent, and ~~vol%~~v/v for O2), the maximum of all steady states for a subject is taken for analysis, and the maximum deviation be compared between Et Control and Control arms using nonparametric Wilcoxon rank sum method.	This is a clarification that is in consistent with word(s) used within the protocol, and does not impact the study design or risk.
28	Section 8.1.8—Analysis of Vasoactive Medications	*In the 3rd sentence:* The vasoactive medication use will be analyzed by ASA status and by preexisting hypertension status.	The addition is related to the stratification variable.
29	Section 8.3—Handling Missing Data	*Under the 2nd paragraph:* For missing values of primary endpoints, multiple imputations will be performed and sensitivity analysis will be conducted for primary endpoints.	This is a clarification that does not impact the study design or risk.
		Third paragraph added: Clinician recorded end tidal target values are considered missing, when a recorded target is not available for a setting adjustment resulting in a significant change in end tidal measurements. If the change in end tidal measurement results in more than 5% v/v O2, 0.9% v/v DES, 0.31% v/v SEV, or 0.15% v/v ISO from the previous end tidal measurement over a period of 2 minutes, then the recorded target data is considered missing. This portion of the data is not used for the purpose of the analysis with the clinician recorded target values.	This added information is related to the potential missing recorded target values from the clinicians.
30	Section 10.1—Foreseeable Adverse Events and Device	*Under the 1st paragraph, 1st sentence added:* Being in this study involves some foreseeable risks.	This is a clarification that does not impact the study design or risk.

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	Effects	*Added sentences after Table 10-1:* Adverse event assessment will be conducted from the time the subject provided consent to the end of the subject's participation in the study. There is always a chance of unexpected risks. Throughout the study, the Sponsor will evaluate and update safety information in study documents.	This is a clarification for existing information in the protocol and conforms to ISO 14155:2011, and does not impact the study design or risk.
31	Section 10.2—Adverse Event Definitions	*Under Unanticipated Serious Adverse Device Event (USADE), 2nd sentence:* In the United States, 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 study documents, will be reported in accordance with 21 CFR ~~§~~812.3 and applicable laws and regulations.	Administrative change.
32	Section 10.4—Management of Serious Adverse Event and Unanticipated Adverse Device Effect Reporting	*First sentence of the 1st paragraph corrected:* All SAEs and/~~-~~or UADEs will be documented as above and reported in writing to the Sponsor within 72 hours of knowledge of the event.	Administrative change.
33	Section 10.5—Follow-up and Use of Collected Data of Subjects with Reported Event	*This section has been added:* Subjects with reported event (AE, SAE, ADE, SADE, UADE, or USADE) shall be followed until the resolution of the event. The Investigator shall submit a follow-up report as indicated in the above-mentioned section. If an event occurred during the study procedure and the subject was withdrawn or discontinued as deemed necessary by the Investigator, any data collected up to the resolution of the event may be used by the Sponsor for the assessment of the event.	This added section conforms to ICH E6 6.9.5 and ISO 14155:2011 Annex A A.7(k).
34	Section 11.1—Early Termination of Subject	*This section was moved from Section 6.5* Early termination of a subject is defined as any situation in which the clinician determines they no longer want to continue with the case, or the clinician may choose to discontinue the Et Control mode during a case. The following objective criteria are utilized to determine when it is appropriate to terminate the subject's participation in the study; additionally, to terminate the Et Control in the investigational arm: • Mean arterial pressure of less than 55 mmHg that is sustained for greater	This is a clarification that consolidates relevant information and does not impact the study design or risk.

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		than 10 minutes; OR • SpO2 less than 90% that is sustained for greater than 10 minutes; OR • With respect to device performance, the Et Control device is not meeting the expected performance requirements such that: ▪ Measured EtO2% is less than 21% for 5 min; OR ▪ Measured ETAA% at steady state deviates from the set EtAA% by more than the following: • Desflurane +/- 2.0 % for 5 min • Sevoflurane +/- 0.6 % for 5 min • Isoflurane +/- 0.3 % for 5 min • An unrecoverable failure that prevents the use of Et control *(Unrecoverable failure is defined as the inability to use Et Control mode because of unrecoverable device malfunction)* The reason for early termination will be recorded on the Electronic Case Report Form. If the Et Control system detects any issues or fault conditions during the case (such as leaks or accuracy issues), the Et Control program may temporarily transition to fall back mode or enter fresh gas mode until the clinician is able to address and resolve the issue. This is not considered auto exit or early termination. This is a design element to help mitigate potential safety risks and correct failure modes. Cases in which there are brief periods of use outside of Et Control based on the algorithm self-exiting will continue to be analyzed as part of the Et Control Arm.	Clarified unrecoverable failure in response to Question #1 under the section "Additional Recommendations and Considerations—Study Design Consideration" of the IDE deficiencies and disapproval Letter dated 14/Jul/2016 from the FDA.
35	Section 11.3—Follow-up and Use of Collected Data of Subjects Withdrawn/Discontinued	*This section has been added; paragraphs moved from Section 6.4:* A 24-hour follow-up will be conducted for subjects that were withdrawn or were discontinued from study participation during the study procedure. Assessment of adverse events and intraoperative awareness shall be collected *(see Section 6.3.4—Twenty-four (24) hour Follow-up Post PACU data collection)*, and shall utilize the Electronic Adverse Events and Intra-Operative Awareness Questionnaire case report forms (CRFs). No additional follow-up will be conducted for subjects that withdrew or were withdrawn from study participation prior to study procedure. Any data collected during the participation of the subject or prior to withdrawal will still be included in the study results and provided to the Sponsor.	This is a clarification that consolidates relevant information and does not impact the study design or risk.

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36	~~11.2 Withdrawal of IRB Approval~~	*This section was moved to Section 12.3 under Section 12—Institutional Review Board (IRB) and Regulatory Filings:* ~~The Investigator is to notify the Sponsor of any withdrawal of IRB approval within 5 working days of such occurrence. If the IRB terminates or suspends its approval of the Study, the Investigator will promptly notify Sponsor and provide a detailed written explanation of the termination or suspension. Upon receipt, the Sponsor will provide written guidelines/instructions on subject withdrawal/termination processes and timelines.~~	This is a clarification that consolidates relevant information and does not impact the study design or risk.
37	Section 12.3—Withdrawal of IRB Approval	*This section was moved from Section 11.2* The Investigator is to notify the Sponsor of any withdrawal of IRB approval within 5 working days of such occurrence. If the IRB terminates or suspends its approval of the Study, the Investigator will promptly notify Sponsor and provide a detailed written explanation of the termination or suspension. Upon receipt, the Sponsor will provide written guidelines/instructions on subject withdrawal/termination processes and timelines.	This is a clarification that consolidates relevant information and does not impact the study design or risk.
38	Section 13—Data Safety Monitoring Board	*Under the 4th paragraph:* The DSMB shall hold meetings at regular intervals or ad hoc, as needed, and will be detailed in the DSMB Charter. The DSMB may make recommendations on the basis of the following established enrollment stopping/pausing criteria (also noted in Section 11.2~~11.1~~—Criteria for Early Termination or Suspension of the Study) to ensure subject safety:	This is a clarification that does not impact the study design or risk.
		The following was added as the 5th paragraph: If the Sponsor is notified of two early subject terminations *(Section 11.1)* or the study stopping criteria *(Section 11.2)* is met, the Sponsor will notify all study sites to pause enrollment and the DSMB shall convene an ad hoc meeting to determine if the terminations were device related safety issues.	This added information from the DSMB Charter is for clarification and inclusion of relevant information, and does not impact the study design or risk.
39	Section 14.1—Management of Data	*Under the 2nd paragraph:* Upon enrollment, all subjects will be assigned a subject~~tudy~~ number and a randomization code. Electronic Case report forms (eCRFs) will use subject~~study~~ numbers only and will not include subject names or other identifiable personal information.	The correction was made to be consistent with the type of data collection system that will be used in the study, and does not impact the study design or risk.
40	Section 14.2—Subject	*Under the 1st paragraph:* Data will be collected from subjects enrolled in this study and ~~submitted to~~ entered	The correction was made to be consistent with the type of data collection system that will be

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	De-identification	into eCRFs provided by GE Healthcare (GEHC). Data collected will be labeled with a de-identified Subject Identification Designation (SID), which consists of the Site number, Clinician ID and~~is the study~~ subject number.~~and randomization code,~~ eCRFs~~and~~ will not contain any identifiable personal information.	used in the study, and does not impact the study design or risk.
41	Section 14.3—Completion of Electronic Case Report Forms (eCRFs)	*Under 1st paragraph, 2nd and 3rd sentences:* The eCRFs will be reviewed by the Sponsor's designated clinical monitor~~,~~ and then transmitted by the monitor to the Contract Research Organization's (CRO) electronic database. All data entered into the eCRF should be verifiable with source documents unless the eCRF is the source itself. *Under 2nd paragraph:* To ensure the quality and integrity of the data, it is the responsibility of the Principal Investigator or designee to ~~in a timely manner,~~ enter data into the eCRFs for each enrolled subject in a timely manner~~t, who is enrolled to participate in this study~~. GEHC will provide eCRFs and will train study staff on data entry using Good Documentation Practices (GDP). eCRF completion guidelines may be provided by the Sponsor to help facilitate training. eCRFs will be completed as information becomes available. *Under 4th paragraph:* During the course of monitoring, if any errors or omissions are found, they shall be brought to the attention of the site designee, who shall make the corrections, as appropriate on the eCRFs. In the event of an eCRF audit or data review once the eCRFs have been ~~pulled from the site~~completed, a data query~~Data Clarification Form (DCF)~~ will be generated and the error, omissions or clarifications will be corrected on the~~se~~ associated eCRF~~forms~~. *Under 5th paragraph:* The Principal Investigator or a Sub-Investigator will electronically sign and date the indicated places on the eCRF. This signature will indicate that a thorough inspection of the data has been made and will thereby certify the contents of the form.	The correction was made to be consistent with the type of data collection system that will be used in the study, and does not impact the study design or risk.
42	Section 14.4—Data Handling and Record Keeping	All documents and data shall be produced and maintained in a manner that assures control and traceability.	Administrative change.

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43	Section 14.5—Record Retention at the Site	*Under 1st paragraph, 1st and 2nd sentences:* All records pertaining to the conduct of the study, including source data, e-CRFs, electronic data ICFs, IRB correspondence, and other study documentation must be retained at the site for inspection at any time by the Sponsor's authorized Study Monitor or designee or regulatory agency; i.e., US Food and Drug Administration (USFDA). These records will be maintained by the site for a minimum of 2 years, per US FDA 21 CFR~~F~~ Part 812.140(d), or a maximum of 3+ years, according to the Sponsors policies; after the investigation termination date or after the date the records are no longer required for purposes of supporting a premarket approval application or notice of completion of a product development protocol. *Under the 1st, 2nd, and 3rd bullets in the 1st paragraph:* ▪ **Source data and documentation**: relevant to data recorded for subject screening and eCRF corroboration (i.e., information in original records, certified copies of original records of clinical findings, observations, or other activities for the study) ▪ **Subject Files**: containing the eCRF worksheets and completed patient eCRFs ▪ Regulatory Binder: containing the protocol and amendments, IRB submissions and approvals, ~~(~~blank and signed/dated~~)~~ ICF(s), and site study logs	Administrative change.
44	Section 16—Publication Policy	*Under 2nd paragraph, 1st sentence:* Data obtained from this study may be used for submission to peer reviewed publications that are consistent with study contracts with prior permission from GE Healthcare.	Administrative change.
45	Section 18—Glossary of Terms	*The following terms and definitions were added:* Adverse Device Effect (ADE): An adverse event related to the use of an investigational medical device [ISO 14155:2011 3.1]. This includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This includes any event that is a result of a user error or intentional misuse of the investigational device [ISO 14155:2011 3.43]. Adverse Event (AE): As defined by EN ISO 14155-2011: any untoward	This is a clarification that does not impact the study design or risk.

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			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.	
		Anticipated Adverse Device Effect	Any adverse event and/or reaction, the specificity or severity of which is consistent with the IRB approved informed consent, protocol, investigator brochure, or product labeling.	
		Clinician	Specialty clinician trained in the administration of anesthesia care, including anesthesiologists, residents, fellows, CRNA, ~~and~~or certified ~~A~~anesthesia ~~A~~assistant.	
		Device deficiency	An inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, such as malfunctions, use errors, and inadequate labelling [ISO 14155:2011 3.15].	
		Early termination of a subject	Any situation in which the clinician determines they no longer want to continue with the case, or the clinician may choose to discontinue the Et Control mode during a case.	
		Heart rate	Defined as the heart rate < 45bpm or > 110bpm for more than 5 minutes.	
		Non-Invasive Blood pressure (NIBP)	Defined as having the systolic blood pressure (SBP) reading < 80 mmHg or > 160 mmHg or mean arterial pressure (MAP) of <60 mmHg or > 120 mmHg for >10 minutes.	
		Non rebreathing system	A breathing system where the patient inspired gases ~~are~~is totally supplied by the gas mixer and the vaporizer.	
		Peripheral Capillary Oxygen Saturation (SpO_2)	Defined as having a value less than 90% for more than 5 minutes.	
		Post-anesthesia discharge time	From the OR discharge to discharge time from the PACU.	

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		Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event [ISO 14155:2011 3.36].	
		Serious Adverse Event (SAE)	As defined by EN ISO 14155 – 2011: an adverse event that d. led to death; e. led to a serious deterioration in the health of the subject, that either resulted in: (5) a life-threatening illness or injury, or (6) a permanent impairment of a body structure or a body function, or (7) in-patient or prolonged hospitalization, or (8) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function; f. led to fetal distress, fetal death or a congenital abnormality or birth defect.	
		Unanticipated adverse device effect (UADE)	As defined by 21 CFR 812.3: means 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 investigational plan 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.	
		Unanticipated serious adverse device effect (USADE)	A serious adverse device effect, which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report [ISO 14155:2011 3.42]. In the United States, 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	

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		death was not previously identified in nature, severity, or degree of incidence in the study documents, will be reported in accordance with 21 CFR §812.3 and applicable laws and regulations. Unrecoverable failure — The inability to use Et Control mode because of unrecoverable device malfunction	
46	Appendix 3—Study Schedule of Procedures	*The following procedures were added:* Surgical History – *marked screening column* Concomitant Medications – *marked screening column* Current Surgery – *marked screening column* Height / Weight / BMI – *marked screening column* Time of Induction – *marked induction and intubation column* Time of Intubation – *marked induction and intubation column* Time of admission to ICU or general ward – *marked PACU discharge column* User Survey [6] – *marked emergence phase column* *The following procedure was corrected:* Mean Arterial Pressure (MAP) – *added a mark under the screening column* *The added footer #6 is as follows:* 6 User survey to be completed after the emergence phase for each case.	These are clarifications that conform to the procedures stated in this protocol, and do not impact the study design or risk.

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		Under the heading, the last column was corrected to reference the added footer: 24 HR POST OPERATIVE [4] *The added footer #4 is as follows:* 4 There will be no follow-up visit after the 24-hour Post-Operative period. *The following was corrected to reference the added footer:* Adverse Event Assessment [5] *The added footer #5 is as follows:* 5 Adverse Event Assessment will be performed from the time the subject provided consent to the end of study participation. *The following statement after the table for Appendix 3 was deleted, which was replaced by footers #4 and #5:* ~~* Subjects will be followed for AE reporting purposes from the time they provided consent to the end of the study. There will be no follow-up visit after the 24-hour Post-Operative period.~~	These are clarifications that do not impact the study design or risk.
47	Appendix 4—Study Site and Investigator List	**Investigator(s):[1]** To be determined prior to start of study. ~~(add/remove rows, as necessary, to account for all sites)~~ Investigator Name, *Title/Credentials, and role (e.g. Principal Investigator, Sub-investigator, Co-investigator, etc.)* *Tel:* X-XXX-XXX-XXXX *e-mail:* investigator@ge.com Site Name *Address:* Address Line 1 Address Line 2 Investigator Name, *Title/Credentials, and role (e.g. Principal Investigator, Sub-investigator, Co-investigator, etc.)* *Tel:* X-XXX-XXX-XXXX *e-mail:* investigator@ge.com Site Name *Address:* Address Line 1 Address Line 2	This is a clarification that does not impact the study design or risk.

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		Investigator Name, *Title/Credentials, and role (e.g. Principal Investigator, Sub-investigator, Co-investigator, etc.)* *Tel:* X-XXX-XXX-XXXX *e-mail:* investigator@ge.com — Site Name *Address:* Address Line 1 Address Line 2 Investigator Name, *Title/Credentials, and role (e.g. Principal Investigator, Sub-investigator, Co-investigator, etc.)* *Tel:* X-XXX-XXX-XXXX *e-mail:* investigator@ge.com — Site Name *Address:* Address Line 1 Address Line 2	
48	Appendix 5—Amendments (Protocol Version 1.0 to 2.0)	A detailed amendment is provided for version 1.0 to version 2.0. Version 1.0 was the first version submitted to the U.S. Food and Drug Administration (US FDA) for the Investigational Device Exemption (IDE) submission, and was not provided to the investigational sites for IRB approval. **Purpose of Amendment:** 4) To make changes as requested by the US FDA, per FDA IDE deficiencies and disapproval letter dated 14/Jul/2016, per IDE #G160132. 5) Sponsor administrative changes. 6) To make general typographical/formatting corrections, in accordance with current standard style guides, American Medical Association (AMA) style, and internal standards of the Sponsor. These changes are not expected to increase subject or operator risk or to adversely impact the scientific integrity or conduct of the study. In the table below, point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough ~~(strikethrough)~~ for each change made in this amendment from the previous version. *(NOTE: In the protocol under this section, this table of point-by-point revisions is inserted after the above paragraphs.)*	*This section has been added to list the above-mentioned changes made to the protocol from version 1 to version 2.*

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APPENDIX 6 - AMENDMENTS (PROTOCOL VERSION 2.0 TO 3.0)

A detailed amendment is provided for version 2.0 to version 3.0. Version 1.0 was the first version submitted to the U.S FDA as part of the IDE application. Version 2.0 was the second version submitted to the U.S. FDA in response to IDE deficiencies and disapproval letter dated 14/Jul/2016 for IDE G160132. Versions 1.0 and 2.0 was not provided to the investigational sties for IRB approval.

Purpose of Amendment:

1) To make changes as requested by the US FDA on 9/Sep/2016 from the interactive question from the review of the IDE #G160132-A001.
2) Sponsor administrative changes.

These changes are not expected to increase subject or operator risk or to adversely impact the scientific integrity or conduct of the study.

In the table below, point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment from the previous version.

Item	Section	Revision or Clarification	Justification
1	Cover Page	Version: 3.0~~2.0~~; 15/Sep/2016~~15/Aug/2016~~	This is a clarification that does not impact the study design or risk.
2	Footer	Ver: 3.0~~2.0~~; 15/Sep/2016~~15/Aug/2016~~	This is a clarification that does not impact the study design or risk.
3	Table of Contents	*Updated table of contents*	This is a clarification that does not impact the study design or risk.
4	List of Figures and Tables	*Updated list of figures and tables*	This is a clarification that does not impact the study design or risk.

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<table>
<tr><th>Item</th><th>Section</th><th>Revision or Clarification</th><th>Justification</th></tr>
<tr><td>5</td><td>Document and Version Control</td><td>
<table>
<tr><th>Revision</th><th>Date (DD/Mmm/YYYY)</th><th>Revision Author</th><th>Comments/Changes</th></tr>
<tr><td>1.0</td><td>02/Jun/2016</td><td>Catherine Cadogan</td><td>Clinical Writer – Initial study protocol for the MASTER Pivotal Study.</td></tr>
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<tr><td>3.0</td><td>15/Sep/2016</td><td>Catherine Cadogan</td><td>Clinical Writer – Protocol Amendment – See Appendix 6 for details of changes made.</td></tr>
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</td><td>This is a clarification that does not impact the study design or risk.</td></tr>
<tr><td>6</td><td>Section 10.2—Adverse Event Definitions</td><td>Correction made to Section 10.2 (1) Non-Invasive Blood Press (NIBP) definition:
(1) Non-Invasive Blood pressure (NIBP): defined as having the systolic blood pressure (SBP) reading < ~~80~~ 70 mmHg or > 160 mmHg or mean arterial pressure (MAP) of <~~60~~ 55 mmHg or > 120 mmHg for >~~10~~ 5 minutes.</td><td>This correction is in response to the request by FDA on 9/Sep/2016 from the interactive question from the review of IDE G160132-A001.</td></tr>
<tr><td>7</td><td>Section 10.4—Management of Serious Adverse Event and Unanticipated Adverse Device Effect Reporting</td><td>Corrected last paragraph:
If additional information (i.e.; outcome of event, date event resolved, additional treatments) is required to submit a follow-up report, the Investigator shall update the AE eCRF and resubmit to the Sponsor's Clinical Affairs.</td><td>Administrative change.</td></tr>
<tr><td>8</td><td>Section 18—Glossary</td><td>Correction made on the Non-Invasive Blood Press (NIBP) definition:
(2) Non-Invasive Blood pressure (NIBP): defined as having the systolic blood pressure (SBP) reading < ~~80~~ 70 mmHg or > 160 mmHg or mean arterial pressure (MAP) of <~~60~~ 55 mmHg or > 120 mmHg for >~~10~~ 5 minutes.</td><td>This correction is in response to the request by FDA on 9/Sep/2016 from the interactive question from the review of IDE G160132-A001.</td></tr>
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Study Title: Multi-site Anesthesia randomized controlled STudy of End tidal control (Et Control) compared to conventional anesthesia Results (MASTER-Anesthesia Trial)
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Item	Section	Revision or Clarification	Justification
9	Appendix 6—Amendments (Protocol Version 2.0 to 3.0)	A detailed amendment is provided for version 2.0 to version 3.0. Version 2.0 was the second version submitted to the U.S. FDA in response to IDE deficiencies and disapproval letter dated 14/Jul/2016 for IDE G160132. Version 2.0 was not provided to the investigational sties for IRB approval. **Purpose of Amendment:** 1) To make changes as requested by the US FDA on 9/Sep/2016 from the interactive question from the review of IDE G160132-A001. 2) Sponsor administrative changes. These changes are not expected to increase subject or operator risk or to adversely impact the scientific integrity or conduct of the study. In the table below, point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment from the previous version. *(NOTE: In the protocol under this section, the table of point-by-point revisions is inserted after the above paragraphs.)*	*This section has been added to list the above-mentioned changes made to the protocol from version 2 to version 3.*

APPENDIX 7 - AMENDMENTS (PROTOCOL VERSION 3.0 TO 4.0)

A detailed amendment is provided for version 3.0 to version 4.0. Version 1.0 was the first version submitted to the U.S FDA as part of the IDE application. Version 2.0 was an amendment submitted to the U.S. FDA in response to IDE deficiencies and disapproval letter dated 14/Jul/2016 for IDE G160132. Version 3.0 was an amendment to include changes as requested by the US FDA on 9/Sep/2016 from the interactive question from the review of the IDE #G160132-A001 and administrative changes. Versions 1.0, 2.0, and 3.0 were not provided to the investigational sties for IRB approval.

Purpose of Amendment:

1) To add the list of investigators and sites in Appendix 4—Study Site and Investigator List that will be participating in this study.
2) Sponsor administrative changes.

These changes are not expected to increase subject or operator risk or to adversely impact the scientific integrity or conduct of the study.

In the table below, point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment from the previous version.

Item	Section	Revision or Clarification	Justification
1	Cover Page	Version: 4.0~~3.0~~; 22/Sep/2016~~15/Sep/2016~~	This is a clarification that does not impact the study design or risk.
2	Footer	Ver: 4.0~~3.0~~; 22/Sep/2016~~15/Sep/2016~~	This is a clarification that does not impact the study design or risk.
3	Table of Contents	*Updated table of contents*	This is a clarification that does not impact the study design or risk.
4	List of Figures and Tables	*Updated list of figures and tables*	This is a clarification that does not impact the study design or risk.

Study Title: Multi-site Anesthesia randomized controlled STudy of End tidal control (Et Control) compared to conventional anesthesia Results (MASTER-Anesthesia Trial)
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Item	Section	Revision or Clarification				Justification
5	Document and Version Control	**Revision**	**Date (DD/Mmm/YYYY)**	**Revision Author**	**Comments/Changes**	This is a clarification that does not impact the study design or risk.
		1.0	02/Jun/2016	Catherine Cadogan	Clinical Writer – Initial study protocol for the MASTER Pivotal Study.	
		2.0	15/Aug/2016	Catherine Cadogan	Clinical Writer – Protocol Amendment – See Appendix 5 for details of changes made.	
		3.0	15/Sep/2016	Catherine Cadogan	Clinical Writer – Protocol Amendment – See Appendix 6 for details of changes made.	
		4.0	22/Sep/2016	Catherine Cadogan	Clinical Writer – Protocol Amendment – See Appendix 7 for details of changes made.	
6	Administrative Structure of Investigation	*Correction made under Research Manager – Telephone:* Tel: [redacted] *Correction made under Biostatistician – Telephone:* Tel: [redacted]				For consistency, this is a clarification that does not impact the study design or risk.
7	Section 10.2—Adverse Event Definitions	*Correction made under Serious Adverse Event (SAE):* Serious Adverse Event: As defined by EN ISO 14155~~—~~2011: an adverse event... c. led to fetal distress, fetal death, or a congenital abnormality or birth defect.				Administrative changes.
8	Section 10.3—Management of Adverse Event Reporting	*Correction made under the 1st sentence in the 1st paragraph:* Any adverse events (AEs) and serious adverse events (SAEs) will be recorded in the ~~subjects~~subject's study record and the Electronic Adverse Event Case Report Form.				Administrative change

Study Title: Multi-site Anesthesia randomized controlled STudy of End tidal control (Et Control) compared to conventional anesthesia Results (MASTER-Anesthesia Trial)
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Item	Section	Revision or Clarification	Justification
9	Section 18—Glossary of Terms	*Correction made under the definition of "High flow anesthesia:"* Anesthesia delivery with fresh gas flow above minute ventilation typically above 5 ~~liter~~liters per min	Administrative change
10	Appendix 4—Study Site and Investigator List	**Investigator(s):**[1] **Edmund Jooste, MD**, *Principal Investigator*, *Tel:* [redacted] — **Duke University**, 2301 Erwin Road, Durham, NC 27710 **Matthew A. Klopman, MD**, *Principal Investigator*, *Tel:* [redacted] — **Emory University Hospital**, 1364 Clifton Road NE, Atlanta, GA 30322 **David Ramsingh, MD**, *Principal Investigator*, *Tel:* [redacted] — **Loma Linda University**, 11234 Anderson Street, Loma Linda, CA 92354 **Melinda Seering, MD**, *Principal Investigator*, *Tel:* [redacted] — **University of Iowa Healthcare**, 200 Hawkins Drive, Iowa City, IA 52242 ~~**Investigator(s):**[1]~~ ~~*To be determined prior to start of study.*~~ ~~Investigator Name, Title/Credentials, and role (e.g. Principal Investigator, Sub-investigator, Co-investigator, etc.)~~ ~~Tel: X XXX XXX XXXX~~ ~~e-mail: investigator@ge.com~~ — ~~Site Name~~ ~~Address: Address Line 1~~ ~~Address Line 2~~ ~~Investigator Name, Title/Credentials, and role (e.g. Principal Investigator, Sub-investigator, Co-investigator, etc.)~~ ~~Tel: X XXX XXX XXXX~~ ~~e-mail: investigator@ge.com~~ — ~~Site Name~~ ~~Address: Address Line 1~~ ~~Address Line 2~~	The change made is the addition of the investigators and sites that will be participating in this study.

Study Title: Multi-site Anesthesia randomized controlled STudy of End tidal control (Et Control) compared to conventional anesthesia Results (MASTER-Anesthesia Trial)
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Item	Section	Revision or Clarification	Justification
		~~Investigator Name, Title/Credentials, and role (e.g. Principal Investigator, Sub-investigator, Co-investigator, etc.)~~ ~~Tel: X XXX XXX XXXX~~ ~~e-mail: investigator@ge.com~~ ~~Site Name~~ ~~Address: Address Line 1~~ ~~Address Line 2~~ ~~Investigator Name, Title/Credentials, and role (e.g. Principal Investigator, Sub-investigator, Co-investigator, etc.)~~ ~~Tel: X XXX XXX XXXX~~ ~~e-mail: investigator@ge.com~~ ~~Site Name~~ ~~Address: Address Line 1~~ ~~Address Line 2~~	
11	Appendix 7—Amendments (Protocol Version 3.0 to 4.0)	APPENDIX 7 - AMENDMENTS (PROTOCOL VERSION 3.0 TO 4.0) A detailed amendment is provided for version 2.0 to version 3.0. Version 2.0 was the second version submitted to the U.S. FDA in response to IDE deficiencies and disapproval letter dated 14/Jul/2016 for IDE G160132. Version 2.0 was not provided to the investigational sties for IRB approval. Purpose of Amendment: 1) To add the list of investigators and sites in Appendix 4—Study Site and Investigator List that will be participating in this study. 2) Sponsor administrative changes. These changes are not expected to increase subject or operator risk or to adversely impact the scientific integrity or conduct of the study. In the table below, point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (strikethrough) for each change made in this amendment from the previous version. ***(NOTE: The above-mentioned table of point-by-point revisions is inserted after the above paragraphs.)***	This section has been added to list the above-mentioned changes made to the protocol from version 3 to version 4.

APPENDIX 8 - AMENDMENTS (PROTOCOL VERSION 4.0 TO 5.0)

A detailed amendment is provided for version 4.0 to version 5.0. Version 1.0 was the first version submitted to the U.S FDA as part of the IDE application. Version 2.0 was an amendment submitted to the U.S. FDA in response to IDE deficiencies and disapproval letter dated 14/Jul/2016 for IDE G160132. Version 3.0 was an amendment to include changes as requested by the US FDA on 9/Sep/2016 from the interactive question from the review of the IDE #G160132-A001 and administrative changes. Version 4.0 was an amendment to add the list of investigators and sites in Appendix 4—Study Site and Investigator List that will be participating in this study and administrative changes. Versions 1.0, 2.0, and 3.0, were not provided to the investigational sties for IRB approval.

Purpose of Amendment:

1) To provide clarification in the protocol as described in the table below.
2) Sponsor administrative changes.

These changes are not expected to increase subject or operator risk or to adversely impact the scientific integrity or conduct of the study.

In the table below, point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment from the previous version.

Item	Section	Revision or Clarification	Justification
1	Cover Page	Version: 5.0~~4.0~~; 21/Oct/2016~~22/Sep/2016~~ *Corrected Zip Code of the Sponsor's address:* Waukesha, WI ~~53005~~53188-1696	This is a clarification that does not impact the study design or risk.
2	Footer	Ver: 5.0~~5.0~~; 21/Oct/2016~~22/Sep/2016~~	This is a clarification that does not impact the study design or risk.
3	Table of Contents	*Updated table of contents*	This is a clarification that does not impact the study design or risk.
4	List of Figures and Tables	*Updated list of figures and tables*	This is a clarification that does not impact the study design or risk.

Study Title: Multi-site Anesthesia randomized controlled STudy of End tidal control (Et Control) compared to conventional anesthesia Results (MASTER-Anesthesia Trial)
Study No: 123.07-2015-GES-0002

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<tr><td>5.0</td><td>21/Oct/2016</td><td>Catherine Cadogan</td><td>Clinical Writer – Protocol Amendment – See Appendix 8 for details of changes made as clarification/administrative change.</td></tr>
</table></td><td>This is a clarification that does not impact the study design or risk.</td></tr>
<tr><td>6</td><td>Study Synopsis – Objectives</td><td colspan="4">Item #4 of the secondary objectives was clarified:
(4) To collect time to discharge from the operating room (OR), which is measured from the time of end of surgery (often defined as procedure end time, last stitch, or placement of last bandage) to time of last breath.</td><td>This is a clarification that does not impact the study design or risk.</td></tr>
<tr><td>7</td><td>Study Synopsis—Eligibility Criteria</td><td colspan="4">Item #3 of the Inclusion Criteria was clarified:
(3) Expected to have airway ~~S~~secured ~~airway~~ with laryngeal mask airway (LMA) or endotracheal tube.</td><td>There is no change to the content. This is a clarification based on what could be known at the time of screening. This clarification does not impact the study design or risk.</td></tr>
<tr><td>8</td><td>Study Synopsis—Sample size and Sites</td><td colspan="4">Under 1st paragraph, 2nd sentence was corrected:
Et Control Arm and Control Arm. A minimum of 15 subject cases is the target enrollment for each of the 3 anesthesia agents (Desflurane, Sevoflurane, and Isoflurane) per arm (only one inhalation anesthetic agent may be used for each enrolled subject in the study arm).</td><td>This is a clarification that does not impact the study design or risk.</td></tr>
</table>

Study Title: Multi-site Anesthesia randomized controlled STudy of End tidal control (Et Control) compared to conventional anesthesia Results (MASTER-Anesthesia Trial)
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Item	Section	Revision or Clarification	Justification
9	Section 3.3.2—Secondary Objective	*Item #4 of the secondary objectives was clarified:* (4) collect time to discharge from the operating room (OR), which is measured from the time of end of surgery *(often defined as procedure end time, last stitch, or placement of last bandage)* to time of last breath.	This is a clarification that does not impact the study design or risk.
10	Section 3.4.3—Other Endpoints	*Item #3 of other endpoints was clarified:* (3) Time to discharge from the operating room (OR) (measured from the end of surgery [often defined as the procedure end time, last stitch, or placement of last bandage] to time of last breath).	This is a clarification that does not impact the study design or risk.
11	Section 5.1—Number of Subjects	*First paragraph was clarified:* A total of 248 Subjects will be enrolled in the study, with approximately 124 subjects enrolled in each arm: Et Control Arm and Control Arm. A minimum of 15 subject cases is the target enrollment for each of the 3 anesthesia agents (Desflurane, Sevoflurane, and Isoflurane) per arm *(only one inhalation anesthetic agent may be used for each enrolled subject in the study arm)*.	This is a clarification that does not impact the study design or risk.
12	Section 5.4—Inclusion Criteria	*Item #4 was corrected for clarification:* 4. ~~Able~~ Expected to have~~te~~ airway secured ~~airway~~ with laryngeal mask airway (LMA) or endotracheal tube	There is no change to the content. This is a clarification based on what could be known at the time of screening. This clarification does not impact the study design or risk.
13	Section 6.2.4—Post Anesthesia Care Unit (PACU) Discharge	*The following note has been added for clarification:* Note: Collection of vital signs at PACU Discharge will be the last vital signs taken at the time patient meets criteria to discharge from PACU.	This is a clarification that does not impact the study design or risk.
14	Section 6.3.1—Preoperative Data Collection	*The following Laboratory Assessment was corrected for clarification:* 7. Laboratory Assessments: females of childbearing potential will have a serum or urine pregnancy test done (prior to randomization) to determine eligibility	This is a clarification that does not impact the study design or risk.

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Item	Section	Revision or Clarification	Justification
15	Section 6.3.2—Operative Procedure Data Collection (Induction/Intubation, Maintenance, and Emergence)	*Under the 2nd bullet, the following items were clarified:* 1. Concomitant Medications: Intravenous medications [name, dose, time administered, time stopped, and rate (if applicable); including intravenous anesthetic agents used prior to intubation] administered from pre-OP through emergence phase 3. Anesthetic agents used prior to intubation *(Note: Record inhaled and intravenous anesthetic agent used prior to intubation. Intravenous anesthetic agent should be recorded in the Intravenous Medication During Study eCRF.)* 6. Operative positioning *(record the primary operating position)* 9. End time of surgery *(often defined as the procedure end time, last stitch, or placement of the last bandage)*	This is a clarification that does not impact the study design or risk.
16	Section 6.3.3—Post Anesthesia Care Unit (PACU) Data Collection	*The following items in this section were corrected for clarification:* Prior to the subject's discharge from PACU *(defined as the time patient meets criteria for discharge from PACU~~subject going home or to the ward~~)*, the following data will need to be collected on the electronic case report form: 2. Time of collection of vital signs *(this will be the last set of vital signs taken at the time patient meets criteria to discharge from PACU)* 7. Intravenous medications [name, dose, time/duration, and rate (if applicable)] administered from emergence through PACU discharge *(defined as the time patient meets criteria to discharge from PACU)*	This is a clarification that does not impact the study design or risk.
17	Section 6.3.4—Twenty-four (24) hours Post PACU Data Collection	*The following paragraph was corrected for clarification:* Collect the following information 24-hours [±8 hours] post PACU discharge *(defined as the time patient meets criteria to discharge from PACU)* for subjects that completed the study and those that were withdrawn or discontinued from study participation during the study procedure.	This is a clarification that does not impact the study design or risk.
18	Section 8.1.4.4—Time to Operating Room (OR) Discharge	*The following sentence was corrected for clarification:* Time to operating room (OR) discharge will be measured from end of surgery *(often defined as procedure end time, ~~of~~ last stitch, or placement of last bandage)* to OR discharge (time of last breath, patient being disconnected from the anesthesia machine).	This is a clarification that does not impact the study design or risk.

Study Title: Multi-site Anesthesia randomized controlled STudy of End tidal control (Et Control) compared to conventional anesthesia Results (MASTER-Anesthesia Trial)
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Item	Section	Revision or Clarification	Justification
19	Section 8.1.7—Analysis of Adverse Events	*The 3rd paragraph was corrected for clarification:* In addition, analysis of adverse events will be performed for each subset of patients defined by the pre-existing hypertension *(defined as a patient treated for hypertension)* status and ASA status.	This is a clarification that does not impact the study design or risk.
20	Section 8.1.9—Other Analysis	*The 4th paragraph was corrected for clarification:* Post-anesthesia discharge time will be summarized and compared between the two study arms using t-test. Post- anesthesia discharge time is defined as OR discharge (patient disconnected from the anesthesia machine) to discharge time from the PACU *(defined as the time patient meets criteria to discharge from PACU)*.	This is a clarification that does not impact the study design or risk.
21	Section 10.1—Foreseeable Adverse Events and Device Effects	*The 2nd sentence in the 1st paragraph was corrected for clarification:* The following are some of the foreseeable adverse events related to general anesthesia that can be observed in both the control and investigational group: nausea, vomiting, hypoxemia, hypercapnia, emergence delay, ~~and~~ agitation, hypertension, hypotension, postoperative pulmonary infection, intraoperative cardiac arrhythmias, myocardial ischemia, myocardial infarction, cardiac arrest, stroke, pulmonary embolism, intraoperative awareness, hypoventilation, hyperventilation, volutrauma, and barotrauma.	This is a clarification that does not impact the study design or risk.
22	Section 18—Glossary of Terms:	*The following terms were corrected for clarification:* End of surgery — Often defined as the procedure end time, last stitch, or placement of the last bandage Post-anesthesia discharge time — From the OR discharge to discharge time from the PACU *(the time patient meets criteria to discharge from PACU)*. *The following term was added in the Glossary as clarification:* Pre-existing Hypertension — Patient that has been treated for hypertension	This is a clarification that does not impact the study design or risk.
23	Appendix 6—Amendments (Protocol Version 2.0 to 3.0)	*The following sentences were added/corrected:* Version 1.0 was the first version submitted to the U.S FDA as part of the IDE application. Versions 1.0 and 2.0 was not provided to the investigational sties for IRB approval.	This is an administrative change that does not impact the study design or risk.

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Item	Section	Revision or Clarification	Justification
24	Appendix 7—Amendments (Protocol Version 3.0 to 4.0)	*The following sentences were corrected.* A detailed amendment is provided for version ~~2~~3.0 to version ~~3~~4.0. Version 1.0 was the first version submitted to the U.S FDA as part of the IDE application. Version 2.0 was ~~the second version~~ and amendment submitted to the U.S. FDA in response to IDE deficiencies and disapproval letter dated 14/Jul/2016 for IDE G160132. Version 3.0 was an amendment to include changes as requested by the US FDA on 9/Sep/2016 from the interactive question from the review of the IDE #G160132-A001 and administrative changes. Versions 1.0, 2.0, and 3.0 ~~was~~ were not provided to the investigational sties for IRB approval.	This is an administrative change that does not impact the study design or risk.
25	Appendix 7—Amendments (Protocol Version 3.0 to 4.0)	*Under Item #11 of the table of point-by-point revisions, the following statement was added at the end of Item #11:* ***(NOTE: The above-mentioned table of point-by-point revisions is inserted after the above paragraphs.)***	This is an administrative change that does not impact the study design or risk.
26	Appendix 8—Amendments (Protocol Version 4.0 to 5.0	*This section has been added to list all the clarifications and administrative changes:* APPENDIX 8 - AMENDMENTS (PROTOCOL VERSION 4.0 TO 5.0) A detailed amendment is provided for version 4.0 to version 5.0. Version 1.0 was the first version submitted to the U.S FDA as part of the IDE application. Version 2.0 was an amendment submitted to the U.S. FDA in response to IDE deficiencies and disapproval letter dated 14/Jul/2016 for IDE G160132. Version 3.0 was an amendment to include changes as requested by the US FDA on 9/Sep/2016 from the interactive question from the review of the IDE #G160132-A001 and administrative changes. Version 4.0 was an amendment to add the list of investigators and sites in Appendix 4—Study Site and Investigator List that will be participating in this study and administrative changes. Versions 1.0, 2.0, and 3.0, were not provided to the investigational sties for IRB approval. Purpose of Amendment: 1) To provide clarification in the protocol as described in the table below. 2) Sponsor administrative changes. These changes are not expected to increase subject or operator risk or to adversely impact the scientific integrity or conduct of the study. In the table below, point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (strikethrough) for each change made in this amendment from the previous version. ***(NOTE: The above-mentioned table of point-by-point revisions is inserted after the above paragraphs.)***	This is an administrative change that does not impact the study design or risk.

APPENDIX 9 - AMENDMENTS (PROTOCOL VERSION 5.0 TO 6.0)

A detailed amendment is provided for version 5.0 to version 6.0. Version 1.0 was the first version submitted to the U.S FDA as part of the IDE application. Version 2.0 was an amendment submitted to the U.S. FDA in response to IDE deficiencies and disapproval letter dated 14/Jul/2016 for IDE G160132. Version 3.0 was an amendment to include changes as requested by the US FDA on 9/Sep/2016 from the interactive question from the review of the IDE #G160132-A001 and administrative changes. Version 4.0 was an amendment to add the list of investigators and sites in Appendix 4—Study Site and Investigator List that will be participating in this study and administrative changes. Versions 1.0, 2.0, and 3.0, were not provided to the investigational sties for IRB approval. Version 4.0 was provided to the investigational sites at the investigator meeting and following the meeting an electronic copy was provided. Version 5.0 was not provided to the investigational sites.

Purpose of Amendment:

1) To provide clarification in the protocol as described in the table below.
2) Sponsor administrative changes.

These changes are not expected to increase subject or operator risk or to adversely impact the scientific integrity or conduct of the study.

In the table below, point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment from the previous version.

Item	Section	Revision or Clarification	Justification
1	Cover Page	Version: 6.0~~5.0~~; 02/Nov/2016~~21/Oct/2016~~	This is a clarification that does not impact the study design or risk.
2	Footer	Ver: 6.0~~50~~; 02/Nov/2016~~21/Oct/2016~~	This is a clarification that does not impact the study design or risk.
3	Table of Contents	*Updated table of contents*	This is a clarification that does not impact the study design or risk.
4	List of Figures and Tables	*Updated list of figures and tables*	This is a clarification that does not impact the study design or risk.

Study Title: Multi-site Anesthesia randomized controlled STudy of End tidal control (Et Control) compared to conventional anesthesia Results (MASTER-Anesthesia Trial)
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<tr><td>6</td><td>Synopsis</td><td colspan="4">Under the Procedures/Methods, the 2nd sentence was correctd
Randomization will be stratified based on ~~clinician~~<u>Investigator</u>, subject's pre-existing hypertension status, and subject's ASA status.</td><td>This is a clarification that does not impact the study design or risk.</td></tr>
<tr><td>7</td><td>Section 3.2—General Design of Study (Descriptive Hypothesis)</td><td colspan="4">The last sentence was corrected as follows:
Stratified randomization will be used based on clinicianInvestigator, subject's pre-existing hypertension status, and subject's ASA status.</td><td>This is a clarification that does not impact the study design or risk.</td></tr>
<tr><td>8</td><td>Section 5.1—Number of Subjects</td><td colspan="4">The 3rd paragraph of this section was clarified:
Each <u>Investigator</u>~~clinician~~ will be performing a minimum of five (5) cases for each arm (Et Control and Control). In situations where the ~~clinician~~ <u>Investigator</u> is unable to complete a minimum of 5 cases in each arm, a Sponsor exception may be obtained. Subjects will be randomized to the Et Control Arm or the Control Arm, and randomization will be stratified</td><td>This is a clarification that does not impact the study design or risk.</td></tr>
</table>

Study Title: Multi-site Anesthesia randomized controlled STudy of End tidal control (Et Control) compared to conventional anesthesia Results (MASTER-Anesthesia Trial)
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Item	Section	Revision or Clarification	Justification
		based on ~~clinician~~Investigator, subject's pre-existing hypertension status, and subject's ASA status.	
9	Section 6.1—Randomization and Enrollment	*The 2nd sentence was corrected as follows:* *Stratified randomization will be used based on clinicianInvestigator, subject's pre-existing hypertension status, and subject's ASA status.*	This is a clarification that does not impact the study design or risk.
10	Section 6.2.6—User Survey	*The 1st sentence was clarified:* The ~~clinician~~ Investigator will complete a User Survey Questionnaire, after completing each subject case.	This is a clarification that does not impact the study design or risk.
11	Section 6.3.1—Preoperative Data Collection	*The definition of "gender" was added for clarification:* 1. **Demographics:** subject's age, gender [the biological sex of the subject], ethnicity, race	This is a clarification that does not impact the study design or risk.
12	Section 14.2—Subject De-identification	*The 2nd sentence of the 1st paragraph was corrected – "Clinician ID was not required for randomization through IxRS."* *Data collected will be labeled with a de-identified Subject Identification Designation (SID), which consists of the Site number, Clinician ID and subject number. eCRFs will not contain any identifiable personal information.*	This is a clarification that does not impact the study design or risk.
13	Glossary	*The following definition was added:* Gender Biological sex of the subject.	This is a clarification that does not impact the study design or risk.
14	Appendix 8	*Item #2 of Appendix 8 was corrected:* 1 | Footer | Ver: ~~45~~.0~~43.0~~; 21/Oct/2016~~22/Sep/2016~~ | This is a clarification that does not impact the study design or risk.	Administrative change.

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Item	Section	Revision or Clarification	Justification
15	Appendix 9	*This section was added to list the changes made in this version* **APPENDIX 9 - AMENDMENTS (PROTOCOL VERSION 5.0 TO 6.0)** A detailed amendment is provided for version 5.0 to version 6.0. Version 1.0 was the first version submitted to the U.S FDA as part of the IDE application. Version 2.0 was an amendment submitted to the U.S. FDA in response to IDE deficiencies and disapproval letter dated 14/Jul/2016 for IDE G160132. Version 3.0 was an amendment to include changes as requested by the US FDA on 9/Sep/2016 from the interactive question from the review of the IDE #G160132-A001 and administrative changes. Version 4.0 was an amendment to add the list of investigators and sites in Appendix 4—Study Site and Investigator List that will be participating in this study and administrative changes. Versions 1.0, 2.0, and 3.0, were not provided to the investigational sties for IRB approval. Version 4.0 was provided to the investigational sites at the investigator meeting and following the meeting an electronic copy was provided. Version 5.0 was not provided to the investigational sites. **Purpose of Amendment:** 1) To provide clarification in the protocol as described in the table below. 2) Sponsor administrative changes. These changes are not expected to increase subject or operator risk or to adversely impact the scientific integrity or conduct of the study. In the table below, point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (strikethrough) for each change made in this amendment from the previous version. ***(NOTE: The above-mentioned table of point-by-point revisions is inserted after the above paragraphs.)***	This is a clarification that does not impact the study design or risk.