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Hypotension Prediction Index Software Guided Hemodynamic Management for Noncardiac Surgery Patients - Blood Pressure Trial –

HPI SMART- BP Trial

A Multicenter, Interventional, Randomized comparison of intraoperative hemodynamic management with or without Hypotension Prediction Index software guidance on postoperative complications

Clinical Trial Protocol and Statistical Analysis Plan

Clinical Trial Protocol version: December 17, 2021
Statistical Analysis Plan version: May 11, 2022

Edwards

Hypotension **P**rediction **I**ndex **S**oftware Guided Hemodynamic **M**anagement for Nonc**ar**diac Surgery Pa**t**ients - **B**lood **P**ressure Trial

HPI SMART- BP Trial

A Multicenter, Interventional, Randomized comparison of intraoperative hemodynamic management with or without Hypotension Prediction Index software guidance on postoperative complications

Clinical Trial Protocol
Trial Number: 2021-04

Revision: C
Date: 17DEC21

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Irvine, CA 92614 USA

Revision B Change Summary

Please note: Punctuation, formatting or clerical changes are not included in the table.

Section (Page)	Change and Reason for Change
Synopsis and Trial Objective (7 & 17)	Updated trial objective to the following: To determine if the use of a protocolized strategy using advanced hemodynamic monitoring with Hypotension Prediction Index (HPI) software guidance for intraoperative hemodynamic management reduces postoperative complication rate in moderate- to high-risk non-cardiac surgery." Reason: To provide further clarification.
Synopsis, Background & General Design (7,10 & 23)	Added "The control arm will be blinded to advanced hemodynamic monitoring with and will only receive blood pressure monitoring data from the arterial line, as per the standard of care." Reason: To provide further clarification for control arm design.
Synopsis, Procedure, and Sample size Justification (7, 35 & 37)	Updated total enrollment to 1486 Reason: To align with statistical analysis plan.
Synopsis, Additional Evaluation (Trial Objective and Endpoints) Additional Evaluation (Statistical Methods) (8,17 & 38)	Updated item 9 to following: Amount of vasoactive drugs; mg (e.g.: phenylephrine, ephedrine, norepinephrine, epinephrine, dobutamine) Added item 10: Amount of intraoperative intravenous analgesics and sedatives Added item 12: Verification of the incidence of the listed postoperative complications may be performed at each site by reviewing historic data up to 6 months prior to study initiation. Reason: To provide further clarification.
Synopsis and Treatment Protocol (8 &24)	Edited Alert phase to state: HPI greater than 85 ➔ alert ➔ treatment per protocol recommendation Edited treatment protocol's figure to display the targeted treatment plan. Reason: To provide further clarification.
Schedule of Events (34)	Added footnote for Creatinine labs to be collected on post-op day 1,2 or 3. Reason: To provide further clarification.

Revision C Change Summary

Please note: Punctuation, formatting or clerical changes are not included in the table.

Section (Page)	Change and Reason for Change
Synopsis & Treatment Protocol (9 & 24)	Added "Clinicians should validate the appropriateness of protocol recommendations, and provide treatment based upon their clinical judgment." Reason: To provide further clarification that clinical judgement is key to treatment.
Additional Evaluations (17 & 39)	Added additional datapoints for analysis Reason: Sensitivity analysis for any missing 30-Day follow-up and treatment protocol compliance analysis
Synopsis, Schema, Schedule of Events & Procedures (10, 27,32)	Removed MoCA; Added: Preo-op Surgical Risk Assessment, Post-Op Neurocognitive Assessments Reason: Change in assessment type
General Design (24)	Added "The HPI Pressure & Flow Optimization Protocol provides recommendations for treatment. Clinicians are instructed to validate the appropriateness of protocol recommendations, and provide treatment based upon their clinical judgment" Reason: Clarification on non-significant risk reasons.
Randomization and Blinding (25)	Changed "Study investigators and staff will be blinded up until the time of the surgery. The staff member(s) involved in the consenting of the patient will be blinded to the randomization assignment and will not be involved in the care of the Trial subject." to "Study investigators will be blinded up until the time of the surgery. The clinician(s) involved in the consenting of the patient will be blinded to the randomization assignment and will not be involved in the care of the Trial subject." Reason: To clarify the randomization and blinding.
Roll-in Subjects (30)	Updated the roll-ins to a max of 5 at a site. The total roll-in cases remain at 60. Reason: To allow for additional roll-in cases at sites that need them.
Procedure (35)	Added "Interventions conducted per treatment protocol and/or outside the treatment protocol will be documented on the eCRF(s). Clinicians should validate the appropriateness of protocol recommendations, and provide treatment based upon their clinical judgment." Reason: To clarify the intervention data that will be collected.
Additional Evaluations (39)	Added "Sensitivity analysis including the review of any influence of surgical position, type of anesthesia, tidal volume etc., on the primary outcome measure, are specified in the SAP." Reason: Clarification on sensitivity analysis.
Anticipated Risks (42)	Added risks related to associated with HPI Pressure and Flow Optimization Protocol Reason: To clarify risks that may be associated with treatment protocol.

STATEMENT OF COMPLIANCE

INVESTIGATOR'S SIGNATURE PAGE

This trial will be carried out in accordance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable state, local and federal regulatory requirements as well as 45 CFR Part 46, 21 CFR Parts 11, 50, 54, 56 and 812.

I will provide copies of the protocol to the Institutional Review Board and all members of the Research team responsible to me who participate in the trial. I will discuss this material with them to ensure that all participating personnel at the Research Site are fully informed regarding the conduct of the protocol.

Once the Institutional Review Board approves the protocol, I will not modify this protocol without obtaining the prior approval of both the Sponsor and the Institutional Review Board. I will submit the protocol modifications and/or any informed consent modifications to the Sponsor and the Institutional Review Board, as applicable, and approval will be obtained before any modifications are implemented. A determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

I will conduct the trial as detailed in the protocol and in accordance with conditions of the approval imposed by the Institutional Review Board and all applicable regulations. I will maintain adequate source documentation records throughout the trial and make them available as requested during monitoring visits. I will maintain device accountability records and will supervise the use of the device involving human subjects. In addition, I will provide all the information requested in the electronic Case Report Forms presented to me by the Sponsor in a manner to assure completeness and accuracy.

I will ensure that the requirements for obtaining informed consent are met. Additionally, I will disclose financial interests in accordance with 21 CFR 54, and certify that such financial interests, if any, will not interfere with my responsibilities as an investigator or influence trial outcomes under my supervision.

I have read the attached protocol and hereby agree that it contains all the necessary details for performing the trial.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

_____

Trial Site Name

Table of Content

SYNOPSIS

Title:	Hypotension Prediction Index (HPI) Software Guided Hemodynamic Management for Noncardiac Surgery Patients – Blood Pressure Trial
Short Title:	HPI SMART-BP Trial
Trial Description:	A multicenter, interventional, randomized trial
Trial Objective:	To determine if the use of a protocolized strategy using advanced hemodynamic monitoring with Hypotension Prediction Index (HPI) software guidance for intraoperative hemodynamic management reduces postoperative complication rate in moderate- to high-risk non-cardiac surgery.
Primary Effectiveness Endpoint:	The primary hypothesis is that the administration of advanced hemodynamic monitoring utilizing the Hypotension Prediction Index (HPI) with a protocolized strategy during moderate-to-high-risk noncardiac surgery reduces composite of severe postoperative complications at 30 days. The composite includes: Major adverse cardiac events MACE (myocardial injury, stroke, non-fatal cardiac arrest, and death), acute kidney injury (AKI), and serious infection. Specifically, we seek to evaluate if the treatment protocol utilizing the technology from Edwards Lifesciences will result in a relative change of at least 25% in the composite complication score when compared to the control arm that will receive an arterial line with only blood pressure monitoring, as per the standard of care.
Trial Devices:	HemoSphere Advanced Monitor, Acumen™ HPI Feature Software, Acumen IQ sensor, FloTrac sensor, and ForeSight Elite Oximetry sensor.
Overall Design:	A multicenter, randomized comparison of intraoperative hemodynamic management with or without a protocolized strategy utilizing Hypotension Prediction Index (HPI) software guidance during moderate-to-high-risk noncardiac surgery.
Trial Population:	Up to 1486 adults undergoing moderate-to-high-risk noncardiac surgery who will be receiving pressure monitoring with an arterial line.
Number of Sites:	Up to Twenty (20) U.S. Sites
Trial Duration:	Total of 24 to 36 months
Participation Duration:	Screening/Baseline; Procedure; Post-Op Days 1-3; ICU; hospital discharge; 30-day Telephone Follow-Up Visit
Inclusion/ Exclusion Criteria	**Inclusion Criteria:** 1. Signed informed consent; 2. Age ≥ 18 years;

3. ASA Physical Status ≥ 2;
4. Noncardiac surgery with expected surgery duration ≥ 2 hours (example include: orthopedic, spine, urology, and general surgery)
5. Planned blood pressure monitoring with an arterial line catheter;
6. General anesthesia;

Exclusion Criteria:

1. Participating in another interventional Trial;
2. Contraindication to arterial blood pressure monitoring;
3. Subjects with a physical site area too limited for proper Sensor placement
4. Serum creatine > 175 µmol/L (>2.0 mg/dL) or CKD stage > 3A
5. Scheduled for intracranial surgery with permissive hypotension;
6. Patient who is confirmed to be pregnant and/or nursing mothers;
7. Patients with an intra-aortic balloon pump (IABP) or ventricular assist device(s);
8. Have a condition that precludes routine or tight blood pressure management such as surgeon request for relative hypotension;
9. Emergency surgery;
10. Require beach-chair positioning;
11. Scheduled for cardiac surgeries
12. Have previously participated in the SMART-BP trial.

Treatment Protocol:	Alert Phase: HPI greater than 85 ➔ alert ➔ treatment per protocol recommendation Monitoring Phase: HPI 50 – 85➔ evaluate flow / vascular tone indices and fluid responsive state. Clinicians should validate the appropriateness of protocol recommendations, and provide treatment based upon their clinical judgment.
Primary Outcome:	A composite of 30-day moderate-to-severe perfusion related postoperative complications. The composite includes: 1. MACE (myocardial injury, stroke, non-fatal cardiac arrest, and death) 2. Acute kidney injury (KDIGO stage 2-3) 3. Serious Infections: pneumonia, deep surgical site or organ space infections, and sepsis
Preoperative Assessments:	Creatinine, Surgical Risk Assessment (NSQIP[1]), Troponin, NT-proBNP

Postoperative Assessments:	Troponin and Post-Op delirium assessment POD 1,2,3; Creatinine POD 2, Post-Operative Morbidity Survey (POMS[7]) POD 3, 30-day Follow-up, World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0[19])
Trial Sponsor:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614 USA

1. INTRODUCTION

Background

With advancements in treating disease, the number of patients undergoing major surgery worldwide is growing.[6] Despite this fact, many patients still experience severe perioperative complications or post-operative mortality.[6] Each year roughly 240 million anesthesia cases are performed worldwide.[3] About 10% of these cases are high risk patients who account for >80% of perioperative deaths.[3] The more common moderate-risk surgery constitutes 40% of surgeries. Of these, about 30% of patients experience minor post-operative complications.[3]

The perioperative period is characterized by hemodynamic instability. Various degrees of hypotension are common during anesthesia, which may cause organ ischemia.[8] There is accumulating evidence that intraoperative hypotension is associated with injury to the heart, kidney, and brain and carries an increased likelihood of mortality in moderate-to high-risk patients.[6] Recent studies have demonstrated a connection between hypotension and adverse outcome events such as acute kidney injury (AKI) and myocardial injury (MI).[20] Post-operative complications, even the minor ones, extend hospital stay and surge healthcare costs, and, more importantly, can reduce long-term survival.[3]

Recent studies have looked at the effects that intraoperative hypotension have on post-operative complications. Long periods of hemodynamic flow-base optimization through cardiac output has shown improvements to reduce complications. One of these trials was the OPTIMISE I trial that aimed to assess the clinical effectiveness of cardiac output-guided hemodynamic therapy during the perioperative period.[14] The meta-analysis for the study indicated that hemodynamic intervention was linked to a reduction in complication rates (intervention 31.5% versus control 41.6%).[14]

In another randomized trial, the effect of individual blood pressure management on reducing organ damage was analyzed.[6] Based on the trial results, only 46.3% patients in the individualized treatment group reported postoperative organ dysfunction compared to that of the standard treatment group which was 63.4%. This study was able to demonstrate a total of 17.1% post-operative organ dysfunction reduction for subjects who received individualized blood pressure management.[6]

The duration of hypotension may have an effect on the resulting organ damage as well.[20] The Hypotension Prediction Index (HPI) algorithm predicts hypotension, which is defined as MAP <65 mmHg for at least one minute, by collecting information from arterial waveform features such as waveform time, amplitude, area, segment slopes, and complexity features.[10] In the HYPE trial, a randomized controlled trial, it was shown that using Hypotension Prediction Index (HPI) software for hemodynamic management reduces intraoperative hypotension compared with the standard of care for patients undergoing elective noncardiac surgery.[21] Based on the results, the subjects in the intervention group experienced a median of 8.0 minutes of hypotension compared to that of the control group which was 32.7 minutes.[21] There was a mean total reduction of 75.5% of hypotension. In another single-center feasibility randomized, blinded prospective interventional trial, there was a substantial reduction of intraoperative hypotension in the HPI group. The rate of hypotensive events in the HPI group was 48%, while the rates in the routine anesthetic care and historic control groups were 87.5% and 80%, respectively. [16]

Currently, there is a minimal amount of evidence linking a reduction in intraoperative hypotension to patient outcome. Moreover, the inclusion of comprehensive flow and hypotension management strategies has also not been evaluated in a robust manner in improving patient postoperative AKI outcome. Precise treatment of perioperative hypotension should be based on a reference to the patient's baseline measurements of BP, cardiac output, stroke volume, heart rate, and systemic vascular resistance (SVR).[11]

Tissue oxygenation will also be measured during the trial using ForeSight Elite oximetry sensors for only observation purposes. Changes in cardiovascular dynamics are induced during major surgery that includes anesthesia. These changes in cardiovascular dynamics can lead to reduction in perfusion of vital organs and contribute to post-operative complications.[12] Different cardiovascular variables besides arterial pressure including arterial oxygen content and cardiac output are regulating and inducing tissue perfusion ad oxygenation. Thus, maintaining or restoring tissue perfusion and oxygenation by optimizing global cardiovascular dynamics can be a propitious concept in improving postoperative outcomes for patients undergoing surgery.[12]

This trial seeks to evaluate the benefit of a protocolized blood pressure management strategy that utilizes a hypotension prediction tool along with a comprehensive advanced hemodynamic assessment to reduce a composite of postoperative complications in patients undergoing non-cardiac surgery. Based onthe literature, [6,10,14] the estimated incidence of the composite primary outcome is expected to be at least 31%. This trial is targeting a relative reduction of at least 25% in the composite outcome within the treatment arm as compared to the control arm control arm that will receive an arterial line with only blood pressure monitoring, as per the standard of care.

2. MEDICAL DEVICES

Device Names

- Acumen™ HPI Feature Software
- Acumen IQ sensor
- FloTrac sensor
- ForeSight Elite oximetry sensors
- HemoSphere advanced monitoring platform

Device Descriptions, Contraindications, and Intended Uses

Acumen™ HPI Feature Software

Description

The Acumen™ HPI Feature Software was initially granted marketing clearance via a de novo request (DEN160044) by the Food and Drug Administration (FDA) on March 16, 2018. It was initially cleared for use on the HemoSphere advanced monitoring platform on November 16, 2018.

The Acumen™ HPI Feature Software provides the clinician with physiological insight into a patient's likelihood of trending toward a hypotensive event (defined as mean arterial pressure ≤ 65 mmHg for at least one minute) and the associated hemodynamic parameters. The Acumen™ HPI Feature Software is intended for use in surgical and non-surgical patients receiving advanced hemodynamic monitoring. The Acumen™ HPI Feature Software is used as decision support to supplement the clinician's assessment of the patient's physiological condition. No therapeutic decisions should be made based solely on the Acumen™ HPI parameter.

The Acumen™ HPI Feature Software, on the HemoSphere advanced monitoring platform, is enabled by the minimally invasive Acumen IQ sensor. The Acumen IQ sensor is the hardware which is connected to an existing radial arterial catheter. Hemodynamic information is calculated and presented on the Edwards HemoSphere advanced monitoring platform. The entire system is comprised of:

- Acumen IQ sensor (hardware): Acumen IQ is the sensor which is connected to the standard arterial catheter tubing from the patient. The sensor relays information to the standard anesthesia monitor in the form of continuous arterial pressure waveform. The sensor also relays information to the Acumen™ HPI Feature Software-enabled HemoSphere Platform.
- Acumen™ HPI Feature Software: The software consists of the Hypotension Prediction Index and other advanced hemodynamic parameters.
- HemoSphere advanced monitoring platform: This is the system monitor which displays the continuous arterial pressure monitoring, HPI, and other advanced hemodynamic parameters.

Acumen IQ Sensor Technology

Description

The Acumen IQ sensor is a sterile, single use kit that monitors pressures when attached to pressure monitoring catheters. When connected to a compatible monitor, the Acumen IQ sensor minimally-invasively measures cardiac output and key hemodynamic parameters, which assist the clinician in assessing the patient's physiologic status and support clinical decisions related to hemodynamic optimization. The disposable sterile cable with a red connector interfaces exclusively with an Edwards cable that is specifically wired for the pressure monitor being used. The disposable sterile cable with a green connector interfaces exclusively with the Edwards cables for use with the Edwards arterial pressure based cardiac output monitoring devices or hardware.

The Acumen IQ sensor has a straight, flow-through design across the pressure sensors with an integral flush device.

Device performance, including functional characteristics, has been verified in a comprehensive series of testing to support the safety and performance of the device for its intended use when used in accordance with the established Instructions for Use.

When used with a compatible monitoring platform, the Acumen IQ sensor provides information regarding the hemodynamic status of the patient, which may lead to improved data driven clinical decision making for medically necessary intervention and/or clinical re-evaluation. When used in conjunction with HPI software, the Acumen IQ sensor assists in providing information regarding the likelihood of a patient trending toward a hypotensive event (defined as mean arterial pressure ≤ 65 mmHg for at least one minute).

Contraindications

There are no absolute contraindications for using the Acumen IQ sensor in patients requiring invasive pressure monitoring.

Acumen IQ Sensor Cleared Indications

The Acumen IQ sensor is indicated for use in intravascular pressure monitoring. It is also indicated for use with the Edwards arterial pressure based cardiac output monitoring devices or hardware to measure cardiac output.

HemoSphere Advanced Monitor with HemoSphere Pressure Cable Cleared Indications (For Use with Acumen IQ Sensor)

The HemoSphere advanced monitor when used with the HemoSphere pressure cable is indicated for use in critical care patients in which the balance between cardiac function, fluid status, vascular resistance and pressure needs continuous assessment. It may be used for monitoring of hemodynamic parameters in conjunction with a perioperative goal directed therapy protocol in a hospital environment.

FloTrac Technology

Description

The FloTrac sensor is a sterile, single use kit that monitors pressures when attached to pressure monitoring catheters. When connected to a compatible monitor, the FloTrac sensor minimally-invasively measures cardiac output and key hemodynamic parameters, which assist the clinician in assessing the patient's physiologic status and support clinical decisions related to hemodynamic optimization. The disposable sterile cable with a red connector interfaces exclusively with an Edwards cable that is specifically wired for the pressure monitor being used. The disposable sterile cable with a green connector interfaces exclusively with the Edwards cables for use with the Edwards arterial pressure based cardiac output monitoring devices or hardware.

The FloTrac sensor has a straight, flow-through design across the pressure sensors with an integral flush device.

FloTrac Sensor Cleared Indications

The FloTrac sensor is indicated for use in intravascular pressure monitoring. It is also indicated for use with the Edwards arterial pressure based cardiac output monitoring devices or hardware to measure cardiac output.

The FloTrac Sensors are cleared for use with the HemoSphere Advanced Monitor with HemoSphere Pressure Cable.

Contraindications

There are no absolute contraindications for using the FloTrac sensor in patients requiring invasive pressure monitoring.

HemoSphere Advanced Monitor with HemoSphere Pressure Cable Cleared Indications (For Use with FloTrac)

The HemoSphere advanced monitor when used with the HemoSphere pressure cable is indicated for use in critical care patients in which the balance between cardiac function, fluid status, vascular resistance and pressure needs continuous assessment. It may be used for monitoring of hemodynamic parameters in conjunction with a perioperative goal directed therapy protocol in a hospital environment.

ForeSight Elite Oximetry Technology

Description
The Sensor, when used in combination with the ForeSight Elite tissue oximeter module or in combination with the ForeSight Elite absolute tissue oximeter, is a single use applied part that allows the clinician to continuously and accurately determine absolute levels of blood oxygenation saturation in the tissue (StO_2).

ForeSight Elite Oximetry Sensors (Large) Cleared Indications
When used in conjunction with the ForeSight Elite absolute tissue oximeter or ForeSight Elite tissue oximetry module: The large Sensor is indicated for monitoring of absolute regional hemoglobin oxygen saturation of blood under the sensor in individuals at risk for reduced flow or no-flow ischemic states. It is intended for use on adults and transitional adolescents ≥ 40 kg.

It is included in the Trial only to obtain reference information under its currently cleared indications.

Contraindications
The ForeSight Elite oximetry sensor is contraindicated for use on patients:

- With a physical site area too limited for proper sensor placement
- With allergic reactions to sensor adhesive
- Undergoing an MRI scan because of associate risk of injury

The ForeSight Elite sensors are cleared for use with the HemoSphere advanced monitor with HemoSphere Tissue Oximetry Module in both pediatric and adult population on the HemoSphere advanced monitoring platform.

HemoSphere Advanced Monitor with HemoSphere Tissue Oximetry Module Cleared Indications
The noninvasive ForeSight Elite tissue oximeter module is intended for use as an adjunct monitor of absolute regional hemoglobin oxygen saturation of blood under the sensors in individuals at risk for reduced-flow or no-flow ischemic states. The ForeSight Elite tissue oximeter module is intended to allow for the display of StO_2 on the HemoSphere advanced monitor. It is indicated for use as follows:

- When used with large sensors, the ForeSight Elite tissue oximeter module is indicated for use on adults and transitional adolescents ≥40 kg.

3. TRIAL OBJECTIVE AND ENDPOINTS

Trial Primary Objective

The primary objective is to determine if the use of a protocolized strategy using advanced hemodynamic monitoring with Hypotension Prediction Index (HPI) software guidance for intraoperative hemodynamic management reduces postoperative complication rate in moderate- to high-risk non-cardiac surgery.

Additional Evaluations

1. Time-to-Adverse Event (Complications) Analysis
    a. Non-Parametric Survival Analysis (KM approach)
    b. Cox Proportional Hazard Model
    c. Mixed effect Cox Proportional Hazard Model
    d. Stratification analysis through applying study sites, gender, race as the stratification factor
    e. Fixed/Mixed effective Poisson regression model applying the count of events as the response
    f. Mixed effective survival model to assess the multiple event cases within patient
2. Hypotension management analysis
    a. Time from alert event to intervention
    b. % alerts with no intervention
    c. Reasons for nonintervention
    d. Amount of hypotension removing nonintervention segments
    e. Agreement analysis; clinical decision vs. treatment algorithm
    f. Overall treatment protocol compliance
3. Area under the curve AUC MAP under the threshold of 55,65,75 mmHg
4. Time Weighted Average (TWA) of intraoperative hypotension (mmHg)
5. Time in target SVV <13% (for valid SVV readings = no arrythmia)
6. Time in target CI >2.5 L/min/m^2[15]
7. Postoperative morbidity survey (POMS) on postoperative day 3
8. Transfusion requirement (mL packed red blood cells)
9. Amounts of intraoperative crystalloid and colloid and vasoactive drugs; mL
10. Amount of vasoactive drugs; mg (e.g.: phenylephrine, ephedrine, norepinephrine, epinephrine, dobutamine)
11. Amount of intraoperative intravenous analgesics and sedatives
12. Brain oxygen saturation – StO_2 using ForeSight Elite tissue oximetry system, time in target
13. Verification of the incidence of the listed postoperative complications may be performed at each site by reviewing historic data up to 6 months prior to study initiation
14. Cost of care
15. Hospital length of stay
16. Hospital readmission within 30 days

Trial Endpoints

The primary outcome endpoint is to demonstrate that adding an advanced hemodynamic monitoring utilizing the Hypotension Prediction Index (HPI) with a protocolized strategy to the information provided by the invasive arterial pressure monitoring during moderate-to-high-risk noncardiac surgery impacts the composite of moderate and severe postoperative complications at 30 days.

A reduction in the composite outcome of least 25% in the treatment arm as compared to the control arm is expected. The composite includes MACE (myocardial injury, stroke, non-fatal cardiac arrest, and death), AKI (KDIGO stage 2-3), and serious infections (pneumonia, deep and organ space surgical site infections, and sepsis).

Outcome definitions

MACE

The components and definition of MACE as a post-operative composite outcome are defined below.

Myocardial injury

Myocardial injury after non-cardiac surgery will be diagnosed by objective screening based on troponin concentrations preoperatively and on the first three postoperative days so long as patients remain hospitalized. MINS is defined as any myocardial infarction (i.e., 4th Universal Definition of myocardial infarction[17]), and any elevated troponin judged to be due to myocardial ischemia (i.e., without evidence of a non-ischemic etiology, e.g. chronic elevation, pulmonary embolism, sepsis, cardioversion, others) that occurred within the first 30 days after surgery.

Myocardial injury will be considered when a postoperative troponin concentration is elevated and believed to be consequent to myocardial ischemia. The thresholds differ depending on the assay generation and type. The following thresholds based on available literature will be used:

1. non-high sensitivity (fourth generation) troponin T ≥0.03 ng/mL;
2. high-sensitivity troponin T ≥65 ng/L; or high-sensitivity troponin T 20-64 ng/L and an increase ≥5 ng/L from baseline;
3. high-sensitivity troponin I (Abbott assay) is ≥60 ng/L[4];
4. high-sensitivity troponin I (Siemens assay) is ≥75 ng/L (Borges, unpublished);
5. troponin I (other assays) is at least twice local 99th percentiles;
6. an increase of at least 20% in patients who have preoperative high-sensitivity troponin concentrations that exceed 80% of the relevant thresholds in items 2-5.

Occasionally, patients will have preoperative troponin concentrations exceeding the thresholds in items 2-5. When that happens, clinicians should try to distinguish acute myocardial injury from chronic elevations. Whenever possible, troponin should be resampled because concentrations will usually change substantially in patients having an acute injury but otherwise remain nearly constant if they represent chronic elevation. For patients with a chronic elevation or an acute injury before surgery, a new myocardial injury after surgery requires identification of a new elevated troponin after surgery as per points 1-5 above, and the troponin

elevation must be a 20% rise beyond the chronic troponin value or beyond the last measurement of the acute preoperative myocardial injury that was clearly demonstrated to have peaked and was coming down.

Nonfatal cardiac arrest

Nonfatal cardiac arrest will be defined as successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation.

Stroke

Strokes will be detected from clinical symptoms lasting at least 24 hours and require imaging evidence consistent with new-onset cerebral ischemic or hemorrhagic injury.

Death

Death will be defined as all-cause mortality through the 30-day follow-up (up to 30-days post-operative).

Serious Infections

Serious infections (pneumonia, deep surgical site, organ/space, and sepsis) within 30 days after the operative procedure is defined according Clavien-Dindo grade II or greater:

Surgical site infection (deep surgical site)

- An infection at the surgical incision site which meets the following criteria:
  - Involves deep soft tissues (e.g., fascial and muscle layers) of the incision and
  - The patient has at least one of the following:
    - Purulent drainage from the deep incision but not from the organ/space component of the surgical site
    - A deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive or not cultured when the patient has at least one of the following symptoms or signs: fever (>38°C), or localized pain or tenderness. A culture-negative finding does not meet this criterion.
    - An abscess or other evidence of infection involving the deep incision is found on direct examination, during surgery, or by histopathologic or radiologic examination
    - Diagnosis of an incisional surgical site infection by a surgeon or attending physician organ space surgical site infection

Surgical site infection (organ/space)

- An infection at the surgical incision site, excluding the fascia or muscle layers, which appears to be related to the surgical procedure and involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure and the patient has at least one of the following:
  - Purulent drainage from a drain that is placed through a stab wound into the organ/space
  - Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/ space
  - An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination Diagnosis of an organ/space surgical site infection by a surgeon or attending physician

Pneumonia

- This is defined as two or more serial chest radiographs with at least one of the following (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease):
  - New or progressive and persistent infiltrates
  - Consolidation
  - Cavitation
- And at least one of the following:
  - Fever (>38°C) with no other recognized cause
  - Leucopenia (<4,000 white blood cells/mm^3) or leucocytosis (>12,000 cells/mm^3)
  - For adults >70 years old, altered mental status with no other recognized cause

- And at least two of the following:
    - New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
    - New onset or worsening cough, or dyspnoea, or tachypnoea
    - Rales or bronchial breath sounds
    - Worsening gas exchange (hypoxia, increased oxygen requirement, increased ventilator demand)

Sepsis

Sepsis within 30 days after the operative procedure is defined according to the criteria of the *Centers for Disease Control and Prevention (CDC)*

Sepsis, severe sepsis, and septic shock criteria

- Sepsis is defined as:
    - Defined focus of infection and
    - At least two systemic inflammatory response syndrome (SIRS) criteria.[2]
        - Criteria for Systemic Inflammatory Response Syndrome (SIRS)
          SIRS is defined by two or more of the following:
            1. Core temperature >38°C or <36°C. (Core temperature was rectal or tympanic). If oral, inguinal, or axillary temperatures were used, 0.5°C were added to the measured value
            2. Heart rate >90/min. If patient had an atrial arrhythmia, record the ventricular rate. If patients have a known medical condition or are receiving treatment that would prevent tachycardia (for example, heart block or beta blockers), they must meet two of the remaining three SIRS criteria.
            3. Respiratory rate > 20/min or a PaCO2 <32 mmHg (4.3 kPa) or mechanical ventilation for an acute process.
            4. White Blood Cell (WBC) count of >12 x 109/l or <4 x 109/l.
- Defined focus of infection is indicated by either an organism grown in blood or sterile site, or an abscess or infected tissue (e.g., pneumonia, peritonitis, urinary tract, vascular line infection, soft tissue, etc.).
- Severe sepsis is defined by sepsis plus at least one organ failure, hypotension or hypoperfusion. Septic shock was sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities

AKI

Postoperative Acute Kidney Injury will be defined by Kidney Disease Improving Global Guidelines (KDIGO) Clinical Practice Guidelines.[9]

AKI is defined as any of the following:

- Increase in SCr by ≥0.3 mg/dL (≥26.5 Lmol/L) within 48 hours; or
- Increase in SCr to≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or

- Urine volume <0.5 mL/kg/h for 6 hours.

AKI is staged for severity according to the following serum criteria (Table 1).

Table 1 Staging of AKI

Stage	Serum creatinine
1	1.5–1.9 times baseline OR ≥0.3 mg/dL (≥26.5 mmol/l) increase
2	2.0–2.9 times baseline
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dL (≥353.6 mmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2

4. TRIAL DESIGN

General Design

A multicenter, interventional, randomized comparison of intraoperative hemodynamic management to determine whether use of a protocolized strategy using advanced hemodynamic monitoring with Hypotension Prediction Index (HPI) software guidance for intraoperative hemodynamic management reduces postoperative complication rate in moderate- to high-risk non-cardiac surgery. There will be two arms in this trial, with both arms receiving arterial line monitoring. The treatment arm will receive guidance from a protocolized strategy using advanced hemodynamic monitoring with Hypotension Prediction Index (HPI) software guidance for intraoperative hemodynamic management. The control arm will be blinded to advanced hemodynamic monitoring and will only receive blood pressure monitoring data from the arterial line, as per the standard of care.

A subject will be considered enrolled in the treatment arm once the subject has signed the informed consent and an Acumen IQ sensor has been connected.

A subject will be considered enrolled in the control arm once they signed informed consent and a FloTrac sensor has been connected.

Subjects will be assigned a 6-7-digit Trial Identification Number (Trial ID). The first three-four numbers will identify the site, and the second set of numbers will identify the subject identification number.

For subjects in the treatment arm an Acumen IQ sensor and ForeSight Elite oximetry sensors will be placed prior to the start of the procedure. All advanced hemodynamic parameters including cardiac output (CO), systemic vascular resistance (SVR), stroke volume (SV), stroke volume variation (SVV), Ea_{Dyn}, dP/dt and vital signs will be collected throughout the duration of the procedure and analyzed according to the Statistical Analysis Plan (SAP).

For subjects in the control arm a FloTrac sensor and ForeSight Elite oximetry sensors will be placed prior to the start of the procedure. The control arm will be blinded to advanced hemodynamic monitoring obtained from the FloTrac and ForeSight sensors and will only receive blood pressure monitoring data from the arterial line, as per the standard of care. All vital signs will be collected throughout the duration of the procedure and analyzed according to the SAP.

Subject participation will include preoperative Trial eligibility screening and consent, planned surgical intervention, post intervention follow up through discharge, and 30 days post procedure. Discontinued subject data will be analyzed under intent-to-treat and data will be used for safety and performance analyses.

This Trial will be conducted in a manner that is consistent with the applicable regulations and in accordance with current Good Clinical Practice (GCP).

In accordance with 21 CFR 812.3(m), this Trial does not meet the definition of a significant risk investigation for the following reasons:

- The devices in the treatment arm are being studied in accordance with the indications for use and intended use granted by FDA and therefore are not investigational devices;

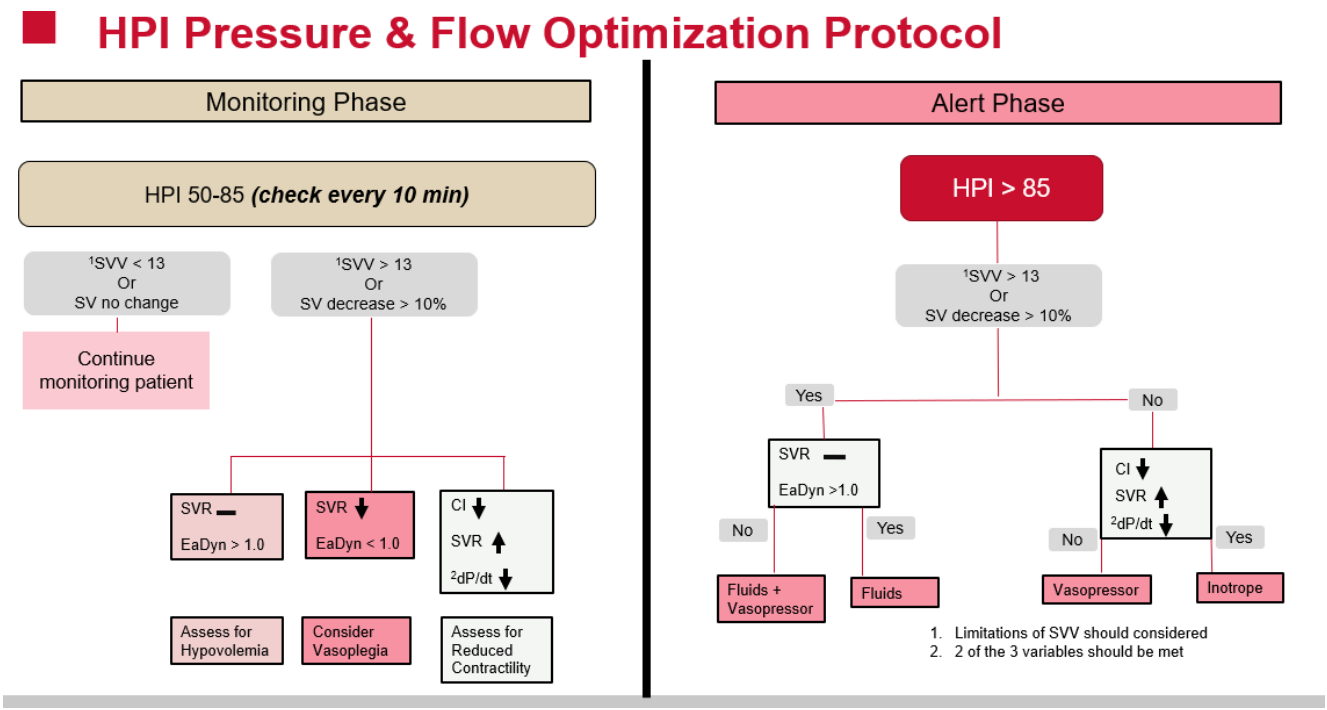
- The devices in the treatment arm are not implants;
- The devices in the treatment arm do not present a potential for serious risk to the health, safety, or welfare of a subject as only subjects requiring an arterial line will be eligible for enrollment in the Trial and;
- The devices in the treatment arm are of substantial importance in diagnosing, mitigating, or treating disease, or otherwise preventing impairment of human health and the general and class II (special) controls provide a reasonable assurance of the safety and effectiveness of adjunctive predictive cardiovascular indicators;
- The Trial relies on the intervention of a learned intermediary prior to initiation of treatment, as the clinicians are utilizing their own clinical judgment in deciding appropriate treatment;
- The HPI Pressure & Flow Optimization Protocol provides recommendations for treatment. Clinicians are instructed to validate the appropriateness of protocol recommendations, and provide treatment based upon their clinical judgment;
- The devices in the treatment arm are not of substantial importance in curing a disease.

Treatment Protocol

Subjects assigned to treatment arm will receive treatment per following guidelines:

- Alert Phase: HPI greater than 85 ➔ alert ➔ treatment per protocol recommendation
- Monitoring Phase: HPI 50 – 85 ➔ evaluate flow / vascular tone indices and fluid responsive state.

Figure 1 : Treatment Protocol for Subjects Enrolled in the Treatment Arm



Note: Clinicians should validate the appropriateness of protocol recommendations, and provide treatment based upon their clinical judgment.

Randomization and Blinding

The randomization for this Trial will be implemented using an Interactive Web Response Systems (IWRS). The Sponsor will be blinded to the randomization codes. Participants will be randomized to either the control or treatment arm at enrollment. Study investigators will be blinded up until the time of the surgery. The clinician(s) involved in the consenting of the patient will be blinded to the randomization assignment and will not be involved in the care of the Trial subject. Once the intent of arterial line placement is confirmed with the anesthesia team, before surgery (the day before or in the morning of surgery), the subject will be randomized to either the treatment or control arm. The arterial line will then be placed. Randomization will be allocated in 1:1 ratio, stratified by site.

Throughout the Trial, the randomization assignment will remain blinded to all parties, with the study investigators and staff being blinded up until the time to surgery. Randomization assignment can be unblinded in the case of a medical emergency that requires the treatment assignment to be known. In this case, an individual subject blind may be broken via the Code Break Module by the Investigator or Medical Reviewer. When possible, the Investigator is to consult with the Medical Reviewer, or designee, prior to breaking the code. The Investigator is to capture the date, time, and reason for breaking the blind in the subject's source notes. Additionally, an independent biostatistician will be unblinded to the randomization codes in order to conduct the interim analysis. All other parties will be blinded to the randomization at time of the interim. After completion of the Trial, the randomization codes will be unblinded, post database lock and with the Trial Sponsor's approval to unblind.

Schema

Figure 2 Enrollment Flow Diagram

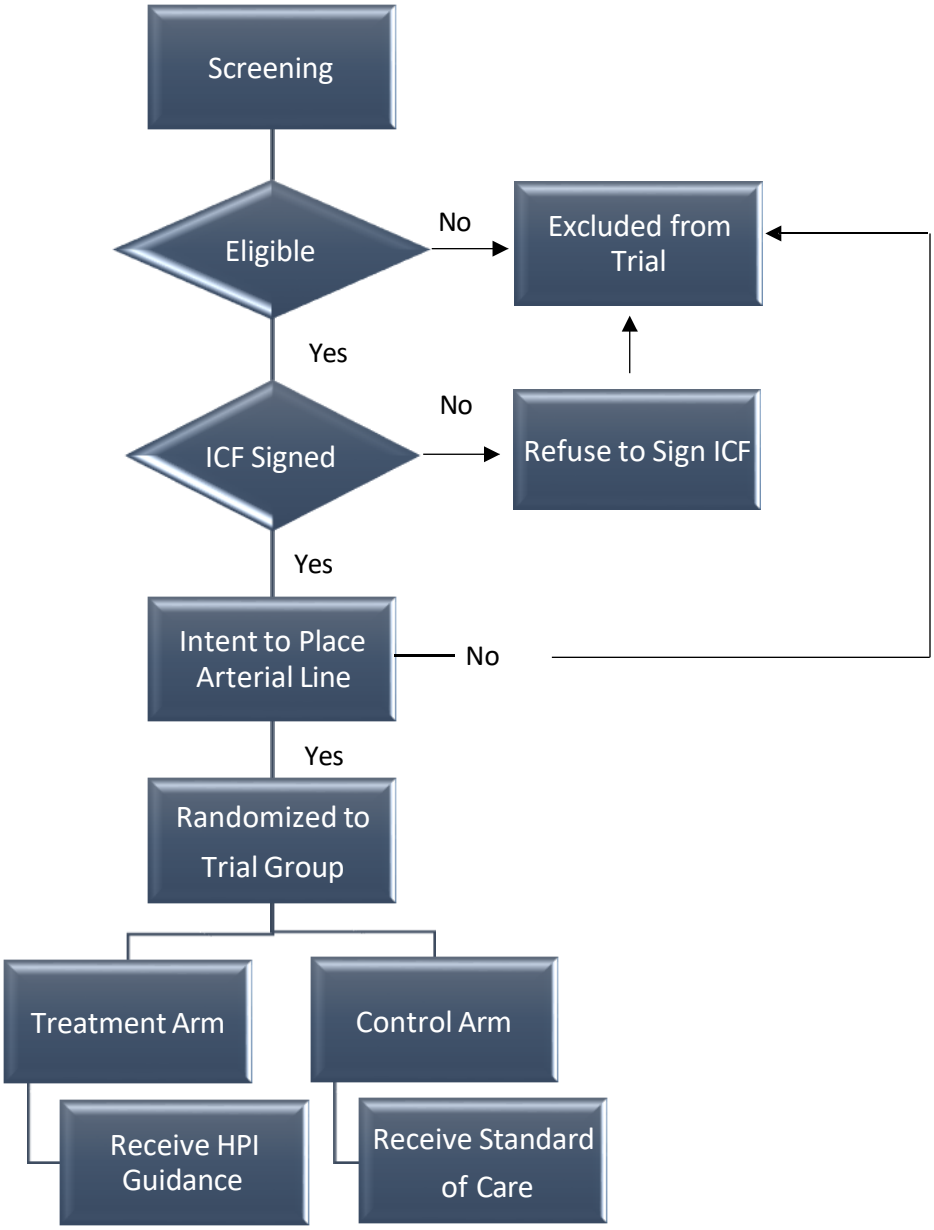
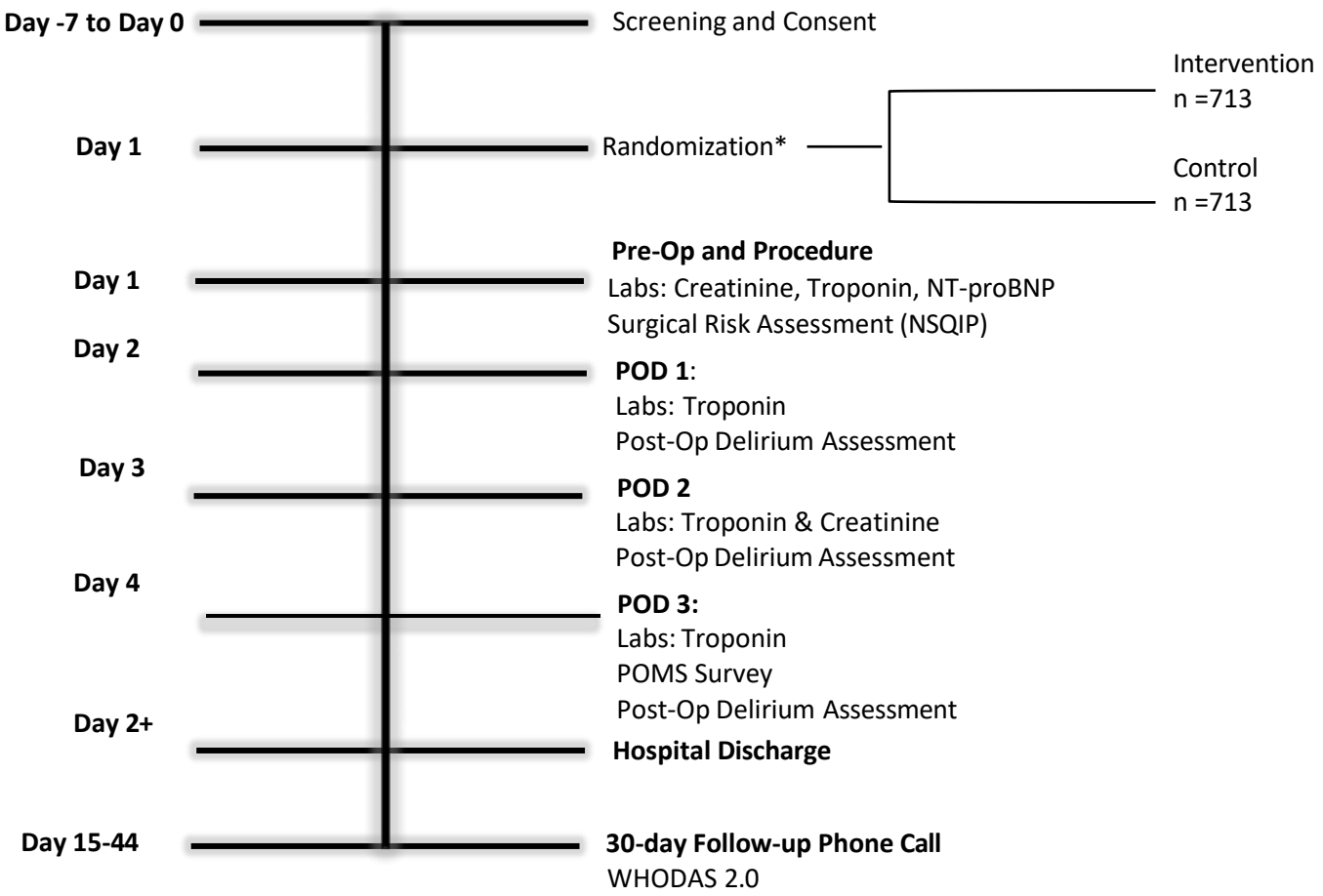


Figure 3 **Enrollment Timeline Diagram**



*Roll-ins not included.

5. SUBJECT CONSENT, SELECTION, AND WITHDRAWAL

General Characteristics of the Proposed Subject Selection

Adults with an ASA classification of ≥ 2 undergoing moderate-to-high-risk noncardiac surgery with expected surgery duration > 2 hours who will be receiving pressure monitoring with an arterial line will be screened for inclusion into the Trial. Only subjects meeting all inclusion criteria will be enrolled. Prior to any Trial procedures, an IRB-approved informed consent form must be signed and dated by the subject or legal guardian. Subjects who have been screened but do not sign an informed consent form will not be considered enrolled and will not have any eCRFs (electronic Case Report Forms) completed.

Informed Consent

Before a subject undergoes any Trial procedures, an informed consent will be obtained utilizing the IRB approved consent form. All consent procedures will be conducted in a manner that is consistent with the applicable regulations and in accordance with Good Clinical Practice (GCP).

During the consent procedure, each potential subject will be given ample time to discuss participation in the Trial and to have any questions or concerns addressed by the Principal Investigator or Investigator. Each subject will be provided with a copy of the IRB approved consent.

Subject Eligibility

All eligible subjects should be screened for Trial eligibility. The Investigator and/or Designee(s) at the Trial site shall review the candidate's eligibility. The Trial site should maintain a cumulative log of all screened subjects in the EDC system.

Inclusion Criteria:

1. Signed informed consent;
2. Age ≥ 18 years;
3. ASA Physical Status ≥ 2;
4. Noncardiac surgery with expected surgery duration ≥ 2 hours (example include: orthopedic, spine, urology, and general surgery)
5. Planned blood pressure monitoring with an arterial line catheter;
6. General anesthesia;

Exclusion Criteria:

1. Participating in another interventional Trial;
2. Contraindication to arterial blood pressure monitoring;
3. Subjects with a physical site area too limited for proper Sensor placement
4. Serum creatine > 175 µmol/L (>2.0 mg/dL) or CKD stage > 3A
5. Scheduled for intracranial surgery with permissive hypotension;
6. Patient who is confirmed to be pregnant and/or nursing mothers;
7. Patients with an intra-aortic balloon pump (IABP) or ventricular assist device(s);
8. Have a condition that precludes routine or tight blood pressure management such as surgeon request for relative hypotension;
9. Emergency surgery;
10. Require beach-chair positioning;
11. Scheduled for cardiac surgeries
12. Have previously participated in the SMART-BP trial.

Screen Failures [or Late Screen Failures]

All eligible subjects should be screened for Study eligibility. The Investigator and/or Designee(s) at the Study site shall review the candidate's eligibility. The Trial site should maintain a cumulative log of all screened subjects in the EDC system.

Early Screen Failure

Early Screen Failures are patients who do not meet the inclusion criteria for participation in this trial (screen failure). Patient may be rescreened if they meet inclusion criteria at a later time. Rescreened participants should be assigned the same participant number as for the initial screening.

Late Screen Failure

Late Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently randomly assigned to the Trial intervention or entered in the Trial.

A Trial ID will be assigned to early screen failures and late screen failures. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, and eligibility criteria.

Enrolled Subjects

A subject will be considered enrolled in the Trial once the subject has signed the informed consent, has been assigned a Trial ID, and an arterial line with either a FloTrac sensor (control arm) or Acumen IQ sensor (treatment arm) has been connected. The Trial ID will be a [6-7-digit] number, the first three-four numbers will identify the site, and the second set of numbers will identify the subject identification number.

Roll-in Subjects

In order to avoid a learning curve bias, up to five (5) Roll-in cases may be performed at a site, as needed, with a maximum total of 60 Roll-in cases in the Trial. Roll-in cases will be analyzed separately from the pivotal cohort.

Early Withdrawal of Subjects

Subjects may voluntarily withdraw consent at any time during the Trial with no loss of benefit or penalty. The Investigator may withdraw any subject if they determine that continued participation in the Trial may be detrimental to the subject's safety and welfare. Subjects withdrawn due to a device complaint or adverse event will be followed through the 30-day telephone follow-up. In addition, if the procedure is aborted early, but after the subject is connected to Trial devices, the subject will be followed for 30 days after the aborted procedure. Each subject withdrawal will be documented on the appropriate eCRF.

Lost to Follow-Up

A participant will be considered lost to follow-up if he or she cannot be reached for the 30-day phone follow-up by the Trial site staff.

The following actions must be taken before a subject is deemed to lost to follow-up:

- The investigator or designee will make every effort to contact with the subject (where possible, three (3) telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or electronic Trial Master File (eTMF).
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the Trial with a primary reason of lost to follow-up.

6. SCHEDULE OF EVENTS & PROCEDURES

Screening

The study staff will review the subject's medical history for eligibility. Once the potential eligibility has been determined, the study will be discussed with the subject and interest in study participation will be determined. Subjects who fulfill all eligibility criteria will be scheduled for surgery within 30 days of the screening visit.

Pre-Procedure

During the pre-procedure period the following data will be collected:

- Labs:
  - Creatinine
  - Troponin
  - NT-proBNP
- Survey
  - Surgical Risk Assessment (NSQIP)

DAY 1 (DAY OF SURGERY)

On the day of the surgery, clinicians will be asked to follow the recommended treatment protocol for subjects enrolled in the treatment arm to reduce the subject's susceptibility to hypotension, (defined as MAP < 65 mmHg for at least one (1) minute), with guidance for decision support from the Hypotension Prediction Index (HPI) Feature Software. There is no restriction on the type of general anesthesia with or without regional anesthesia administered during the surgery.

The subjects in the treatment arm who are undergoing the planned non-cardiac surgery will have a radial arterial catheter inserted for pressure monitoring. The catheter will be connected to an Acumen IQ sensor and to the HemoSphere advanced monitoring platform with the Hypotension Prediction Index (HPI) Feature Software. The ForeSight Elite oximetry sensors will also be placed on subject's forehead to collect tissue oximetry data for observational purposes.

The subjects enrolled in the control arm will have a radial arterial catheter inserted for pressure monitoring and will have ForeSight Elite oximetry sensors placed on their forehead. The catheter will be connected to a FloTrac sensor and to the HemoSphere advanced monitoring platform, however the clinician will not be able to visualize the HemoSphere advanced monitoring platform and will not have information from FloTrac and ForeSight sensors. The subjects will be treated per standard of care, which includes radial arterial catheter monitoring for blood pressure monitoring.

The study staff may access intraoperative care data from the electronic anesthesia information management system. A designated study staff will be present during the procedures to collect data live. At the completion of the surgery, the hemodynamic monitoring data will be downloaded from HemoSphere advanced monitoring platform.

DAYS 2-4 (POD 1-3)

The following data will be collected post-operation at Days (POD) 1, 2 & 3:

- Post-Operative Day 1
  - Any fluid and vasoactive medications
  - Obtain post-operative complications
  - Labs: Troponin
  - Post-Op delirium assessment (4AT[5] or 3D-CAM[17])

- Post-Operative Day 2
  - Obtain post-operative complications
  - Record adverse events
  - Labs: Creatinine and Troponin
  - Post-Op delirium assessment (4AT or 3D-CAM)

- Post-Operative Day 3
  - Obtain post-operative complications
  - Record adverse events
  - Labs: Troponin
  - POMS survey post-operation
  - Post-Op delirium assessment (4AT or 3D-CAM)

If the subject is discharged prior to any of the above schedule of events, a telephone call is sufficient to collect the appropriate required data.

Discharge from the ICU / hospital

The following data will be collected at discharge from the ICU / hospital:

- Obtain post-operative complications
- Record adverse events
- Concomitant Medications: medication that was administered post-operation

30-Day Follow-up

The following data will be collected at 30 days post-procedure via telephone if the subject is no longer in the hospital:

- Obtain post-operative complications
- Record adverse events
- Mortality determination
- WHODAS 2.0 Survey

Schedule of Events (SoE)

Table 2: Schedule of Events

Trial Procedure / Exam	Subject Screening	Pre-Procedure	Procedure	Post-OP Day 1	Post-OP Day 2	Post-OP Day 3	Discharge	30-Day Follow Up (±14 Days)
Obtain Informed Consent	X							
Perform Inclusion / Exclusion Evaluation	X							
Obtain Medical History / Subject Demographics [1]	X							
Assign Subject ID	X							
Assign Trial Arm	X							
Enter Subject Data into Monitor[3]			X					
Vital Signs			X					
Monitoring Duration			X					
Data download from Monitor[3]			X					
Obtain Fluid and Vasoactive Medication Administration Record [2]			X	X				
Obtain post-operative complications, if applicable			X	X	X	X	X	X
Labs: Creatinine [4]		X			X			
Labs: Troponin		X		X	X	X		
Labs: NT-proBNP		X						
POMS [5]						X		
NSQIP Surgical Risk Assessment[5]		X						
Post-Op delirium assessment (e.g., 4AT or 3D-CAM)[5]				X	X	X		
WHODAS 2.0[5]								X
Complete eCRFs	X	X	X	X	X	X	X	X
Record Adverse Events, if applicable			X	X	X	X	X	X
Obtain ICU / Hospital discharge Information							X	X
Phone Contact 30-day follow up / Mortality Determination								X

[1] Medical History / Subject Demographics / Surgical and Clinician Demographics can be obtained prior to procedure, either at the screening visit or on the day of procedure.

[2] Can be collected via the hospital record system anytime on the day of procedure or thereafter.

[3] To be conducted for subjects assigned to treatment arm

[4] To be collected on post-op day 1, 2 or 3.

[5] To be collected if data or subject is available.

Procedure

The HPI SMART-BP Trial will collect data from up to 1486 subjects at up to 20 study sites across the United States. Up to 60 subjects may be included as roll-ins and will be analyzed separately from the pivotal cohort. Subjects will be randomly assigned to the interventional or control arms. The maximum number of subjects enrolled at each site will not exceed 20% of the total study population.
A subject will be considered enrolled in the Trial once the subject has signed the informed consent, has been assigned a Trial ID, an arterial line with either a FloTrac sensor (control arm) or Acumen IQ sensor (treatment arm) has been connected. Subjects may be screened for eligibility and consented on the day of surgery.

Subject participation will include preoperative study eligibility screening and consent, planned surgical intervention, Post-Op Day 1-3, ICU, hospital discharge, and 30 days post-procedure. Discontinued subject data will be analyzed under intent-to-treat and data will be used for safety and performance analyses.

The subjects enrolled in the treatment arm will have a radial arterial catheter inserted for pressure monitoring and will have ForeSight Elite oximetry sensors placed on their forehead. The catheter will be connected to an Acumen IQ sensor and to the HemoSphere advanced monitoring platform which includes the AcumenTM Hypotension Prediction Index (HPI) feature software. The Acumen HPI software will provide clinicians with information and physiological insight regarding the likelihood of a subject trending towards a hypotensive event (defined as mean arterial pressure ≤ 65 mmHg for at least one minute). A secondary screen with associated hemodynamic parameters is available to the clinicians for additional quantitative information regarding the subject's physiological condition. When the Hypotension Prediction Index (HPI) exceeds 85 for two consecutive 20-second updates or reaches 100 at any time, a popup alert will appear on the monitor and clinicians can activate the secondary screen to review all hemodynamic parameters. The anesthesia team will receive a protocolized hemodynamic management strategy and will determine the amount and timing of intravenous fluids and vasopressor or ionotropic drugs to be given to subject. Interventions conducted per treatment protocol and/or outside the treatment protocol will be documented on the eCRF(s). Clinicians should validate the appropriateness of protocol recommendations, and provide treatment based upon their clinical judgment.

The subjects enrolled in the control arm will have a radial arterial catheter inserted for pressure monitoring and will have ForeSight Elite oximetry sensors placed on their forehead. The catheter will be connected to a FloTrac sensor and to the HemoSphere advanced monitoring platform; however, the clinician will not be able to visualize the HemoSphere advanced monitoring platform and will not have information from FloTrac and ForeSight sensors. The subjects will be treated per standard of care, which includes radial arterial catheter monitoring for blood pressure monitoring. Patients in the control arm will not have a defined MAP threshold for hypotension and will not receive protocolized hemodynamic management. The anesthesia team will determine the amount and timing of intravenous fluids and vasopressor or inotropic drugs to be given to subject.

For subjects enrolled in both arms, creatinine values and Surgical Risk Assessment (NSQIP) will be collected during the perioperative period. Troponin values and Post-Op delirium assessment (4AT or 3D-CAM) for POD 1-3, creatinine values for POD 2, POMS survey for POD 3, and 30-day survey will be accessed post operatively.

7. STATISTICAL METHODS

Statistical Analysis Plan (SAP)

There will be a formal SAP, separate from this Trial protocol. A formal SAP will be completed prior to database lock and the analysis of any Trial endpoints data. The SAP will detail the planned statistical analyses. The subsections below summarize the planned analyses.

Primary Outcome Endpoint

The primary outcome endpoint is to determine if the use of a protocolized strategy using advanced hemodynamic monitoring with Hypotension Prediction Index (HPI) software guidance for intraoperative hemodynamic management reduces postoperative complication rate in moderate- to high-risk non-cardiac surgery. The composite includes MACE (myocardial injury, stroke, non-fatal cardiac arrest, and death), AKI, and serious infections (pneumonia, deep and organ space surgical site infections, and sepsis).

Sample Size Justification

The goal of this study is to assess if the use of Hypotension Prediction Index (HPI) software guidance impacts the incidence of postoperative morbidity and mortality in the adult population undergoing moderate-to-high-risk noncardiac surgery (with a pressure monitoring with an arterial line). A relative reduction in the composite outcome within the treatment arm is expected. For a group sequential analysis, following the O'Brien and Fleming methodology, a sample size was calculated for a two-sample comparison of rates (two-sided). The hypothesis are as follows:

H_0: p_0-$p_1 \geq 0$

H_1: $p_0 \neq p_1$

Assuming at least a 25% relative change in rate for the treatment (p_1) arm, a type I error (0.05), a power of 80%, and a reference rate of 0.31 (p_0) based on a meta-analysis [6,10,14] , a sample size of 1426 subjects are needed. An additional 60 subjects may be included as roll-ins, which results in a total enrollment potential of 1486 subjects.

Analysis Populations

Modified Intent-to-treat (mITT)
Modified Intent-to-treat (mITT) is defined as the study subjects who were exposed to the study product and will therefore be included in the effectiveness and safety analysis datasets. All randomized study subjects who have satisfied the population criteria will be classified in the designated population and will only be included in analyses for which they have available data. The mITT population will also be used to present exploratory analyses by the randomized treatment arm. The safety population is defined as all randomized subjects who were exposed to the study product; thus, the safety population will therefore be identical to the mITT population if all randomized subjects are exposed to the study product. The safety population will be used to present the safety summaries by actual treatment received.

Per Protocol Analysis

A per protocol analysis is defined as a dataset of subjects who completed enrollment as written in the protocol, (e.g., No protocol deviations occurred during the non-cardiac surgical procedures).

Analysis Methods

The following z-statistic will be used to judge if the Hypotension Prediction Index (HPI) software can reduce postoperative morbidity and mortality:

$$z = \frac{\hat{p} - \hat{p} - 0}{\sqrt{(\frac{x_0 + x_1}{n_0 + n_1})\,(1 - \frac{x_0 + x_1}{n_0 + n_1})\,(\frac{1}{n_0} + \frac{1}{n_1})}}$$

Here x_0 and x_1 are the amount of events that occurred in the reference arm and test arm respectively, thus, $\hat{p}_0 = \frac{x_0}{n_0}, \hat{p}_1 = \frac{x_1}{n_1}$ are the proportion of events that occurred in the reference arm and test arm, respectively, n_0, n_1 are the number of subjects in reference arm and test arm respectively. The pooled standard error is given by $\sqrt{(\frac{x_0+x_1}{n_0+n_1})(1-\frac{x_0+x_1}{n_0+n_1})(\frac{1}{n_0}+\frac{1}{n_1})}$. The z-statistic will be calculated using data from the complete case population and it will be compared to the critical z-value ($z(\alpha', n_0+n_1-2)$ to judge if the null hypothesis can be rejected. Here α' is the adjusted type I error rate (adjusted for interim analysis). Moreover, the degree of freedom is given by, n_0+n_1-2. The 95% CI is given by $\hat{p}-\hat{p} \pm z_\alpha \sqrt{(\frac{x_0+x_1}{n_0+n_1})(1-\frac{x_0+x_1}{n_0+n_1})(\frac{1}{n_0}+\frac{1}{n_1})}$ The other analysis methods are detailed in the statistical analysis plan.

Additional Evaluations

The continuous variables will be evaluated using the parametric two sample t-test (or the Welsh t-test if unequal variance or the Wilcox-Mann Whitney test if non-normally distributed) and categorical/binary variables will be evaluated using a chi-squared test (Fisher's exact if low counts). Logistic regression will be used to evaluate incidence of AKI with other variables being used as co-variates. Time-to-event variables will be evaluated by survival analysis models (Kaplan-Meier or Cox Proportional Hazards). Summary statistics and statistical comparison will be presented in tables with point estimates (odds ratios or log odds), standardized errors, and 95% CI. There will be no multiplicity adjustment for performing multiple hypothesis tests of exploratory outcomes, unless specified otherwise.

Sensitivity analysis including the review of any influence of surgical position, type of anesthesia, tidal volume etc., on the primary outcome measure, are specified in the SAP.

The following data will also be explored:

1. Time-to-Adverse Event (Complications) Analysis
    a. Non-Parametric Survival Analysis (KM approach)
    b. Cox Proportional Hazard Model
    c. Mixed effect Cox Proportional Hazard Model
    d. Stratification analysis through applying study sites, gender, race as the stratification factor
    e. Fixed/Mixed effective Poisson regression model applying the count of events as the response
    f. Mixed effective survival model to assess the multiple event cases within patient
2. Hypotension management analysis
    a. Time from alert event to intervention
    b. % alerts with no intervention
    c. Reasons for nonintervention
    d. Amount of hypotension removing nonintervention segments
    e. Agreement analysis; clinical decision vs. treatment algorithm
    f. Overall treatment protocol compliance
3. Area under the curve AUC MAP under the threshold of 55,65,75 mmHg

4. Time Weighted Average (TWA) of intraoperative hypotension (mmHg)
5. Time in target SVV <13% (for valid SVV readings = no arrythmia)
6. Time in target CI >2.5 L/min/m[15]
7. Postoperative morbidity survey (POMS) on postoperative day 3
8. Transfusion requirement (mL packed red blood cells)
9. Amounts of intraoperative crystalloid and colloid and vasoactive drugs; mL
10. Amount of vasoactive drugs; mg (e.g.: phenylephrine, ephedrine, norepinephrine, epinephrine, dobutamine)
11. Amount of intraoperative intravenous analgesics and sedatives
12. Brain oxygen saturation – StO_2 using ForeSight Elite tissue oximetry system, time in target
13. Verification of the incidence of the listed postoperative complications may be performed at each site by reviewing historic data up to 6 months prior to study initiation
14. Cost of care
15. Hospital length of stay
16. Hospital readmission within 30 days

Planned Interim Analyses

Assuming a power of 80% and a relative reduction of at least 25% in the composite score (reference proportion=0.31) with three total looks (two interim analysis, one final), the critical values for each time point were chosen to preserve an overall type-1 error rate of 0.05. The O'Brien and Fleming methodology was used to determine the boundary rule for deciding when to stop the trial prematurely. Futility was included. A relative reduction in the composite outcome within the treatment arm is expected. The alpha at each interim and the maximum number of observations are chosen so that the overall significance level is the probability of detecting the treatment difference under the null hypothesis. The table below shows the critical values:

Analysis	Information Rate	Effectiveness Boundary z-value (Upper, Lower)	Futility Boundary z-value (Upper, Lower)
First Interim Analysis	50%	(2.96259, -2.96259)	(0.40273, -0.40273)
Second Interim	75%	(2.35898, -2.35898)	(1.12741, -1.12741)
Final Analysis	100%	(2.01404, -2.01404)	(2.01404, -2.01404)

8. RISK ANALYSIS

Anticipated Risks

Edwards will monitor for safety, which includes those potentially associated with the use of Trial devices and their components. There may be additional risks and discomforts that are not known at this time.

Any events associated with the Trial devices will be reported in accordance with the Medical Device Reporting (Complaints) regulation (21 CFR Part 803).

Below is a list of general anticipated risks associated with the type of surgeries and procedures, which may be conducted as standard of care.

- Risks related to transplantation of donor organ:
  - Death
  - Explant of donor organ
  - Hemorrhage
  - Organ transplant failure
  - Respiratory Failure
  - Sepsis/Infection

- Risks related to other surgical or patient factors:
  - 30-day mortality
  - Cardiac arrest
  - Cardiac arrhythmia
  - Hemorrhage
  - Ileus
  - Nausea and vomiting
  - Pneumonia
  - Prolonged Hospital length of stay
  - Prolonged ICU length of stay
  - Pulmonary embolism
  - Sepsis
  - Transfusion need
  - Wound infection

Below is a list of anticipated risks that may be associated with the use of the Acumen IQ/FloTrac sensor:

The vascular access obtained is standard clinical care for the adult population and the addition of the Acumen IQ/FloTrac sensor is and is not expected to impose any additional risk to the patient. There is no measurable increased infectious risk with the temporary use of the Acumen IQ/FloTrac sensor.

Below is a list of anticipated risks that may be associated with the use of ForeSight Elite oximetry Sensors:

- Allergic reaction to adhesive on sensors
- Skin irritation

In addition to the risks mentioned above, use of the HPI Pressure & Flow Optimization Protocol may lead to undertreatment or overtreatment with vasoactive drugs or fluids.

Under- or overtreatment may result in the following anticipated risks:

- Heart failure
- Profound hypotension
- Hypertension
- Cardiac ischemia
- Tachyarrhythmia
- Bradycardia

Risk Management

The HemoSphere advanced monitoring platform, Acumen IQ sensor, FloTrac sensor, ForeSight Elite oximetry sensor and Hypotension Prediction Index (HPI) Feature Software have been tested to an established regimen of safety and performance testing (as applicable) required prior to use in human subjects in these clinical studies. This regimen includes requirements under applicable standards and regulations for packaging, shelf life, biocompatibility, microbiology, chemistry, sterility, electrical, mechanical and fatigue testing.

The indications and intended use of the HemoSphere advanced monitoring platform with Acumen™ Hypotension Prediction Index (HPI) feature software and Acumen IQ sensor remain unchanged from those previously cleared by FDA.

Table 3: Trial Devices and Indication for use

Device	Indication for use
HemoSphere Advance Monitoring Platform with Acumen Hypotension Prediction Index	The Acumen HPI feature software is intended for use in surgical or non-surgical patients receiving advanced hemodynamic monitoring. The Acumen HPI feature is considered to be additional quantitative information regarding the patient's physiological condition for reference only and no therapeutic decisions should be made based solely on the Acumen Hypotension Prediction Index (HPI) parameter.
Acumen IQ Sensor	The Acumen IQ sensor is indicated for use in intravascular pressure monitoring. It is also indicated for use with the Edwards arterial pressure based cardiac output monitoring devices or hardware to measure cardiac output.
FloTrac Sensor	The FloTrac sensor is indicated for use in intravascular pressure monitoring. It is also indicated for use with the Edwards arterial pressure based cardiac output monitoring devices or hardware to measure cardiac output. The FloTrac Sensors are cleared for use with the HemoSphere Advanced Monitor with HemoSphere Pressure Cable.
ForeSight Elite oximetry Sensor	The large ForeSight Elite oximetry Sensor is indicated for monitoring of absolute regional hemoglobin oxygen saturation of blood under the sensor in individuals at risk for reduced flow or no-flow ischemic states. It is intended for use on adults and transitional adolescents ≥ 40 kg.

Benefits

There are no guaranteed benefits to Trial participation. However, this will be the first prospective, multicenter, interventional, randomized controlled Trial that will highlight the potential effect the Hypotension Prediction Index (HPI) plus a treatment protocol has on morbidity and mortality.

9. REPORTABLE EVENTS

Recording and Reporting of Adverse Events

The Investigator and/or Designee(s) will determine whether any adverse events (AEs) have occurred. An AE is defined as any untoward medical occurrence in a clinical Trial of a Trial Device regardless of the causal relationship of the problem with the device or, if applicable, other Trial treatment or diagnostic product(s). Information for AEs with the Trial devices will be collected from the time a subject begins the Trial related procedure and/or is exposed to Trial product(s). AEs will also be collected during surgical intervention, post intervention, discharge and through the follow-up. AEs may be volunteered by subjects, clinicians, elicited from questioning by Investigator and/or Designee(s), or collected via observation. When a device or Trial related AE is suspected all available event information and will be provided to the Clinical Events Committee.

Once an AE/SAE/UADE is confirmed as such, event, date of onset, severity, duration, treatment (if required), resolution (or ongoing), assessment of seriousness, relationship to Trial procedure and relationship to device will be recorded on the appropriate eCRF or SAE Report Form and submitted as necessary by the Investigator and/or Designee(s). Any suspected AEs related to the Trial Device or Trial procedure must be reported to the Sponsor or Designee within 24 hours of first awareness of the event.

Severity of an AE

The following guidelines will be used to describe the severity of the AE:

- Mild – Event requires minimal or no treatment and do not interfere with the subject's daily activities.
- Moderate – Event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Event interrupts a subject's usual daily activity and may require systemic drug therapy or other intervention. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."

Relationship of an AE

The evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, Trial-related procedures, accidents, and other external factors. In a device Trial, the Trial product(s) must always be suspect.

Causality of relationship to the Trial product(s) will be judged by the Investigator who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. Causality of relationship will also be reviewed by the Investigator, and independently by a Medical Reviewer, as follows:

Not related:

- An event is clearly not and cannot be related to the Trial product(s), and/or evidence exists that the event is definitely related to another etiology. Note: Reporting of these events to the Sponsor or designee within 5 working days of first awareness of the event is not required unless the event was related to the Investigational Device or Trial.

Possibly Related:

- There is some evidence to suggest a causal relationship may exist; however, the event could have been produced by another cause (e.g., treatment, condition). Note: Reporting of these events to the Sponsor or designee within 5 working days of first awareness of the event is required.

Related:

- A relationship can be directly attributed to the use of the Investigational Device. Note: Reporting of these events to the Sponsor or designee within 24 hours of first awareness of the event is required.

Recording and Reporting of Adverse Device Effects

An adverse device effect (ADE) is defined as an AE related to the use of a Trial medical device. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation or operation, or any malfunction of the investigation device. It also includes any AE resulting from use error or from intentional misuse of the Trial Device.

ADEs must be reported to the Sponsor or designee, within 24 hours of first awareness of the event. Notification should be done via email, fax, telephone, or direct communication followed by direct entry of AE/SAE data into the eCRF. In addition, the Trial site will report confirmed ADEs related to their IRB in accordance with the IRB's/IEC's requirements. ADEs will also be reported to the FDA, as required.

Recording and Reporting of Serious Adverse Event

A serious adverse event (SAE) is defined as an AE that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Recording and Reporting of Serious Adverse Device Effects

A serious adverse device effect (SADE) is an ADE that has resulted in any of the consequences or characteristics of a SAE.

SADEs must be reported to the Sponsor or designee, within 24 hours of first awareness of the event. Notification should be done via email, fax, telephone, or direct communication followed by direct entry of AE/SAE data into the eCRF. In addition, the Trial site will report confirmed SADEs their IRB in accordance with the IRB's/IEC'S requirements. SADEs will also be reported to the FDA, as required.

Recording and Reporting of Unanticipated Adverse Device Events

Unanticipated adverse device effect (UADE) is defined in 21 CFR 812.3(s) as 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 supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. In contrast, an anticipated adverse device effect is an effect which by its nature, incidence, severity, or outcome has been identified in the risk analysis report.

UADEs must be reported to the Sponsor or designee within 24 hours and submitted to the reviewing IRB as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.

All AEs related to the Trial Device or Trial will be reviewed by the Investigator and/or Designee(s) and Sponsor. These AEs will be followed until they are adequately resolved, explained by the Investigator and/or Designee(s), until subject has completed follow-up, terminated the Trial early, is lost to follow-up or has been withdrawn from the Trial.

Recording and Reporting of Deaths

Events resulting in death during the subject's enrollment in this Trial are not expected to occur as a result of participation in the Trial. In the event of subject death, every reasonable effort should be made to obtain a copy of the autopsy report and/or death summary. Information on the date and cause of death and its relationship to the Trial device will be determined by the Investigator and/or Designee and recorded on the appropriate AE eCRF and submitted on an SAE Report Form as necessary.

Recording and Reporting of Adverse Events Associated with Commercial Components

Any adverse event associated with an FDA cleared component will be recorded as a device complaint and reported via the MDR program (21 CFR Part 803). Complaints will also be reported to the IRB in accordance with each IRB's/IEC's requirements. Device complaints should be reported to the Sponsor as soon as the site becomes aware of the complaint. The Sponsor may request further information and documentation from the site when complications and/or malfunctions are observed and reported.

Recording and Reporting of Pre-Existing Conditions

Pre-existing medical conditions and symptoms due to pre-existing medical conditions, surgery or admission to ICU will not be recorded as adverse events. The admission of a critically ill patient in the intensive care unit is commonly due to one or several serious medical conditions and/or a major surgery, which may cause changes and abnormalities of blood chemistry, diagnostic and physiological parameters. In the event there is a deterioration of a pre-existing medical condition or symptoms due to the use of the Trial product(s) or a Trial related procedure, then the review of the event will be initiated, and an AE will be recorded if it meets the definition. Any events occurring prior to the exposure to the Trial product(s) or Trial related procedure will be recorded as medical history.

Reporting Adverse Events to the FDA

Confirmed UADEs will be evaluated by the Medical Reviewer. The FDA, all participating principal investigators, and their reviewing IRBs/IECs will be informed no later than 10 working days after Edwards Lifesciences or designee first becomes aware of the effect.

Reporting Adverse Events to the Responsible IRB

In accordance with applicable policies of the IRB, the Investigator will report, any observed or volunteered confirmed adverse event that is determined to be (1) unexpected; (2) related or possibly related to the research; and/or (3) involves increased or greater risk of harm to participant(s) or others than was previously known or approved by the IRB. AE reports will be submitted to the IRB in accordance with the IRB policies and procedures.

Confirmed UADEs will be evaluated, and the reviewing IRB will be informed of the results of the Trial no later than 10 working days after Edwards or when the designee first becomes aware of the effect.

Recording and Reporting AE Time Period

At each Trial visit, the Investigator and/or Designee(s) will inquire about the occurrence of AE/SAEs/ADEs/SADEs/UADEs since the last visit. AE/SAEs/ADEs/SADEs/UADEs will be followed until they are adequately resolved, explained by the Investigator and/or Designee(s), until subject has completed follow-up, terminated the Trial early, is lost to follow-up or has been withdrawn from the Trial.

10. INDEPENDENT SAFETY COMMITTEES

Medical Reviewer

The role of the Medical Reviewer is to adjudicate pre-specified adverse events in a consistent and unbiased manner throughout the course of the trial. The Medical Reviewer is an independent, qualified physician whose medical specialty may include anesthesiology. The Medical Reviewer will adjudicate serious adverse events that are possibly related to the surgical procedure or the Acumen™ Hypotension Prediction Index (HPI) Feature Software or death. The Medical Reviewer will notify the site or Sponsor if additional potential adverse events are identified during the adjudication process.

Data Safety Monitoring Board

An independent (4-Member) Data Safety Monitoring Board (DSMB) will be established to oversee the Trial outcome. Members of the DSMB must be free of significant conflicts of interest (e.g., Financial, intellectual, professional, or regulatory), or measures should be in place to minimize perceived conflict of interest. Members of the DSMB are also experts in all scientific disciplines needed to interpret the data and ensure Trial participant safety, including an independent biostatistician. The DSMB will meet via teleconference a minimum of semiannually or at least two (2) times over the course of the Trial. The DSMB manual of operation (MOP) will be maintained by the Sponsor as part of the clinical Trial project plan. The DSMB MOP will outline membership and voting procedures as well as DSMB Meeting documentation and communication. The DSMB meetings will include an open session where the Sponsor will present Trial updates, review trends for device malfunctions, protocol deviations and subject withdrawal reasons to communicate Trial progress. The Investigators may attend the open session.

In addition to the open portion of the DSMB meetings, there will be closed sessions that will only be attended by the DSMB members.

The DSMB will perform the following activities during the closed session of the meetings:

- Assess primary safety endpoint
- Assess participant risk versus benefit, performance of Trial sites, and other factors that can affect Trial safety outcome
- Review factors external to the Trial when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the Trial
- Make recommendations to Edwards Lifesciences, IRB, and investigators concerning continuation or conclusion of the Trial based solely on safety evaluation
- Protect the confidentiality of the Trial data and the results of monitoring

To mitigate any potential release of Trial results, the analysis of safety endpoint will be led by the independent biostatistician serving on the DSMB. The biostatistician will have no contact with the Sponsor or any Trial sites. Furthermore, the identification of the other DSMB members will not be shared with the sites during the conduct of the Trial.

Stopping Rules

Continuation or discontinuation of the trial will be based upon the DSMB's evaluation of trial safety. This study will be stopped prior to its completion if: (1) the intervention is associated with adverse events that call into question the safety of the intervention, (2) any new information becomes available during the trial that necessitates stopping the trial and/or (3) Based on the results of interim analysis.

11. RECEIVING, STORAGE, AND RETURN OF DEVICES

Receipt of Device Supplies

A packing list will accompany all device shipments. This list will include the inventoried product with receipt date and investigator and/or designee signature.

Storage

The HemoSphere advanced monitoring platform and all Trial product(s) shall be stored in a secure and clean area complying with the storage instructions provided in the labeling.

Device Accountability

The Investigator and/or delegated-Trial personnel shall keep records documenting the receipt, use, return, and disposal of the devices. Only the Investigator, delegated-Trial Personnel and/or designee(s) (i.e., Assisting Clinician(s)) may use the devices. The Investigator will supervise the use of the devices in Trial subjects. The Trial site shall account for which system/device was used for which subject as well as for the return of the system/device.

Return of Devices

The Principal Investigator or designee is responsible for returning the unused product back to the Sponsor.

12. CONFIDENTIALITY AND PRIVACY

Information about Trial subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Consistent with these regulations, a signed authorization will be obtained that informs each subject of the following:

- What protected health information (PHI) will be collected from subjects in this Trial
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

No subject demographic data or medical information will be used or shared outside the Sponsor and site staff unless an unanticipated adverse device effect (UADE) is reported. If a UADE is reported, all efforts will be made to keep subject information confidential. The Sponsor is dedicated to maintaining the confidentiality and privacy of subjects who volunteer to participate in the Trial. The Trial Investigator and the Trial site personnel are responsible for maintaining confidentiality throughout the clinical Trial. The Sponsor and Sponsor designated Trial personnel will have access to the data collected. The hard copies of the source documentation are to be maintained in a secure area with limited access.

To protect subject confidentiality, the subject's name must not appear anywhere on CRFs, or supporting documentation removed from the site. All subject identifiers (e.g., social security number) will be obliterated from all photocopies of source documents that have been removed from the site. All Trial documents will identify the subject by a subject Trial identification number and Protocol number assigned by the Sponsor (if applicable).

In the event that a subject revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled Trial period.

13. DATA HANDLING AND RECORD KEEPING

Source

Source data are all information, original records of clinical findings, observations, or other activities in a Trial necessary for the reconstruction and evaluation of the Trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, source worksheets that have been certified as source, and records kept at the pharmacy, at the laboratories, and at medical-technical departments involved in the Trial.

Required data for this Trial are to be recorded in the subject's file and/or via eSource and/or on worksheets, certified as source, for source documentation and data verification. Some of the source documentation generated during the Trial may also be the electronic data from the Monitor, laboratory data, or printout from Radiometer and YSI. Data may also be entered directly onto the eCRF during the visit. Because of the potential for errors, inaccuracies, and illegibility in transcribing data onto eCRFs, the Investigator must permit inspection of source documents by the Sponsor, and inspection by local and regulatory authorities.

Data Entry Timelines

It is recommended that electronic case report forms (eCRFs) be completed within 24 hours of data availability, but not more than 10 working days after completion of assessments.

14. CHANGES TO THE PROTOCOL

Changes to the research covered by this protocol must be implemented by formal protocol amendment. All amendments to the protocol must be initiated by the Sponsor.

Protocol amendments must not be implemented without prior IRB approval. Documentation of amendment approval by the Investigator and IRB or IEC must be provided to the Sponsor or its authorized representative. When the change(s) involve only logistic or administrative aspects of the Trial, the IRB only needs to be notified.

15. PROTOCOL DEVIATION

Any deviations from the protocol will be documented on the protocol deviation eCRF. The Investigator/or Designee shall be responsible for the reporting of any deviations deemed reportable to the IRB.

Deviations shall be reported to the Sponsor, regardless of whether they are medically justifiable, pre-approved by the sponsor, or taken to protect the subject in an emergency. Subject-specific deviations will be reported on the appropriate eCRF.

Non-subject specific deviations (e.g., unauthorized use of a device outside the Trial, etc.) will be reported in writing. The investigator will also adhere to procedures for reporting Trial and subject specific deviations to their IR/IEC in accordance with their specific IRB's/ IEC's reporting policies and procedures.

16. DATA COLLECTION METHODS

Trial data will be captured utilizing electronic Case Report Forms (eCRFs) including the 30-day follow-up call as well as downloaded files captured directly via the use of the HemoSphere advanced monitor. Data collected from the HemoSphere advanced monitor will be downloaded at the end of each catheterization procedure and stored on a USB stick. USBs will be stored in a secure location at the site, accessible only to Trial site personnel. The HemoSphere data on USBs may be shipped to the Sponsor at any point in time of the Trial per the request of the Sponsor.

17. RECORD RETENTION

It is the Investigator's responsibility to retain Trial essential documents during the investigation and for a minimum period of two (2) years after the investigation is terminated or completed, or the records are no longer required for the purposes of supporting a premarket approval application or a notice of completion of a product development protocol. These documents should be retained for a longer period if required by an agreement with the Sponsor. In such an instance, it is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

18. TRIAL DOCUMENTATION

Trial Records

Edwards will maintain accurate, complete, and current records relating to the conduct of the Trial.
Records to be maintained by Edwards Lifesciences and the Trial site include but are not limited to:

- Trial protocol and all amendments, if applicable
- IRB approved Informed Consent
- IRB approval letter, including informed consent form
- IRB membership list, or alternative notification of IRB being duly constituted or Department of Health and Human Services Multiple Projects Assurance Number
- IRB correspondences
- Trial training logs
- Device accountability records
- Required reports, if applicable

The following records must be maintained for each subject enrolled in the Trial:

- Signed informed consent form
- All completed eCRFs
- Supporting documentation of any adverse events

Trial Reports

Designated site personnel shall prepare and submit the following accurate and complete reports in a timely manner to the IRB and FDA, if applicable:

- Report of an Unanticipated Adverse Device Effects (UADEs) as soon as possible, but in no event later than 10 working daysafter the first awareness of the event. After an internal evaluation, Edwards shall report the results of such evaluation to FDA and to all reviewing IRBs/IECs and participating investigators within 10 working days after receipt of notice of the effect.
- Withdrawal of IRB approval within 5 working days to Edwards. Thereafter, Edwards shall notify FDA and all reviewing IRBs/IECs and participating investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the notification of withdrawal of approval.
- Progress reports will be submitted to the IRB as required and no less than yearly.
- Deviation from the Trial protocol to protect the subject's life or physical well-being in an emergency will be reported to Edwards as soon as possible, but in no event later than 5 working days after the emergency occurred. Non-emergency deviations will be reported to the IRB, as required. If deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB shall be notified.
- A final written report is submitted to the IRB within 6 months after completion or termination of the Trial as required.
- Upon request by the reviewing IRB or FDA, Edwards will provide accurate, complete, and current information about any aspect of the investigation.
- Use of the Trial device without informed consent will be reported to Edwards and the IRB within 5 working days after the use occurs. Thereafter, Edwards shall notify FDA within 5 days of receipt of notice.

Communication Procedures

Edwards will utilize an electronic regulatory binder to maintain required Trial documentation including applicable correspondences during the course of the Trial.

19. TRIAL MONITORING, AUDITING, AND INSPECTING

Site Selection

The Trial site(s) for this Trial will be pre-screened by the Sponsor. The Principal Investigator will be selected based on their training and experience with this type of research activity and available subject population. The Sponsor will provide the Investigator with information, Trial specific training, and supplies necessary to conduct the Trial.

Trial Monitoring Plan

A Monitoring Plan will be created to address monitoring arrangements and the extent of source data verification. A Trial monitor will be assigned to monitor the progress of the Trial by the Sponsor. The Trial monitor may be either an employee of the Sponsor or contracted. The Trial monitor will be responsible for reviewing eCRFs and monitoring the Trial site routinely to observe Trial progress and to verify that the Trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements. The Investigator must permit inspection of the source documents, regulatory binders and other Trial related documents provided by the Sponsor.

Trial monitoring visits will be scheduled throughout the duration of the Trial between the Trial monitor and the Investigator and/or Designee at a mutually convenient and available time. These visits will assure that the facilities are still acceptable, the Protocol and investigational plan are being followed, the IRB has been notified of approved Protocol changes as required, complete records are being maintained, appropriate timely reports have been made to the Sponsor and the IRB, device and device inventory are secure and the Investigator is carrying out all agreed activities. Any personnel changes must be reported to the Trial monitor immediately.

All eCRFs will be maintained in a validated EDC system and data anomalies, missing data, or unclear data will be queried as necessary throughout the Trial for clarification/resolution by the Principal Investigato r or delegated-site personnel.

Interim Monitoring Activities
The Sponsor has the obligation to monitor the conduct of this Trial to ensure that the Trial is conducted in accordance with the protocol, Edwards Lifesciences procedures and 21 CFR 812.46 Monitoring Investigations.

Interim monitoring visits (onsite or remote) will be conducted to evaluate the progress of the Trial, verify the rights, well-being, and protection of the patients, and verify that the reported clinical Trial data is accurate, complete, and verifiable from the electronic medical records and source documents. Monitoring visits will be made in accordance with the Monitoring Plan.

Site Close-Out Visit

The Investigator will be notified in writing upon termination or completion of the Trial. The Sponsor retains the right to suspend or prematurely terminate this clinical investigation at any time. Upon completion or premature termination of the Trial, the Trial monitor will perform a close-out visit.

A site will be considered closed when the following criteria are met:

- Last subject completes 30-day follow-up
- All data queries are resolved
- A site closeout visit is completed
- The IRB is notified in writing of site and Trial closure in accordance with their requirements

Auditing and Inspecting

In the event that audits are initiated by the Sponsor or national/international regulatory authorities, the Investigator shall allow access to the original medical records and provide all requested information, as applicable. The Investigator will permit Trial-related monitoring, audits, and inspections by the Research Quality Assurance Office, IRB, the Sponsor, and government regulatory bodies, of all Trial related documents (e.g., source documents, regulatory documents, data collection instruments, Trial data etc.). The Investigator will ensure the capability for inspections of applicable Trial-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

20. TRIAL EARLY TERMINATION

Edwards retains the right to temporarily suspend or prematurely terminate this Trial at any time if there is sufficient reasonable cause. Written notification, documenting the reason for Trial suspension or termination, will be provided by the Sponsor to Principal Investigator and regulatory authorities. If the Trial is prematurely terminated or suspended, the Principal Investigator will promptly inform Trial subjects, and the IRB, and will provide the reason(s) for the termination or suspension.

If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the IRB or regulatory authorities, Edwards shall suspend the Trial while the risk is assessed by the Data Safety Monitoring Board (DSMB). Edwards shall terminate the clinical investigation if an unacceptable risk is confirmed.

21. ETHICS

Ethical and Scientific Conduct of the Clinical Research Trial

The Trial may only commence once IRB approval and regulatory approval, as applicable, are received. This Trial will be conducted in compliance with the Protocol approved by the IRB, the relevant federal regulations, and IRB policies and procedures and according to Good Clinical Practice standards.

The Investigator shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of medical and clinical research practice and the applicable regulations. The Investigator will provide copies of the current Trial Protocol to all Trial site personnel responsible for Trial conduct.

As the Sponsor of this clinical Trial, Edwards Lifesciences has the overall responsibility for the conduct of the Trial, including assurance that the Trial meets the regulatory requirements of the pertinent regulatory agencies. Edwards Lifesciences will also ensure compliance with the signed clinical agreement, the Protocol, the requirements of applicable regulations, and any conditions of Trial approval by the IRB.

The Sponsor may transfer Trial related duties and functions to a CRO. Transferred duties and functions will be specified in a written agreement. Ultimate responsibility for the quality and integrity of the Trial resides with the Sponsor.

22. FINANCIAL DISCLOSURES

Appropriate financial disclosures will be obtained from all Principal Investigators and Sub-Investigators and additional personnel listed on the Statement of the Investigator. The Investigator will provide sufficient and accurate financial disclosure information to the Sponsor prior to Trial start-up, and again during the course of the trial. The Principal Investigators and Sub-Investigators shall promptly update the Sponsor if any relevant changes occur during the course of the investigation.

23. CONFLICT OF INTEREST POLICY

The independence of this Trial from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this Trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The Sponsor requires that all conflicts of interest be disclosed and will establish a mechanism for the management of all reported dualities of interest.

24. PUBLICATIONS

At the conclusion of the Trial, a manuscript may be prepared for publication in a scientific journal. The Sponsor reserves the right to review any manuscripts prior to submission. The Trial will be entered into a clinicaltrials.gov.

25. ACRONYMS AND ABBREVIATIONS

Acronym	Entire Word
ADE	Adverse Device Effect
AE	Adverse Event
AKI	Acute Kidney Injury
ASA	American Society of Anesthesiologists
BP	Blood Pressure
CI	Cardiac Index
CO	Cardiac Output
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP or gCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HPI	Hypotension Prediction Index
HR	Heart Rate
Hr	Hour
ICF	Informed Consent Form
ICU	Intensive Care Unit
IRB	Institutional Review Board
ITT	Intent-to-Treat
KDIGO	Kidney Disease: Improving Global Outcomes
MI	Myocardial injury
MINS	Myocardial Injury after Noncardiac Surgery
mL	Milliliters
mITT	Modified Intent-to-Treat
N	Total Sample Size
NCT	National Clinical Trial
NSQIP	National Surgical Quality Improvement Program
PI	Principal Investigator
POD	Post-Operative Day
POM	Postoperative morbidity survey
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
StO_2	Peripheral tissue oxygen saturation
Sub-I	Sub-Investigator
SV	Stroke Volume
SVI	Stroke Volume Index
SVV	Stroke Volume Variation
SVR	Systemic Vascular Resistance
UADE	Unanticipated Adverse Device Effect
3D-CAM	3-Minute Diagnostic Interview for Confusion Assessment Method defined Delirium
4AT	4 A's Test

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Edwards Lifesciences

STATISTICAL ANALYSIS PLAN

Protocol Title:	Hypotension Prediction Index Software Guided Hemodynamic Management for Noncardiac Surgery Patients - Blood Pressure
Protocol Number:	2021-04
SAP Version:	A
SAP Date:	May 11, 2022
[redacted]	[redacted]

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Glossary of Terms

ABBREVIATION	DEFINITION OR DESCRIPTION
AE	Adverse Event
ADE	Adverse Device Effect
AKI	Acute kidney injury
AUC	Area Under Curve
Alpha (α)	Type I error
α'	Adjusted type I error
Beta (β)	Type II error
CC	Complete case population
CEC	Clinical Events Committee
CI	Confidence Intervals
CSR	Clinical study report
dpt	Disposable Blood Pressure Transducer
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ES	Effect Size
ESKD	End Stage Kidney Disease
GCP	Good Clinical Practice
GSD	Group Sequential Design
H_0	Null hypothesis
H_1	Alternative hypothesis
HPI	Hypotension Prediction Index
IRB	Institutional Review Board
KDIGO	Kidney Disease Improving Global Outcomes
MACE	Major Adverse Cardiovascular Events
MAP	Mean Arterial Pressure
mITT	Modified Intention-To-Treat
MINS	Myocardial Injury After Noncardiac Surgery
MOCA	Montreal Cognitive Assessment
POMS	Postoperative Morbidity Survey
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
TWA	Time weighted average

1. INTRODUCTION

This statistical analysis plan (SAP) specifies the statistical methods to be implemented for the analysis of data collected within the scope of Edwards Lifesciences's Protocol 2021-04, Hypotension Prediction Index Software Guided Hemodynamic Management for Noncardiac Surgery Patients-Blood Pressure Trial and provides detailed instructions as to how clinical data analysis will be performed.

All statistical analysis will be performed using SAS 9.4 or later version. Results obtained from the analyses specified in the SAP will become the basis of the clinical study report (CSR) for this protocol. Any deviations from the SAP must be documented in the CSR.

2. STUDY DESIGN

2.1 Study Objectives

The primary objective of this study is to evaluate the benefit of a protocolized blood pressure management strategy that utilizes a HPI along with a comprehensive advanced hemodynamic assessment to reduce a composite of postoperative complications in patients undergoing non-cardiac surgery. The study population is subjects ≥ 18 years of age undergoing moderate-to-high-risk non-cardiac surgery with pressure monitoring with an arterial line.

2.2 Overall Study Design and Plan

This is a multicenter, interventional, randomized clinical study with treatment and control arms focusing on intraoperative hemodynamic management with or without hypotension prediction index software guidance. A noncardiac surgery patient will be enrolled in the study once the subject has signed the informed consent form, has been assigned a study identification number, an arterial line has been placed and the subject is randomized to the treatment or control arm. In The subjects enrolled in the treatment arm will have a radial arterial catheter inserted for pressure monitoring. The catheter will be connected to an Acumen IQ sensor and to the HemoSphere advanced monitoring platform which includes the Acumen™ Hypotension Prediction Index (HPI) feature software. In the control arm, the physician will use standard of care (with a FloTrac sensor) management per physician judgement. Section 5 in study protocol lists all inclusion/ exclusion criteria used to screen and enroll study patients. Section 4 of the protocol details the trial design.

An adapted group sequential design will be utilized for this clinical study, and to determine stopping rules, or to re-estimate the sample size by interim analysis outcomes [10, 12, 14, 17]. Adapted group sequential study design allows for one or more planned interim analyses when a prespecified stopping criteria is chosen. If the first interim analysis outcomes provide evidence for the necessity to enroll more patients, study sample size will be reassessed to determine the new appropriate sample size [1,10]. When there is sufficient evidence from study data collected at present stage in addition to the data collected from previous study stage, the clinical trial could be stopped early for already achieving the study objectives. A type I error (α) spending function will be used to design stopping boundaries for effectiveness, while allowing flexibility in how many interim analyses are designed, and at what time point they are conducted [4]. The methodology from O'Brien, Harrington, and Fleming [16] will be used to determine the effectiveness stopping criteria for prespecified first interim analysis, the secondary interim analysis, and the final analysis with 50%, 75%, and 100% information respectively. Many literatures proposed different methodologies from weighted combining test statistics to weighted combining p value from interim analyses to preserve type I error (α). The O'Brien-Fleming methodology, the conservative approach, spend little type I error (α) at the time of interim analyses and lead to boundary values at the final stage that

are close to those from fixed sample designls, [16]1. The O'Brien-Fleming formulae (to preserve the familywise error rate, a) is denoted as follows, $PH_0(IZ_11< ci, \ldots, IZk\text{-}il < ck\text{-}l \bullet IZkI ::?: ck) = ak,$ *where* ci = *cp(K,*a), where ci represents the positive critical values corresponding to stopping boundaries and the trial stops at an interim-i where *IZi*I ::?: ci. In this clinical trial, the O'Brien-Fleming methodology will be used to split the type I error (a) for each interim analysis, and also used to calculate critical value to judge if receives or rejects the null hypothesis. If the Z-statistic is close to the critical boundary value but the null hypothesis could not be rejected. By adapted group sequential study design principles, the study sample size will be re-assessed for the purpose to achieve the study objective by a third-party, independent, un-blinded statistician who will not unblind the study statistician and hence does not involve and alpha penalty. It is noted that a group sequential design with one(50%) interim analysis can reduce the expected sample size of a clinical trial by roughly 15% [3, 11, 171].

2.3 Sample Size Consideration

Meta-analysis approach is used to optimally integrate the valid information collected from literature. Here, the statistics (pooled effect sizes (ES)) from the meta-analysis construct the composite endpoint for the reference (control) group. Composite endpoint is comprised of the following components: **(1)** MACE (myocardial injury [2]I, stroke, non-fatal cardiac arrest, and death), (2) AKI (KDIGO stage 2-3), and (3) infection (pneumonia, deep surgical site, and organ space surgical site).

The event rate (pooled effect size) of the control arm to be given is 0.31. This event rate was calculated using the weighted average methodology where the final event rate is based on the sample sizes as the weight from following manuscripts, Futier et al. 171, Pearse et al. I[13]I, and Maheshwari et al. I[9]I_The algorithm formula is: $ES = \frac{r.c:eight\ xEs)\_}{weight}$ Moreover, for manuscripts in which individuals who experienced MINS, stroke or death simultaneously were observed, an adjustment was conducted so that there is no overcounting within the meta-analysis. The event rate for the components MACE, AKI, and infection is as 0.06788, 0.10217, and 0.17182 respectively. Please see algorithm listed below the table using in the meta-analysis and final composite endpoint computation.

Sample Size				AKI(%)	Infection (%)	
				Renal	Deep Surgical Site	Organ Space Sure:ical Site
n=145	aT	Q.	$;.5	17.9	0	24.8
n =364	2.'2'	Q	3.0	4.7	01	9.9
n =108	·4::0:	1.4,	(J:1)3	18.5	31.5 [3]	0
Composite	6.288			10.217	17.182	

$$Compilation\ Composite = 1 - (1 - 0.06788) * (1 - 0.10217) * (1 - 0.17182) = 0.30690$$

Although there are other derivations of the meta-analysis including Fleiss's inverse variance methodology [15]1(Please see appendix section 12.1, 12.2, and 12.3), this conservative control arm final composite endpoint estimate (0.31) is selected to estimate sample size for this clinical trial, due to this being more reflective of what is observed in clinical practice. A 25% reduction of the composite endpoint by the treatment arm is expected for this trial, which is used in sample size

' Did not report deep alone, this statistic was merged with other infection types.
[2] MINS rate was adjusted for overcounting, original rate for MINS 7/108 (6 7%) 5/108 (4.6%)
[3] Deep Surgical Site Infection rate was adjusted for overcounting, original rate 35/108 (32.4%) 34/108 (315%)

estimation, and is supported by the integrated evidence from physician clinical experience, scientific publications, and previous clinical trial results.

The hypothesis setting for this study used in sample size estimation is:

Ho: Pi 2:: Po
H1:P1 $<$ Po

where p_1 and p_0 are the proportions of composite endpoint in treatment arm and control arm, respectively.

Moreover, two interim analyses will be designed at 50% and 75% subject enrollment with 30-day follow-up data, to assess the composite endpoint (pooled event rate) between treatment and control arms. To determine when the trial can be stopped prematurely for effectiveness, the O'Brien-Fleming methodology [16]1was used to determine the stopping boundary (alpha spending function). The O'Brien-Fleming methodology preserves the overall type I error across all interim analyses[16]. The overall type I error used for this one tail hypothesis test study is 0.025. If the Z-statistics is close to boundary value but could not reject null hypothesis, possibly the study sample size will be reassessed for the purpose to achieve study objective.

With these trial parameter and hypothesis settings, and two designed interim analyses plus a final analysis, 1486 subjects (including 15% attrition, including a maximum of 60 roll-ins) are needed for this clinical trial. The sample size is estimated with PASS2021. The critical *Z* value and the corresponding *p* value for effectiveness boundary are displayed in the following table for interim analysis and final analysis. By the study objective and experiment design, in effectiveness analysis if the *Z* value calculated by the data available at each study stage (interim analysis and final analysis) is less or equal the critical *Z* value listed in effectiveness boundary column, the null hypothesis will be rejected, and the study stops for the study objective is achieved. To simplify the interim analysis decision making procedure, the lower limit of the reference arm accumulated subjects with complication, and the upper limit of treatment arm accumulated subjects with complication are designed by the study design parameters, the study arm accumulated sample size at each analysis stage, and effectiveness boundary (critical Z value) estimated by O'Brien-Fleming methodology.

Analysis	Information Rate	Alpha Spending Function	Effectiveness Boundary Critical Z value	P-Value
First Interim	50%	O'Brien-Fleming	-2.96259	0.00153
Second Interim	75%	O'Brien-Fleming	-2.35898	0.00916
Final Analysis	100%	O'Brien-Fleming	-2.01404	0.02200

Analysis	Information Rate	Proportion of Control Subject with Complications	Required Reduction Rate	Control Arm Limit (2::)	Treatment Arm Limit (<)	Subject Ratio(<)*
First Interim	50%	0.31	0.33	111	74	0.67
Second Interim	75%	0.31	0.21	167	131	0.78
Final Analysis	100%	0.31	0.16	222	186	0.84

Note:* Subject Ratio=Treatment Arm Limit/Control Arm Limit.

2.4 Randomization and Blinding

The enrolled subjects will be randomized to treatment arm and control arm with 1:1 ratio. To avoid the selection bias caused by study team, the randomization will be done automatically by the Electronic Data Capture (EDC) system.

Randomization will occur after verifying an arterial line that is placed during the study procedure. A block randomization scheme with alternating block sizes of 4 and 6 subjects will be generated by study subject enrolled at each study site. No other stratification factors will be considered in randomization. By the random number generated for each subject within the randomization block, the web-based program will produce a cutoff value to ensure equal allocation between the treatment and control arms. The randomization code for each subject will be maintained by the study coordinator at the study site. The treatment allocation will be unblinded once the surgery operation starts.

3. STUDY ENDPOINT

The primary hypothesis is that the administration of advanced hemodynamic monitoring utilizing the Hypotension Prediction Index (HPI) with a protocolized strategy during moderate-to-high-risk noncardiac surgery reduces composite of severe postoperative complications.

3.1 Primary Effectiveness Endpoint

The primary objective of this study is that the administration of a protocolized strategy utilizing advanced hemodynamic monitoring with a hypotension prediction index software reduces composite of severe postoperative complications identified within 30 days post-operative period.

The primary outcome variable is a composite endpoint that includes major adverse cardiac events (MACE), acute kidney injury (AKI), and serious infection (pneumonia, deep surgical site, sepsis, and organ space surgical site infection). Myocardial injury will be diagnosed based on troponin concentrations preoperatively. MINS is defined as any myocardial infarction (i.e., 4th Universal Definition of myocardial infarction17), and any elevated troponin judged to be due to myocardial ischemia (i.e., without evidence of a non-ischemic etiology, e.g. chronic elevation, pulmonary embolism, sepsis, cardioversion, others) that occurred within the first 30 days after surgery. Strokes will be detected from clinical symptoms lasting at least 24 hours. Mortality is confined to a 30-day post-operative window. Postoperative acute kidney injury will be defined by the Kidney Disease Improving Global Guidelines (KDIGO). Surgical infection site (pneumonia, deep surgical site, and organ space) within 30 days after the operative procedure is defined according Clavien-Dindo grade II or greater. Please see the study protocol for more detailed criteria.

3.2 Exploratory Analysis Datapoints

The following measures will also be investigated for this study:

1. Time-to-Adverse Event (Complications) Analysis
    a. Non-Parametric Survival Analysis (KM approach)
    b. Cox Proportional Hazard Model
    c. Mixed effect Cox Proportional Hazard Model
    d. Stratification analysis through applying study sites, gender, race as the stratification factor
    e. Fixed/Mixed effective Poisson regression model applying the count of events as the response
    f. Mixed effective survival model to assess the multiple event cases within patient

2. Hypotension management analysis
    a. Time from alert event to intervention
    b. % alerts with no intervention
    c. Reasons for nonintervention
    d. Amount of hypotension removing nonintervention segments
    e. Agreement analysis; clinical decision vs. treatment algorithm
    f. Overall treatment protocol compliance
3. Hypotension duration (minute) is the summation of hypotension instance duration, defined as the consecutive measurements with MAP<65 lasting at least 1 minute.
4. Area under the curve (AUC) with the MAP threshold of 55,65,75 mmHg
5. Time Weighted Average (TWA) of intraoperative hypotension (mmHg)
6. Time in target SVV <13% (for valid SVV readings = no arrythmia)
7. Time in target CI >2.5 L/min/m15
8. Postoperative morbidity survey (POMS) on postoperative day 3
9. Transfusion requirement (mL packed red blood cells)
10. Amounts of intraoperative crystalloid and colloid and vasoactive drugs; mL
11. Amount of vasoactive drugs; mg (e.g.: phenylephrine, ephedrine, norepinephrine, epinephrine, dobutamine)
12. Amount of intraoperative intravenous analgesics and sedatives
13. Brain oxygen saturation – StO2 using ForeSight Elite tissue oximetry system, time in target
14. Verification of the incidence of the listed postoperative complications may be performed at each site by reviewing historic data up to 6 months prior to study initiation
15. Cost of care
16. Hospital length of stay
17. Hospital readmission within 30 days

Please see appendix section 12.9 for TWA calculation.

4. ANALYSIS POPULATIONS

4.1 Modified Intent-to-treat (mITT)

Modified Intent-to-treat (mITT) is defined as the study subjects who were exposed to the study product and will therefore be included in the effectiveness and safety analysis datasets. All randomized study subjects who have satisfied the population criteria will be classified in the designated population and will only be included in analyses for which they have available data. The mITT population will also be used to present exploratory analyses by the randomized treatment arm. The safety population is defined as all randomized subjects who were exposed to the study product; thus, the safety population will therefore be identical to the mITT population if all randomized subjects are exposed to the study product. In this clinical study, the primary effectiveness endpoint is a composite measurement of MINS, AKI, and serious infection adverse events, mITT will be the target population in interim, and final effectiveness analysis. The Roll-in subjects designed for the training purpose to avoid a learning curve bias will be analyzed separately. The safety population will be used to present the safety summaries by actual treatment received.

4.2 Full Analysis Population (FAS)

The full analysis population is defined as all pivotal subjects with valid intra-operative measurements during non-cardiac surgery, and with at least one valid post-operative measurement. It will be applied in primary and secondary effectiveness sensitivity analysis.

4.3 Per Protocol Population (PP)

A per protocol analysis population is defined as a group of pivotal subjects who enrolled into study and completed all operations as written in the protocol (e.g., No major protocol deviations occurred during the non-cardiac surgical procedures). It will be applied in primary and secondary effectiveness sensitivity analysis.

4.4 Complete (Evaluable) Case Population (CC)

The complete case population is defined as all pivotal subjects who complete surgery, have valid post-operative data and follow-up records, and exit this study by designed procedure within protocol. It is the population used in primary and secondary effectiveness endpoint sensitivity analysis in final analysis.

4.5 Roll-in Subject

To prevent a learning curve bias, up to five (5) Roll-in cases may be performed at a site, as needed, with a maximum total of 60 Roll-in cases in the Trial. Roll-in cases will be analyzed separately from the pivotal cohort.

4.6 Screen Failures

Late screen failures are defined as subjects who consent to participate in the clinical trial and but are not subsequently randomly assigned to the trial intervention or entered in the trial. So, the subjects are not exposed to FloTrac sensor or Acumen IQ sensor and are not treated as part of the study. Late screen failures will be represented in summary tables by counts and percentages. Please see study protocol for more detailed criteria.

5. DEFINITIONS

5.1 Analysis Dates and Days

Subjects who fulfill all eligibility criteria will be scheduled for surgery and followed for 30 days post-surgery. The 30-day follow-up has a ±14-day window (see protocol for more detailed information). Pre-procedure data collection includes: (1) Pre-op Surgical Risk Assessment, and (2) the lab values: creatine, troponin, and NT-proBNP. On post-op day 1 the following data will be collected: (1) the lab value troponin, (2) post-op complication, and (3) fluid and vasoactive medications. On post-op day 2 the following data will be collected: (1) the lab values: creatinine and troponin, (2) adverse events, and (3) post-operative complications. The POMS will be given on postoperative day 3, further, the POMS may be entered into the system until after the third day. Other post-op day 3 data include: (1) the lab value troponin, (2) Post-Op Neurocognitive Assessments, (3) post-op complications, (4) adverse events, and (5) post-op complications. Lastly, for 30-day follow up the following will be evaluated: (1) post-op complications, (2) adverse events, and (3) the WHODAS 2.0 survey.

5.2 Analysis Window

There is no analysis window for this study. Please see the protocol for more detailed procedure information.

6. DATA AND ANALYSIS CONVENTIONS

6.1 General Conventions

The baseline characteristics and demographics, the medical history data of each study subject will be collected during the subject screening process and recorded on an electronic case report form (eCRF). The hemodynamic measurement data will be downloaded from HemoSphere advanced monitoring platform.

All endpoints will be presented using descriptive statistics by assigned treatment group; continuous variable will be summarized with the mean, standard deviation (SD), median, and interquartile range (IQR); binary and categorical variables will be presented using count and percentage.

Other summaries (e.g., minimum, maximum, standard error, 95% intervals, coefficient of variation (CV) or %CV, odd ratio) will be used as appropriate. Sample sizes shown with summary statistics are the number (n) of patients with non-missing values. All percentages should be rounded and reported to a single decimal place (xx.x%). If percentages are reported as integers, percentages greater than 0% but <1% will be reported as <1%, whereas percentages greater than 99% but <100% will be reported as >99%. A percentage of 100% will be reported as 100%.

For categorical endpoints, logistic regression and the approximate Z test will be performed on the primary outcomes and exploratory analysis. Summary statistics and p-values from the statistical comparison will be displayed in result report. The p-value will present with three decimals. P-values less than 0.001 will be reported as <0.001. Additionally, ad-hoc analyses may be conducted as deemed appropriate.

An independent Data Safety Monitoring Board (DSMB) will evaluate the data at interim.

6.2 Handling of Missing Data

Missing data are defined as those instances in which data collection was attempted yet failed for some reason (i.e., due to technological, procedural, and/or subject dropout). Demographic and baseline characteristics are collected from the study subjects as part of screening. Subjects who do not meet all criteria will not be enrolled into this study. Subjects who are not randomized are considered as screening failures. Data for screening failure subject will not be captured.

If missing data are not related to the subject's eligibility criteria, missing data will be presented as not reported in the demographic and baseline characteristics summary statistics table. These subjects will be included in all analysis. However, if the missing data are related to the subject's eligibility, this will be considered a protocol deviation, and in this case, the study data from this subject will be reviewed internally, to determine if the subject should be excluded from analysis set.

The hemodynamic measurements are downloaded from the monitor platform. Theoretically, there should be no missing data. If there are missing values in the hemodynamic parameters download from monitor platform caused by any reason, the last value will be carried forward.

For binary or categorical data that are missing as defined above, single imputation will be used. For continuous data that are missing as defined above, statistical imputation using the multiple imputation (MI) method.

By the data from similar clinical trial sponsored by Edwards LifeSciences, missing value of the primary effectiveness endpoint is really rare (less than 1%). In case, more than 5% study subjects with missing primary effectiveness endpoint, imputation techniques with different missing mechanisms (multiple imputation approach with assumption missing at complete random, missing at random, or tipping point analysis approach for missing not at random), mentioned in National Research Council publication [18], will apply to impute the missed values. Sensitivity analysis for primary

effectiveness endpoint will conduct on pivotal mITT data with imputed values to check the robustness of statistical analysis outcome.

With assumption missing primary effectiveness endpoint at random or complete at random (missing primary effectiveness endpoint unrelated to the actual value of primary effectiveness endpoint), 20 different datasets will be exported from multiple imputation approach. With exact the same statistical analysis method, the p value from the sensitivity analysis on imputed data should be consistent to the statistical hypothesis test result with valid pivotal mITT dataset.

With tipping point analysis approach for the missing primary effectiveness endpoint related to actual primary endpoint value, multiple imputed datasets are exported corresponding to all possible imputations. By the p-value from statistical analysis on all these imputed datasets, if a reasonable majority of statistical hypothesis tests have the same outcome as it from valid pivotal mITT dataset statistical hypothesis test, this statistical outcome would be considered robust.

Please see section 8.3 and 8.4 for outliers and sensitivity analysis.

7. SUMMARY OF BASELINE INFORMATION

7.1 Patient Enrollment and Accountability

The following will be tabulated via frequency and percentage into a summary table:

- Number of included and randomized patients
- Number of randomized patients by treatment groups
- Number of active sites
- Number of included and randomized patients by treatment groups
- Number of included and randomized patients by site
- Number and percentage of patients having finished the study normally by treatment groups
- Reason of withdrawal will also be tabulated and a listing of reason of withdrawal will be produced
- Normal study end (yes/no) and if no, reason

Moreover, subjects who withdraw from the study will be tabulated with the reasons for the withdrawal. Compliance with study visits will also be presented. Please refer to section 4 for enrolled subject definition. Also, please see the protocol for the enrollment diagram and enrollment timeline diagram.

7.2 Demographics and Baseline Characteristics

The baseline characteristics and demographics of each study subject will be collected during the subject screening process. For subject demographics, age, sex, race, ethnicity, and other demographic variables will be used for each summary. All outcomes will be presented using descriptive statistics; normally distributed data by the mean and standard deviation (SD) and skewed distributions by the median and interquartile range (IQR). The sample size of non-missing values will be reported for summary tables as well as frequency (count and percentage) of illegible and eligible will be represent by a Consolidated Standards of Reporting Trials (CONSORT) consort diagram. The number and reasons for drop-out, lost-to-follow-up, or withdrawal will be presented by frequency and percentage.

7.3 Medical History and Prior Intervention

The subject's medical historical data will be recorded on an electronic case report form (eCRF). Historical data will be summarized into tables with continuous variables being represented by medians and interquartile ranges and categorical

variables being represented by counts and percentages.

7.4 Baseline Risk Assessments

Demographic data will be summarized into tables with continuous variables represented by median and interquartile ranges. Categorical demographic variables will be represented by counts and percentages

The vascular access obtained is standard clinical care for the adult population and the addition of the Acumen IQ sensor or FloTrac sensor is not expected to impose any additional risk to the patient. There is no measurable increased infectious risk with the temporary use of the Acumen IQ sensor or FloTrac sensor. Below is a list of anticipated risks that may be associated with the use of the ForeSight Oximetry Sensors:

- Allergic reaction to adhesive on sensors
- Skin irritation

7.5 Procedural Information

Procedural data (procedure setting and procedure measurements) will be summarized into tables with continuous variables being represented by medians and interquartile ranges and categorical variables being represented by counts and percentages. Moreover, a specifications document is created for each statistical output (table, listing, or figure) and it will contain, at the minimum:

- Title and footnote information
- Column headers
- If the output includes a figure then a detailed description of the figure
- Variables, procedures, and/or calculation logic used in the statistical output
- Ad Hoc or Post Hoc analyses
- Formulas for derived procedures

8. STATISTICAL ANALYSIS OF STUDY ENDPOINTS

8.1 Primary Effectiveness Endpoint

The primary objective is to determine if the use of a protocolized strategy using advanced hemodynamic monitoring with Hypotension Prediction Index (HPI) software guidance for intraoperative hemodynamic management reduces postoperative complication rate in moderate- to high-risk non-cardiac surgery patient. The treatment group (Acumen ID sensor) will be compared to control arm receiving standard of care (FloTrac sensor). This analysis will be conducted on the mITT population only with pivotal study subject. With null hypothesis, the Z-statistic will be used to judge if the hypotension prediction index software can reduce postoperative morbidity and mortality:

$$Z = \frac{\hat{p} - \hat{p}}{\sqrt{\frac{\hat{p} * (1 - \hat{p})}{n_1} + \frac{\hat{p} * (1 - \hat{p})}{n_0}}}$$

Here x_0 and x_1 are composite endpoint events in the reference arm and treatment arm respectively; thus, $\hat{p} = \frac{x_0}{n_0}$, $\hat{p} = \frac{x_1}{n_1}$ are the proportion of events in the reference arm and treatment arm, respectively; n_0, n_1 are the number of subjects in

reference arm and treatment arm respectively; $\frac{\hat{p}_0*(1-\hat{p}_0)}{n_0}$, $\frac{\hat{p}_1*(1-\hat{p}_1)}{n_1}$ is the variances of the proportion of events in reference arm ($\hat{p}_0$), and in test arm ($\hat{p}_1$) respectively. The Z-statistic will compare to the critical Z-value to judge if the null hypothesis could be rejected.

By the study designed parameter table in section 2.3 and the *Z* statistic calculated at each study stage with the trial data collected at present stage in addition to data collected in previous stage or stages, following judgement will be conducted for interim analysis and final analysis. For first and second interim analyses, if the calculated *Z* value is equal to or less than the critical *Z* value in the effectiveness boundary column, the null hypothesis will be rejected, and the study will stop for achieving the study objective; if the calculated *Z* statistic is greater than critical *Z* value for effectiveness but it is close to the critical value but could not reject null hypothesis, the study continues to next step, and the study sample seize will be reassessed by the principles of adapted group sequential study design. If it is necessary, more study subject will be enrolled for the purpose to achieve the study objectives. For final analysis, if the calculated *Z* statistic is equal to or less than the critical *Z* value listed in effectiveness boundary column, the null hypothesis will be rejected, and the alternative hypothesis will accept, the study objective is achieved, otherwise, the null hypothesis will accept, the study objective will be not achieved.

8.2 Exploratory Evaluations

For all endpoints listed in section 3.2, the continuous variables will be evaluated with linear fixed/mixed effect regression model on the treatment effectiveness adjusted by subject's baseline and demographic, medical history variables, and surgery related covariates. The categorical/binary variables, and count variables will be evaluated with generalized linear model or mixed generalized linear model on the effectiveness of treatment adjusted by all relevant covariates. Time-to-event variables will be evaluated by survival analysis models (Kaplan-Meier or Cox Proportional Hazards). The re-current time to event variable will be analyzed with frailty cox proportion hazard model. Sub-group analysis will be conducted based upon study design factors and baseline characteristics.

8.3 Outliers

Suspected outliers for this study will be considered as the observation that lie outside of the pre-defined clinical bounds. Outliers may be evaluated via summary statistics (interquartile or standard deviation rules), graphical methods (boxplots or histograms) or statistical test. For continuous outcomes, formal statistical test includes the Grubbs (or Dixon's Q), or Tietjen-Moore test can be used as well as the cutoff observation being within 1.5 units of the interquartile range. All methods of measurements will be recorded for all devices and included as part of the data set. Once outliers are identified, the principal investigator will assess the validity of the data.

8.4 Sensitivity Analysis

Sensitivity analysis will be performed for primary endpoint. For primary effective endpoint, sensitivity analysis will be conducted with all study subjects from FAS, PP, or CC population to check if the similar conclusion could be drawn. If there are more than 5% study subjects with missing primary endpoint in test arm, the imputed endpoint with missing at complete random, or missing not at random will replace the missing value for each study subject, the sensitivity analysis on this imputed mITT pivotal dataset will be conducted to check if the similar conclusion could be drawn. Then check if the variation among study sites will affect the statistical comparison between study arms. Next check if the study cohorts (roll-

in, pivotal) will change the analytical conclusion. Finally, bootstrap approach will be applied to check if sample size effect the analytical result.

The effect of the following factors on the primary effectiveness endpoint will be analyzed:

- MAP threshold (<55, 60, 70 mmHg) and the length of time in hypotension episode definition (20, 40, and 80 seconds)
- NSQIP score vs ASA score
- Regional anesthesia vs general anesthesia
- Surgery technique (open or laparoscopic) vs hemodynamic changes
- Patient positioning vs hemodynamic changes
- Surgery type vs hemodynamic changes
- Survival analysis
- Arterial line vs Arterial line + CVP monitoring
- Onset of HPI Alert vs time of intervention
- Amount of vasopressors/fluids/inotropes administered vs time of intervention (start & stop time)
  - Stratified by cohort
- Tidal volume

9. ANALYSIS OF SAFETY

9.1 Deaths

Any deaths that occur during this study will be summarized by frequencies and percentages. The frequency distribution and percentage of death related to a specific medical device will be presented. Evaluation of death has a 30-day post-op window. Death is considered an unexpected serious adverse event in the context of this study.

9.2 Adverse Events

The safety data will be summarized for all subjects in the safety population. Safety will be assessed through summary of adverse events. The frequency and percentage of AEs and SAEs will be reported in summary tables by treatment group. Plots showing the incidence of AEs and SAEs and their relative risk (with 95% confidence interval) will also be produced.

Any other serious adverse events that occur during this study will be summarized by frequencies and percentages. The frequency distribution and percentage of any adverse events related to a specific medical device will be presented. The following categories will be on the summary table:

- AEs-All
- AEs-Serious
- AEs Treatment-related
- AEs by seriousness criterion
- AEs that lead to study withdrawal

10. CHANGES FROM PROTOCOL SPECIFIED ANALYSES

There are no changes to the protocol specified analyses at this time. If protocol deviations occur during the study, they will be tabulated via frequency and percentage and presented in a summary table. Definition of minor and major deviations can be found in the protocol.

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12. APPENDIX

12.1 Alternative Computation of the Reference

Sample Size				AKI(%)	Infection (%)			
				Renal	Sepsis	Pneumonia	Deep Surgical Site Infection	Organ Space Surgical Site Infection
n=145	0396,°	- >	S...-	17.9%	26.2%	11.0%	0%	24.8%
n =364	> —		·a.mt.	4.7%	NA	10.7%	0%4	9.9%
n=108		1	0;93K	**18.5%**	**NA**	**NA**	31.5%[6]	0%

12.1.1 MACE, AKI, Infection (Sepsis, Pneumonia, Deep, and Organ)

This composite contains: (1) MINS, (2) Stroke, (3) Death, (4) AKI, (5) Sepsis, (6) Pneumonia, (7) Deep Surgical Site Infection, and (8) Organ Space Surgical Site Infection. The composite score is given by 0.55.

$$MACE = \frac{145(0.007+0.000+0.055)+364(0.022+0.000+0.030)+108(0.046+0.074+0.0093)}{145+364+108}$$

$$AKI = \frac{145(0.179)+364(0.047)+108(0.185)}{145+364+108}$$

$$Infection = \frac{145(0.262+0.110+0.000+0.248)+364(0.107+0.099)+108(0.315+0.000)}{145+364+108}$$

	AKI Composite	Infection Composite
a--	**0.10217**	0.38549

$$Composite\ Score = 1 - ((1 - 0.06788) * (1 - 0.10217) * (1 - 0.38549)) = 0.55554$$

12.1.2 MACE, AKI, Infection {Pneumonia, Deep, and Organ)

This composite contains: (1) MINS, (2) Stroke, (3) Death, (4) AKI, (5) Pneumonia, (6) Deep Surgical Site Infection, and (7)

[4] Did not report deep alone, this statistic was merged with other infection types.
[5] MINS rate was adjusted for overcounting, original rate for MINS 7/108 (6 7%) 5/108 (4.6%)
[6] Deep Surgical Site Infection rate was adjusted for overcounting, original rate 35/108 (32.4%) 34/108 (315%)

Organ Space Surgical Site Infection. The composite score is given by 0.49.

$$MACE = \frac{145(0.007 + 0.000 + 0.055) + 364(0.022 + 0.000 + 0.030) + 108(0.046 + 0.074 + 0.0093)}{145 + 364 + 108}$$

$$AKI = \frac{145(0.179) + 364(0.047) + 108(0.185)}{145+364+108}$$

$$Infection = \frac{145(0.110 + 0.000 + 0.248) + 364(0.107 + 0.099) + 108(0.315 + 0.000)}{145 + 364 + 108}$$

MACE Composit	AKI Composite	Infection Composite
0.06788	**0.10217**	0.32392

$$Composite\ Score = 1 - ((1 - 0.06788)^* (1 - 0.10217)^* (1 - 0.32392)) = 0.49397$$

12.2 Fleiss's Inverse Variance

All the meta-analysis, using the weighted mean effect sizes will be compared to Fleiss's inverse variance methodology (6). This methodology allows for aggregates over multiple variables while minimizing the variance of the weighted average. It is noted that when the variances are equal, then the inverse variance average becomes the traditional average. The formula (pooled effect size), for binary outcomes is represented as follows, $O = \frac{\sum_{k=1}^{k} wke}{Wk}$ where wk is the reciprocal of the variance and O represents a measure of the generic effect size for each k-study. Moreover, each variable is weighted in inverse proportion to its variance, this is considered the inverse standard error. Moreover, for manuscripts in which individuals who experienced MINS or stroke, or death simultaneously were observed, an adjustment was made so that there is no overcounting within the meta-analysis.

Sample Size	'Mqff4'			AKI(%)	Infection (%)			
	MINS		hath	Renal	Sepsis[7]	Pneumonia	Deep Surgical Site Infection	Organ Space Surgical Site Infection
n=145	0:.1"		5.5'6	17.9%	26.2%	11.0%	0%	24.8%
n =364			3ml	4.7%	NA	10.7%	0%8	9.9%
n =108	uw-	)!;fl	0 9395	18.5%	NA	NA	31.5%10	0%

Component	Composite Value	Model	Tau²	Test of Heterogeneity (p Value)
	D.OB&	……, ...Effects	0.0001	0.1004
	0..0041	Randonf -	<dOtJOI	IIOI36
AKI	0.1332	Effects:: Random Effects	0.0088	0,0568 < 0.0001
Sepsis	0.2620	----	-	----
Pneumonia	0.1080	Random Effects	0.0000	0.9168

[7] Cannot run inversive variance method on, only 1 paper reported statistics on this measure.
[8] Did not report deep alone, this statistic was merged with other infection types.
[9] MINS rate was adjusted for overcounting, original rate for MINS 7/108 (6 7%) 5/108 (4.6%)
[10] Deep Surgical Site Infection rate was adjusted for overcounting, original rate 35/108 (32.4%) 34/108 (31.5%)

Deep Surgical Site Infection	0.0346	Random Effects	0.0006	<0.0001
Organ Space Surgical Site Infection	0.1102	Random Effects	0.0089	<0.0001

If heterogeneity was present in the meta-analysis, this was adjusted for by using a random effects model. It is noted the following for random effects: (1) results apply beyond the included studies, (2) there is no common fixed parameter, and (3) the summary effect is an estimate of the mean distribution of the true effects. [15] Moreover, the DerSimonian-Laird estimator was used to estimate Tau[11].

For this study, a more conservative methodology of weighted sums was selected based upon the sample sizes due to this being more reflective of what is observed in clinical practice.

12.2.1 MACE, AKI, Infection (Deep and Organ)

The individual event rates for the components MACE, AKI, and infection are as follows, 0.0506, 0.1332 and 0.1448. The composite score is given by 0.2962.

$$Composite\ Score = 1 - ((1 - 0.0506) * (1 - 0.1332) * (1 - 0.1448)) = 0.2962$$

12.2.2 MACE, AKI, Infection (Pneumonia, Deep, and Organ)

The individual event rates for the components MACE, AKI, and infection are as follows, 0.0506, 0.1332, and 0.2528. The composite score is given by 0.3851.

$$Composite\ Score = 1 - ((1 - 0.0506) * (1 - 0.1332) * (1 - 0.2528)) = 0.3851$$

12.2.3 MACE, AKI, Infection (Sepsis, Pneumonia, Deep, and Organ)

The individual event rates for the components MACE, AKI, and infection are as follows, 0.0506, 0.1332, and 0.5148. The composite score is given by 0.6007.

$$Composite\ Score = 1 - ((1 - 0.0506) * (1 - 0.1332) * (1 - 0.5148)) = 0.6007$$

12.3 Time Weighted Average (TWA) Computation

AUC (minute*mmHg) for a hypotension instance is calculated by the following:

$$Aue = \sum_{i=1}^{m} \frac{(t_{i+1} - t_i)}{60} * \left(65 - \frac{MAPi + MAPi+1)}{2}\right)$$

Thus, TWA is given by:

$$TWA = \frac{Aue}{lm}$$

Where the unit of *TWA* is given by *mmHg* and 4n is the length of measurement of study subject in minutes given by:

$$4n = last\ valid\ EV1000\ measure\ time - first\ valid\ EV1000\ measure\ time$$

[11] This is a test for between-study heterogeneity; Occurs when, $Tau^2 > 0\%$

13. PEER REVIEW REQUEST, PER SAP INSTRUCTION (DOC-0089205)

Yes	Name of Reviewer:	No	Reason Peer Review not Needed:
þ	[redacted]	☐	