NCT05083403

A randomized trial of the Hypotension Prediction Index in the CArdiac operating room and the intensive caRE unit

HPI CARE Trial

Clinical Trial Protocol and Statistical Analysis Plan

Clinical Trial Protocol Version: August 24, 2023

Statistical Analysis Plan Version: May 7, 2024

A randomized trial of the Hypotension Prediction Index in the CArdiac operating room and the intensive caRE unit

HPI CARE Trial

Clinical Trial Protocol
Study Number: 2020-19

Revision: F
Date:24AUG23

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Revision F Change Summary

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

Section (Page)	Change and Reason for Change
Randomization and Blinding (20)	Removed Biostatistician requirement to be blinded. Reason: Biostatistician do not have to be blinded for the purpose of this trial.
Randomization and Blinding (21)	Updated HPI Pressure & Flow Optimization Protocol to add SVV as a parameter to be reviewed Reason: Per PI and Edwards study team request

Revision E Change Summary

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

Section (Page)	Change and Reason for Change
Synopsis and Exclusion Criteria (11 & 24)	Updated exclusion criteria #5 to state "Subjects with pre-op or pre-pump or post-pump LVEF <15%". A footnote was also added for further clarification. Reason: PI request
Trial Endpoints (17 & 18)	Added additional evaluations Reason: PI Request
Schema and SOE (21 & 27)	Added day of procedure and POD labs Reason: PI request
Secondary Endpoint (31)	Added list of Secondary Endpoints Reason: PI Request
Additional Evaluations (32)	Added additional evaluations Reason: PI Request
Protocol Deviations (44)	Added clarification on recording the protocol deviations. Reason: Per Edwards guidelines

Revision D Change Summary

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

Section (Page)	Change and Reason for Change
Synopsis and Exclusion Criteria (10 & 23)	Added footnote to exclusion #9 Reason: To further clarify the definition of severe PAH
Schema and SOE (20 & 25)	Added day of procedure and POD1-3 labs Reason: PI request
Trial Endpoints & Statistical Methods (16 & 29)	Added two new additional evaluations: 1) Subgroup analysis of primary endpoint stratified by mechanical ventilation vs extubated (ICU setting) 2) Subgroup analysis of primary endpoint stratified by OR vs ICU setting Reason: PI interest as post hoc analyses
Trial Design (19)	Updated the CI guidance to < 1.8 Reason: PI request, as that reflects Institution's standard practice

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 and Subject Eligibility (9 & 21)	Updated exclusion criteria # 9 to "Subjects with known or identified with pulmonary systolic pressures> 70mmHg or mean pressures > 55mmHgsevere PAH as determined by a pre-operative echo or intraoperative Swan-Ganz" Reason: To add further clarification
Synopsis and Subject Eligibility (9 & 21)	Removed "ForeSight Elite" from exclusion #1 Reason: Using ForeSight is optional. Made the change for clarification
Background (10)	Added "The ForeSight Elite technology must not be used for clinical judgment and will only collect data in the background." Reason: Clarification on the use for ForeSight sensors
Device Names (14)	Added "The use of ForeSight Elite sensors is optional in this trial and is for data collection purposes only. The clinician can choose to not use the sensors." Reason: Clarification on the use for ForeSight sensors
Randomization and Blinding (18)	Added "Measure baseline MAP and/or CO/CI in the pre-induction period, once the arterial line goes in the operating room." For monitoring phase Reason: Clarification and additional details on Monitoring Phase
Randomization and Blinding (18)	Updated "CI decrease > 10% and/or MAP decrease > 20 % below baseline to CI decrease > 20% and/or MAP decrease > 30 %below baseline" in the treatment protocol. Reason: Physician guidance
Schema (18)	Added "The randomization assignment must not be revealed to the clinicians until surgery. If a clinician randomizes the subject, they must not be the involved in the care of the subject in the OR. A clinical research coordinator or a designee who is delegated to consent and/or randomize the subjects, may be unblinded to the randomization assignment to set up the devices in the OR accordingly. However, the delegated coordinator/designee must not reveal the randomization assignment to clinician prior to start of the surgery. " Reason: To provide clarification on randomization
Schema (20)	Updated randomization timeline to be on days 0-1 Reason: Clarification on when randomization can be done
Schema (20)	Updated screening timeline to start on day -14-0 Reason: Clarification on when screening can be done
Procedure (26)	Added "The initiation of HPI in the CVICU will not start until 15-30 minutes after the HPI arm subject arrives in the CVICU. Once HPI is initiated in the CVICU, HPI-based interventions will be held for at least 5 minutes before extubation and will also be held for at least another 5 minutes after extubation." Reason: To add clarification on procedures in the CVICU
Risk Management (31)	Adde "The optional use of the noninvasive ForeSight Elite sensors also does not add any additional risks" Reason: To add clarification on the risks associated with using ForeSight sensors

Revision B Change Summary

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

Section (Page)	Change and Reason for Change
Medical Devices and Trial Design (10 & 17)	Removed K and DEN numbers Reason: No longer applicable
General Design (16)	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.
General Design (16)	Removed "ForeSight, a non-invasive sensor, is being used according to indications for use and intended use granted by FDA." Reason: No longer applicable
Randomization and Blinding (17)	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.
Anticipated Risks (30)	Added risks related to associated with HPI Pressure and Flow Optimization Protocol Reason: To clarify risks that may be associated with treatment protocol.
Throughout the protocol	Made clerical updates throughout Reason: To add additional clarity

STATEMENT OF COMPLIANCE

INVESTIGATOR'S SIGNATURE PAGE

This HPI CARE Study 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

_____

Study Site Name

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SYNOPSIS

Title:	A randomized trial of the **H**ypotension **P**rediction **I**ndex in the **CA**rdiac operating room and the intensive ca**RE** unit
Short Title:	**HPI CARE** Trial
Trial Description:	A prospective single center randomized controlled trial to determine if guided hemodynamic management with the Acumen HPI technology in the OR and ICU can reduce the mean duration of hypotension in cardiac surgery patients requiring cardiopulmonary bypass.
Trial Objective:	Primary Objective: To determine whether the use of the Acumen™ HPI Feature Software to guide hemodynamic management in patients undergoing cardiac surgery requiring cardiopulmonary bypass reduces the mean duration of hypotension (defined as MAP < 65 mmHg) from the post-bypass period in the cardiac operation room (OR) and the cardiovascular intensive care unit (CVICU).
Primary Effectiveness Endpoint:	Assessment if the use of the Acumen™ HPI Feature Software reduces the mean duration of hypotension (defined as MAP < 65mmHg) from the post-bypass period to the first 8-hour ICU period as compared with the control group.
Primary Safety Endpoint:	Serious adverse events through 30 days as indicated below: • Serious intraoperative and post-operative complications between each cohort • Device-related serious adverse events (SAEs)
Trial Devices:	HemoSphere Advanced Monitoring Platform, Acumen™ HPI Feature Software, ForeSight Elite Sensors, Acumen IQ Sensors
Overall Design:	A single center randomized controlled trial to determine whether the use of the Acumen™ HPI Feature Software reduces the mean duration of hypotension post-bypass.
Trial Population:	Up to 350 subjects will be enrolled, up to 175 in the HPI arm and up to 175 in the non-HPI arm. Subjects recruited and enrolled should be scheduled for cardiopulmonary bypass surgery and should be receiving blood pressure monitoring with a radial arterial line with or without a Swan-Ganz catheter for pulmonary artery pressures and continuous cardiac output. Potentially qualifying subjects will be evaluated during their preoperative clinic visits. Subjects must be at least 18 years of age at the time of screening.
Number of Sites:	One site in United States
Trial Duration:	Total of 2 years (24 months); this includes an approximate enrollment period of 18 months.

Participation Duration:	Screening/Baseline; Day of Surgery; Post-Op Day 1; Post-Op Day 2-7; Discharge; 30-Day Follow-Up
Inclusion/ Exclusion Criteria	**Inclusion Criteria** 1. Subjects who are at least 18 years of age 2. Subjects who have signed the Informed Consent Form 3. Subjects with planned pressure monitoring with an arterial line 4. Subjects with planned sternotomy 5. Subjects with planned general anesthesia 6. Subjects who have ASA Physical Status ≤ 4 7. Subjects with planned cerebral oximetry monitoring 8. Subjects with planned overnight hospitalization 9. Subjects with planned cardiopulmonary bypass (CPB) "on-pump" surgery **Exclusion Criteria** 1. Subjects with a physical site area too limited for proper sensor placement 2. Subjects with contraindications for arterial line placement 3. Subjects participating in another (interventional) study 4. Subjects in whom an intraoperative MAP target will be < 65 mmHg 5. Subjects with pre-op or pre-pump or post-pump LVEF <15%[1] 6. Subjects requiring heart transplant 7. Subjects with pre-existing circulatory support devices or planned circulatory support devices post-bypass 8. Subjects requiring emergency surgery 9. Subjects with known or identified severe PAH (defined as pulmonary systolic pressures> 70mmHg or mean pressures > 55mmHg) as determined by a pre-operative echo or intraoperative Swan-Ganz[2] 10. Subjects with cardiovascular instability in the operating room necessitating the need to go back on bypass for a subsequent run
Trial Sponsor:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614 USA

[1] Pre-operative echo will take precedence over pre-pump echo. In the event of discrepancy on numbers, a final decision will be made based on a discussion between the PI and the cardiac anesthesiologist performing the pre-pump echo.

[2] Severe PAH is qualified as PA systolic pressure >70mmHg and/or mean pressure >55mHg as documented on a pre-operative echo or cardiac catheterization. Or in the absence of these a sustained pressure as above after the insertion of a Swan-Ganz for at least 60 minutes in the pre-bypass period. All severe PAH pressure values should be attributed to an irreversible etiology in the best clinical judgement of the treating team to meet exclusion criteria.

1. INTRODUCTION

Background

Though many studies have been conducted exploring the risks of intraoperative hypotension during non-cardiac surgery, intraoperative hypotension during cardiac surgery and post-cardiac surgery is relatively unexplored. Previous studies have demonstrated that in adult cardiac surgery patients, hypotension upon anesthesia-to-ICU drop-off is more frequent than previously thought, and this may be associated with adverse effects [1].

In addition, previous studies have also shown that the association between intraoperative hypotension and in-hospital mortality varies across different baseline risk profiles; specifically, in intermediate-risk patients (defined by CARE score of 3-4), post-CPB hypotension is a potentially modifiable risk factor for mortality. In these intermediate-risk patients, hemodynamic goal-directed therapies may improve survival [2].

Minimally invasive technologies have been developed to monitor hemodynamic parameters. The Acumen IQ sensor is a minimally invasive solution for advanced hemodynamic monitoring; the monitor automatically calculates key flow parameters every 20 seconds. Continuous clarity provided by the HemoSphere system offers proactive decision support to manage hemodynamic instability and ensure adequate perfusion.

Studies have shown that HPI is capable of providing accurate and continuous predictions of upcoming hypotensive episodes and is superior to commonly measured perioperative hemodynamic variables in terms of its predictive ability [3]. There is an unmet need in cardiac surgery and the cardiovascular intensive care unit (CVICU), as there is a lack of research into the impact that reduced hypotension may have on this patient population, and studies have not yet been conducted to determine whether hemodynamic goal-directed therapies could improve survival in these patients.

The primary objective of the trial is to assess the Acumen™ HPI Feature Software in post-CPB patients in the OR and CVICU for up to 8-hours to determine whether the use of this software will lead to a reduction in the mean duration of hypotension. The trial population will be adults who are at least 18 years of age undergoing CPB cardiac surgery.

In addition, ForeSight Elite sensors, which are cleared for adult use, can be used optionally in this trial with the HemoSphere advanced monitoring platform to collect observational data on tissue oximetry. The ForeSight Elite technology must not be used for clinical judgment and will only collect data in the background. The ForeSight Elite Sensors provide the benefit of continually monitoring tissue oxygen saturation with accuracy and precision [4].

2. MEDICAL DEVICES

Device Names

- HemoSphere Advanced Monitoring Platform
- Acumen™ HPI Feature Software
- ForeSight Elite Sensors
- Acumen IQ Sensors

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 by the Food and Drug Administration (FDA). It was later cleared for use on the HemoSphere Advanced Monitoring Platform.

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 is enabled by the minimally invasive Acumen IQ sensor. The Acumen IQ sensor is the hardware which is connected to an existing 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 Indicator 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 Technology

Description

The Acumen IQ Sensor is a sterile, single-use kit that monitors pressures when attached to pressure monitoring catheters. When connected to the HemoSphere Advanced Monitoring Platform, 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 cable with a red connector interfaces exclusively with an Edwards cable that is specifically wired for the pressure monitor being used. The 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.

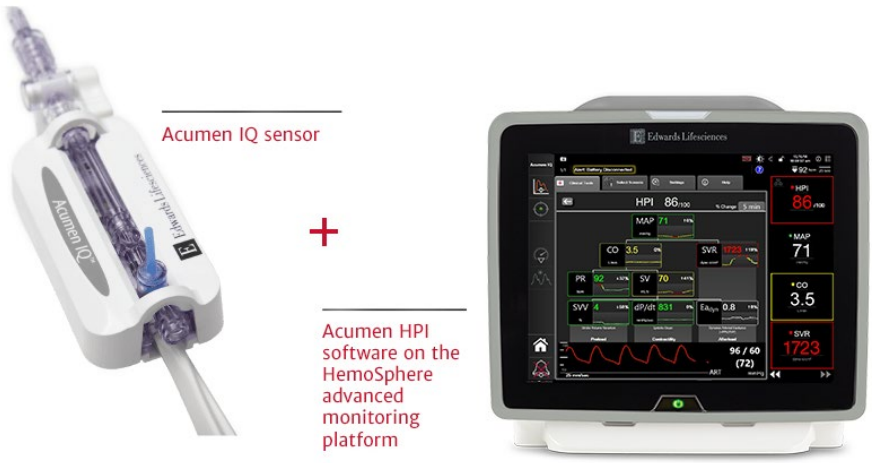


Figure 1. Acumen IQ Sensor and Acumen HPI Software

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

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.

Contraindications

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

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

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

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 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 measures hemoglobin allowing the clinician to continuously and accurately determine absolute levels of blood oxygenation saturation in the tissue (StO_2).

- ForeSight Elite Sensors have been cleared in both the pediatric and adult population on the HemoSphere Advanced Monitoring Platform. However, only adults will be studied during this clinical trial.

Figure 2. ForeSight Elite Technology

ForeSight Elite Sensors Cleared Indications
When used in conjunction with the FORE-SIGHT ELITE absolute tissue oximeter or FORE-SIGHT ELITE tissue oximetry module: The 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.

Contraindications

The ForeSight Elite 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 associated 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.

Note: The use of ForeSight Elite sensors is optional in this trial and is for data collection purposes only. The clinician can choose to not use the sensors.

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.

HemoSphere Advanced Monitor with HemoSphere Oximetry Cable Cleared Indications

The HemoSphere advanced monitor when used with the HemoSphere oximetry cable and Edwards oximetry catheters is indicated for use in adult and pediatric critical care patients requiring monitoring of venous oxygen saturation (SvO_2 and $ScvO_2$) and derived hemodynamic parameters in a hospital environment. Refer to the Edwards oximetry catheter indications for use statement for information on target patient population specific to the catheter being used. *Refer to the Intended Use statement for a complete list of measured and derived parameters available for each patient population.*

3. TRIAL OBJECTIVE AND ENDPOINTS

Trial Objectives

The objective of the study is to determine whether the use of the Acumen™ HPI Feature Software to guide hemodynamic management in the cardiac operating room (OR) post-CPB and the cardiovascular intensive care unit (CVICU) reduces the mean duration of hypotension (defined as MAP < 65 mmHg) as compared with the control group. The study is being performed in this patient population to provide information that cannot be readily obtained through additional non-clinical assessments.

Trial Endpoints

The primary endpoint is the reduction in the mean duration of hypotension (defined as MAP < 65 mmHg) post-bypass to the first 8-hour ICU period as compared with the control group.

Time of hypotension will be calculated as the sum of the following:

- From at least within 10 minutes of administration of Protamine in the post-CPB period until skin closure in the cardiac operating room (OR Period)
- Within 60 minutes upon arrival to CVICU and through the first 8 hours in the cardiac intensive care unit (CVICU Period)

Excluding a period of 15 minutes prior and 15 minutes after tracheal extubation

The following secondary endpoints will be analyzed:

- Additional definitions of hypotension:
  - Time Weighted Average (TWA) of MAP < 65 mmHg in the OR Period (T1)
  - TWA of MAP<65 mmHg in the CVICU Period (T2)
  - TWA of MAP < 65 mmHg in the CVICU Period, pre extubation (T3)
  - TWA of MAP < 65 mmHg in the CVICU Period, post extubation (T4)
  - Mean duration in minutes of MAP < 65 mmHg in the time periods of T1, T2, T3 and T4
  - Mean duration in minutes of MAP < 60 mmHg in the time periods of T1, T2, T3 and T4
  - Mean duration in minutes of MAP < 55 mmHg in the time periods of T1, T2, T3 and T4
  - Mean duration in minutes of MAP < 50 mmHg in the time periods of T1, T2, T3 and T4

- Clinical endpoints:
  - Acute kidney injury (AKI)[7], as defined by the modified KDIGO criteria, stages 1, 2 and 3
  - Neurocognitive deficit, as evaluated by the MMSE, CAM-ICU 7, and bCAM assessments. [bCAM will be used for delirium screening for patients who are deemed ready for transfer to the floor per ICU attending team's assessment, even if they are physically in the ICU]
  - Periprocedural Myocardial injury, measured with high-sensitivity Troponin I and defined by a threshold of 70 times the upper reference limit[6]. or >1400 pg/ml

The primary safety endpoints are serious adverse events through 30 days as indicated below:

- Serious intraoperative and post-operative complications
- Device-related serious adverse events and adverse events

The exploratory evaluations are indicated below:

- Subgroup analysis of primary and secondary endpoints by age stratification
- Subgroup analysis of primary and secondary endpoints by gender
- Subgroup analysis of primary and secondary endpoints by race
- Protocol adherence to HPI alert, as defined by >50% HPI alerts with documented intervention per the suggested treatment algorithm within a 5 minute timeframe
- Difference in time spent in hypertension defined as TWA of MAP>110, >120 and >130 mmHg post-cardiopulmonary bypass CPB) through the first 8-hour ICU period as compared with the control group.
- In-hospital mortality rate
- Incidence of cerebral desaturations defined as total time below 10% relative to baseline NIRS values.
- Percent of monitoring time with CO or CI within 10% relative to pre-induction baseline
- ICU Length of Stay
- Hospital Length of Stay
- Time to extubation
- SOFA scores
- New onset atrial fibrillation, detected prior to ICU discharge

4. TRIAL DESIGN

General Design

A single-center randomized controlled trial to determine whether use of the Acumen™ HPI Software Feature to guide hemodynamic management in cardiac surgery post-CPB and up to 8-hours post-CPB reduces the mean duration of hypotension (defined as MAP < 65 mmHg). The results of the HPI arm will be compared with a control group (non-HPI arm). In the control group, the clinician will use non-protocolized standard of care management per clinician and provider judgement.

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 group 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 group are not implants;
- The devices in the treatment group 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;
- The devices in the treatment group are of substantial importance in diagnosing, mitigating, or treating disease, or otherwise preventing impairment of human health and Class II (general and 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 group are not of substantial importance in curing disease.

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).

Randomization and Blinding

Subjects will be randomized into two arms, the HPI arm and the non-HPI arm. The randomization will be done automatically by the Electronic Data Capture (EDC) system. The subject will be blinded. Due to the nature of the interventions, the investigators and treating anesthesiologist, anesthesia nurse, intensivist and critical care nurse will not be masked to group allocation.

The HPI arm will utilize the HemoSphere Advanced Monitoring Platform with the Acumen™ HPI Software Feature. The treating cardiac anesthesiologist/anesthesia nurse in the operating room and the critical care

nurses/intensivists/advance practice providers in the ICU will be trained to understand Acumen™ HPI Software Feature and the advanced hemodynamic parameters provided. The treating anesthesiologist, anesthesia nurse, intensivist, and critical care nurse will be provided with guidance by means of a flowchart suggesting what to treat and what the cause of hypotension is (see Figure 3. HPI Arm Protocol). Timing of treatment and choice of treatment is then left to the discretion of the attending intensivist and critical care nurse.

In the non-HPI arm, clinicians will be using non-protocolized standard of care to treat subjects.

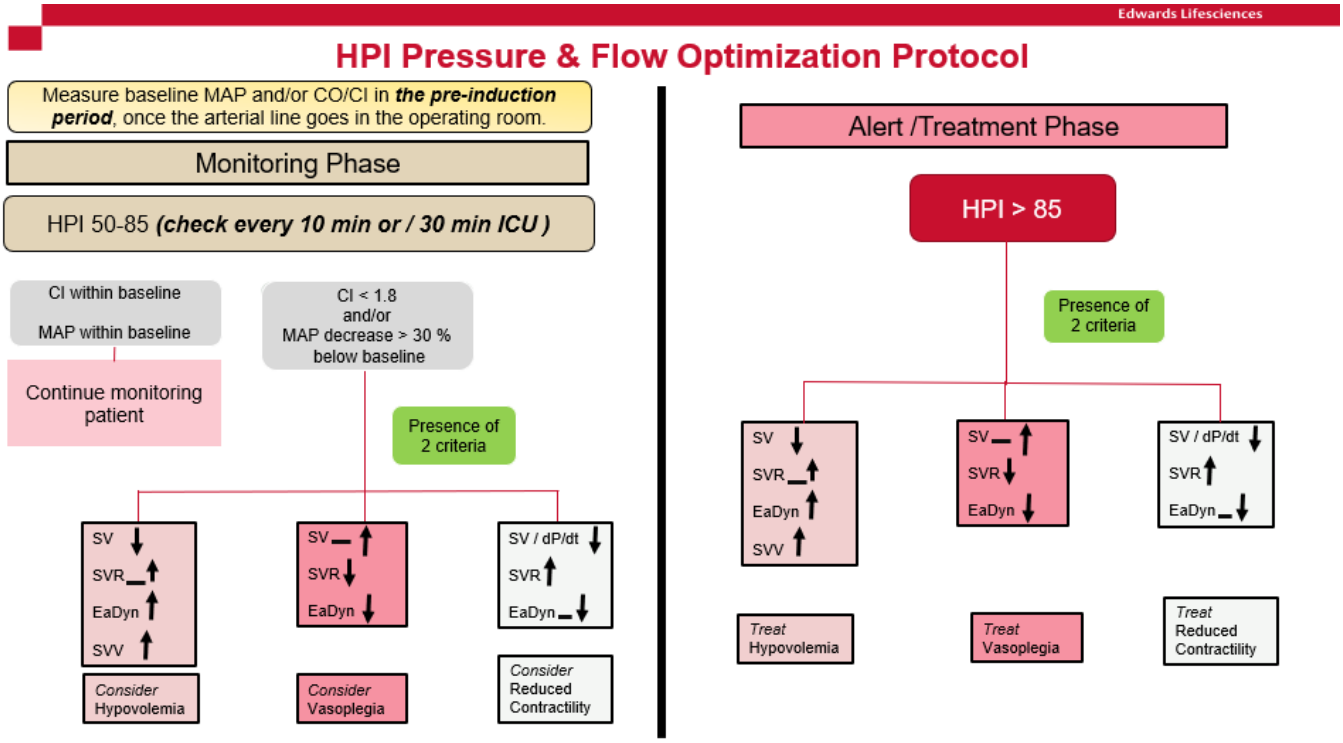


Figure 3. HPI Arm Protocol

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

Schema

Screening and consenting subjects will occur during the pre-anesthesia visit. Once the subject is consented, the subject will undergo a Mini-Mental State Examination (MMSE).

After the subject has consented and prior to surgery, the subject will be randomized into the HPI arm or the non-HPI arm (control group). The randomization assignment must not be revealed to the clinicians until surgery. If a clinician randomizes the subject, they must not be the involved in the care of the subject in the OR. A clinical research coordinator or a designee who is delegated to consent and/or randomize the

subjects, may be unblinded to the randomization assignment to set up the devices in the OR accordingly. However, the delegated coordinator/designee must not reveal the randomization assignment to clinician prior to start of the surgery.

A baseline Creatinine, NT pro-BNP and Troponin will be drawn on the day of procedure. Any fluids and vasoactive medications administered, intraoperative complications, and adverse events that occurred during the procedure will be collected.

After surgery on post-operation day 1 (or within 24 hours of extubation), any fluids and vasoactive medications, post-operative complications, and adverse events will be collected. Troponin will be drawn and an MMSE will be administered.

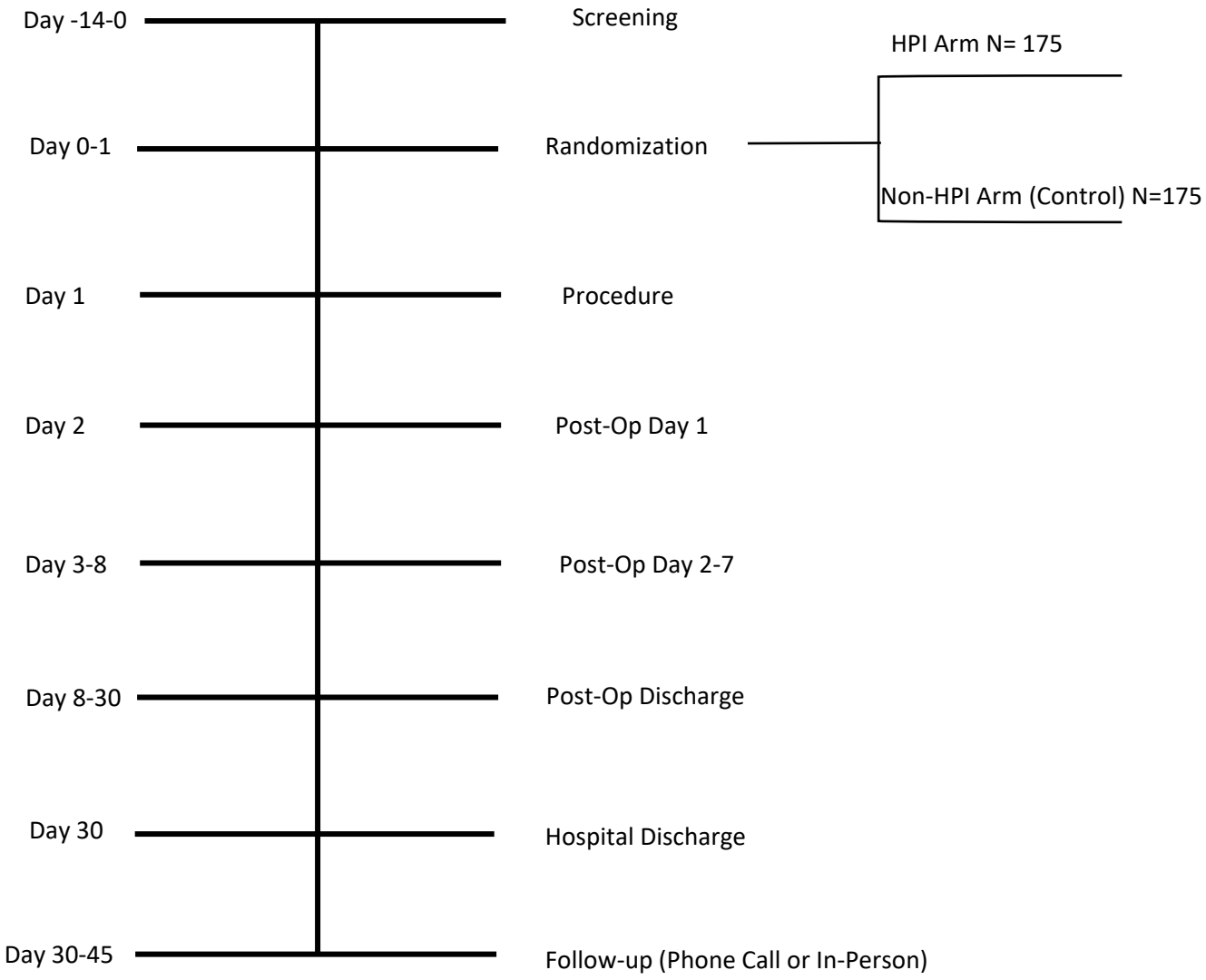
Before hospital discharge (generally post-operation day 2-7, but may vary), another MMSE will be administered. Troponin and NT pro-BNP will be drawn POD1, 2, 3. Creatinine will be drawn POD 1, 2, 3.

While the subject is in the ICU, an ICU-specific Confusion Assessment Method (CAM-ICU 7) will be administered twice daily. This assessment will be administered for up to 7 days post-operation in the ICU or until the subject is transferred to the hospital floor.

While the subject is located on the hospital floor, a Brief Confusion Assessment Method (bCAM) be administered twice daily. This assessment will be administered until post-operation day 7 or until hospital discharge (whichever comes first).

Additional information will be collected when the subject is discharged. A 30-day follow up will take place 30 days (±15 days) post-operation, either by phone call or in-person. If the follow-up takes place in-person, an MMSE will be administered at that time.

Figure 4. Sample Timeline Diagram



5. SUBJECT CONSENT, SELECTION AND WITHDRAWAL

General Characteristics of the Proposed Subject Selection

Up to 350 subjects (including 5 roll-in subjects) scheduled for cardiopulmonary bypass surgery (including CABG, valve and or a combination) and receiving pressure monitoring with an arterial line, who are at least 18 years of age will be enrolled in the trial. Only subjects meeting all inclusion criteria who have provided informed consent will be enrolled. Subjects who have been screened but did not sign an informed consent form will not be considered enrolled and will not have any eCRFs (electronic Case Report Forms) completed. The subject will be considered enrolled once the Acumen IQ sensor is connected to the arterial line.

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 Study site shall review the candidate's eligibility. The trial site should maintain a cumulative log of all screened subjects that are eligible in participating.

Inclusion Criteria

1. Subjects who are at least 18 years of age
2. Subjects who have signed the Informed Consent Form
3. Subjects with planned pressure monitoring with an arterial line
4. Subjects with planned sternotomy
5. Subjects with planned general anesthesia
6. Subjects who have ASA Physical Status ≤ 4
7. Subjects with planned cerebral oximetry monitoring
8. Subjects with planned overnight hospitalization
9. Subjects with planned cardiopulmonary bypass (CPB) "on-pump" surgery

Exclusion Criteria

1. Subjects with a physical site area too limited for proper sensor placement
2. Subjects with contraindications for arterial line placement
3. Subjects participating in another (interventional) study
4. Subjects in whom an intraoperative MAP target will be < 65 mmHg

5. Subjects with pre-op or pre-pump or post-pump LVEF <15%[1]
6. Subjects requiring heart transplant
7. Subjects with pre-existing circulatory support devices or planned circulatory support devices post-bypass
8. Subjects requiring emergency surgery
9. Subjects with known or identified severe PAH (defined as pulmonary systolic pressures> 70mmHg or mean pressures > 55mmHg) as determined by a pre-operative echo or intraoperative Swan-Ganz[2]
10. Subjects with cardiovascular instability in the operating room necessitating the need to go back on bypass for a subsequent run

[1] Pre-operative echo will take precedence over pre-pump echo. In the event of discrepancy on numbers, a final decision will be made based on a discussion between the PI and the cardiac anesthesiologist performing the pre-pump echo.

[2] Severe PAH is qualified as PA systolic pressure >70mmHg and/or mean pressure >55mHg as documented on a pre-operative echo or cardiac catheterization. Or in the absence of these a sustained pressure as above after the insertion of a Swan-Ganz for at least 60 minutes in the pre-bypass period. All severe PAH pressure values should be attributed to an irreversible etiology in the best clinical judgement of the treating team to meet exclusion criteria.

Screen Failures [or Late Screen Failures]

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the trial intervention or entered in the trial. 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 demography, 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 Study Identification Number (Study ID), an arterial line has been placed and Acumen IQ sensor has been connected. The Study ID will be an 874-XXX (6-digit) number; the first three numbers will identify the site, and the second set of numbers will identify the subject identification number. Roll-in cases will be assigned a unique Study ID and be analyzed separately from the pivotal cohort. There will be an identification number assigned to each investigator. The ID for each subject will remain the same throughout enrollment at each site.

Roll-in Subjects

In order to avoid a learning curve bias, up to five (5) Roll-in cases may be performed per site. Roll-in cases will be assigned a unique Study ID and will be analyzed separately from the Pivotal cohort. There will be an identification number assigned to each investigator. The ID for each investigator will remain the same throughout enrollment at each site.

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 follow-up. In addition, if the procedure is aborted early, but after the subject is exposed to trial product, 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 fails to return the 30-day follow-up phone call after 3 attempts and is unable to be contacted by the trial site staff.

The following actions must be taken if a participant fails to return to the clinic for a required trial visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the trial.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 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 participant's medical record or trial file.
- 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

Schedule of Events

Study Procedure / Exam	Subject Screening	Procedure	Day 1 Post-Op	Day 2-7 Post-Op	Discharge	30-Day Follow Up (±15 Days)
Obtain Informed Consent	X					
Perform Inclusion / Exclusion Evaluation	X					
Obtain Medical History / Subject Demographics[1]	X					
MMSE	X		X	X[2]		X[3]
Assign Subject ID		X				
Randomize Subject		X				
Enter Subject Data into Monitor		X				
Vital Signs		X				
NT pro-BNP		X	x	X[4]		
Troponin		X	X	X[4]		
Creatinine		X	X	X[5]		
ABG Labs		X				
Basic Labs		X				
Monitoring Duration		X				
Data download from Monitor		X				
Obtain Fluid and Vasoactive Medication Administration Record[6]		X	X			
CAM			X[7]	X[8]		
Complete eCRFs	X	X	X	X	X	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] MMSE will likely take place between Day 2-7 Post-Op, but this may vary.
[3] Only required for patients who will be returning to Wake Forest Baptist Medical Center for 30-day follow up
[4] Troponin and NT Pro-BNP to be drawn on POD 1, 2 and 3
[5] Creatinine to be collected on POD 1, 2 and 3
[6] Can be collected via the hospital record system anytime on the day of procedure or thereafter.
[7] CAM will be administered twice during post-op Day 1. While in the ICU, CAM-ICU 7 will be utilized. Once the subject is transferred to the hospital floor, bCAM will be utilized.
[8] CAM will be administered twice per day until Day 7 Post-Op or until the subject is discharged (whichever occurs first). While in the ICU, CAM-ICU 7 will be utilized. Once the subject is transferred to the hospital floor, bCAM will be utilized.

Record Adverse Events, if applicable		X	X	X	X	X
30-day follow up / Mortality Determination						X

Procedure

On the day of the procedure, the subject will be randomized into the HPI arm or the non-HPI arm (control group). If the subject is randomized into the HPI arm, the clinician will receive trial research nurse support and will use the Acumen™ HPI Software Feature with the Acumen IQ Sensor to monitor the subject. The initiation of HPI in the CVICU will not start until 15-30 minutes after the HPI arm subject arrives in the CVICU. Once HPI is initiated in the CVICU, HPI-based interventions will be held for at least 5 minutes before extubation and will also be held for at least another 5 minutes after extubation.

All subjects, regardless of randomization, will be equipped with an Acumen IQ Sensor. If the subject is not randomized into the HPI arm, the clinician will use non-protocolized standard of care.

7. STATISTICAL METHODS

Statistical Analysis Plan (SAP)

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

Primary Effectiveness Endpoint

The primary objective of this trial is to determine whether the use of the Acumen™ HPI Feature Software to guide hemodynamic management in critically ill patients in the cardiac operating room (OR) and the cardiovascular intensive care unit (CVICU) reduces the duration (t[mins]) of hypotension below a threshold of Mean Arterial Pressure (MAP), defined as MAP <65mmHg.

Sample Size Justification

In the HPI CARE Trial, the reduction of the mean duration of hypotension in the operating room (OR) and intensive care unit (ICU), is the primary endpoint. The following statistical hypotheses are designed and used for the sample size estimation.

$$H_n: \mu_1 \geq \mu_0$$

$$H_a: \mu_1 < \mu_0$$

where μ_1, μ_0 are the mean hypotension duration of the test arm and reference arm, respectively.

Because there are no publications available targeting hypotension management in the ICU, the sample size estimation is conducted based on the summary statistics from OR measurement. By the summary statistics (mean and standard deviation) of hypotension duration from post-CPB and closed chest [3,5], the following statistics are calculated and applied in sample size estimation: hypotension mean=29 (minutes), standard deviation=29.4 (minutes).

By clinical study design, type I error $\alpha = 0.025$ (one side test), test power$= (1 - \beta) = 0.80$, the expected hypotension duration reduction rate by HPI software and the treatment protocol is 30%, the expected ratio of hypotension duration standard deviation divided by the mean hypotension in the test arm will be 1.10 (obtained from a previous non-cardiac OR HPI study, Edwards Lifesciences), with SAS PROC POWER, the estimate of sample size is 171 per group. $\beta$is type II error.

Primary Safety Endpoint

The primary safety endpoint is to assess all serious intraoperative and post-operative adverse events through 30 days, including serious device-related events.

Analysis Populations

A. mITT population

The Modified intent-to-treat (mITT) population is composed of all subjects who pass the screen (inclusion/exclusion) evaluation, sign the inform consent form (ICF), are assigned a subject ID, and are randomized to a study group. This includes roll-in and pivotal subjects.

B. FAS population

FAS (full analysis set) population is composed of all pivotal subjects with valid HemoSphere observations.

C. PP population

The per protocol (PP) population is composed of all pivotal subjects without protocol deviations.

D. CC population

The complete cases (CC) population is composed of all the pivotal subjects who complete surgery and complete the trial.

Analysis Methods for the Primary Endpoint

The primary study objective is to evaluate if the use of HPI software in conjunction with a treatment protocol can statistically reduce the study patient's hypotension duration by the measurements taken in the cardiac OR and ICU, which has been shown to correlate with morbidity and mortality. By the hypotheses designed in sample size calculation, the following t statistics will be used to judge if the hypotension duration of the study arm with HPI software is statistically shorter or smaller than the control arm without HPI software.

$$t = \frac{\widehat{\mu_1} - \widehat{\mu_0}}{\sqrt{S_p^2(\frac{1}{n_1} + \frac{1}{n_0})}}$$

Here $\widehat{\mu_1}, \widehat{\mu_0}$ is the mean hypotension duration estimation of the test arm and reference arm, respectively. The pooled variance, $S_p^2 = \frac{(n_1-1)*S_1^2+(n_0-1)*S_0^2}{n_1+n_0-2}$, n_1, n_0 is the final valid subjects in test arm and reference arms respectively, S_1^2 and S_0^2 are the variance estimates of the test arm and reference arm respectively.

By the t statistics calculated with the data from clinical operation, compares to the critical t value ($t(\alpha', n_1 + n_2 - 2)$ to judge if null hypothesis is rejected. Here $\alpha'$is the split type I error by study design for interim analysis and the final analysis, $n_1 + n_2 - 2$ is the degree of freedom.
For the interim analysis, by Pocock methodology with one-sided t test, $\alpha' = 0.015$. If p value deduces from the actual t value with $n_1 + n_2 - 2$ degrees of freedom is less than α', $H_n$will be rejected.

For the final analysis, using the Pocock methodology, with one-sided t test, $\alpha' = 0.015$. A similar computation will be done at the interim analysis.

All the other statistical methodology used in sensitivity analysis, safety analysis, and exploratory analysis will be detailed in the SAP.

Note: In this study, the sample size is not big enough to ignore the approximate property with Z score test, especially in the interim analysis.

Planned Interim Analyses

To monitor the effectiveness and safety of HPI software on hypotension management in cardiac surgery and ICU, one interim analysis is planned and will be conducted at the time that half of the enrolled study subjects complete surgery and the hemodynamic measurements are downloaded from the monitoring platform.

To compensate for the early look at the data during the interim analysis, using the Pocock methodology, for this study design, 11% extra study subjects will be enrolled. Considering drop-out through ICF withdrawal, subjects lost to follow-up, and roll-in subjects for training, another 10% attrition is added for subject enrollment; the final sample size is 175 subjects per group.

Secondary Endpoints

The following secondary endpoints will be analyzed per the SAP:

- TWA of MAP < 65 mmHg in the OR Period (T1)
- TWA of MAP<65 mmHg in the CVICU Period (T2)
- TWA of MAP < 65 mmHg in the CVICU Period, pre extubation (T3)
- TWA of MAP < 65 mmHg in the CVICU Period, post extubation (T4)
- Mean duration in minutes of MAP < 65 mmHg in the time periods of T1, T2, T3 and T4
- Mean duration in minutes of MAP < 60 mmHg in the time periods of T1, T2, T3 and T4
- Mean duration in minutes of MAP < 55 mmHg in the time periods of T1, T2, T3 and T4
- Mean duration in minutes of MAP < 50 mmHg in the time periods of T1, T2, T3 and T4

Clinical endpoints:

- Acute kidney injury (AKI)[7], as defined by the modified KDIGO criteria, stages 1, 2 and 3.
- Neurocognitive deficit, as evaluated by the MMSE, CAM-ICU 7, and bCAM assessments.
- Periprocedural Myocardial injury, measured with high-sensitivity Troponin I and as defined a threshold of 70 times the upper reference limit[6]. or >1400 pg/ml

Additional Evaluations

The following additional evaluations will be included and are considered exploratory:

- Subgroup analysis of primary and secondary endpoints by age stratification
- Subgroup analysis of primary and secondary endpoints by gender
- Subgroup analysis of primary and secondary endpoints by race
- Protocol adherence to HPI alert, as defined by >50% HPI alerts with documented intervention per the suggested treatment algorithm within a 5 minute timeframe
- Difference in time spent in hypertension defined as TWA of MAP>110, >120 and >130 mmHg post-cardiopulmonary bypass CPB) through the first 8-hour ICU period as compared with the control group.
- In-hospital mortality rate
- Incidence of cerebral desaturations defined as total time below 10% relative to baseline NIRS values.
- Percent of monitoring time with CO or CI within 10% relative to pre-induction baseline
- ICU Length of Stay
- Hospital Length of Stay
- Time to extubation
- SOFA scores
- New onset atrial fibrillation detected prior to ICU discharge

8. RISK ANALYSIS

Anticipated Risks

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

All trial devices are commercially available. Any events associated with any commercially available trial device 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 cardiopulmonary bypass surgery:
  - Death
  - Hemolysis
  - Capillary leak syndrome
  - Post-perfusion syndrome
  - Air embolism
  - Formation of blood clots
  - Acute respiratory distress syndrome
  - Systemic inflammatory response
  - Organ failure
  - Bleeding

- 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 Sensor:
The vascular access obtained is standard clinical care for the adult population and the addition of the Acumen IQ 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.

Below is a list of anticipated risks that may be associated with the use of ForeSight Elite 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 trial devices have been tested to an established regimen of safety and performance testing and have been cleared by the US FDA in adults.

The current risks identified for using these products do not outweigh the benefit the patient will receive. Furthermore, this trial is:

1) Being conducted on patients who are already planned to receive an arterial line and the addition of Acumen IQ sensor do not add to the invasiveness of the trial. The optional use of the noninvasive ForeSight Elite sensors also does not add any additional risks. As such, the risks do not outweigh the benefits.

Benefits
There are no guaranteed benefits from a subject's participation in this trial.

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 Medical Reviewer.

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 devices or trial procedure must be reported to the Sponsor or Designee within 24 hours of first awareness of the event.

Classification 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.
- Serious – Serious 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 the 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 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 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 the medical devices in this trial. 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 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 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 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; however, 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 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 Clinical Events Committee. The FDA, all participating principal investigators and their reviewing IRBs 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

Independent Medical Reviewer

A Medical Reviewer will oversee the safety progress. The Medical Reviewer must be free of significant conflicts of interest (e.g., Financial, intellectual, professional, or regulatory), and is an expert in all scientific disciplines needed to interpret the data and ensure participant safety.

The Medical Reviewer will perform the following activities:

- Adjudicate all adverse events based on whether the events were:
  - Serious/Non-Serious
  - Anticipated/Unanticipated
  - Related to procedure and/or device

The Medical Reviewer will provide an immediate adjudication [within 48 hours] of unanticipated adverse device effects [UADE] in terms of anticipation, severity, and relatedness to trial devices.

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 used of the device 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 Device

The Principal Investigator 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 Study. 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 Study 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.) for which no eCRF is available will be captured in study documentation (i.e., note-to-file) that includes the investigator's signature and will be provided to the sponsor. The sponsor will maintain oversight of non-subject specific deviations using an internal tracking tool. The investigator will also adhere to procedures for reporting trial and subject specific deviations to their IRB in accordance with their specific IRB's reporting policies and procedures.

16. DATA COLLECTION METHODS

Trial data will be captured utilizing electronic Source (eSource) and electronic Case Report Forms (eCRFs) including the 30-day follow-up 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 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. STUDY DOCUMENTATION

Study Records

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

- Study 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
- Study training logs
- Device accountability records
- Required reports, if applicable

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

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

Study 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 days after 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 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 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 study 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 study 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 study 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 study documentation including applicable correspondences during the course of the study.

19. STUDY MONITORING, AUDITING, AND INSPECTING

Site Selection

The Study site(s) for this Study 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, Study specific training, and supplies necessary to conduct the Study.

Study Monitoring Plan

A Monitoring Plan will be created to address monitoring arrangements and the extent of source data verification. A Study monitor will be assigned to monitor the progress of the Study by the Sponsor. The Study monitor may be either an employee of the Sponsor or contracted. The Study monitor will be responsible for reviewing eCRFs and monitoring the Study site routinely to observe Study 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 Study related documents provided by the Sponsor.

Study monitoring visits will be scheduled throughout the duration of the Study between the Study 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 Study 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 Study for clarification/resolution by the Principal Investigator or delegated-site personnel.

Interim Monitoring Activities

The Sponsor has the obligation to monitor the conduct of this study to ensure that the study 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 study, verify the rights, well-being, and protection of the patients, and verify that the reported clinical study 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 Study. The Sponsor retains the right to suspend or prematurely terminate this clinical investigation at any time. Upon completion or premature termination of the Study, the Study 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 study 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 Study-related monitoring, audits, and inspections by the Research Quality Assurance Office, IRB, the Sponsor, and government regulatory bodies, of all Study related documents (e.g., source documents, regulatory documents, data collection instruments, Study data etc.). The Investigator will ensure the capability for inspections of applicable Study-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 study suspension or termination, will be provided by the Sponsor to Principal Investigator and regulatory authorities. If the study 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 study while the risk is assessed by the Medical Reviewer. Edwards shall terminate the clinical investigation if an unacceptable risk is confirmed.

21. ETHICS

Ethical and Scientific Conduct of the Clinical Research Study

The Study may only commence once IRB approval and regulatory approval, as applicable, are received. This Study 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 Study Protocol to all Study site personnel responsible for Study conduct.

As the Sponsor of this clinical Study, Edwards Lifesciences has the overall responsibility for the conduct of the Study, including assurance that the Study 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 Study approval by the IRB.

The Sponsor may transfer study 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 Study 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.

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 Study, a manuscript may be prepared for publication in a scientific journal. The Sponsor reserves the right to review any manuscripts prior to submission. The Study will be entered into a clinical trial registry databank such as clinicaltrials.gov.

25. ACRONYMS AND ABBREVIATIONS

Acronym	Entire Word
ADE	Adverse Device Effect
AE	Adverse Event
ASA	American Society of Anesthesiologists
BP	Blood Pressure
CI	Cardiac Index
CCO	Continuous Cardiac Output
CO	Cardiac Output
CEC	Clinical Events Committee
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
HR	Heart Rate
Hr	Hour
ICC	Intra-Cluster Correlation
ICF	Informed Consent Form
ICO	Intermittent Cardiac Output
ICU	Intensive Care Unit
IRB	Institutional Review Board
ITT	Intent-to-Treat
mL	Milliliters
mITT	Modified Intent-to-Treat
N	Total Sample Size
NCT	National Clinical Trial
PAC	Pulmonary Artery Catheters
PI	Principal Investigator
PR	Pulse Rate
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SpO_2	Peripheral Capillary 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

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Edwards Lifesciences

STATISTICAL ANALYSIS PLAN

Protocol Title:	A randomized trial of the Hypotension Prediction Index in the cardiac operating room and the intensive care unit
Study Number:	2020-19
SAP Version:	Revision A
SAP Date:	May 7, 2024
SAP Author:	[redacted]

CONFIDENTIAL

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Glossary of Terms

ABBREVIATION	DEFINITION OR DESCRIPTION
ADE	Adverse device effect
AE	Adverse event
AKI	Acute kidney injury
AUC	Area under curve
α	Type I error in hypothesis test and sample size estimation
β	Type II error in hypothesis test and sample size estimation
CEC	Clinical events committee
CI	Cardiac index
CI	Confidence Intervals
CO	Cardiac output
CPB	Cardiopulmonary bypass
CSR	Clinical study report
CVICU	Cardiovascular intensive care unit
DIA	Diastolic blood pressure
dP/dt	Maximal slope of the arterial pressure upstroke
Eadyn	Dynamic arterial elastance
eCRF	Electronic case report form
GCP	Good clinical practice
H_n	Null hypothesis
H_a	Alternative hypothesis
HPI	Hypotension prediction index
ICU	Intensive care unit
ICF	Informed consent form
IRB	Institutional review board
MAP	Mean a arterial pressure
OR	Operating room
Post CPB	Post cardiopulmonary bypass
PR	Pulse rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SV	Stroke volume
SVI	Stroke volume index
SVV	Stroke volume variation
SYS	Systolic blood pressure
TWA	Time weight 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, 2020-19 (version F), A randomized trial of the Hypotension Prediction Index in the cardiac operating room and the intensive care unit, provides detailed instructions to study data analysis. If there are conflictions between SAP and other study documents related to data analysis, SAP will be the final document that we will follow.

The primary analyses will be done using SAS, Version 9.4 or later version installed in Edwards Lifesciences' Server. The computation of hypotension duration for each hypotension instance, subject's total hypotension duration, and all other relevant endpoints will be completed with global macro function written with SAS, which is developed and maintained by department of critical care, Edwards Lifesciences.

R will be the support software used in a few applications, such as draw publication quality plots, and application of advanced statistical models in the analysis.

2. STUDY DESIGN

2.1. Study Objectives

The objective of the study is to determine whether the use of the AcumenTM HPI Feature Software to guide hemodynamic management in the cardiac operating room (OR) post-CPB and the cardiovascular intensive care unit (CVICU) reduces the mean duration of hypotension (defined as MAP < 65 mmHg) as compared with the control group. The study is being performed in this patient population to provide information that cannot be readily obtained through additional non-clinical assessments.

2.2. Overall Study Design

This study is a single-center randomized controlled trial to determine whether use of the Acumen HPI Software Feature to guide hemodynamic management in cardiac surgery post-CPB and up to 8-hours post-CPB reduces the amount of hypotension (defined as MAP < 65 mmHg). The results of the HPI arm will be compared with a control group (non-HPI arm). In the control group, the clinician will use non-protocolized standard of care management per clinician and provider judgement.

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 HPI arm are being studied in accordance with the indications for use and intended use granted by FDA in DEN160044 (March 16, 2018), and therefore are not investigational devices.
- The devices in the treatment group are not implants.

- The devices in the treatment group 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 trial relies on the intervention of a learned intermediary prior to initiation of treatment. The devices in the treatment group are of substantial importance in diagnosing, mitigating, or treating disease, or otherwise preventing impairment of human health; however, as described in the de novo classification letter for DEN160044 (March 16, 2018), the Class II (special) controls provide a reasonable assurance of the safety and effectiveness of adjunctive predictive cardiovascular indicators, and specifically, the AcumenTM HPI Software Feature, met the special controls as established by FDA; and the devices in the treatment group are not of substantial importance in curing disease.

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).

2.3. Study Subject Randomization Schema

Subjects will be randomized into two arms, the HPI arm and the non-HPI arm. The randomization will be done automatically by the Electronic Data Capture (EDC) system. To keep the subject balance between HPI arm and control group (1:1), sequentially, 2, or 4, or 6 study subjects passed the qualification screening with yes for all inclusion criteria and no for all exclusion criteria, signed the IFC form, assigned the subject ID, form a subject block. The randomization allocation of study subject will conduct within each block depending on the random number generated from uniform distribution, the block specified cutoff probability will be selected to guarantee half of the subjects will go to the control group and another half will be assigned to the HPI arm. The probability cutoff point to assign a subject to HPI arm or control group will variate among blocks, which is determined by the random seed and the uniform random number produced for each study subject.

Due to system limitations with the electronic data capture (EDC) system, there is a manual process for handling screen failures who are randomized (late screen failures). There is a small chance that some randomization assignments will be skipped due to these screen failures (partially filled blocks), or some randomization assignments given out more than once. These issues may introduce bias in the study. Should these events occur, an additional sensitivity analysis will take place. If randomization assignments are skipped, the study will be assessed to ensure a reasonable balance exists between the cohorts. The collected baseline variables will be compared to ensure that both cohorts are well matched.

In the event that some of the randomizations are given out twice, a sensitivity analysis will be performed to determine if the duplicate randomization caused any difference in the results. This sensitivity analysis on the primary endpoint will remove all subjects who were included in the duplicate randomization and the results will be compared to the primary endpoint to ensure the results are consistent. If they are consistent between the main analysis and the sensitivity analysis, then it will be determined that there was no bias created. If the results of the sensitivity analysis differ significantly, then both the results for the primary endpoint and the sensitivity analysis will be presented.

2.4. Sample Size Considerations

2.4.1. Hypothesis Test Setting

It is anticipated that the alert function of the Acumen™ HPI Feature Software will reduce the hypotension duration by a clinically relevant amount, which is derived by the consecutive measurements with MAP<65 (mmHg) lasting at least 1 minutes (see appendix). By the HPI CARE study objective, following one-side hypotheses test settings will be designed and applied in sample size estimation and data analysis.

$$H_n: \mu_{HPI} \geq \mu_{ctr}$$
$$H_a: \mu_{HPI} < \mu_{ctr}$$

Here, μ_{HPI}, μ_{ctr} is the mean number of minutes of hypotension duration of HPI arm study subjects and that of control group study subjects respectively.

2.4.2. Experiment Design Parameter

It is frequently encountered upon intensive care unit (ICU) admission, where patients become hypotensive in the immediate post-operative period, shortly after the arrival from the operating room (OR). Hypotension upon anesthesia-to-ICU drop-off is more frequent than previously reported and may be associated with adverse clinical outcomes[9]. Many studies have been conducted exploring the risks of intraoperative hypotension during non-cardiac surgery, also there are literatures focusing on the hemodynamic management in operating room during cardiac surgery, but up to now, no valid evidence available from hemodynamic management operation for the patients discharged to ICU could be applied in sample size simulation for HPI CARE study. The association between the severity and duration of intraoperative hypotension and postoperative stroke in patients undergoing cardiac surgery was evaluated in a retrospective cohort study of 7,457 consecutive adult patients who underwent cardiac surgery with the aid of cardiac pulmonary bypass[9]. From this study, following summary statistics (table 1) are drawn that will be integrated in sample size simulation for HPI CARE study. Recently, a single medical center prospective cohort feasibility clinical study is designed and executed to evaluate the use of the HPI in cardiac surgeries requiring cardiopulmonary bypass (CPB) [13]. Totally 37 subjects were enrolled for this study. By 33 valid subjects, the mean total intraoperative hypotension duration is 9 minutes, and the corresponding stand deviation is 15 (minutes) for close chest period in whole cardiac surgery procedure, which will be integrated together with the summary statistics from post cardiac pulmonary bypass (see table 1) in the sample size simulation.

Table 1: Summary Statistics of intraoperative hypotension during post-Cardiac Pulmonary bypass period[9]

MAP(mmHg)	Stroke (n=111) Mean±STD (minutes)	No Stroke (n=7346) Mean±STD (minutes)	All Patients (n=7457) Mean±STD (minutes)
<55	9.2±20.00	3.8±11.10	3.88±11.30
55-64	23.5±27.30	16.0±18.60	16.11±18.78
<65 (Derived)	32.7±33.84	19.8±21.66	19.99±21.92*

Note: *The mean and STD of hypotension duration will be used in sample size estimation.

2.4.3. Sample Size Estimate

Because there is no valid evidence available for the hemodynamic management from literature on intensive care unit, in this simulation only the information from closed chest stage and post cardiac pulmonary bypass stage are integrated.

By HPI CARE study objectives, clinical study design, and hypotheses test settings, a one side hypothesis test is the standard method, type I error for this test is 0.025, test power=0.80, control group mean hypotension duration=29 minutes, its stand deviation=29.49, the expected reduction is 30%, by the HPI arm result from non-cardiac clinical study, the ratio between hypotension duration STD and mean is around 1.10. The estimated subjects for each arm by 1:1 allocation is 142 from the simulation completed by SAS PROC POWER. Considered lost follow up, withdraw informed consent form, et al, 10% attrition will put on the estimated sample size. It is 157 subjects for HPI arm and control group.

Variable	Control Group (non-HPI arm)	Test Group (HPI Arm)

Mean hypo (minutes)	29 min	20.3 min
SD of Mean hypo minutes	29.49 min	22.33 min
Alpha (overall, one-sided)	0.025	---
Sides	One-Sided	---
Power	0.8	---
Sample size	142	142
Dropout rate	10%	10%
Sample size (subjects)	157	157

3. STUDY ENDPOINTS

3.1. Primary Endpoint

Assessment if the use of the Acumen HPI Feature Software reduces the mean duration of hypotension (defined as MAP < 65mmHg) from the post-bypass period to the first 8-hour ICU period as compared with the control group.

3.2. Primary Safety Endpoint

Serious adverse events through 30 days as indicated below:

- Serious intraoperative and post-operative complications between each cohort
- Device-related serious adverse events (SAEs).

3.3. Secondary Endpoints

The following secondary endpoints will be analyzed:

- Additional definitions of hypotension:
  - Time Weighted Average (TWA) of MAP < 65 mmHg in the OR Period (T1)
  - TWA of MAP<65 mmHg in the CVICU Period (T2)
  - TWA of MAP < 65 mmHg in the CVICU Period, pre extubation (T3)
  - TWA of MAP < 65 mmHg in the CVICU Period, post extubation (T4)
  - Mean duration in minutes of MAP < 65 mmHg in the time periods of T1, T2, T3 and T4
  - Mean duration in minutes of MAP < 60 mmHg in the time periods of T1, T2, T3 and T4
  - Mean duration in minutes of MAP < 55 mmHg in the time periods of T1, T2, T3 and T4
  - Mean duration in minutes of MAP < 50 mmHg in the time periods of T1, T2, T3 and T4
- Clinical endpoints:
  - Acute kidney injury (AKI)7, as defined by the modified KDIGO criteria, stages 1, 2 and 3
  - Neurocognitive deficit, as evaluated by the MMSE, CAM-ICU 7, and bCAM assessments. [bCAM will be used for delirium screening for patients who are deemed ready for transfer to the floor per ICU attending team's assessment, even if they are physically in the ICU]
  - Periprocedural Myocardial injury, measured with high-sensitivity Troponin I and defined by a threshold of 70 times the upper reference limit6. or >1400 pg/ml

3.4. Exploratory Endpoints

The exploratory evaluations are indicated below:

- Subgroup analysis of primary and secondary endpoints by age stratification
- Subgroup analysis of primary and secondary endpoints by gender
- Subgroup analysis of primary and secondary endpoints by race
- Protocol adherence to HPI alert, as defined as by >50% HPI alerts responded to with HPI suggested interventions with documented intervention per the suggested treatment algorithm within a 5-minute timeframe.
- Difference in time spent in hypertension defined as Time weighted average (TWA)TWA of MAP>110, >120 and >130 mmHg post-cardiopulmonary bypass CPB) through the first 8-hour ICU period as compared with the control group.
- In-hospital mortality rate
- Incidence of cerebral desaturations defined as total time below 10% relative to baseline NIRS values.
- Percent of monitoring time with CO or CI within 10% relative to pre-induction baseline
- ICU Length of Stay
- Hospital Length of Stay
- Time to extubation
- New onset atrial fibrillation, detected prior to ICU discharge

4. ANALYSIS POPULATIONS

A subject will be considered enrolled in the trial once the subject has signed the informed consent, has been assigned a Study Identification Number (Study ID), an arterial line has been placed and Acumen IQ has been connected. The Study ID will be an 874-XXX (6-digit) number; the first three numbers will identify the site, and the second set of numbers will identify the subject identification number. Roll-in cases will be assigned a unique Study ID and be analyzed separately from the pivotal cohort. There will be an identification number assigned to each investigator. The ID for each subject will remain the same throughout enrollment at each site.

4.1. Modified ITT (mITT) Population

The mITT population is composed of all subjects who pass the screen (inclusion/exclusion) evaluation, sign the inform consent form (ICF), are assigned a subject ID, and are randomized to a study group, an arterial line has been placed and the FloTrac or Acumen IQ Sensor has been connected.

4.2. Full Analysis Set (FAS) Population

The FAS population is a subset of the mITT population and will consist of all enrolled pivotal subjects who undergo cardiac surgery ≥ 2 hours duration with the aid of cardiopulmonary bypass, have one postoperative assessment, and have valid hemodynamic observations.

4.3. Per Protocol (PP) Population

The per protocol (PP) population is a subset of the subjects in the FAS who are more compliant with the protocol and is characterized by criteria such as the following: i) the completion of a certain pre-specified minimal exposure to the treatment regimen; ii) the availability of measurements of the primary endpoint(s); iii) the absence of any major protocol violations including the violation of entry criteria.

4.4. Complete Case (CC) Population

The CC population is composed of all the pivotal subjects who complete surgery and complete the trial.

4.5. Roll-in Subjects

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

4.6. Screen Failure

Screen failures are defined as subjects who consent to participate in the clinical trial but who are not randomly assigned to a trial arm. Screen failures will be represented in subject accountability table by counts and percentages. Screen failures also includes study subjects who were included in the study but did not meet all the inclusion criteria.

5. DEFINITIONS

5.1. Analysis Dates and Days

Reference Start Date (Day 0)

On the day of the surgery, the start of the study is defined as when the arterial line has been connected and after initial stabilization (max 15 minutes). The date of the surgery will be used as the reference start date (day 0).

If a subject has multiple procedure forms, we will present information on the procedure with the earliest date where the site has indicated that the arterial line was placed.

If no form has this indicated, then the procedure information corresponding to the procedure with the earliest date that indicated an arterial line was placed will be used. If no form has this listed, then the date of the earliest procedure will be used.

Last Participation Date

The Last Participation Date is defined as the last date recorded. This will be the study exit date if the subject has exited the study or the latest date the subject was known to be alive and on study.

Treatment Start Date

The Treatment Start Date is defined as the date of the surgery.

Study Day

Study Day = Date – Reference Start Date

Last Participation Day

Last Participation Day = Last Participation Date – Reference Start Date

Note: Last Participation Day is used as the censor day for any survival analysis.

5.2. Analysis Windows

No analysis windows will be used for this study. If some visits are far outside of the time, then a sensitivity analysis that removes the out of window visits may be performed to assess the impact of the out of window visits.

6. DATA AND ANALYSIS CONVENTIONS

6.1. General Conventions

The baseline characteristics and demographics of each study subject will be collected during the subject

screening process.

Descriptive summaries will follow the conventions below:

- For continuous variables, summary statistics will include sample size, mean, median, standard deviation (SD), and/or standard error (SE), Q1, Q3, minimum, and maximum.
- For categorical (including ordinal) variables, summaries will include the count and percentage of subjects in each category.
- Time-to-event variable summaries will include the number of subjects with the event and Kaplan-Meier estimates at given time points. Standard errors will be calculated using Greenwood's formula.

All analyses will be performed using SAS® Software version 9.4 or later (SAS Institute, Inc., Cary, NC) unless otherwise specified.

6.2. Handling of Missing Data

Demographic and baseline characteristics are collected from the study subjects as part of screening. If missing data are not related to the subject's eligibility criteria, missing data will be presented by the valid sample size in the demographic and baseline characteristics summary statistics table. Subjects with missing data will be included in the final 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 the final analysis set.

Algorithms for imputing the missing dates of safety events are given below. Generally, the safety event date will be assigned as the earliest possible date that is on or after the procedure date.

- If the year is unknown, then the date will be imputed using the procedure date
- If the month is unknown, then:
  - If the year matches the year of the procedure date, then impute the month and day using the procedure date
  - Otherwise, assign the procedure month
- If the day is unknown, then:
  - If the month and year match the month and year of the procedure date, then impute the day using the procedure date
  - Otherwise, assign '01'

Unless otherwise noted, no other data imputation will be made.

7. SUMMARY OF BASELINE INFORMATION

7.1. Subject Accountability

A summary table will provide the total number of subjects screened, enrolled, and who have completed the clinical trail. The subjects eligible for this study and compliant with each follow-up contact will be summarized descriptively. Subjects withdrawn from study, lost follow-up, and lost with other reasons will be tabulated together with their reasons.

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 such as age, sex, race, ethnicity, and other demographic variables will be used for each summary. All measurements will be presented using descriptive statistics; continuous variables, such as age, body height, body weight, body mass index, will be summarized as described in section 6.1.

The CONSORT (Consolidated Standards of Reporting Trials) Flow Diagram will be drawn to represent study subjects count and its percentage dynamics from subject qualification screening, eligible subject enrollment, and intervention (randomization) allocation, follow-up, and data analysis.

7.3. Medical History

Patient's medical historical data will be recorded with electronic case report form (eCRF). Medical historical data will be summarized into tables with continuous variables being represented by mean, stand deviation, median, and ranges, and categorical variables being represented by counts and percentages.

7.4. Procedural Information

Procedure data including the surgery classification, planned surgical technique, duration, and procedural interventions will be summarized.

8. STATISTICAL ANALYSIS OF STUDY ENDPOINTS

8.1. Primary Effectiveness Endpoint

Primary objective of this clinical study is to determine whether the use of the AcumenTM HPI Feature Software to guide hemodynamic management in patients undergoing cardiac surgery requiring cardiopulmonary bypass reduces the mean duration of hypotension (defined as MAP < 65 mmHg) from the post-bypass period in the cardiac operation room (OR) and the cardiovascular intensive care unit (CVICU). With MAP measurements sampled during post-CPB and up to first 8 hour in ICU, downloaded from the advanced hemodynamic monitoring platform, the primary effectiveness endpoint the hypotension duration of study subject is calculated with the algorithm illustrated in sample size estimation section 2.4.3.

The primary effectiveness endpoint will be analyzed on the FAS population.

8.1.1. Summary Statistics and Statistical Comparison

The computed total hypotension duration of study subject allocation in the HPI arm and control group will be summarized using descriptive statistics including mean, median, minimum, maximum, standard deviation, Q1 (first quantile), and Q3 (third quantile), and present these descriptive statistics by study arms in the summary table. Additionally, the p-value from a two sample mean t-test will be provided to test the difference.

8.1.2. Primary Effectiveness Endpoint Analysis

We will test the following hypothesis:

$$H_n: \mu_{HPI} \geq \mu_{ctr}$$
$$H_a: \mu_{HPI} < \mu_{ctr}$$

Here μ_{HPI}, μ_{ctr} are the mean number of minutes of hypotension duration of HPI arm study subjects and that of control group study subjects respectively.

A two-sample t-test will be used to judge if the hypotension duration of HPI arm is statistically shorter or smaller than the outcomes of control group without HPI software. We will use the following:

$$t = \frac{\widehat{\mu_1} - \widehat{\mu_0}}{\sqrt{S_p^2(\frac{1}{n_1} + \frac{1}{n_0})}}$$

Here $\widehat{\mu_1}$, $\widehat{\mu_0}$ are the mean hypotension duration estimation of HPI arm and control group, respectively, the pooled variance $S_p^2 = \frac{(n_1-1)*S_1^2+(n_0-1)*S_0^2}{n_1+n_0-2}$, n_1, n_0 is the final valid subjects in HPI arm and control group respectively, S_1^2, S_0^2 is the variance estimates of HPI arm, and control group respectively.

By the t statistics calculated with the data collected during clinical operation, compares to the critical t value $(t(\alpha', n_1 + n_0 - 2)$ to judge if null hypothesis is rejected. Here $\alpha'$is the split type I error by study design for interim analysis and the final analysis, $n_1 + n_0 - 2$ is the degree of freedom.

For the interim analysis, by Pocock methodology [15-16] with one-sided t test, $\alpha' = 0.0154$. If $\widehat{\mu_1} - \widehat{\mu_0}$ is negative, and the actual p value calculated from the t statistics based on designed null hypothesis from the trial outcomes is less than α', H_{null}will be rejected. Following conclusion will be drawn: the application HPI software system in hemodynamic management statistically reduces the hypotension duration in HPI arm.

8.1.3. Sensitivity Analysis

The objective of sensitivity analysis is to guarantee the robustness of the statistical analysis conclusion drawn from statistical hypothesis test. Following sensitivity analyses are designed in this study:

A. Modification of hypotension definition:
   A1. The effectiveness of the threshold of MAP on statistical conclusion, check the analytical conclusion sensitivity to changes of the MAP threshold value to define hypotension instance from 50 mmHg to 70 mmHg with step=5 mmHg.
   A2. The time length cut off used in hypotension instance definition, check the analytical conclusion sensitivity to changes of the cut off time length from 20 seconds to 80 seconds with step=20 seconds.
B. The effectiveness of sample size:
   B1. With bootstrap method, draw analytical conclusion by analysis based on the sub-set of study data sampled from the whole study data, check the consistency between the whole data analysis result and the simulated sub-dataset analysis result.
   B2. Including the study subject with missing covariate information or cohort structure in the analytical dataset, check the consistency between the analysis with all study subject and on the analysis result with FAS subject.

8.1.4. Interim Analysis

To monitor the effectiveness and safety of HPI software on hypotension management in cardiac surgery and ICU for study patient requiring cardiac pulmonary bypass, one interim analysis is planned and will be conducted at the time that half of the enrolled study subjects' complete surgery and the hemodynamic measurements are downloaded from the monitoring platform.

To compensate for the early look at the data during the interim analysis, using the Pocock methodology, for this study design, 11~12% extra study subjects will be enrolled. Considering drop-out through withdraw ICF, lost follow-up, and roll-in subjects for training et al, another 10% attrition is added for subject enrollment, considering the study subject randomization, the final sample size is 175 subjects per group.

This interim analysis focuses on the primary effectiveness endpoint, the subject total hypotension duration during post-cardiac pulmonary bypass stage and the first 8 hours for patients in intensive care unit. The reduction of mean hypotension duration between the HPI arm and control group will be tested by t (student) statistics with $n_1 + n_2 - 2$ degree of freedom. If the corresponding p value of this t statistics is less than the critical p value=0.0154 (the type I error allocation by the study design) together with the mean hypotension

minutes of HPI arm study subject is smaller than the number of control group study subject, the null hypothesis is rejected. By this interim analysis result, the study team will make a decision whether stop the clinical study or continue until the maximum study subjects are enrolled and the study is completed.

8.2. Primary Safety Endpoint

The safety endpoint will be analyzed using the modified Intent-to-Treat population (mITT population) as defined in Section 3.

Serious adverse events through 30 days as indicated below:

- Serious intraoperative and post-operative complications between each cohort
- Device-related serious adverse events (SAEs)

8.2.1. Primary Safety Endpoint Analysis

By the occurrence or proportion of the serious complication, and the serious adverse device event (ADE) among study subjects within each HPI arm, a two-sample t-test for proportions will be used for the statistical comparison.

$$t = \frac{\widehat{p_1} - \widehat{p_0}}{\sqrt{\widehat{p_{pool}} * \left(1 - \widehat{p_{pool}}\right)\left(\frac{1}{n_1} + \frac{1}{n_0}\right)}}$$

Here $\widehat{p_1}$, $\widehat{p_0}$ are the complication, and serious ADE occurrence proportion as the estimates of population occurrence probability of HPI arm ($\widehat{p_1} = \frac{x_1}{n_1}$) and control group ($\widehat{p_0} = \frac{x_0}{n_0}$) respectively, $\widehat{p_{pool}}$ is the pooled event occurrence probability derived with following algorithm $\widehat{p_{pool}} = \frac{x_0 + x_1}{n_0 + n_1}$, n_1, n_0 is the final valid subjects in HPI arm and control group respectively, x_1, x_0 is the events (AE) recorded in study subjects of HPI arm and control group respectively. If the p value from this analysis is less than 0.025 and the proportion difference in t statistic calculation is negative, it is the expected result. Following conclusion will be drawn that the application of HPI software system can statistically decrease the complications and SAE occurrence.

8.3. Multiplicity Adjustment

The family-wise Type I error rate between the primary efficacy and safety endpoints will be controlled using a hierarchical gatekeeping method. If the primary efficacy endpoint is not passed, then the safety endpoints will not be tested either. If the primary endpoint is passed, then the secondary endpoints will be tested using a one-sided α at the same level as the primary endpoint.

8.4. Secondary Endpoints

The following secondary endpoints will be calculated.

8.4.1. Additional Definitions of Hypotension

For each of the following definitions of hypotension, the time weighted average (TWA) of MAP or the mean duration will be calculated for each arm and the difference between the two arms. A 95% confidence interval will be calculated using the t-distribution. These additional definitions of hypotension will be calculated for the FAS population.

- Time Weighted Average (TWA) of MAP < 65 mmHg in the OR Period (T1)
- TWA of MAP<65 mmHg in the CVICU Period (T2)
- TWA of MAP < 65 mmHg in the CVICU Period, pre extubation (T3)
- TWA of MAP < 65 mmHg in the CVICU Period, post extubation (T4)
- Mean duration in minutes of MAP < 65 mmHg in the time periods of T1, T2, T3 and T4
- Mean duration in minutes of MAP < 60 mmHg in the time periods of T1, T2, T3 and T4
- Mean duration in minutes of MAP < 55 mmHg in the time periods of T1, T2, T3 and T4
- Mean duration in minutes of MAP < 50 mmHg in the time periods of T1, T2, T3 and T4

8.4.2. Clinical Endpoints

The following clinical endpoints will be analyzed. The clinical endpoints will be analyzed on the mITT population.

- Acute kidney injury (AKI), as defined by the modified KDIGO criteria, overall and by stage 1, 2 and 3
- Neurocognitive deficit, as evaluated by the MMSE, CAM-ICU 7, and bCAM assessments. [bCAM will be used for delirium screening for patients who are deemed ready for transfer to the floor per ICU attending team's assessment, even if they are physically in the ICU]
- Periprocedural Myocardial injury, measured with high-sensitivity Troponin I and defined by a threshold of 70 times the upper reference limit or >1400 pg/ml

For each of the clinical endpoints, the rate in each arm and the difference in the rates for the arms will be presented.

8.5. Subgroup Analyses

Subgroup analyses will be performed for the primary effectiveness, the primary safety, and the secondary endpoints. For each subgroup, the appropriate summary statistics will be presented for each arm individually and for the difference between the two arms. Where appropriate, a 95% confidence interval for the difference may also be presented. Subgroups will include but not limited to:

- Subgroup age stratification
- Subgroup gender
- Subgroup race (white versus non-white)

These subgroup analyses are not powered and no formal hypothesis testing will be performed.

8.6. Exploratory Analyses

The following exploratory analyses will be performed. These analyses will be presented for the FAS population.

- Protocol adherence to HPI alert, as defined by >50% HPI alerts with documented intervention per the suggested treatment algorithm within a 5-minute timeframe

For each subject, it is likely that there will be several decisions necessary. Each decision will be made separately, and the overall rate of compliance will be calculated.

A full definition of the compliance algorithm, can be found in section 12.2.

- Difference in time spent in hypertension defined as TWA of MAP>110, >120 and >130 mmHg post-cardiopulmonary bypass CPB) through the first 8-hour ICU period as compared with the control group.

The time spent in hypertension will be calculated in a similar manner to the primary endpoint. The only difference will be that we are looking for the amount of time above the hypertension thresholds instead of below it. The average time will be calculated by arm and the difference will also be presented.

- In-hospital mortality rate

The mortality rate will be calculated as a simple proportion for each arm and for the difference between the two arms.

- Incidence of cerebral desaturations defined as total time below 10% relative to baseline NIRS values.

For each subject, the baseline NIRS value will be established at The time below 10%

- Percent of monitoring time with CO or CI within 10% relative to pre-induction baseline

The baseline CO and CI will be calculated pre-induction. The percent of the monitoring time within 10% of the baseline value will be calculated and presented by and for the difference between the arms.

- Hospital Length of Stay (days)

The hospital length of stay will be calculated starting with the procedure time until the subject is discharged. LoS will be calculated and presented by and for the difference between the arms.

- ICU Length of Stay (hours)
- Time to extubation (hours)

The time to extubation will be calculated as the amount of time from intubation until extubation. The average time will be presented by arm and the difference will also be presented.

- New onset atrial fibrillation, detected prior to ICU discharge

The proportion of patients with new onset afib will be presented by arm and the difference between the two arms.

9. ANALYSIS OF SAFETY

9.1. Deaths

All deaths that occur for subjects during the study will be presented as the incidence rate and the relationship with the study device and the procedure. Deaths will be summarized for the mITT population by arm.

9.2. Adverse Events

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).

An adverse device effect (ADE) is defined as an AE related to the use of the medical devices in this trial. 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. 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. A serious adverse device effect (SADE) is an ADE that has resulted in any of the consequences or characteristics of a SAE.

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.

All ADEs, SAEs, SADEs, and UADEs reported for this study will be summarized overall and for events occurring by timepoint (overall, day 0, and days 1-30 days). Only events with onset on or after the procedure date (Day 0) will be summarized in tables. All events that occur before the procedure will be presented in corresponding data listings. These events will be analyzed on the mITT population.
Summaries of incidence rates (frequencies and percentages), severity (serious adverse event [SAE] or not), and relationship to procedure and/or device of individual events will be prepared where data is available and presented by arm.

9.3. Imputation for Missing Dates for Safety Events

Algorithms for imputing the missing dates of safety events are given below.

- If the year is unknown, then the date will be imputed using the procedure date
- If the month is unknown, then:
    - If the year matches the year of the procedure date, then impute the month and day using the procedure date
    - Otherwise, assign 'January'

- If the day is unknown, then:
  - If the month and year match the month and year of the procedure date, then impute the day using the procedure date
  - Otherwise, assign '01'

9.4. Risk Assessments

The safety data will be summarized for all subjects in the safety population (mITT). Safety will be assessed through summarizing adverse events and judging the compliance with study treatment. The frequency and percentage of AEs and SAEs will be reported in summary tables by treatment group. Safety data will not be subjected to any imputation and will be summarized on an observed case basis. Plots showing the incidence of AEs and SAEs and their relative risk (with 95% confidence interval) will also be produced.

10. CHANGES FROM PROTOCOL SPECIFIED ANALYSIS

The protocol calls for an additional analysis of the SOFA score. This score was not collected in the electronic data capture (EDC) system, so it will not be reported.

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12. APPENDIX

12.1. Algorithm to Derive Primary Effectiveness Endpoint

The primary effectiveness endpoint of this study is the number of minutes of the intraoperative hypotension instance which is defined as a mean arterial pressure (MAP) below 65 for at least one minute experienced by patients in the cardiac operating room (OR) post-CPB and the cardiovascular intensive care unit (CVICU) up to first 8 hours for patients undergoing cardiac surgery requiring cardiopulmonary bypass, which is calculated with following mathematical procedure.

12.1.1. Detecting the start time and end time of hypotension instance.

The monitoring platform usually samples the cardiac parameters in 20 second intervals. There are rare, sampled measurements that MAPs are exact 65 mmHg for which marks the start time and end time of the hypotension instance. For majority of hypotension instances, the start time point and the end time point with MAP=65 need to be calculated by the consecutive two MAP measurements, one with MAP<65 and one with MAP>65 (intersection point A and B illustrated in Figure 1).

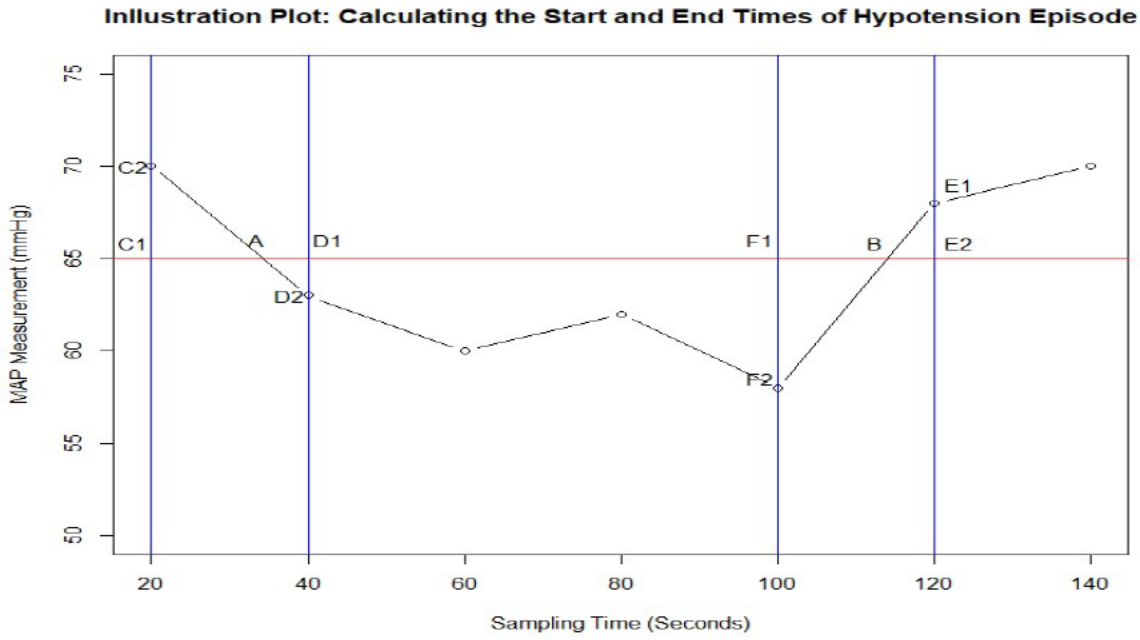

Figure 1. An illustration plot of hypotension instance start time and end time calculation

In Figure 1, the duration (the number of minutes) of this hypotension instance is calculated through $\frac{t_B - t_A}{60}$. t_A, t_B is the time corresponding the point $A, and\ B$ in the plot respectively, which is the intersection point of the line segment of MAP=65 with the line segment from a measurement point with MAP>65 to a point with MAP<65 (instance starting point A), the intersection point of the line segment of MAP=65 with the line segment from a measurement point with MAP<65 to a point with MAP>65 (ending point B). By linear interpolation method or similarity of two right angle triangles, have:

$$t_A = 20 + \overline{C1A} = 20 + 20 \cdot \frac{\overline{C2C1}}{\overline{C2C1} + \overline{D2D1}} = 20 * (1 + \frac{MAP_{C2} - 65}{MAP_{C2} - MAP_{D2}})$$

$$t_B = 100 + \overline{F2B} = 100 + 20 \cdot \frac{\overline{F2F1}}{\overline{F2F1} + \overline{E2E1}} = 100 + 20 \cdot \frac{65 - MAP_{F2}}{MAP_{E1} - MAP_{F2}}$$

Here MAP_{C2} is the MAP value corresponding to the measurement point with time=20 seconds, $MAP_{D2}$is the MAP value corresponding to the measurement point with time=40 seconds, $MAP_{F2}, MAP_{E1}$is the MAP value corresponding to the measurement point with time=100 and 120 seconds respectively.

12.1.2. Calculating the duration of hypotension instance

Hypotension duration for this instance is time at point B minus time at point A.

$$Instance\ duration = (t_B - t_A)/60 = (100 + 20 \cdot \frac{65 - MAP_{F2}}{MAP_{E1} - MAP_{F2}} - 20 - 20 \cdot \frac{MAP_{C2} - 65}{MAP_{C2} - MAP_{D2}})/60$$
$$= (80 + 20 \cdot (\frac{65 - MAP_{F2}}{MAP_{E1} - MAP_{F2}} - \frac{MAP_{C2} - 65}{MAP_{C2} - MAP_{D2}}))/60$$

If $Instance\ duration \geq 1$ minutes, it is a hypotension instance counted in subject total hypotension duration calculation.

12.1.3. Calculating subject total hypotension duration

$$Total\ hypotension\ duration\ (Subject) = \sum_{i=1}^{n} ith\ hypotension\ instance\ duration$$

Here n is the hypotension instances, if $n = 0$, then this subject's hypotension duration is 0.

12.1.4. Calculating AUC of each hypotension instance, and subject AUC, the additional endpoint

With following trapezoid equation, the AUC (minute*mmHg) for a hypotension instance is calculated.

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

Here i is the index for consecutive observations, $MAP = 65$ for the start and end points of this hypotension instance, MAP_i, MAP_{i+1} is the MAP value (≤ 65) at i, i+1 measurement time respectively.

Subject AUC: $AUC = \sum_{j=1}^{n} AUC_j$

Here n is the total hypotension instances, if n=0 then subject $AUC = 0$.

12.1.5. Calculating Subject TWA, the additional endpoint

With the subject total AUC, TWA is calculated with following equation:

$$TWA = \frac{AUC}{l_m}$$

The unit of TWA is *mmHg*. Here l_m is the length of measurement of study subject in minutes,

$$l_m = last\ valid\ EV1000\ measure\ time - first\ valid\ EV1000\ measure\ time$$

IF $AUC = 0$, then $TWA = 0$ too. Usually l_m is less than surgery duration.

12.2. Algorithm to Derive Compliance

From the protocol, compliance to the study procedure is defined by the following algorithm:

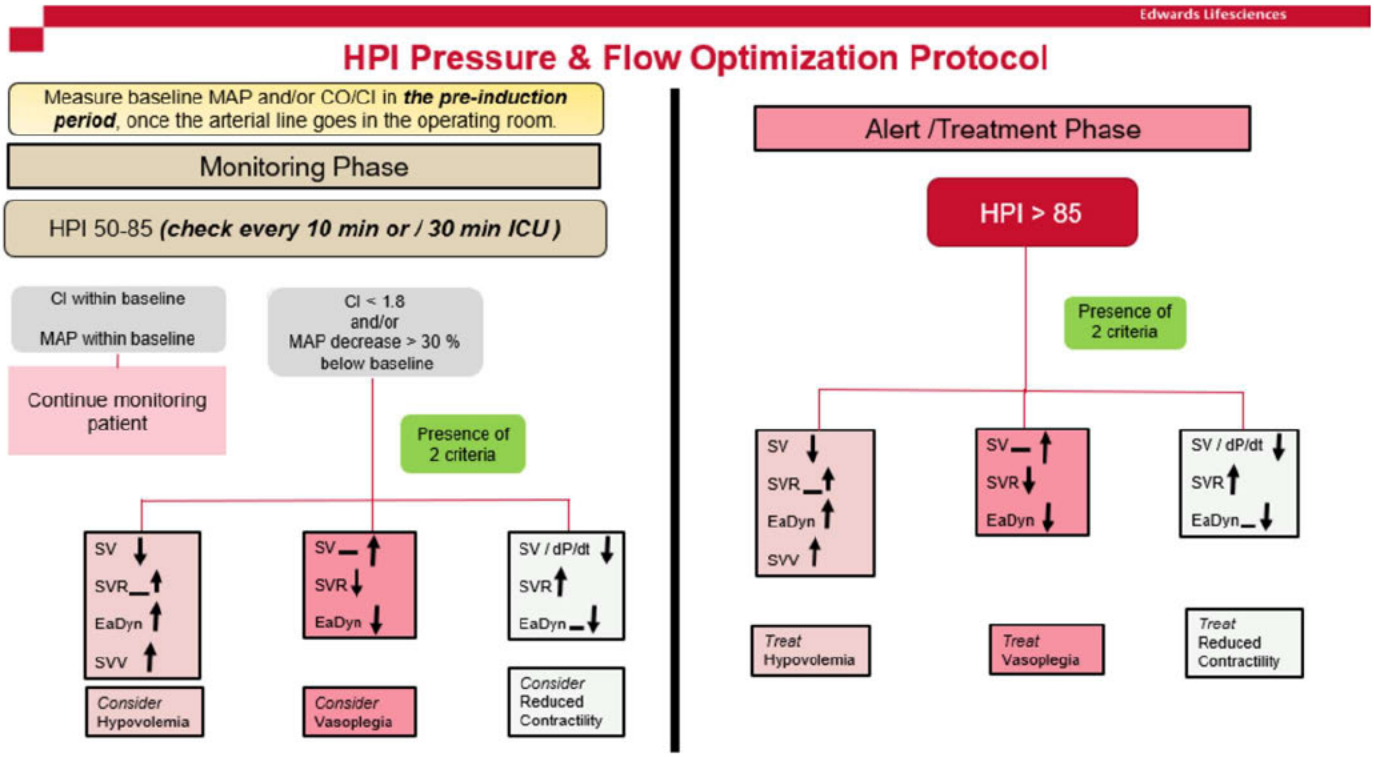

Figure 1: HPI Pressure and flow optimization protocol for HPI CARE.

Compliance is defined as

- Any event that lasts less than 2 minutes will be considered an artefact and will be considered a success
- Any event where an intervention occurred from the start time of the HPI alert until 5 minutes after the alert
- Any event where any recommended treatment was ongoing at the time of the start of the alert, with correct defined per the flow diagram
- Any event where any recommended treatment was concluded within 1 minute before the start of an alert. It is assumed that these interventions are in response to a rapidly increasing HPI value

Non-compliance is defined as all other events

- No intervention noted
- No Action, Patient Appears Stable
- Recommendation made (Fluids), provider declined per clinical judgment
- Recommendation made (Inotrope), provider declined per clinical judgment
- Recommendation made (Vasopressor), provider declined per clinical judgment
- If the incorrect treatment was given per the flow diagram

To determine whether the recommendation made matches the treatment given per the flow diagram, we will do as follows.

- Compare the values for SV, SVV, SVR, EaDyn, and dP/dt at the time the alert was triggered with the values recorded 3 minutes prior (now - prior). This will give us the change in each value. For each of these, we will use the table below to determine the recommended treatments:

SV	SVR	EaDyn	dp/dt	SVV		Give Fluids	Give Vasopressor	Give Inotrope
Down	Down	Down	Down	Down		No	Yes	Yes
Down	Down	Down	Down	Neutral		No	Yes	Yes
Down	Down	Down	Down	Up		Yes	Yes	Yes
Down	Down	Down	Neutral	Down		No	Yes	Yes
Down	Down	Down	Neutral	Neutral		No	Yes	Yes
Down	Down	Down	Neutral	Up		Yes	Yes	Yes
Down	Down	Down	Up	Down		No	Yes	Yes
Down	Down	Down	Up	Neutral		No	Yes	Yes
Down	Down	Down	Up	Up		Yes	Yes	Yes
Down	Down	Neutral	Down	Down		No	No	Yes
Down	Down	Neutral	Down	Neutral		No	No	Yes
Down	Down	Neutral	Down	Up		Yes	No	Yes
Down	Down	Neutral	Neutral	Down		No	No	Yes
Down	Down	Neutral	Neutral	Neutral		No	No	Yes
Down	Down	Neutral	Neutral	Up		Yes	No	Yes
Down	Down	Neutral	Up	Down		No	No	Yes
Down	Down	Neutral	Up	Neutral		No	No	Yes
Down	Down	Neutral	Up	Up		Yes	No	Yes
Down	Down	Up	Down	Down		Yes	No	No
Down	Down	Up	Down	Neutral		Yes	No	No
Down	Down	Up	Down	Up		Yes	No	No
Down	Down	Up	Neutral	Down		Yes	No	No
Down	Down	Up	Neutral	Neutral		Yes	No	No
Down	Down	Up	Neutral	Up		Yes	No	No
Down	Down	Up	Up	Down		Yes	No	No
Down	Down	Up	Up	Neutral		Yes	No	No
Down	Down	Up	Up	Up		Yes	No	No
Down	Neutral	Down	Down	Down		Yes	No	Yes
Down	Neutral	Down	Down	Neutral		Yes	No	Yes
Down	Neutral	Down	Down	Up		Yes	No	Yes
Down	Neutral	Down	Neutral	Down		Yes	No	Yes
Down	Neutral	Down	Neutral	Neutral		Yes	No	Yes
Down	Neutral	Down	Neutral	Up		Yes	No	Yes
Down	Neutral	Down	Up	Down		Yes	No	Yes
Down	Neutral	Down	Up	Neutral		Yes	No	Yes
Down	Neutral	Down	Up	Up		Yes	No	Yes
Down	Neutral	Neutral	Down	Down		Yes	No	Yes
Down	Neutral	Neutral	Down	Neutral		Yes	No	Yes

SV	SVR	EaDyn	dp/dt	SVV		Give Fluids	Give Vasopressor	Give Inotrope
Down	Neutral	Neutral	Down	Up		Yes	No	Yes
Down	Neutral	Neutral	Neutral	Down		Yes	No	Yes
Down	Neutral	Neutral	Neutral	Neutral		Yes	No	Yes
Down	Neutral	Neutral	Neutral	Up		Yes	No	Yes
Down	Neutral	Neutral	Up	Down		Yes	No	Yes
Down	Neutral	Neutral	Up	Neutral		Yes	No	Yes
Down	Neutral	Neutral	Up	Up		Yes	No	Yes
Down	Neutral	Up	Down	Down		Yes	No	No
Down	Neutral	Up	Down	Neutral		Yes	No	No
Down	Neutral	Up	Down	Up		Yes	No	No
Down	Neutral	Up	Neutral	Down		Yes	No	No
Down	Neutral	Up	Neutral	Neutral		Yes	No	No
Down	Neutral	Up	Neutral	Up		Yes	No	No
Down	Neutral	Up	Up	Down		Yes	No	No
Down	Neutral	Up	Up	Neutral		Yes	No	No
Down	Neutral	Up	Up	Up		Yes	No	No
Down	Up	Down	Down	Down		Yes	No	Yes
Down	Up	Down	Down	Neutral		Yes	No	Yes
Down	Up	Down	Down	Up		Yes	No	Yes
Down	Up	Down	Neutral	Down		Yes	No	Yes
Down	Up	Down	Neutral	Neutral		Yes	No	Yes
Down	Up	Down	Neutral	Up		Yes	No	Yes
Down	Up	Down	Up	Down		Yes	No	Yes
Down	Up	Down	Up	Neutral		Yes	No	Yes
Down	Up	Down	Up	Up		Yes	No	Yes
Down	Up	Neutral	Down	Down		Yes	No	Yes
Down	Up	Neutral	Down	Neutral		Yes	No	Yes
Down	Up	Neutral	Down	Up		Yes	No	Yes
Down	Up	Neutral	Neutral	Down		Yes	No	Yes
Down	Up	Neutral	Neutral	Neutral		Yes	No	Yes
Down	Up	Neutral	Neutral	Up		Yes	No	Yes
Down	Up	Neutral	Up	Down		Yes	No	Yes
Down	Up	Neutral	Up	Neutral		Yes	No	Yes
Down	Up	Neutral	Up	Up		Yes	No	Yes
Down	Up	Up	Down	Down		Yes	No	Yes
Down	Up	Up	Down	Neutral		Yes	No	Yes
Down	Up	Up	Down	Up		Yes	No	Yes
Down	Up	Up	Neutral	Down		Yes	No	Yes

SV	SVR	EaDyn	dp/dt	SVV		Give Fluids	Give Vasopressor	Give Inotrope
Down	Up	Up	Neutral	Neutral		Yes	No	Yes
Down	Up	Up	Neutral	Up		Yes	No	Yes
Down	Up	Up	Up	Down		Yes	No	Yes
Down	Up	Up	Up	Neutral		Yes	No	Yes
Down	Up	Up	Up	Up		Yes	No	Yes
Neutral	Down	Down	Down	Down		No	Yes	Yes
Neutral	Down	Down	Down	Neutral		No	Yes	Yes
Neutral	Down	Down	Down	Up		No	Yes	Yes
Neutral	Down	Down	Neutral	Down		No	Yes	No
Neutral	Down	Down	Neutral	Neutral		No	Yes	No
Neutral	Down	Down	Neutral	Up		No	Yes	No
Neutral	Down	Down	Up	Down		No	Yes	No
Neutral	Down	Down	Up	Neutral		No	Yes	No
Neutral	Down	Down	Up	Up		No	Yes	No
Neutral	Down	Neutral	Down	Down		No	Yes	Yes
Neutral	Down	Neutral	Down	Neutral		No	Yes	Yes
Neutral	Down	Neutral	Down	Up		No	Yes	Yes
Neutral	Down	Neutral	Neutral	Down		No	Yes	No
Neutral	Down	Neutral	Neutral	Neutral		No	Yes	No
Neutral	Down	Neutral	Neutral	Up		No	Yes	No
Neutral	Down	Neutral	Up	Down		No	Yes	No
Neutral	Down	Neutral	Up	Neutral		No	Yes	No
Neutral	Down	Neutral	Up	Up		No	Yes	No
Neutral	Down	Up	Down	Down		No	Yes	No
Neutral	Down	Up	Down	Neutral		No	Yes	No
Neutral	Down	Up	Down	Up		Yes	Yes	No
Neutral	Down	Up	Neutral	Down		No	Yes	No
Neutral	Down	Up	Neutral	Neutral		No	Yes	No
Neutral	Down	Up	Neutral	Up		Yes	Yes	No
Neutral	Down	Up	Up	Down		No	Yes	No
Neutral	Down	Up	Up	Neutral		No	Yes	No
Neutral	Down	Up	Up	Up		Yes	Yes	No
Neutral	Neutral	Down	Down	Down		No	Yes	Yes
Neutral	Neutral	Down	Down	Neutral		No	Yes	Yes
Neutral	Neutral	Down	Down	Up		Yes	Yes	Yes
Neutral	Neutral	Down	Neutral	Down		No	Yes	No
Neutral	Neutral	Down	Neutral	Neutral		No	Yes	No
Neutral	Neutral	Down	Neutral	Up		Yes	Yes	No

SV	SVR	EaDyn	dp/dt	SVV		Give Fluids	Give Vasopressor	Give Inotrope
Neutral	Neutral	Down	Up	Down		No	Yes	No
Neutral	Neutral	Down	Up	Neutral		No	Yes	No
Neutral	Neutral	Down	Up	Up		Yes	Yes	No
Neutral	Neutral	Neutral	Down	Down		No	No	Yes
Neutral	Neutral	Neutral	Down	Neutral		No	No	Yes
Neutral	Neutral	Neutral	Down	Up		Yes	No	Yes
Neutral	Neutral	Neutral	Neutral	Down		No	No	No
Neutral	Neutral	Neutral	Neutral	Neutral		No	No	No
Neutral	Neutral	Neutral	Neutral	Up		Yes	No	No
Neutral	Neutral	Neutral	Up	Down		No	No	No
Neutral	Neutral	Neutral	Up	Neutral		No	No	No
Neutral	Neutral	Neutral	Up	Up		Yes	No	No
Neutral	Neutral	Up	Down	Down		Yes	No	No
Neutral	Neutral	Up	Down	Neutral		Yes	No	No
Neutral	Neutral	Up	Down	Up		Yes	No	No
Neutral	Neutral	Up	Neutral	Down		Yes	No	No
Neutral	Neutral	Up	Neutral	Neutral		Yes	No	No
Neutral	Neutral	Up	Neutral	Up		Yes	No	No
Neutral	Neutral	Up	Up	Down		Yes	No	No
Neutral	Neutral	Up	Up	Neutral		Yes	No	No
Neutral	Neutral	Up	Up	Up		Yes	No	No
Neutral	Up	Down	Down	Down		No	Yes	Yes
Neutral	Up	Down	Down	Neutral		No	Yes	Yes
Neutral	Up	Down	Down	Up		Yes	Yes	Yes
Neutral	Up	Down	Neutral	Down		No	Yes	Yes
Neutral	Up	Down	Neutral	Neutral		No	Yes	Yes
Neutral	Up	Down	Neutral	Up		Yes	Yes	Yes
Neutral	Up	Down	Up	Down		No	Yes	Yes
Neutral	Up	Down	Up	Neutral		No	Yes	Yes
Neutral	Up	Down	Up	Up		Yes	Yes	Yes
Neutral	Up	Neutral	Down	Down		No	No	Yes
Neutral	Up	Neutral	Down	Neutral		No	No	Yes
Neutral	Up	Neutral	Down	Up		Yes	No	Yes
Neutral	Up	Neutral	Neutral	Down		No	No	Yes
Neutral	Up	Neutral	Neutral	Neutral		No	No	Yes
Neutral	Up	Neutral	Neutral	Up		Yes	No	Yes
Neutral	Up	Neutral	Up	Down		No	No	Yes
Neutral	Up	Neutral	Up	Neutral		No	No	Yes

SV	SVR	EaDyn	dp/dt	SVV		Give Fluids	Give Vasopressor	Give Inotrope
Neutral	Up	Neutral	Up	Up		Yes	No	Yes
Neutral	Up	Up	Down	Down		Yes	No	Yes
Neutral	Up	Up	Down	Neutral		Yes	No	Yes
Neutral	Up	Up	Down	Up		Yes	No	Yes
Neutral	Up	Up	Neutral	Down		Yes	No	No
Neutral	Up	Up	Neutral	Neutral		Yes	No	No
Neutral	Up	Up	Neutral	Up		Yes	No	No
Neutral	Up	Up	Up	Down		Yes	No	No
Neutral	Up	Up	Up	Neutral		Yes	No	No
Neutral	Up	Up	Up	Up		Yes	No	No
Up	Down	Down	Down	Down		No	Yes	Yes
Up	Down	Down	Down	Neutral		No	Yes	Yes
Up	Down	Down	Down	Up		No	Yes	Yes
Up	Down	Down	Neutral	Down		No	Yes	No
Up	Down	Down	Neutral	Neutral		No	Yes	No
Up	Down	Down	Neutral	Up		No	Yes	No
Up	Down	Down	Up	Down		No	Yes	No
Up	Down	Down	Up	Neutral		No	Yes	No
Up	Down	Down	Up	Up		No	Yes	No
Up	Down	Neutral	Down	Down		No	Yes	Yes
Up	Down	Neutral	Down	Neutral		No	Yes	Yes
Up	Down	Neutral	Down	Up		No	Yes	Yes
Up	Down	Neutral	Neutral	Down		No	Yes	No
Up	Down	Neutral	Neutral	Neutral		No	Yes	No
Up	Down	Neutral	Neutral	Up		No	Yes	No
Up	Down	Neutral	Up	Down		No	Yes	No
Up	Down	Neutral	Up	Neutral		No	Yes	No
Up	Down	Neutral	Up	Up		No	Yes	No
Up	Down	Up	Down	Down		No	Yes	No
Up	Down	Up	Down	Neutral		No	Yes	No
Up	Down	Up	Down	Up		Yes	Yes	No
Up	Down	Up	Neutral	Down		No	Yes	No
Up	Down	Up	Neutral	Neutral		No	Yes	No
Up	Down	Up	Neutral	Up		Yes	Yes	No
Up	Down	Up	Up	Down		No	Yes	No
Up	Down	Up	Up	Neutral		No	Yes	No
Up	Down	Up	Up	Up		Yes	Yes	No
Up	Neutral	Down	Down	Down		No	Yes	Yes

SV	SVR	EaDyn	dp/dt	SVV		Give Fluids	Give Vasopressor	Give Inotrope
Up	Neutral	Down	Down	Neutral		No	Yes	Yes
Up	Neutral	Down	Down	Up		Yes	Yes	Yes
Up	Neutral	Down	Neutral	Down		No	Yes	No
Up	Neutral	Down	Neutral	Neutral		No	Yes	No
Up	Neutral	Down	Neutral	Up		Yes	Yes	No
Up	Neutral	Down	Up	Down		No	Yes	No
Up	Neutral	Down	Up	Neutral		No	Yes	No
Up	Neutral	Down	Up	Up		Yes	Yes	No
Up	Neutral	Neutral	Down	Down		No	No	Yes
Up	Neutral	Neutral	Down	Neutral		No	No	Yes
Up	Neutral	Neutral	Down	Up		Yes	No	Yes
Up	Neutral	Neutral	Neutral	Down		No	No	No
Up	Neutral	Neutral	Neutral	Neutral		No	No	No
Up	Neutral	Neutral	Neutral	Up		Yes	No	No
Up	Neutral	Neutral	Up	Down		No	No	No
Up	Neutral	Neutral	Up	Neutral		No	No	No
Up	Neutral	Neutral	Up	Up		Yes	No	No
Up	Neutral	Up	Down	Down		Yes	No	No
Up	Neutral	Up	Down	Neutral		Yes	No	No
Up	Neutral	Up	Down	Up		Yes	No	No
Up	Neutral	Up	Neutral	Down		Yes	No	No
Up	Neutral	Up	Neutral	Neutral		Yes	No	No
Up	Neutral	Up	Neutral	Up		Yes	No	No
Up	Neutral	Up	Up	Down		Yes	No	No
Up	Neutral	Up	Up	Neutral		Yes	No	No
Up	Neutral	Up	Up	Up		Yes	No	No
Up	Up	Down	Down	Down		No	Yes	Yes
Up	Up	Down	Down	Neutral		No	Yes	Yes
Up	Up	Down	Down	Up		Yes	Yes	Yes
Up	Up	Down	Neutral	Down		No	Yes	Yes
Up	Up	Down	Neutral	Neutral		No	Yes	Yes
Up	Up	Down	Neutral	Up		Yes	Yes	Yes
Up	Up	Down	Up	Down		No	Yes	Yes
Up	Up	Down	Up	Neutral		No	Yes	Yes
Up	Up	Down	Up	Up		Yes	Yes	Yes
Up	Up	Neutral	Down	Down		No	No	Yes
Up	Up	Neutral	Down	Neutral		No	No	Yes
Up	Up	Neutral	Down	Up		Yes	No	Yes

SV	SVR	EaDyn	dp/dt	SVV		Give Fluids	Give Vasopressor	Give Inotrope
Up	Up	Neutral	Neutral	Down		No	No	Yes
Up	Up	Neutral	Neutral	Neutral		No	No	Yes
Up	Up	Neutral	Neutral	Up		Yes	No	Yes
Up	Up	Neutral	Up	Down		No	No	Yes
Up	Up	Neutral	Up	Neutral		No	No	Yes
Up	Up	Neutral	Up	Up		Yes	No	Yes
Up	Up	Up	Down	Down		Yes	No	Yes
Up	Up	Up	Down	Neutral		Yes	No	Yes
Up	Up	Up	Down	Up		Yes	No	Yes
Up	Up	Up	Neutral	Down		Yes	No	No
Up	Up	Up	Neutral	Neutral		Yes	No	No
Up	Up	Up	Neutral	Up		Yes	No	No
Up	Up	Up	Up	Down		Yes	No	No
Up	Up	Up	Up	Neutral		Yes	No	No
Up	Up	Up	Up	Up		Yes	No	No

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

Yes	Name of Reviewer:	No	Reason Peer Review not Needed:
☐		X	The original SAP was peer reviewed and most of the changes to this version are to bring it in line with the latest protocol. No substantial changes to statistical methodology were made.