NCT04465370

Pediatric Cardiac **O**utput Monitorin**G** **O**bservational **Study**

(**POGO Study**) **A Prospective, Single-Arm, Nonrandomized, Observational Study of Cardiac Output Monitoring in Pediatric Patients**

Clinical Trial Protocol and Statistical Analysis Plan

Clinical Trial Protocol version: November 20, 2022
Statistical Analysis Plan version: December 2, 2020

Pediatric Cardiac **O**utput Monitorin**G** **O**bservational **Study** (**POGO Study**)

A Prospective, Single-Arm, Nonrandomized, Observational Study of Cardiac Output Monitoring in Pediatric Patients

Clinical Study Protocol
Study Number: 2019-08
IDE Number: G190308

Revision: E
Date: November 20, 2020

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Revision B Change Summary

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

Section (Page)	Change and Reason for Change
Synopsis & Study Design (7 & 17)	Updated number of sites to up to 5 Reason: To meet enrollment goal within 12 months of commencement
Schedule of Events & Procedures (26)	Removed reference of thermodilutions analyses Reason: SAP provides details of analysis
Independent Safety Committees (36)	Clarified the structure of the DSMB meetings Reason: To ensure it is clear that efforts to mitigate operational bias are in place

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, Study Objective & Statistical Methods (8, 16 & 22)	Limited secondary effectiveness endpoint to a single focus on CO, as determined by the Critchley and Critchley method of percent error calculation. Also added exploratory analyses comparisons of CI, as determined by the Critchley and Critchley method of percent error calculation and CI as determined by the Bland-Altman method of bias. Reason: To align with revised statistical analysis plan
Data Safety Monitoring Board (37)	Updated to indicate DSMB's role in study oversight Reason: Clarified that DSMB will solely evaluate study safety and base its recommendation to continue the study on this assessment. There is no planned interim analysis, thus DSMB will not assess effectiveness.

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Revision D Change Summary

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Section (Page)	Change and Reason for Change
Synopsis, Subject Selection and Withdrawal (8, 19)	Edited inclusion criteria #4 to read "For those Subjects who have had a cardiac transplant, Subjects must be at least two weeks post cardiac transplantation." Reason: To qualify and better clarify that pre-transplant cardiac catherization evaluations are allowable. For only those Subjects who have undergone cardiac transplantation, those Subjects will need to wait at least 2 weeks after the transplant to be eligible for the study.

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, Subject Selection and Withdrawal (8, 19)	Edited exclusion criteria to include the following additional exclusions: 6. Documented ≥ moderate pulmonary hypertension (PAPm > 25 mmHg, PVRI > 3.0 WUxm2) 7. Presence of intracardiac shunting (i.e., ASD, VSD) 8. Aorto-pulmonary collaterals 9. ≥ Moderate tricuspid regurgitation, per echocardiogram criteria 10. > Moderate Aortic or pulmonary regurgitation, per echocardiogram criteria 11. Persistent cardiac arrythmias during the cardiac catheterization period (> 3min) 12. Vascular abnormalities of the arterial system (i.e., connective tissue disorders, mid-aortic syndrome) Reason: Additional clarity to ensure intended exclusion of patients whose pathophysiologic state may result in intermittent and/or prolonged states in which the cardiac output from the right side of the heart may differ from the cardiac output from the left side of the heart.

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INVESTIGATOR'S SIGNATURE PAGE

This study will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and 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 Study team responsible to me who participate in the Study. I will discuss this material with them to ensure that all participating personnel at the Study 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.

I will conduct the study 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 study and make them available as requested during monitoring visits. I will maintain device accountability records and will supervise the used 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 study outcomes under my supervision.

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

Investigator's Signature	Date
Investigator's Printed Name	
Study Site Name	

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SYNOPSIS

Title:	**P**ediatric Cardiac **O**utput Monitorin**G** **O**bservational **Study**
Short Title:	**POGO Study**
Study Objective:	The primary objective of the study is to assess Cardiac Output Monitoring in pediatric subjects by comparing FloTrac and ClearSight system to intermittent thermodilution Swan-Ganz, in order to expand the indications of FloTrac, ClearSight and Swan-Ganz thermodilution pulmonary artery catheter to the pediatric population 12 to 18 years of age.
Study Devices:	HemoSphere advanced monitoring platform, intermittent thermodilution Swan-Ganz, FloTrac, ClearSight system, ForeSight Elite sensors
Overall Design:	A prospective, single-arm, nonrandomized, observational study to assess the cardiac output (CO) monitoring methods in pediatric subjects.
Study Population:	Up to 108 eligible Subjects in a single arm Males and Females, 12 to 18 years of age at the time of screening.
Number of Sites:	Up to five (5) U.S. sites
Study Duration:	Total of 9 to 12 months
Participation Duration:	Screening/Baseline; Procedure; 30-day Telephone Follow-Up Visit
Inclusion/ Exclusion Criteria:	**Inclusion Criteria** 1. Subjects who are 12 to 18 years of age 2. Subjects who have signed the Informed Consent Form 3. Subjects who are projected to receive Swan-Ganz catheter as part of procedure/standard of care with intermittent cardiac output measures 4. For those Subjects who have had a cardiac transplant, Subjects must be at least two weeks post cardiac transplantation 5. Subjects with planned pressure monitoring with an arterial line **Exclusion Criteria** 1. Subjects with contraindications for Pulmonary Artery Catheters Placement and monitoring (recurrent sepsis, or with hypercoagulopathy); 2. Subjects with contraindications for Arterial Line Placement; 3. Subjects with an extreme contraction of the smooth muscle in the arteries and arterioles in the lower arm and hand (i.e., Raynaud's Disease). 4. Subjects with a physical site area too limited for proper Sensor placement 5. Subjects with finger size less than the smallest finger cuff size

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	6. Documented ≥ moderate pulmonary hypertension (PAPm > 25mmHg, PVRI > 3.0 WUxm2) 7. Presence of intracardiac shunting (i.e., ASD, VSD) 8. Aorto-pulmonary collaterals 9. ≥ Moderate tricuspid regurgitation, per echocardiogram criteria 10. > Moderate Aortic or pulmonary regurgitation, per echocardiogram criteria 11. Persistent cardiac arrythmias during the cardiac catheterization period (> 3min) 12. Vascular abnormalities of the arterial system (i.e., connective tissue disorders, mid-aortic syndrome)
Primary Effectiveness Endpoint:	Demonstrate that monitoring of cardiac output with Swan-Ganz, FloTrac, and ClearSight system is comparable as determined by the Bland-Altman method of bias.
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.
Secondary Effectiveness Endpoint:	Demonstrate that monitoring of cardiac output with Swan-Ganz, FloTrac, and ClearSight system is comparable as determined by the Critchley and Critchley method of percent error calculation.
Study Sponsor:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614 USA
Study Director:	[redacted]
Study Manager:	[redacted]

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1. INTRODUCTION

Background

In the critically ill, traditional vital signs may be late indicators of compromised or inadequate oxygen delivery to the tissues, potentially delaying intervention and putting the patient at greater risk. The ability to monitor blood oxygenation early is critical. The pursuit of measuring blood flow through the heart has resulted in the development of different techniques for its quantification. The three main methodologies to measure cardiac output are the Fick method, dye dilution, and thermodilution techniques [9]. The Fick method is the "gold standard" for cardiac output determinations in adults and is based on the principles developed by Adolph Fick in the 1870's. Fick's concept proposes that the uptake or release of a substance by an organ is the product of blood flow through that organ and the difference between the arterial and venous values of the same substance. The Fick principle reflects the extraction of oxygen through the systemic circulation and is dependent on arterial and pulmonary arterial oxygen levels, hemoglobin and the maximum amount of oxygen consumption by the body in a given period (VO2 max). Thus, the Fick principle involves the blood oxygenation process through the lungs and oxygen delivery to the tissues, where it is added and removed by a flow limited mechanism. By measuring the amount of oxygen carried by the blood, the total amount of blood needed to carry oxygen through the lungs could be calculated. This value then reflects the output of the heart [9].

An intermittent thermodilution method applies the Steward Hamilton indicator dilution principles, using temperature change as the indicator. A known amount of solution with a known temperature is injected into the right side of the circulation and continuously withdrawn and measured at a constant rate from the arterial side. This resultant curve is plotted against time and cardiac output is calculated using the Stewart-Hamilton Equation. This curve is similar to the one produced by the indicator dilution method. A modified Stewart-Hamilton equation is used to calculate the cardiac output, taking into consideration the change in temperature as the indicator. Modifications include the measured temperature of the injectate and the patient's blood temperature, along with the specific gravity of the solution injected [9].

Minimally invasive technologies have been developed to monitor CO. FloTrac is a minimally invasive solution for advanced hemodynamic monitoring that automatically calculates key flow parameters every 20 seconds. Continuous clarity provided by the FloTrac system offers proactive decision support to manage hemodynamic instability and ensure adequate perfusion. In addition to minimally invasive technologies, noninvasive technologies such as the ClearSight system offer proactive decision support to optimize perfusion. The ClearSight system provides advanced hemodynamic parameters and continuous noninvasive blood pressure (BP) from a finger cuff and extends the benefits of continuous hemodynamic monitoring to a broad patient population, including patients in whom an arterial line would not typically be placed [10].

The Swan-Ganz pulmonary artery catheter (PAC) is considered the gold standard to validate new CO monitoring devices. The Swan-Ganz PAC consists of an intravenous device placed in the pulmonary artery allowing measurement of cardiac output, pulmonary artery pressures [1] as well as cardiac filling pressures. Since its initial presentation by Swan in 1970 [2], several modifications were made on the initial catheter that allowed for intermittent monitoring of cardiac output, stroke volume (SV), systemic vascular resistance (SVR) and mixed venous saturation (SvO_2) [1,3]. Technology for cardiac output (CO) and blood volume measurements has been developed using existing central venous and peripheral arterial catheters (PAC), such that

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transcardiopulmonary thermodilution of blood with a small saline bolus is detected with ultrasound sensors attached to an extracorporeal arteriovenous loop [4].

There is an unmet need in the pediatric population, as there are currently no clinically practical, accurate or precise methods for measuring cardiac output (CO). During his research in 1920, Alfred Blalock, M.D., a pioneer of pediatric congenital cardiac surgery found that "the repeated removal of blood is usually associated with a decline in the cardiac output from 30 to 50% below the normal level before a marked diminution in the mean blood pressure occurs" [4,5]. Even though it has been nearly 100 years since Dr. Blalock demonstrated the importance of cardiac output in global cardiovascular circulation, even with its shortcomings, blood pressure remains the gold standard for hemodynamic monitoring of cardiovascular function in critically ill pediatric patients [6]. Cardiac output is measured very rarely in the pediatric population; however, it is vital for oxygen delivery. In this population, the methods used for cardiac output monitoring continue to be a poor surrogate, not validated or inaccurate. Cardiac output measurement is an essential part of hemodynamic monitoring and management of all critically ill patients, including pediatric patients of all ages and sizes [7].

The primary objective of the study is to assess Cardiac Output Monitoring in pediatric subjects by comparing FloTrac, ClearSight system to intermittent thermodilution Swan-Ganz, in order to expand the indications of FloTrac, ClearSight and Swan-Ganz thermodilution pulmonary artery catheter to the pediatric population 12 to 18 years of age. The study population will be children ages 12 to 18 who are at least 2 weeks post cardiac transplant.

The ForeSight Elite sensors, which are cleared for pediatric use, will be used in this study with the HemoSphere advanced monitoring platform to collect additional data on tissue oximetry. The ForeSight Elite Sensors provide the benefit of continually monitoring oxygen saturation of tissue with accuracy and precision.

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2. MEDICAL DEVICES

Device Names

- HemoSphere Advanced Monitoring Platform (including ClearSight Module)
- Swan-Ganz thermodilution pulmonary artery catheter
- FloTrac Sensor
- ClearSight System (includes pressure controller/wrist unit, Heart Reference Sensor and finger cuff)
- ForeSight Elite Sensors (commercially available in adults and pediatric populations)

Device Descriptions, Contraindications and Intended Uses

Swan-Ganz Technology

Description

The Swan-Ganz thermodilution catheters provide diagnostic information to rapidly determine hemodynamic pressures and cardiac output when used with a compatible cardiac output computer. The Swan-Ganz technology will be used for the intermittent cardiac output measurements. There will be two sets of four repeated intermittent cardiac output measurements.

- Swan Ganz Thermodilution Catheters: K160084 cleared in adults. Devices are investigational in pediatric population.

Swan-Ganz Thermodilution Pulmonary Artery Catheter Cleared Indications

The Swan-Ganz thermodilution catheters are indicated for the assessment of a patient's hemodynamic condition through direct intracardiac and pulmonary artery pressure monitoring, cardiac output determination, and for infusing solutions.

The distal (pulmonary artery) port also allows sampling of mixed venous blood for the assessment of oxygen transport balance and the calculation of derived parameters such as oxygen consumption, oxygen utilization coefficient, and intrapulmonary shunt fraction.

Swan-Ganz Thermodilution Pulmonary Artery Catheter Proposed Indications

Swan-Ganz thermodilution catheters are indicated for the assessment of a patient's hemodynamic condition through direct intracardiac and pulmonary artery pressure monitoring, cardiac output determination, and for infusing solutions.

The distal (pulmonary artery) port also allows sampling of mixed venous blood for the assessment of oxygen transport balance and the calculation of derived parameters such as oxygen consumption, oxygen utilization coefficient, and intrapulmonary shunt fraction. Indicated for use in adults and pediatric patients 12-18 years of age.

Contraindications

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No absolute contraindications to the use of flow-directed pulmonary artery catheters exist. However, a patient with a left bundle branch block may develop a right bundle branch block during catheter insertion, resulting in complete heart block.

HemoSphere Advanced Monitor with HemoSphere Swan-Ganz Module Cleared Indications
The HemoSphere advanced monitor when used with the HemoSphere Swan-Ganz module and Edwards Swan-Ganz catheters is indicated for use in adult and pediatric critical care patients requiring monitoring of cardiac output (continuous [CO] and intermittent [iCO]) and derived hemodynamic parameters in a hospital environment. It may be used for monitoring hemodynamic parameters in conjunction with a perioperative goal directed therapy protocol in a hospital environment.

The are no changes to the HemoSphere Advanced Monitor with HemoSphere Swan-Ganz Module since the specific patient population indications are provided as part of the Swan-Ganz catheter IFU (see below).

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

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

- FloTrac Sensors (classic): K152980 are cleared in adults. Devices are investigational in pediatric population.

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

FloTrac Sensor Proposed Indications
The FloTrac sensor is indicated for use in intravascular pressure monitoring. It is also indicated for use with the Edwards arterial pressure based cardiac output monitoring devices or hardware to measure cardiac output. Indicated for adult and pediatric patients 12-18 years of age.

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

The FloTrac Sensors are cleared for use with the HemoSphere Advanced Monitor with HemoSphere Pressure Cable (K180881).

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

The are no changes to the HemoSphere Advanced Monitor with HemoSphere Pressure Cable since the specific patient population indications are provided as part of the FloTrac sensor IFU (see below).

ClearSight Technology

Description
The ClearSight finger cuffs, when used with an appropriate Edwards monitoring system, provide continuous, noninvasive hemodynamic monitoring. The ClearSight finger cuffs utilize the volume-clamp method to measure blood pressure with an inflatable bladder wrapped around the middle phalanx of the finger. The cardiac output measurements from the ClearSight technology will be compared to the intermittent cardiac output measurements from the Swan-Ganz technology.

- ClearSight Finger Cuffs: K190130 are cleared in adults for use with EV1000NI. Investigational device for use with HemoSphere Advanced Monitoring Platform.

The ClearSight technology is not cleared in the US for use with the HemoSphere Advance Monitor Platform. The non-invasive ClearSight technology is currently available in the US on a different Edwards' platform (EV1000NI - K160552) but is investigational on the HemoSphere advanced monitor.

Contraindications
In some patients with extreme contraction of the smooth muscle in the arteries and arterioles in the lower arm and hand, such as may be present in patients with Raynaud's disease, blood pressure measurement can become impossible.

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HemoSphere Advanced Monitor with HemoSphere ClearSight Module Proposed Indications
The HemoSphere advanced monitor when used with the HemoSphere ClearSight module, pressure controller and a compatible Edwards finger cuff are indicated for adult patients over 18 years of age and pediatric patients 12-18 years of age in which the balance between cardiac function, fluid status and vascular resistance needs continuous assessment. It may be used for monitoring hemodynamic parameters in conjunction with a perioperative goal directed therapy protocol in a hospital environment. In addition, the noninvasive system is indicated for use in patients with co-morbidities for which hemodynamic optimization is desired and invasive measurements are difficult. The HemoSphere advanced monitor and compatible Edwards finger cuffs noninvasively measures blood pressure and associated hemodynamic parameters.

ClearSight Finger Cuff Proposed Indications
The ClearSight finger cuffs are indicated for adult patients over 18 years of age and pediatric patients 12-18 to noninvasively measure blood pressure and associated hemodynamic parameters when used with EV1000 clinical platform NI or HemoSphere advanced monitoring platform.

The HemoSphere Advanced Monitoring Platform is a multi-parameter, multi-technology, hemodynamic platform. The goal of this platform is to provide users with a single point in which they can utilize any of Edwards' hemodynamic disposables. The HemoSphere advanced monitoring platform is composed of a primary HemoSphere Monitor. The HemoSphere advance monitoring platform interfaces with external technology specific modalities in the form of modules or Smart-Cables. Each modality is designed to connect to a specific type of Edwards disposable product as discussed above, and interface to the HemoSphere Monitor via a digital interface. The commercially available HemoSphere Advanced Monitoring Platform is cleared for use with the disposables presented above.

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 (StO2).

- ForeSight Elite Sensors: K180003, in both pediatric and adult population on the HemoSphere Advanced Monitoring Platform (not seeking expansion, only included to obtain additional information under its current indications)

ForeSight Elite Sensors (Medium) Cleared Indications
When used in conjunction with the ForeSight Elite absolute tissue oximeter or FORE-SIGHT ELITE tissue oximetry module: The medium Sensor is indicated for monitoring of absolute regional hemoglobin oxygen saturation of blood under the sensor in individuals at risk for reduced flow or no-flow ischemic states. It is intended for use on pediatric subjects ≥ 3 kg.

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ForeSight Elite Sensors (Large) Cleared Indications

When used in conjunction with the FORE-SIGHT ELITE absolute tissue oximeter or FORE-SIGHT ELITE tissue oximetry module: The large Sensor is indicated for monitoring of absolute regional hemoglobin oxygen saturation of blood under the sensor in individuals at risk for reduced flow or no-flow ischemic states. It is intended for use on pediatric subjects ≥ 40 kg.

There are no proposed indications for ForeSight Elite technology since Edwards is not seeking indications expansion. It is included in the study only to obtain reference information under its currently cleared indications for pediatric patients.

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 associate risk of injury

The ForeSight sensors are cleared for use with the HemoSphere Advanced Monitor with HemoSphere Tissue Oximetry Module (K190205) in both pediatric and adult population on the HemoSphere Advanced Monitoring Platform (not seeking expansion, only included to obtain additional information under its current indications)

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 StO2 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.
- When used with medium sensors, the ForeSight Elite tissue oximeter module is indicated for use on pediatric subjects ≥3 kg.
- When used with small sensors, the ForeSight Elite tissue oximeter module is indicated for cerebral use on pediatric subjects <8 kg and non-cerebral use on pediatric subjects <5kg.

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 (SvO2 and ScvO2) 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.*

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3. STUDY OBJECTIVE

The primary objective of the study is to assess Cardiac Output Monitoring in pediatric subjects by comparing FloTrac, ClearSight and the Fick principle (using Swan Ganz) to intermittent thermodilution Swan-Ganz, in order to expand the indications of FloTrac, ClearSight and Swan-Ganz thermodilution pulmonary artery catheter to the pediatric population 12 to 18 years of age.

Study Endpoints

The primary effectiveness endpoint is to demonstrate that monitoring of cardiac output (CO) with Swan-Ganz, FloTrac, and ClearSight is comparable as determined by the Bland-Altman method of bias.

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

The secondary effectiveness endpoint is to demonstrate that monitoring of cardiac output (CO) with Swan-Ganz, FloTrac, and ClearSight is comparable as determined by the Critchley and Critchley method of percent error calculation.

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4. STUDY DESIGN

General Design

This study is an observational study in the U.S. Up to 108 eligible Subjects will be enrolled at up to five (5) study sites. A subject will be considered enrolled in the study once the subject has signed the informed consent and a Swan-Ganz thermodilution pulmonary artery catheter has been deployed, a FloTrac has been connected, the ClearSight finger cuff has been attached or ForeSight Elite sensors have been placed. The Study ID will be a 6-digit number, the first three numbers will identify the site, and the second set of numbers will identify the subject identification number.

A Swan-Ganz catheter, FloTrac transducer, ClearSight finger cuff and ForeSight Elite sensors will be placed prior to the start of the catheterization procedure. Intermittent cardiac output and other hemodynamic parameters will be collected throughout the duration of the procedure and analyzed according to the Statistical Analysis Plan.

Data collected in this study will support in expanding the current indications of Swan-Ganz, FloTrac and ClearSight into the pediatric population.

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

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5. SUBJECT SELECTION AND WITHDRAWAL

General Characteristics of the Proposed Subject Selection

Subjects 12 to 18 years of age, with planned catheterization procedure, at least 2 weeks post cardiac transplantation, who are projected to receive an arterial line and a Swan-Ganz catheter as part of the procedure/standard of care with intermittent cardiac output measures will be screened for inclusion into the Study. Only subjects meeting all inclusion criteria will be enrolled.
Prior to any Study procedures, an IRB approved informed consent form must be signed and dated by the subject or legal guardian. Subjects who have been screened but do not sign an informed consent form will not be considered enrolled and will not have any eCRFs (electronic Case Report Forms) completed.

Informed Consent

Before a subject undergoes any Study 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 Study 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.

Inclusion Criteria

1. Subjects who are 12 to 18 years of age
2. Subjects who have signed the Informed Consent Form
3. Subjects who are projected to receive Swan-Ganz catheter as part of procedure/standard of care with intermittent cardiac output measures
4. For those Subjects who have had a cardiac transplant, Subjects must be at least two weeks post cardiac transplantation
5. Subjects with planned pressure monitoring with an arterial line

Exclusion Criteria

1. Subjects with contraindications for Pulmonary Artery Catheters placement and monitoring (recurrent sepsis, or with hypercoagulopathy);
2. Subjects with contraindications for Arterial Line Placement;
3. Subjects with an extreme contraction of the smooth muscle in the arteries and arterioles in the lower arm and hand (i.e., Raynaud's Disease).
4. Subjects with a physical site area too limited for proper Sensor placement
5. Subjects with finger size less than the smallest finger cuff size
6. Documented ≥ moderate pulmonary hypertension (PAPm > 25mmHg, PVRI >3.0 WUxm2)
7. Presence of intracardiac shunting (i.e., ASD, VSD)
8. Aorto-pulmonary collaterals
9. ≥ Moderate tricuspid regurgitation, per echocardiogram criteria
10. > Moderate Aortic or pulmonary regurgitation, per echocardiogram criteria
11. Persistent cardiac arrythmias during the catheterization period (> 3min)

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12. Vascular abnormalities of the arterial system (i.e., connective tissue disorders, mid-aortic syndrome)

Subject Screening

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

Early Withdrawal of Subjects

Subjects may voluntarily withdraw consent at any time during the study with no loss of benefit or penalty. The Investigator may withdraw any subject if they determine that continued participation in the study may be detrimental to the subject's safety and welfare. Each subject withdrawal will be documented on the appropriate eCRF.

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6. STATISTICAL METHODS

Primary Effectiveness Endpoint

The primary objective of this study is to demonstrate that monitoring of cardiac output with Sawn-Ganz, FloTrac, and ClearSight system is comparable as determined by the Bland-Altman method of bias.

Sample Size Justification

Sample size consideration for bias

The bias between the matched pairs of CO measurements, as determined by the Bland-Altman method, must be smaller than the minimum clinical difference δ, which is the value that is large enough to claim difference.

The hypothesis for bias is:

H0: bias <-δ or bias >δ

H1: -δ≤ bias ≤δ

H0 is the null hypothesis (i.e. the difference between matched pairs of CO values of the two systems is larger than δ), H1 is the alternative hypothesis (i.e. the difference between matched pairs of CO values of the two systems is within the range of δ). A meta-analysis conducted a comprehensive search of 21 published medical literature to assess the accuracy and precision of minimally invasive CO monitoring systems used in children when compared with CO monitoring reference methods [8]. Among the 21 studies, 19 studies (90%) showed a bias range of -0.5 to 0.5 L/min. Based on these data, the clinical minimum difference δ was set at 0.5 L/min, i.e. bias is expected to be -0.5< bias < 0.5 l/min. This value is smaller in magnitude than the 0.8 l/min floor that the US FDA had previously considered for CO comparisons. The meta-analysis also shows that 19 out of 21 published studies had standard deviation (SD) no more than 1.0 L/min.

In this study eight repeated measurements (m=8 sub samples) or sub sample sections will be taken during the cardiac catherization case, thus intra-cluster correlation ecoefficiency ICC is a factor to be considered in sample size estimation. Here $ICC = \frac{\delta_s^2}{\delta_s^2+\delta_{ss}^2}$. $\delta_s^2$is the variance component of study subject. $\delta_{ss}^2$is the variance component of sum sample. By literature the ICC in children ranges from 0.94 to 0.98. The variation of study subject is dominant. Fixed the study subjects, the more sub-samples taken the less δ_{ss}^2will be by a factor 1/m. This will reduce the total variance applied in sample size calculation. Using ICC=0.98, and SD=1 (Variance=1) as an example, for m=8, as an example, for m=8, the stand deviation used in sample size estimation is $SD = \sqrt{0.98 * 1 + \frac{1-0.98}{8}} = 0.991211..$

The sample size calculation for this hypothesis is based on the one-sample t-test for equivalence. The desired outcome is to reject the null hypothesis at the 0.05 significance level. For this equivalence test of bias, two comparisons will be performed: FloTrac vs Swan-Ganz and ClearSight vs Swan-Ganz. In order to preserve the overall type 1 error rate at 0.05, the Bonferroni Correction will be used to adjust for multiple comparisons.

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Assuming a true mean bias of 0.0 and a SD of 1.0 l/min in the cardiac output, the sample size required for δ=0.5, alpha=0.05, and power=90% to reject the null hypothesis is 45, ignoring the ICC. After considering ICC for eight repeated measures (m=8), a sample size of 54 Subjects in needed. After considering a 34.5% rejection rate for hemodynamic instability, 10% lost to follow-up rate and 6 Roll-in Subjects for the learning curve, a total of 102 (96 evaluable Pivotal Subjects and 6 Roll-in Subjects) will be enrolled.

Adjusting for multiple comparisons, considering there will be two target devices and a reference device pairs, simultaneously, 108 total Subjects will be enrolled in this study.

Sample size consideration for percent error

The Critchley and Critchley method of percent error (PE) calculation will be compared to 30%. The Precision will be considered as acceptable if PE is less than 30 %.

The hypothesis for PE is a one-sided test:
H0: PE > 30%
H1: PE ≤ 30%

The sample size calculation for this hypothesis was based on the one-sided T-test. The desired outcome is to reject the null hypothesis at the 0.05 significance level. Assuming a true mean of 30% and a conservative SD assumption of 70%, the sample size required for power=90% to reject the null hypothesis is 49.

Because the study is designed with sub samples (repeated measurements) or sub sample sections (m= 8), ICC is a factor needing to be considered in the sample size estimation. When eight repeated measures (m=8) are performed, the SD=69.38%. The corresponding sample size necessary is 49.

For PE, a sample size of n=60 will be used in the study design, after considering two pairwise comparisons between 2 devices with a reference device. In addition, after considering a 34.5% rejection rate for hemodynamic instability, 10% lost to follow-up rate, 102 evaluable subjects will be targeted. To account for the learning curve and 6 additional Roll-in Subjects will be enrolled, totaling 108 Subjects enrolled in the study.

Calculation of Cardiac Index (CI)

Adjusting cardiac output (CO) with study subject body surface area (BSA) results in the derivation of cardiac index (CI). This adjustment for body surface area, in the study pediatric population (12 to 18 years old), will result in a smaller bias and percent error between test device and reference device. The standard deviation estimate will also be smaller, at the same scale, thus, the sample size estimate decreases. Sample size estimates for bias and percent error for CI is detailed in the SAP.

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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

All enrolled subjects with evaluable data will be included in the analysis of effectiveness endpoint, and all enrolled subjects will be included in the analysis of safety endpoint.

The analysis set is composed of all evaluable subjects with valid CO matched pair measurements from the target medical device system (FloTrac and ClearSight systems) and the reference medical device system (the Swan-Ganz thermodilution pulmonary artery catheter).

Evaluable subjects are those with non-rejected intermittent thermodilutions who have completed the 30-day telephone follow up period.

Analysis Methods

The primary effectiveness endpoints will be accessed using the testing method described in the Sample Size Justification section. Additionally, descriptive statistics will be used to summarize data. Mean, SD, median, 25^{th} (Q1) and 75^{th} (Q3) percentiles, minimum, and maximum will be reported for continuous variables; frequency and percentage of subjects will be reported for categorical variables. Further details of the analysis method will be described in the Statistical Analysis Plan for this study.

Secondary Effectiveness Endpoint

The secondary effectiveness endpoint is to demonstrate that monitoring of cardiac output (CO) with Swan-Ganz, FloTrac and ClearSight is comparable, as determined by the Critchley and Critchley method of percent error.

Additional Evaluations

The following additional evaluations will be included and considered exploratory:

- Comparison analysis of CI as determined by the Bland-Altman method of bias calculation with confidence intervals
- Comparison analysis of CI as determined by the Critchley and Critchley method of percent error calculation with confidence intervals
- Subgroup analysis of primary and secondary endpoint by age stratification
- Subgroup analysis of primary and secondary endpoint by gender
- Subgroup analysis of primary and secondary endpoint by race
- Subgroup analysis of primary and secondary endpoint by site

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- Comparison of cardiac output from FloTrac, ClearSight and Swan-Ganz technologies to the Fick principle
- Evaluation of hemodynamic parameters that are collected by the FloTrac, ClearSight, Swan-Ganz technologies, including:
    - Cardiac Output (CO)
    - Cardiac Index (CI)
    - Pulse Rate (PR)
    - Stroke Volume (SV)
- Evaluation of other hemodynamic parameters that will be collected during the catherization procedure, as prespecified in the SAP

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7. 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 investigational devices for use in this study 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-study personnel shall keep records documenting the receipt, use, return, and disposal of the devices. Only the Investigator, delegated-Study Personnel and/or designee(s) (i.e., Assisting Clinician(s)) may use the devices. The Investigator will supervise the used of the device in Study subjects. The Study 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.

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8. SCHEDULE OF EVENTS & PROCEDURES

Schedule of Events

The following matrix shows the scheduled assessments through the end of the Study (30-Day Follow Up).

Study Procedure / Exam	Subject Screening	Procedure	Discharge	30-Day Follow Up (±14 Days)
Obtain Informed Consent	X			
Perform Inclusion / Exclusion Evaluation	X			
Obtain Medical History / Subject Demographics[1]	X			
Assign Subject ID		X		
Enter Subject Data into Monitor		X		
Vital Signs		X		
Monitoring Duration		X		
Data download from Monitor		X		
Obtain Fluid and Vasoactive Medication Administration Record[2]		X		
Complete eCRFs	X	X	X	X
Record Adverse Events, if applicable		X	X	X
Phone Contact 30-day follow up / Mortality Determination				X

The duration of individual study participation is expected to be 30 days (±14 days) after procedure.

Data collection will occur during the study via the HemoSphere platform and electronic case report forms (eCRFs). The 30-day follow-up phone contact will be recorded on the applicable eCRF.

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

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

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Intermittent Thermal Dilution Assessment(s)

Using the Swan-Ganz thermodilution pulmonary artery catheter, two series of four (4) intermittent dilutions should be administered by the Investigator while in the cath lab. The dilution curves are analyzed and averaged to give one (1) CO value.

CO measured by the ClearSight and FloTrac systems will be simultaneously compared with the CO measured by the Swan-Ganz catheter using the thermodilution method. There will be 2 sets of 4 measurements recorded over a 30-second interval, during the Swan-Ganz thermodilution bolus injection. Those 4 measurements will be pair-matched by time in the ClearSight and FloTrac systems. The same number of measurements that will be recorded during the Swan-Ganz thermodilution will be recorded for the ClearSight and FloTrac devices. The following thermodilution procedure will be used:

A 10 ml sample of iced glucose solution (5%) will be drawn through an iced injectate container (CO-SET+ or any other container that meets the requirements, as determined by the investigator) and injected in a steady manner. Four TD CO determinations will output, preferably within 5 minutes. From there, three values, will be averaged to obtain one single value. Each thermodilution curve will be visually checked before acceptance. The dilution curve will be automatically corrected for the temperature of the blood and of the injectate measured at the entrance of the catheter lumen. Values for temperatures will be stored together with the thermodilution values. The entire series of four thermodilution estimates will be rejected if, during an injection, the HemoSphere advanced monitor displays an alert signal, if the injectate temperature is above 10 °C, or when the curve of the dilution is abnormal. In case of rejection, the entire series of four thermodilutions will be repeated.

Hemodynamics and respiratory rate must be stable during the TD series, since variability violates the assumption of stability that is required for the TD technique. Sponsor-instream review of the TD series will occur after each catheterization to determine if hemodynamic variability occurred and the site team will be retrained on the importance of conducting the TD technique during hemodynamic stability.

Clinical Study Completion or Early Termination

The IRB will be notified upon completion or premature termination of the study. Edwards retains the right to suspend or prematurely terminate this clinical study at any time.

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 Data Safety Monitoring Board (DSMB). Edwards shall terminate the clinical investigation if an unacceptable risk is confirmed.

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.

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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 study, etc.) will be reported in writing. The investigator will also adhere to procedures for reporting study and subject specific deviations to their IRB in accordance with their specific IRB's reporting policies and procedures.

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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 study, the IRB only needs to be notified.

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9. 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.

Any events associated with a commercially available study device (Fore-Sight Elite Tissue Oximetry Sensors) will be reported in accordance with the Medical Device Reporting (Complaints) regulation (21 CFR Part 803), while events associated with the investigational devices (remainder of devices in this study) will be reported under the IDE program (812.150).

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

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

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

Below is a list of anticipated risks that may be associated with the use of Swan-Ganz thermodilution pulmonary artery catheter:

- Allergic reaction to latex
- Cardiac arrhythmias
- Complete heart block

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- Knotting
- Nitroglycerin absorption
- Perforation of the pulmonary artery
- Pneumothorax
- Pulmonary infarction
- Thrombocytopenia
- Thrombophlebitis
- Thrombosis
- Tricuspid and pulmonic valve damage
- Right bundle branch block
- Sepsis/Infection

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

Below is a list of anticipated risks that may be associated with the use of the ClearSight finger cuff:

- Discoloration of digit distal to the cuff
- Discomfort where the cuff is applied
- Pain associated with inflation of the cuff
- Slight numbness of the fingertip

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

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Risk Management

The study devices have been tested to an established regimen of safety and performance testing and, with the exception of the ClearSight Module used in the HemoSphere platform, have been cleared by the US FDA in adults. The ClearSight technology has been cleared for use in adults with the EV1000 Monitor; however, it has not been cleared for use with the HemoSphere advanced monitoring platform.

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

1) Being conducted on patients who are already planned to receive an arterial line and a Swan Ganz catheter and the addition of FloTrac and ClearSight do not add to the invasiveness of the study,
2) Being conducted on patients who are already planned to receive thermodilutions
3) An observational study as opposed to an interventional study
4) Not relying on the data obtained from the FloTrac and ClearSight to treat patients

Collecting data does not introduce any new risks in relation to these products. Regarding the ClearSight Module used in the HemoSphere platform, thorough testing has been performed to show that this system functions as intended. As such collectively, the risks do not outweigh the benefits.

Benefits

There are no guaranteed benefits from a subject's participation in this study. However, the ForeSight Elite Sensors are cleared for pediatric use and provide the benefit of continually monitoring oxygen saturation of tissue with accuracy and precision. When desaturation of tissue occurs, the following may occur:

- Cognitive disfunction
- Extended time on mechanical ventilation
- Extra days spent in the hospital or intensive care unit (ICU)
- Increased post-operative nausea and vomiting

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10. 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 Study of an Investigational Device regardless of the causal relationship of the problem with the device or, if applicable, other Study treatment or diagnostic product(s). Information for AEs with the study devices will be collected from the time a subject begins the study procedure and is exposed to Study products. AEs will also be collected during surgical intervention, post intervention, discharge and through the 30-day 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 study related AE is suspected all available event information and will be provided to the Clinical Events Committee.

Once an AE/SAE/UADE is confirmed as such, event, date of onset, severity, duration, treatment (if required), resolution (or ongoing), assessment of seriousness, relationship to Study 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 Investigational Device or Study procedure must be reported to the Sponsor or designee within 5 working days of first awareness of the event.

Recording and Reporting of Adverse Device Effects

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

Causality of relationship to the Investigational Device will be judged by the Investigator, and reviewed independently by the Clinical Events Committee, as follows:

Not related:

- An event is clearly not and cannot be related to the Investigational Device. Reporting is not required per protocol unless the event was related to the Investigational Device or Study.

Possibly Related:

- A relationship may exist but could have been produced by another cause (e.g., treatment, condition).

Related:

- A relationship can be directly attributed to the use of the Investigational 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 Study 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.

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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 Study 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 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 Investigational Device or Study 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 or been withdrawn from the Study.

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Recording and Reporting of Deaths

Events resulting in death during the subject's enrollment in this Study are not expected to occur as a result of participation in the Study. 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 Study 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.

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 Study products or a Study 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 study 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.

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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 Study no later than 10 working days after Edwards or when the designee first becomes aware of the effect.

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11. INDEPENDENT SAFETY COMMITTEES

Clinical Events Committee

An independent (3-Member) Clinical Events Committee (CEC) will be established to oversee the safety progress. Members of the CEC must be free of significant conflicts of interest (e.g. Financial, intellectual, professional, or regulatory), and are experts in all scientific disciplines needed to interpret the data and ensure study participant safety. The CEC will meet via teleconference a minimum of two (2) times over the course of the study. The CEC may also meet for an ad hoc review of data in the event that a UADE is reported. The CEC charter will be maintained by the Sponsor as part of the clinical study project plan. The CEC charter will outline membership and voting procedures as well as CEC Meeting documentation and communication.

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

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Data Safety Monitoring Board

An independent (4-Member) Data Safety Monitoring Board (DSMB) will be established to oversee the Study outcome. Members of the DSMB must be free of significant conflicts of interest (e.g. Financial, intellectual, professional, or regulatory) and are experts in all scientific disciplines needed to interpret the data and ensure study participant safety, including an independent biostatistician. The DSMB will meet via teleconference a minimum of one (1) time over the course of the study. The DSMB manual of operation (MOP) will be maintained by the Sponsor as part of the clinical study project plan. The DSMB MOP will outline membership and voting procedures as well as DSMB Meeting documentation and communication. The DSMB meetings will include an open session where the Sponsor will present study updates, review trends for device malfunctions, protocol deviations and subject withdrawal reasons to communicate study progress. The Investigators may attend the open session.

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

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

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

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

Stopping Rules

Continuation or discontinuation of the study will be based upon the DSMB's evaluation of study safety. The DSMB may recommend stopping the study based solely on any safety concerns.

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12. DATA HANDLING AND RECORD KEEPING

Confidentiality

Information about Study 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 Study
- 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 Study. The Study Investigator and the Study site personnel are responsible for maintaining confidentiality throughout the clinical Study. The Sponsor and Sponsor designated Study 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 Study 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 Study period.

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Source Documents

Source data are all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the study. 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 study.

Required data for this Study are to be recorded in the subject's file and/or in worksheets, certified as source, for source documentation and data verification unless otherwise specified. Protocol deviation information can be recorded directly on the Protocol Deviation eCRF. Some of the source documentation generated during the Study may be either a worksheet, the electronic data from the Monitor, laboratory data, or printout from Radiometer and YSI. 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. Because of the potential for errors, inaccuracies, and illegibility in transcribing data onto eCRFs, the Investigator must permit inspection of the source documents.

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13. DATA COLLECTION METHODS

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

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14. RECORD RETENTION

It is the Investigator's responsibility to retain Study 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.

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15. 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.

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- 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.

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Communication Procedures

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

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16. 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 compliance with Study Protocol. 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 missing or unclear data will be queried as necessary throughout the Study. The Sponsor may request further information and documentation when complications and/or malfunctions are observed and reported.

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.

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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.).

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17. 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.

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18. 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.

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19. 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.

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20. 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
SpO2	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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STATISTICAL ANALYSIS PLAN

Protocol Title:	**A Prospective, Single-Arm, Nonrandomized, Observational Study of Cardiac Output Monitoring in Pediatric Patients**
Protocol Number:	#2019-08
SAP Version:	**B**
SAP Date:	**December 2, 2020**
SAP Author:	[redacted]

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Revision B Change Summary

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

Section (Page)	Change and Reason for Change
Subject Eligibility Criteria (18)	Edited exclusion criteria to include the following additional exclusions: *"6. Documented ≥ moderate pulmonary hypertension (PAPm > 25 mmHg, PVRI > 3.0 WUxm2)* *7. Presence of intracardiac shunting (i.e., ASD, VSD)* *8. Aorto-pulmonary collaterals* *9. ≥ Moderate tricuspid regurgitation, per echocardiogram criteria* *10. > Moderate Aortic or pulmonary regurgitation, per echocardiogram criteria* *11. Persistent cardiac arrythmias during the cardiac catheterization period (> 3min)* *12. Vascular abnormalities of the arterial system (i.e., connective tissue disorders, mid-aortic syndrome)"* Reason: Additional clarity to ensure intended exclusion of patients whose pathophysiologic state may result in intermittent and/or prolonged states in which the cardiac output from the right side of the heart may differ from the cardiac output from the left side of the heart.

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Glossary of Terms

ABBREVIATION	DEFINITION OR DESCRIPTION
ABP	Arterial Blood Pressure
AE	Adverse Event
ADE	Adverse Device Effect
Alpha	Type I error in hypothesis test
Beta	Type II error in hypothesis test
BSA	Body Surface Area
CEC	Clinical Events Committee
CI	Cardiac Index
CI	Confidence Intervals
CO	Cardiac Output
CSR	Clinical study report
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
H0	Null hypothesis
H1	Alternative hypothesis
MAP	Mean Arterial Pressure
ICC	Intra-cluster correlation coefficient
IRB	Institutional Review Board
PAC	Pulmonary Artery Catheter
PE	Percent Error
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SV	Stroke Volume
TD	Thermodilution

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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 #2019-08, "**A Prospective, Single-Arm, Nonrandomized, Observational Study of Cardiac Output Monitoring in Pediatric Patients**", and provides detailed instructions as to how each analysis will be performed.

Results obtained from the analyses specified in the SAP will become the basis of the clinical study report (CSR) for this protocol. Any deviations from the SAP must be documented in the CSR.

2. STUDY DESIGN

2.1 Study Objectives

The primary objective of the study is to assess Cardiac Output Monitoring in pediatric subjects by comparing FloTrac™ and ClearSight™ to intermittent thermodilution Swan-Ganz™, in order to expand the indications of FloTrac™, ClearSight™ and Swan-Ganz Intermittent Thermodilution Catheter to the pediatric population 12 to 18 years of age.

2.2 Overall Study Design and Plan

This is an observational study in the U.S. A subject will be considered enrolled in the study once the subject has signed the informed consent, a Swan-Ganz catheter has been deployed, a FloTrac has been connected, a ClearSight finger cuff has been attached and ForeSight Elite sensors have been placed. The Study ID will be a 6-digit number, the first three numbers will identify the site, and the second set of numbers will identify the subject identification number. Subjects will be enrolled in age group, 12 to 18 years of age.

A Swan-Ganz catheter, FloTrac transducer, ClearSight finger cuff and ForeSight Elite sensors will be placed prior to the start of the surgery. There will be 2 sets of 4 intermittent cardiac output measurements recorded, each over a 30 second interval during the bolus injection. Measures for FloTrac and ClearSight will be retrospectively matched by time point to the Swan-Ganz catherization data. Intermittent cardiac output and other hemodynamic parameters will be collected throughout the duration of the surgery. For each study subject two sets of four repeated measurements will be taken in the cardiac catherization lab. Data collected in this study will support in expanding the current indications of Swan-Ganz, FloTrac and ClearSight into the pediatric population.

In order to avoid a learning curve bias, up to 6 roll-in subjects will be enrolled, which is counted in the final sample size in study. The collected data from the roll-in cohort will be analyzed separately from the pivotal study subjects.

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A modified intent-to-treat (mITT) principle will be applied. Through investigator professional judgement and statistical principles, this study will be conducted in a manner that is consistent with the applicable regulations and in accordance with current Good Clinical Practice (GCP).

All methods of measurements will be recorded for all devices and included as part of the data set. Edwards will conduct analyses both with and without observations that are determined to be outliers. Once outliers are identified, the Principal Investigator will assess the validity of the data.

2.2.1 Cardiac Output

Cardiac output will be continuously measured by FloTrac and ClearSight, while cardiac output will be intermittently measured by the Swan-Ganz catheter, using the thermodilution method. During a 5- minute period of thermodilution and cardiac output determination, each subject will be assessed for hemodynamic stability. Should there be any instability, the bolus will be rejected. All data will be recorded and any rejected values will be clearly identified in the eCRF.

The rejection criteria that will be used to determine hemodynamic instability are detailed below:

- FloTrac and ClearSight will display mean arterial pressure (MAP). If MAP varies > 15% during the 30-sec period of each intermittent thermodilution, the bolus will be rejected.
    i. If more than 1 result is greater than 15% of the mean or the prespecified rejection criteria is met, discard the entire series, and repeat the series of four thermodilutions.
        - Note: The likely cause for 2, 3 or 4 results being greater than 15% of the mean is technique dependent, i.e., shooting the thermodilution either fast, slow or drawing up the incorrect amount of fluid.
    ii. If none the results are greater than 15% of the mean or the prespecified rejection criteria is not met, discard one result that is furthest from the mean.
- FloTrac and ClearSight will also display Pulse rate. If Pulse varies > 15% during the 30-sec period of each ITD, the bolus will be rejected.
    i. If more than 1 result is greater than 15% of the mean or the prespecified rejection criteria is met, discard entire series, and repeat the series of four thermodilutions.
        - Note: The likely cause for 2, 3 or 4 results being greater than 15% of the mean is technique dependent, i.e., shooting the thermodilution either fast, slow or drawing up the incorrect amount of fluid.
    ii. If none the results are greater than 15% of the mean or the prespecified rejection criteria is not met, discard one result that is furthest from the mean.
- ClearSight will display Physiocal. If Physiocal is not at least 30 beats, the bolus will be rejected.

For Cardiac Output comparisons of FloTrac and ClearSight to Swan-Ganz ITD, all hemodynamic monitors will be time aligned.

The CO values from ClearSight and FloTrac for the analyses will be prepared as follows:

- Determine the averaging window corresponding with each bolus injection

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- Average the CO over the 30 second period
- Determine the average of 3 of 4 CO values

The CO values from Swan-Ganz ITD for analyses will be prepared as follows:

- Determine the CO from each of the 3 of 4 accepted bolus injections
- Determine the average of 3 of 4 CO values

The CO values from Swan-Ganz ITD for analyses will be prepared as follows:
- Determine the CO from each of the 3 of 4 accepted bolus injections
- Determine the average of 3 of 4 CO values

2.3 Sample Size Consideration

2.3.1 Sample size consideration for bias

The bias between the matched pairs of CO measurements, as determined by the Bland-Altman method, must be smaller than the minimum clinical difference δ, which is the value that is large enough to claim difference.The hypothesis for bias is:

H0: bias <-δ or bias >δ
H1: -δ≤ bias ≤δ

H0 is the null hypothesis (i.e. the difference between matched pairs of CO values of the two systems is larger than δ), H1 is the alternative hypothesis (i.e. the difference between matched pairs of CO values of the two systems is within the range of δ). A meta-analysis conducted a comprehensive search of 21 published medical literature to assess the accuracy and precision of minimally-invasive CO monitoring systems used in children when compared with CO monitoring reference methods [8]. Among the 21 studies, 19 studies (90%) showed a bias range of -0.5 to 0.5 L/min. Based on these data, the clinical minimum difference δ was set at 0.5 L/min, i.e. bias is expected to be -0.5< bias < 0.5 l/min. This value is smaller in magnitude than the 0.8 l/min floor that the US FDA had previously considered for CO comparisons. The meta-analysis also shows that 19 out of 21 published studies had standard deviation (SD) no more than 1.0 L/min.

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In this study eight repeated measurements (m=8 sub samples) or sub sample sections will be taken during the cardiac catherization case, thus intra-cluster correlation ecoefficiency ICC is a factor to be considered in sample size estimation. Here $ICC = \frac{\delta_s^2}{\delta_s^2+\delta_{ss}^2}$. $\delta_s^2$is the variance component of study subject. $\delta_{ss}^2$is the variance component of sum sample. By literature the ICC in children ranges from 0.94 to 0.98. The variation of study subject is dominant. Fixed the study subjects, the more sub-samples taken the less δ_{ss}^2will be by a factor 1/m. This will reduce the total variance applied in sample size calculation. Using ICC=0.98, and SD=1 (Variance=1) as an example, for m=8, the stand deviation used in sample size estimation is $SD = \sqrt{0.98 * 1 + \frac{1-0.98}{8}} = 0.991211.$

The sample size calculation for this hypothesis is based on the one-sample t-test for equivalence. The desired outcome is to reject the null hypothesis at the 0.025 significance level. For this equivalence test of bias, two comparisons will be performed: FloTrac vs Swan-Ganz and ClearSight vs Swan-Ganz. In order to preserve the overall type 1 error rate at 0.05, the Bonferroni Correction will be used to adjust for multiple comparisons. Assuming a true mean bias of 0.0 and a SD of 1.0 l/min in the cardiac output, the sample size required for δ=0.5, alpha=0.025, and power=90% to reject the null hypothesis is 45, ignoring the ICC. After considering ICC for eight repeated measures (m=8), adjusting for multiple comparisons, considering comparisons of between two target devices and a reference device pairs, simultaneously, a sample size of 60 Subjects is needed. After considering a 34.5% rejection rate for hemodynamic instability, 10% lost to follow-up rate, and 6 roll-in Subjects for the learning curve, up to 108 (102) evaluable Pivotal Subjects and 6 Roll-in Subjects) will be enrolled into the study.

By simulating the study results with a mixed effect model, using repeated measurement data collected from a similar study, although the sample size estimate from this approach is conservative, it is reasonable and rational.

2.3.2 Sample size consideration for percent error

The Critchley and Critchley method of percent error (PE) calculation will be compared to 30%. The Precision will be considered as acceptable if PE is less than or equal to 30%.
The hypothesis for PE is a one-sided test:
H0: PE > 30%
H1: PE ≤ 30%

In a meta-analysis paper published in 2010, Peyton and Chong suggested that acceptable agreement should be a percentage error of 30% or less, which has become a widely quoted criterion.

In a paper published by Odor, Bampoe, and Cecconi, “PE is calculated by dividing the limits of agreement by the mean value of measurements taken using the reference method of CO monitoring in the required population. A PE cut of ± 30% has been suggested as a pragmatic guide for clinicians to determine whether a new measurement technique represents a good alternative to the reference standard. The basis of this approach is that the level of precision should be at least equivalent to the reference standard i.e. thermodilution, which is ± 20%. Since random error in measurement is compounded during combination of two precisions, with two measurements at ± 20% equating to a total error of ± 28.3%, the total PE is commonly rounded to ± 30%. Thus, finding a percentage error

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of less than ± 30% equates to the new tested technique having an error similar to the reference standard, which should therefore be considered acceptable."

The sample size calculation for this hypothesis was based on the one-sided T-test. The desired outcome is to reject the null hypothesis at the 0.025 significance level. Assuming a true mean of 30% and a conservative SD assumption of 70%, the sample size required for power=90% to reject the null hypothesis is 49. With Bonferroni adjustment for two comparison between three target device systems, enrollment of 60 subjects is required.

Additionally, in the paper "A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques," Critchley LA and Critchley JA constructed an error gram from the percentage errors from the test and reference methods to determine acceptable limits between methods. They graphically showed that limits of agreement of up to +/-30% were acceptable for PE.

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Because the study is designed with sub samples (repeated measurements) or sub sample sections (m=8), ICC is a factor needing to be considered in the sample size estimation. By similar assumption and calculation in section 2.3.1, for m=8, the SD=69.38%, the corresponding sample size necessary is 49. For PE, a sample size of n=60 will be used in the study design, after considering two pairwise comparisons between 2 devices with a reference device. In addition, after considering a, 34.5% rejection rate for hemodynamic instability, 10% lost to follow-up rate, up to 102 evaluable subjects will be targeted. To account for the learning curve, 6 additional roll-in subjects will be enrolled (up to 3 at each site), totaling 108 Subjects enrolled in the study.

2.3.3 Sample size consideration for bias calculated with cardiac index

The bias between the matched pairs of CI measurements, as determined by the Bland-Altman method, must be smaller than the minimum clinical difference δ, which is the value that is large enough to claim difference.

The hypothesis for bias is:
H0: bias <-δ or bias >δ
H1: -δ≤ bias ≤δ

Because there are no valid publications found through internet searching to design the settings in sample size estimation based on CI, the relation between CI and CO is used in sample size estimation here. Cardiac index (CI) is defined as cardiac output (CO)/body surface area (BSA). By the results from Cattermole G. N., Leung P. Y. M., Mak P. S. K. et al. 2010 and Cattermole G. N., Leung P. Y. M., Ho G. Y. L. et al. 2017, the BSA value for kid with age ≥8 is greater than 1, target on Chinese population in Hong Kong. For the age group from 12 to 18 years, it is around 1.5. If the study subjects are from developed country the BSA value possibly will be larger. If the study targets at developing country population, this value possibly will be smaller. By this consideration BSA=1.2 is used in bias adjustment and the SD adjustment. The SD used in sample size estimation for CI will be 0.85 ($SD_{CI} \approx \frac{SD_{CO}}{BSA} \approx 0.85$).

In this study eight repeated measurements or sub sample sections for each study subject will be taken during the cardiac catherization case, thus intra-cluster correlation ecoefficiency ICC is a factor to be considered in sample size estimation. Here $ICC = \frac{\delta_s^2}{\delta_s^2+\delta_{ss}^2}$. $\delta_s^2$is the variance component of study subject. $\delta_{ss}^2$is the variance component of sum sample. By literature the ICC in children ranges from 0.94 to 0.98. The variation of study subject is dominant. Fixed the study subjects, the more sub-samples taken the less δ_{ss}^2will be by a factor 1/m. This will reduce the total variance applied in sample size calculation. Using ICC=0.98, and SD=1 (Variance=1) as an example, as an example, for m=8, the adjusted variance will be $0.98 * 0.7225 + (1 - 0.98) * \frac{0.7225}{8} = 0.70985$ and the SD=0.8425.

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The sample size calculation for this hypothesis was based on the one-sample t-test for equivalence. The desired outcome is to reject the null hypothesis at the 0.025 significance level. Assuming a true mean bias of 0.0 and a SD of 0.85 l/min in the cardiac Index, the sample size required for δ=0.5, alpha=0.025, and power=90% to reject the null hypothesis is 33 ignoring the ICC. After considering ICC the sample size is also 33 for m=8. After considering a 34.5% rejection rate for hemodynamic instability, 10% lost to follow-up rate, and 6 roll-in subjects for the learning curve, up to 61 evaluable subjects will be enrolled. For two pairwise comparisons considering two target device with the reference device, the sample size is 108. For situations where variation from study subject is dominant, adding repeated measurements is not an efficient method in sample size estimation.

Adjusting cardiac output (CO) with study subject body surface area (BSA) results in the derivation of cardiac index (CI). This adjustment for body surface area, in the study pediatric population (12 to 18 years old), will result in a smaller bias and percent error between test device and reference device. The standard deviation estimate will also be smaller, at the same scale. By the result from publish literatures, the conservative median of BSA 1.2 is used in this adjustment, which will decrease the standard deviation. Thus, the sample size estimate decreases obviously.

2.3.4 Study subject allocation between age groups

In statistical analysis, balance study design have more analysis power, and interpolation is always much more dependable than extrapolation. For our study device there are more evidence available in the adult population. Considering study subject properties and two surgical sites, 6 roll-in subject will be tested in age group 12-18.

2.3.5 Target Sample Size Requirement

Power(%)	Bias (n)	PE (n)
90	92	102
85	81	87
80	75	79

(Note: original sample size estimate for Bias and PE were adjusted for Bonferroni (two pairwise comparisons), 34.5% rejection rate for hemodynamic instability, 10% lost to follow-up rate, and 6 roll-in subjects for the learning curve. The target sample will include 102 evaluable subjects. Six additional roll-in's will comprise the training cohort.)

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3. STUDY ENDPOINTS

The primary effectiveness endpoint is to demonstrate that monitoring of cardiac output (CO) with Swan-Ganz, FloTrac, and ClearSight is comparable as determined by the Bland-Altman method of bias.

The secondary endpoint analyses will include:

- CO, assessed using include using the Critchley and Critchley method of percent error calculation

Two comparisons will be performed for each of three endpoints described above: FloTrac vs Swan-Ganz and ClearSight vs Swan-Ganz.

The primary and secondary efficacy endpoints will be analyzed using the evaluable analysis set as defined in Section 5.

The primary safety endpoint is to assess all serious intraoperative and post-operative adverse events through 30 days, including serious device-related events. The safety endpoint will be analyzed using the safety analysis set as defined in Section 5.

3.1 Primary effectiveness endpoint

By the CO measurement from Swan-Ganz, FloTrac, and ClearSight, and Fick principle, the variable bias (X) is derived for statistical analysis:

$$x_{ij} = CO_{tij} - CO_{rij}$$

Where x_{ij} is the bias of ith subject and jth matched pair repeated measurements, CO_{tij} is CO measurement of the ith subject at jth repeated measurement of test device, such as Swan-Ganz, FloTrac, and ClearSight, CO_{di} is the CO measurement of ith subject at jth repeated measurement of reference device the Swan-Ganz thermodilution pulmonary catheter. Here $i = 1, \dots, n$ (the estimated sample size, 102), $j = 1, \dots, m$ (the planned repeated measurements, 8).

3.1.2 97.5% Confidence Intervals for bias using bootstrap and limit of agreement methods

Bootstrap method will be used to estimate two-sided 97.5% confidence intervals for all CO and CI bias measures under study. This will be performed for all analysis datasets as well as those data with rejected data. Results will be compared.

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3.2 Secondary effectiveness endpoints

$$PE_{ij} = 100 * \frac{|CO_{tij} - CO_{rij}|}{CO_{rij}} = 100 * \frac{|x_{ij}|}{CO_{rij}}$$

3.2.1 PE derived by CO

The percent error is derived as follow:

$$PE_{ij} = 100 * \frac{|CO_{tij} - CO_{rij}|}{CO_{rij}} = 100 * \frac{|x_{ij}|}{CO_{rij}}$$

where PE_{ij} is the percent error of ith subject at jth repeated measurement of FloTrac and ClearSight with CO measurements from the Swan-Ganz thermodilution pulmonary catheter, as the reference.

3.3 Explatory analyses

3.3.1 Bias derived by CI

By the CI measurement from Swan-Ganz, FloTrac, and ClearSight, the variable bias (X) is derived for statistical analysis:

$$x_{ij} = CI_{tij} - CI_{rij} = (CO_{tij} - CO_{rij})/BSA$$

Where x_{ij} is the bias of ith subject and jth matched pair repeated measurements of CI, CI_{tij} is CI measurement of the ith subject at jth repeated measurement by FloTrac and ClearSight, CI_{rij} is the CI measurement of ith subject at jth repeated measurement of reference device, Swan-Ganz ITD, on the same study subject. Here $i = 1, \ldots, n$ (the estimated sample size, 102), $j = 1, \ldots, m$ (the planned repeated measurements, 8). And BSA is the body surface area of this study subject.

$$PE_{ij} = 100 * \frac{|CO_{tij} - CO_{rij}|}{CO_{rij}} = 100 * \frac{|x_{ij}|}{CO_{rij}}$$

3.3.2 PE derived by CI

The percent error of CI is derived as follow:

$$PE_{ij} = 100 * \frac{|CI - CI_{rij}|}{CI_{rij}} = 100 * \frac{|x_{ij}|}{CI_{rij}} = 100 * \frac{\left|\frac{CO_{tij}}{BSA} - \frac{CO_{rij}}{BSA}\right|}{\frac{CO_{rij}}{BSA}} = 100 * \frac{[CO_{tij} - CO_{rij}]}{CO_{rij}}$$

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where PE_{ij} is the percent error of CI measurement of ith subject at jth repeated measurements by FloTrac and ClearSight, using Swan-Ganz ITD CI measurement as the reference. BSA is the body surface area of this study subject. Here the PE calculated by CI is the same as calculated by CO. Therefore, this fact will be noted and present in the final report.

$$x_{ij} = CO_{tij} - CO_{rij}$$

3.4 Explatory analyses

3.4.1 98.75% Confidence Intervals for PE using bootstrap method (derived by CO and CI)

Bootstrap method will be used to estimate one-sided confidence for PE, CO and CI measures under study. This will be performed for all analysis datasets as well as those datasets with rejected data. Results will be compared.

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4. ANALYSIS POPULATIONS

The analysis set is composed of all evaluable subjects with valid CO matched paired measurements from the target medical device system (Swan-Ganz™, FloTrac™, and ClearSight™), the Fick principle and the reference medical device system (a Swan-Ganz thermodilution catheter). Evaluable subjects are those with non-rejected intermittent thermodilutions who have completed the 30-day telephone follow up period.

5. DEFINITIONS

5.1. Enrolled Subject

A subject will be considered enrolled in the study once the subject has signed the informed consent, a Swan-Ganz catheter has been deployed, a FloTrac has been connected, a ClearSight finger cuff has been attached and/or ForeSight Elite sensors have been placed.

5.2. Evaluable Subject

An evaluable subject is one who has valid CO pair measurements that were not rejected and also has completed the 30-Day follow up.

5.3. Modified Intent-to-treat (mITT)

Modified Intent-to-treat (mITT) is defined as the study subjects who were exposed to the study product and will therefore be included in the effectiveness and safety analysis datasets.

5.4. Per Protocol Analysis

A per protocol analysis is defined as a dataset of subjects who completed the cardiac catherization as written in the protocol. No protocol deviations occurred during the cardiac catherization procedure.

5.5. Pivotal Cohort

The pivotal cohort are subjects who were enrolled after the roll-in period. The pivotal cohort will be analyzed separately from the roll-in cohort.

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5.6. Roll-in Cohort

The roll-in cohort are the first 1-3 subjects enrolled at the site that the study investigator uses to confidently perform the intermittent thermodilution. This group of patients will analyze separately from the pivotal subjects.

5.7. Screen Failure

A screen failure is a study subject who does not meet all inclusion criteria or fails at least one of exclusion criteria.

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. The subject's medical historical data will be recorded on an electronic case report form (eCRF). The CO measurement data will be downloaded from hemodynamic monitor (Hemosphere advanced monitoring platform). The Roll-in cohort data will be analyzed separately.

The data analyses will be conducted with SAS 9.4 software system. Bland Altman analyses will be performed for bias and precision measures. Limits of agreement will be calculated.

6.2 Handling of Missing Data

Missing data are defined as those instances in which data collection was attempted yet failed for some reason (i.e. due to technological, procedural, and/or subject constraints). 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.

The CO measurements are downloaded from the hemodynamic monitor. Theoretically, there should be no missing data. For data that are missing as defined above, statistical imputation using the SAS imputation method will be utilized.

6.3 Handling of Invalid Data

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After downloading the data from the hemodynamic monitors, abnormal observations will be checked and evaluated for hemodynamic stability. Should there be any instability, the result will be rejected. All data will be recorded, and any rejected values will be clearly identified in the eCRF.

The rejection criteria that will be used to determine - hemodynamic instability are detailed below:

- Mean arterial pressure (MAP): If MAP varies > 15% during the 30-sec period of each intermittent thermodilution, the bolus will be rejected.
- Pulse rate: If Pulse varies > 15% during the 30-sec period of each ITD, the bolus will be rejected.
- PhysioCal: If PhysioCal is not at least 30 beats, the bolus will be rejected.
-

Upon taking four (4) thermodilution measurements and given the above criteria for classifying data as invalid, Edwards proposes to remove the one measurement that is the greatest outlier of the four. If upon the rare occasion two or more outliers measure greater than 15% from the mean, within a series of measurements, or hemodynamic instability results when these observations are taken, the clinician will repeat the series. If this scenario of repeating the series is missed by the clinican during the clinical procedure and discovered by the statisticians during data review, the outliers will be analyzed separately. In addition to the results for the collected parameters, the number of subjects with less than 3 and number of subjects with at least 3 valid values, and results of subjects will be tabulated separately, and reported. Those subjects who have less than 3 valid measurements and were missed for repeated testing by the clinician performing the thermodilutions will be considered as protocol deviations or protocol violations.
Additionally, a supplementary exploratory analysis will be reported using all the recorded values (valid and invalid) to assess the impact of the excluded values.

7. SUMMARY OF BASELINE INFORMATION

7.1 Subject Eligibility Criteria

Inclusion Criteria

1. Subjects who are 12 to 18 years of age
2. Subjects who have signed the Informed Consent Form
3. Subjects who are projected to receive Swan-Ganz catheter as part of procedure/standard of care with intermittent cardiac output measures
4. For those Subjects who have had a cardiac transplant, Subjects must be at least two weeks post cardiac transplantation Subjects
5. Subjects with planned pressure monitoring with an arterial line

Exclusion Criteria

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1. Subjects with contraindications for Pulmonary Artery Catheters Placement and monitoring (recurrent sepsis, or with hypercoagulopathy);
2. Subjects with contraindications for Arterial Line Placement;
3. Subjects with an extreme contraction of the smooth muscle in the arteries and arterioles in the lower arm and hand (i.e., Raynaud's Disease).
4. Subjects with a physical site area too limited for proper Sensor placement
5. Subjects with finger size less than the smallest finger cuff size
6. Documented ≥ moderate pulmonary hypertension (PAPm > 25 mmHg, PVRI > 3.0 WUxm2)
7. Presence of intracardiac shunting (i.e., ASD, VSD)
8. Aorto-pulmonary collaterals
9. ≥ Moderate tricuspid regurgitation, per echocardiogram criteria
10. > Moderate Aortic or pulmonary regurgitation, per echocardiogram criteria
11. Persistent cardiac arrythmias during the cardiac catheterization period (> 3min)
12. Vascular abnormalities of the arterial system (i.e., connective tissue disorders, mid-aortic syndrome)"

7.2 Demographics and Baseline Characteristics

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

7.3 Medical History

The subject's medical historical data will be recorded on an electronic case report form (eCRF). The CO measurement data will be downloaded from hemodynamic monitor (Hemosphere advanced monitoring platform).

7.4 Risk Assessments

Any events associated with a commercially available study device will be reported in accordance with the Medical Device Reporting (Complaints) regulation (21 CFR Part 803), while events associated with the investigational device will be reported under the IDE program (812.150). .

Below is a list of anticipated risks that may be associated with the use of Swan-thermodilution pulmonary artery catheter.

- Perforation of the pulmonary artery
- Pulmonary infarction
- Cardiac arrhythmias
- Knotting
- Sepsis/Infection
- Right bundle branch block
- Complete heart block

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- Tricuspid and pulmonic valve damage
- Thrombocytopenia
- Pneumothorax
- Thrombophlebitis
- Nitroglycerin absorption
- Thrombosis
- Allergic reaction to latex

FloTrac sensor

The vascular access obtained is standard clinical care and the addition of the FloTrac arterial transducer is standard procedure and does not impose any additional risk to the patient. There is no measurable increased infectious risk with the temporary use of the FloTtrac sensor.

Below is a list of anticipated risks that may be associated with the use of the ClearSight finger cuff.

- Discomfort where the cuff is applied
- Discoloration of digit distal to the cuff
- Pain associated with inflation of the cuff
- Slight numbness of the fingertip

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

- Allergic reaction to sensors
- Skin irritation

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7.5 Study Procedure

The schedule of events is illustrated in the following table.

Study Procedure / Exam	Subject Screening	Procedure	30-Day Follow Up (±14 Days)
Obtain Informed Consent	X		
Perform Inclusion / Exclusion Evaluation	X		
Obtain Medical History / Subject Demographics[1]	X		
Assign Subject ID		X	
Enter Subject Data into Monitor		X	
Vital Signs		X	
Monitoring Duration		X	
Data download from Monitor		X	
Obtain Fluid and Vasoactive Medication Administration Record[2]		X	
Record Adverse Events, if applicable		X	X
Phone Contact 30-day follow up / Mortality Determination			X

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

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

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8. STATISTICAL ANALYSIS OF STUDY ENDPOINTS

8.1 Primary Endpoint

The primary objective of this study is to demonstrate that monitoring of cardiac output with Sawn-Ganz, FloTrac, and ClearSight is comparable as determined by the Bland-Altman method of bias. To demonstrate this comparability, the bias calculation will be assessed separately.

Summary statistics and statistical comparison

The CO measurements from both investigational and reference device systems will be summarized using descriptive statistics including mean, median, minimum, maximum, standard deviation, Q1 (first quantile), and Q3 (third quantile). Additionally, p values from paired t-test will be provided to test the difference.

8.1.2 Primary endpoint analysis with Bias calculated by CO

The primary endpoint of the bias between the matched pairs of CO measurements as determined by the Bland-Altman method will be tested as below using the one sample t-test.

The hypothesis for bias is:

H0: bias <-0.5 or bias >0.5
H1: -0.5≤ bias ≤0.5
See section 3.1 for details.

8.1.3 Limits of Agreement

Limits of agreement will be computed using Bland-Altman methods. Components of the one-way analysis of variance will be used to estimate variance of multiple between-device differences for the same subject. These components of variance measures include the mean square for subjects (SS), and residual mean square (RMS). The differences between the average difference across subjects will be estimated from the difference between SS and RMS. This difference will be divided by $M=((\sum m_i)^2 - \sum m_i^2)/(n-1)*(\sum m_i)$, where n = total number of subjects, and m_i is the number of pairwise difference measurements for the *ith* subject. The estimated component of variance, which represents the heterogeneity, is estimated as (SS – RMS)/M. The total variance (TV) for single differences on different subjects is estimated by the sum of these two components: TV = (SS – RMS)/M + RMS. The resulting lower and upper limits of agreement will be estimated with 97.5% confidence mean(diff) ± 1.984*TV for a two-sided test.

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We want agreement to be the same or at least similar over the range of CO and CI measurements. Plots of the difference bias between device pairings (ClearSight vs Swan-Ganz, and FloTrac vs Swan-Ganz), for CO and CI measurements, on average of the two device measurements will be performed, with reference lines including zero, mean difference, and lower and upper limits of agreement. Two-sided 97.5% LOA will be calculated for bias between device pairings[9]. The statisticians will determine whether the standard deviation of the mean difference is constant or non-constant for each measure. The mean difference and standard deviation about the mean difference will be estimated for all measurements. The difference measures will be tested for heterogeneity using components of variance methods. The variance for single differences between device pairs of measurements, on different subject, will be plotted. Also, mean difference will be plotted on the order in which observations are recorded for each subject.

Visual check of the bias spread pattern and deviation using scatter plots of bias and/or percent error versus Fick principle reference mean CO, and scatter plot of bias and the percent error versus target device mean CO, with reference lines zero and limits of agreement (δ[OBJ]$\delta\delta$to the plot will be performed.

8.2 Secondary Endpoint

8.2.1 Percent Error calculated by CO as the secondary endpoint

The secondary endpoint of the percent error between the matched pairs of CO measurements as determined by the Critchley and Critchley method will be tested as below using the one sample t-test. The hypothesis for PE is:

H0: PE > 30%
H1: PE ≤ 30%

8.3 Sensitivity Analysis

8.3.1 Sensitivity analysis on study subject

To determine the effectiveness of study subject on the analytical results, following sensitivity analysis will be conducted by artificially removing one or a few study subjects. The expected result is that no study subject or group of study subjects are influence subjects on the analytical result.

8.3.2 Sensitivity analysis on reference device

To determine the effectiveness of reference device on the test device in the analytical results, different reference devices will be applied in sensitivity analysis. The expected result is that the reference device performance is stable and consistency, which is not the influence factor for the analytical result.

8.4 Exploratory Analyses

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The following exploratory analyses will be preformed

- Comparison analysis of CI calculated for Bias as determined by Bland Altman method with confidence intervals.
- Comparison analysis of CI as determined by the Critchley and Critchley method of percent error calculation with confidence intervals
- Subgroup analysis of primary and secondary endpoint by age stratification
- Subgroup analysis of primary and secondary endpoint by gender
- Subgroup analysis of primary and secondary endpoint by race
- Subgroup analysis of primary and secondary endpoint by site
- Comparison of cardiac output from FloTrac, ClearSight and Swan-Ganz technologies to the Fick principle

8.4.1 Validation of Accuracy and Consistency

Considering the variation of CO measurement from both device systems among patients, applying patient and patient age group as potential classification factors, the conclusion from 8.1.2 will be validated with bootstrap method through the 97.5% coverage intervals, which should be within the range from -δ to δ. These analyses will be presented within clinical study report.

8.4.2 Variance component analysis

With mixed effect model, the derived variable bias as the response, study site, surgery team, and subject as the random variable, estimate the variance component of each factor to trace the main source of variability, which will benefit to future variation control. This analysis will be present in the clinical study report.

8.5 Interim analysis

No interim analysis is planned for this study.

8.6 Analysis of other hemodynamic parameters

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Below is a table of other hemodynamic parameters measures that will be collected in this study.

Table 1. Measures by Device and Endpoint

	Device				
Parameters	Swan Ganz	FloTrac	ClearSight	ForeSight	Endpoints
Cardiac Output (CO)	X	X	X		Primary (Bland Altman), Secondary (Percent Error)
Cardiac Index (CI)	X	X	X		None (exploratory analyses - descriptive stats)
Central Venous Pressure (CVP)		X			None (exploratory analyses - descriptive stats)
Diastolic Blood Pressure (DIA(ART)/DIA(PAP))		X			None (exploratory analyses - descriptive stats)
Dynamic Arterial Elastance (Ea(dyn))		X	X		None (exploratory analyses - descriptive stats)
Intermittent cardiac index (iCI)	X				None (exploratory analyses - descriptive stats)
Intermittent cardiac output (iCO)	X				None (exploratory analyses - descriptive stats)
Intermittent systemic vascular resistance (iSVR)	X				None (exploratory analyses - descriptive stats)
Intermittent systemic vascular resistance index (iSVRI)	X				None (exploratory analyses - descriptive stats)
Mean Arterial Pressure (MAP)		X	X		None (exploratory analyses - descriptive stats)
Mean pulmonary artery blood pressure (MPAP)		X			None (exploratory analyses - descriptive stats)
Noninvasive Arterial Diastolic Pressure (DIA(NI))			X		None (exploratory analyses - descriptive stats)
"Noninvasive arterial systolic blood pressure (SYS(NI))"			X		None (exploratory analyses - descriptive stats)
Pulmonary artery diastolic blood pressure (DIA(PAP))		X			None (exploratory analyses - descriptive stats)
Pulmonary artery systolic blood (SYS(PAP))		X			None (exploratory analyses - descriptive stats)
Pulse Pressure Variation (PPV)		X	X		None (exploratory analyses - descriptive stats)
Pulse Rate (PR)	X	X	X		None (exploratory analyses - descriptive stats)
Stroke volume (SV)	X	X	X		None (exploratory analyses - descriptive stats)
Stroke volume index (SVI)	X	X	X		None (exploratory analyses -

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Table 1. Measures by Device and Endpoint					
					descriptive stats)
Stroke Volume Variation (SVV)		X	X		None (exploratory analyses - descriptive stats)
Systemic arterial diastolic blood pressure (DIA (ART))		X			None (exploratory analyses - descriptive stats)
Systemic arterial systolic blood pressure (SYS(ART))		X			None (exploratory analyses - descriptive stats)
Systemic vascular resistance (SVR)		X	X		None (exploratory analyses - descriptive stats)
Systemic vascular resistance index (SVRI)		X	X		None (exploratory analyses - descriptive stats)
Systolic Pressure (SYS(ART)/SYS(PAP))		X			None (exploratory analyses - descriptive stats)
Systolic Slope (dP/dt)		X	X		None (exploratory analyses - descriptive stats)
StO2 - 1 (cerebral)				X	None (exploratory analyses - descriptive stats)
StO2 - 2 (cerebral)				X	None (exploratory analyses - descriptive stats)

9 ANALYSIS OF SAFETY

9.1 Adverse Events

The adverse events data will be summarized with frequency counts and percentages. The frequency distribution and percentage of adverse event related to a specific medical device will be presented. The primary safety endpoint will include summary of intraoperative and post-operative adverse events, discharge through 30 days followup, related or unrelated to the devices under study.

9.2 Deaths and Other Serious Adverse Events

Death or other serious adverse events that occur during this study will be summarized with frequencies and percentages.

10 CHANGES FROM PROTOCOL SPECIFIED ANALYSES

There are no changes to the protocol specified analyses at this time.

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DOC-0089208 Rev. A (This template is required by DOC-0089205)

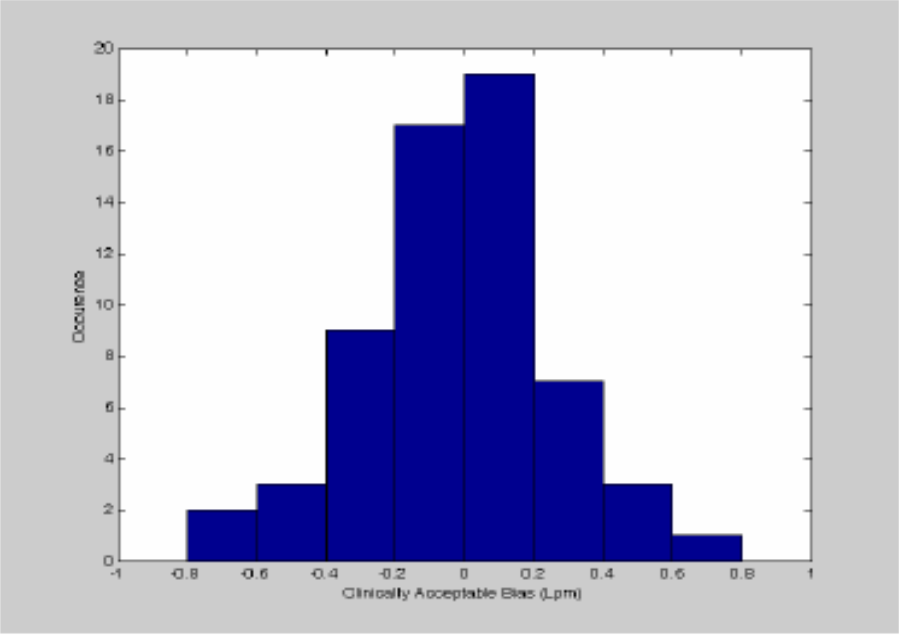
12 APPENDIX

13 LITERATURE SEARCH/REVIEW

For the original FloTrac submission in 2004 and the publication (Nusmeier, van Der Hoeven, and Lemson, 2010), an abstract search was performed to compile relevant clinical data on the accuracy and acceptance criteria of various injectate and continuous cardiac output measurements (iCO, and CCO). PubMed was searched using the keywords “continuous” OR “Fick’ OR pulse contour" OR “TD”) AND "cardiac output" AND “precision”, to identify published literature that reported performance comparisons of cardiac output measurements. A total of 97 abstracts of published articles were found as a result of the search.

Review of the abstracts showed that 42 of them were irrelevant. Of the 42 that were not taken into consideration, 17 reported on pre-clinical studies, 21 had insufficient statistics and 4 did not provide performance comparison of cardiac output. Hence, 55 abstracts were deemed relevant to this analysis. Ten out of 55 abstracts reported accuracy in terms of cardiac index. The remaining 45 abstracts contained 75 pairs of Bland-Altman comparisons. Fourteen of the 75 Bland-Altman comparison pairs were reported as marginal or unacceptable, the remaining 61 pairs from 38 abstracts were reported as clinically acceptable [32-69].

Figure 1 indicates a histogram of the bias reported in the 61 comparisons. The range of bias reported as clinically acceptable was [-0.79 …0.63]. However, from the histogram, it can be seen that only three of the reported values were outside +/- 0.6 l/min. Thus, the literature advocated outer limits of +/- 0.6 l/min for the bias of a Bland-Altman comparison of cardiac output values.



Since then, several CO validation studies against pulmonary and transpulmonary thermodilution with the noninvasive technology have been performed. The analysis of 10 of these studies [70-79] showed a bias range of 0.0 to 0.6 L/min, with an average of 0.24 ± 0.19 L/min. Based on these data and after discussion with the Data Management and Bio-center of the National Center for Cardiovascular

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Diseases (Professor Wei LI), the performance criterion was set at 0.5 L/min, i.e. bias is determined to be -0.5< bias < 0.5 l/min. This value is smaller in magnitude to the 0.8 l/min floor that the US FDA had previously considered for CO comparisons.

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

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

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