synchronized cardiac assist

Cardiac Assist
for Cardiogenic Shock and High Risk PCI
The Synchritude Registry

PROTOCOL NUMBER: 1.0

VERSION: 1.1

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Sponsor

XENIOS AG
Im Zukunftspark 1
74076 Heilbronn
Germany

www.i-cor.com
T +49 7131 2706 0
F +49 7131 2706 299
info@xenios-ag.com

Clinical Monitor:

MAXIS Medical GmbH
Karpfenweg 12
60327 Frankfurt am Main
Germany
Tel: +49.69.2400.3626
Fax: +49.69.2400.3627
Email: maxisoperations@maxismedical.com

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Abbreviations:

ACT	Activated clotting time
AE	averse event
AG	Aktiengesellschaft
ALT	alanine aminotransferase
APS-II	Acute Physiological Score II
aPTT	Activated partial thromboplastin time
AST	aspartate aminotransferase
AT III	Antithrombin III
bpm	beats per minute
BSA	body surface area
BUN	Blood urea nitrogen
CABG	Coronary Artery Bypass Grafting
°C	degrees centigrade
CE	conformité européenne
cm	centimeters
CO_2	Carbon dioxide
CONSORT	Consolidated Standards of Reporting Registrys
CRF	Case Report Form
CRP	c-reative protein
DR-AE	device-related adverse effects
DR-SAE	Device Related Serious Adverse Events
EC	Ethical Committee
ECG	Electrocardiogram
ECMO	extracorporeal membrane oxygenation
EEP	energy equivalent pressure
ESC	European Society of Cardiology
EU	European Union
F_{IO2}	Fractional Inspired Oxygen concentration
GCP	Good Clinical Practice
fHb	free hemoglobin
h	hour
IABP	intra-aortic balloon counterpulsation
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
ID	Identification
INR	international normalized ratio
ISO	International Organization for Standardization
LAVDs	left ventricular assist devices
L/min	liters/minute
LV	Left ventricle
MAP	Mean arterial pressure
MCP-1	Monocyte chemoattractant protein-1
MEDDEV	Medical Devices Directive
ml/min/m^2	milliliters/minute/meter-squared
mm Hg	millimeters of Mercury
mmol/l	millimol/liter
NAG	N-acetyl-beta-D-glucosaminidase
NAGL	Neutrophil gelatinase-associated lipocalin
S_{VO2}	mixed venous hemoglobin saturation
MODS	multiple organ dysfunction syndrome
NO	nitric oxide
O_2	Oxygen
PAI-1	plasminogen activator inhibitor-1
PIC	patient informed consent forms
PaO_2	partial pressure of oxygen in blood
PCI	Percutaneous coronary intervention
PEEP	positive end-expiratory pressure

PHI	protected health information
PI	Primary Investigator
ROSC	return of spontaneous circulation
RV	Right ventricle
SAE	Serious Adverse Event
SAPS	Simplified Acute Physiology Score
SHE	surplus hemodynamic energy
SOFA	Sequential Organ Failure Assessment
SD	standard deviation
tPA	tissue plasminogen activator
UADE	unanticipated adverse device effect
vWF	Von Willebrand factor

Executive Summary

SPONSOR:	i-COR® XENIOS AG
PROTOCOL TITLE:	**Cardiac Assist for Cardiogenic Shock and High Risk PCI (The Synchritude Registry)**
DEVICE:	i-COR® SYNCHRONIZED CARDIAC ASSIST INTENDED USE: Synchronized Cardiac Assist to enhance perfusion and oxygenation in the setting of combined heart-lung failure or in high risk percutaneous intervention procedures in the cardiac catheterization laboratory.
OBJECTIVES:	The purpose of this study is to perform post-market surveillance and evaluate prospectively the performance of the i-COR® SYNCHRONIZED CARDIAC ASSIST device in patients with cardiogenic shock or in patients undergoing high risk percutaneous intervention procedures in the catheterization lab.
DESIGN:	The Synchritude Registry is a prospective, non-randomized, multi-center, open-label registry of the performance of the i-COR® SYNCHRONIZED CARDIAC ASSIST device in patients with cardiogenic shock or in patients undergoing high risk percutaneous intervention procedures in the cardiac catheterization lab.
PATIENT POPULATION	Patients treated with the i-COR® SYNCHRONIZED CARDIAC ASSIST device in the setting of cardiogenic shock or undergoing high risk PCI.
SAMPLE SIZE:	Up to 300 patients
CLINICAL SITES:	Up to 30 clinical sites in Germany, Austria and France
OUTCOMES TO BE COLLECTED:	DEVICE PERFORMANCE: Technical success (defined as the ability to implant the i-COR® SYNCHRONIZED CARDIAC ASSIST device and establish synchronized cardiac assist without serious adverse events). CLINICAL EFFECTIVENESS: Device performance success (defined as the ability to establish synchronized cardiac assist and maintain or improve tissue oxygenation) assessed before and immediately post-procedure (acute) in each patient.
FOLLOW-UPS:	All patients will be studied at baseline and immediately after each patient is stabilized on cardiac assist.

INCLUSION: PATIENTS WHO PHYSICIANS HAVE SELECTED FOR TREATMENT WITH the iCOR® SYNCHRONIZED CARDIAC ASSIST device and who are being treated for:

- High-risk PCI
- Cardiogenic Shock

Patient or legal caregiver has provided written consent prior to data collection

EXCLUSION:

- Coma with fixed pupils not induced by drugs
- Mechanical causes for cardiogenic shock (ventricular septal defect of papillary muscle rupture)
- Severe peripheral arterial occlusive disease or other vascular abnormalities precluding insertion of femoral arterial or venous catheters
- Previous known aortic regurgitation greater than grade II
- Contra-indications for anticoagulation
- Severe hemolysis of any cause

1 Introduction: Description and research purpose of the study

1.1 Background and rationale: Explanation of the study purpose

Patients with cardiac dysfunction often present with reduced cardiac output, reduced blood pressure (hypotension), tachycardia and inadequate tissue perfusion. When severe and caused by a primary cardiac event (a myocardial infarction, for example), this is called cardiogenic shock. Cardiogenic shock is defined as a failure of cardiac pumping function which results in an increasing centralization of circulation, inadequate blood supply and inadequate oxygen supply to vital organs. This can cause confusion, agitation, somnolence in cases of reduced cerebral perfusion, oliguria or anuria in cases of reduced renal perfusion, gastrointestinal symptoms in cases of reduced mesenteric perfusion, and pale, cool, damp, mottled skin in cases of reduced peripheral perfusion (Hochman *et al.*, 1999; Dickstein *et al.*, 2008).

Myocardial infarction is the most common cause of cardiogenic shock and is responsible for shock in over 70% of cases, (Hochman *et al.*, 1999; Hochman, 2003). With rapid treatment of a myocardial infarction – "Every minute counts!" – and restoration of coronary circulation through acute coronary intervention, prehospital fibrinolysis, anticoagulation and combined anti-platelet therapy, the fatality rate due to myocardial infarctions has been reduced to less than 25 % in recent years. However, if cardiogenic shock occurs, the incidence of which is 4-8% (Hochman, 2003; Dickstein *et al.*, 2008; Howlett, 2011) the fatality rate following myocardial infarction remains high, between 50-70%, despite all interventional revascularization methods and optimized medical therapy (Hochman *et al.*, 1999; Dickstein *et al.*, 2008; Howlett, 2011). The prognosis for cardiogenic shock is not only dependent upon the magnitude of the reduction in heart function, but also on the extent of organ hypoperfusion and the severity of multiple organ dysfunction syndrome (MODS), which may develop as a consequence of tissue hypoperfusion.

Rapid myocardial revascularization (percutaneous coronary intervention or coronary artery bypass grafting) and drug-based therapy following myocardial infarction aim to achieve hemodynamic stabilization and thereby reduce end organ damage. When not initially successful and cardiogenic shock develops, medical support of cardiac function and blood pressure may be necessary. Medical therapy for combined heart-lung failure consists of optimizing preload, reducing afterload, augmenting inotropic function of the heart and supplemental oxygen therapy and mechanical ventilation with elevated fractional inspired oxygen concentrations and positive end expiratory pressure, if necessary to ensure adequate oxygenation of the arterial blood. Vasoactive substances (inotropes, vasopressors) are often necessary to increase myocardial function (cardiac output) and support blood pressure. These drugs, however, increases myocardial oxygen consumption, leading to an increased risk for myocardial ischemia and cardiac arrhythmia. Too often in the setting of severe combined heart-lung failure, these medical measures are inadequate, and mechanical circulatory support is necessary. In general, mechanical support should be considered at an "early stage" to improve outcomes (Sayer *et al.*, 2012).

Given the persistently high mortality of acute myocardial infarction when complicated by cardiogenic shock, there is still a need for effective mechanical cardiac assist that provides effective cardiorespiratory support in the setting of combined heart-lung failure. Synchronized cardiac assist is a new procedure used to generate physiological, heart-synchronous circulatory support that has not yet been tested systematically or used extensively in humans. In synchronized cardiac assist, blood is pumped through blood vessels to an extracorporeal membrane oxygenator, oxygenated there, and then reperfused into the body. Assisted blood flow occurs primarily during diastole and is synchronized to the heart beat by monitoring the ECG and using the ECG as a trigger to turn the pump on and off. Pumping function is generally accomplished using a centrifugal or diagonal pump. The output of the pump is regulated with a control device. Flow rates of up to 7 L/min can be achieved, but for most clinical applications, a blood flow rate of 2-5 L/min is sufficient. The key element of

every extracorporeal gas exchange system is the oxygenator, which receives deoxygenated blood via the pump. These hollow fiber diffusion oxygenators largely determine, along with the blood flow rate, the oxygenating capacity of the membrane. Carbon dioxide removal can be controlled by changing the gas flow rate (in L/min, "sweep gas") across the blood perfused hollow fiber gas exchange surface. The higher the blood CO_2 content, the higher this gas flow rate must be set (0.5 – 15 L/min). In order to achieve sufficient blood flow rates and optimal extracorporeal oxygenation, large lumen intravascular catheters are needed. The Seldinger technique is used to cannulate the femoral artery and vein to place these large bore catheters (Hecker *et al.*, 2012).

i-COR® combines extracorporeal membrane oxygenation with a small extracorporeal pump that is capable of delivering high blood flow synchronized to the heart beat (the ECG) so that the augmentation of cardiac output with well-oxygenated blood occurs during diastole and does not represent an increased afterload on the heart during systole. The purpose of the Synchritude Registry is to study the performance of the CE marked i-COR® Synchronized Cardiac Assist device to optimize the performance of the device in the setting of cardiogenic shock following or associated with cardiac ischemic events and in the setting of high risk percutaneous intervention procedures in the cardiac catheterization lab.

1.2 Description of prior basic research

Shepard et al. (Shepard *et al.*) published a seminal investigation highlighting the difference between continuous and pulsatile blood flow. They found that the mechanically measurable pressure, or the recording of the relevant pressure curve in the artery, is insufficient as an index of organ perfusion. They noted that if was more important to quantify the energy that is transported in a given segment of a vessel during a specific time period. This information is required to fully understand peripheral perfusion and regional microcirculation and to develop physiological systems for mechanical support of the cardiovascular system that simulate the natural pulsatile flow in the arterial system. These authors proposed a specific quantitative description of the effect of blood flow generated by the heart, or by cardiac support systems, to a) facilitate the comparison of the physiological effects of pulsatile and non-pulsatile flow, b) to differentiate between potentially different effects of different types of pulsatile flow, and c) to associate these effects with cardiovascular control mechanisms and with the design of an artificial heart.

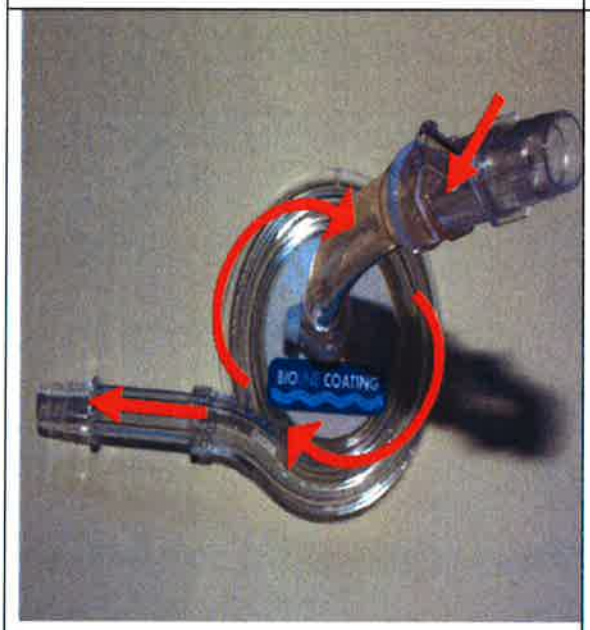
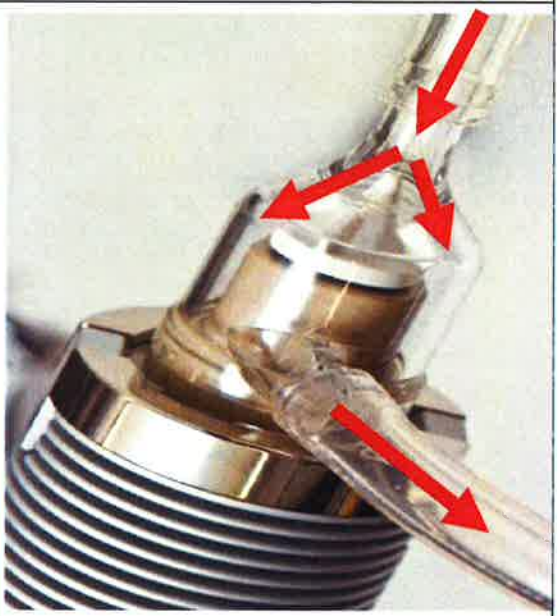
Shepard et al. developed a quantitative mathematical description of the pressure and flow that permits a precise description of pulsatile flow and facilitates the comparison between different forms of pulsating flow. They calculated the total energy of the flow at a specific location, which was associated with determining the amplitude and phase of the pressure, the flow rate and the energy and frequency spectra. They expressed the total energy of a flow as 'energy equivalent pressure' (EEP) and compared it with the mean pressure. The EEP encompasses the idea that starting from the aortic root, hemodynamic energy is transmitted into the periphery by the blood flow both through the axial movement of the blood and through a spring-like recoil of the aortic wall following its expansion.

As an example, they estimated an energy equivalent pressure (EEP) and mean pressure in a patient suffering from high blood pressure who had undergone surgery for renal artery stenosis. The mean pressure below the origin of the renal artery was 110 mmHg, and the calculated EEP was 128 mmHg. The difference of 18 mmHg represented the hemodynamic energy of 24,000 ergs/cm³ and reflects the difference between pulsatile and non-pulsatile flow at the same mean pressure. The greater EEP reflects the additional energy in the pulsatile flow pattern and indicates that to obtain a similar flow in distal vessels, a stable, unvarying mean pressure of 128 mm Hg would have been necessary to achieve the same flow benefit that was present during pulsatile flow at a mean pressure of only 110 mm Hg.

In animal models of pulsatile and non-pulsatile flow in extra-corporeal systems, Ündar et al. (1999) demonstrated that even when no significant differences were found for MAP, the EEP was significantly higher in those animals supported by pulsatile flow when compared with the

non-pulsatile group ($p<0.001$). These findings have been translated into humans where pulsatile mechanical circulatory support yields better results than an optimum medicinal therapy, as measured using 1-year survival rates (Guan *et al.*, 2010). Human organs and cells are naturally programmed to detect and process dynamic changes in pressure and flow. Mechanotransduction in the vascular endothelium is based on the reaction to shear stress and pulse pressure. The flow profile acts directly on endothelial cell regulation of apoptosis, angiogenesis, atherosclerosis, vascular remodeling and systemic blood pressure. Endothelial cell function depends on the frequency, mean value and amplitude of the mechanical impulse (Soucy *et al.*, 2013). It is insufficient to describe pulsatility using pulse pressure or the pulse pressure index. Determination of the EEP as the quotient of the product of the integral of flow and pressure change divided by the integral of flow change, and the calculation of surplus hemodynamic energy (SHE) from the difference between EEP and MAP is better suited to describe the hemodynamic energy and physiological benefits made available by a given pulse. Calculation of SHE captures the additional energy in the pulsatile flow that is not represented by the MAP.

The geometry of the blood pumps used has an important influence upon the mechanical stress on blood cells and thereby the destruction of red blood cells (hemolysis) and activation of platelets, which can be associated with thromboembolic complications during ECMO. Currently, there are three main categories of blood pump available, depending on the manufacturer: Centrifugal, axial, and diagonal flow. With a centrifugal blood pump design, high pressure and low flow rates can be generated, while with an axial design, high flow rates and low pressure can be generated. A diagonal design allows for the generation of high flow rates as well as high pressures (Giersiepen *et al.*, 1990; Reul & Akdis, 2000; Toomasian & Bartlett, 2011). The combined high flow rates and low pressures associated with the diagonal pump design meet important requirements for pulsatile blood pump systems, and the operating characteristics of diagonal pumps are desirable for use in veno-arterial combined cardiac and respiratory support in the setting of cardiogenic shock. The ability to generate high flow rates quickly with a low pressure head is important to allow synchronized cardiac assist during diastole.

Centrifugal blood pump design	Diagonal blood pump design
	

Centrifugal pumps are particularly well-suited to generate pulsatile flow since they can be activated and inactivated quickly. Patel et al. (2014) recently published the first *in vitro* study on the ECG controlled pulsatile operation of the i-COR® diagonal pump in a veno-arterial extracorporeal life support circulatory system with an iLA® membrane oxygenator and 3/8" tubing. Ventricular salvos, ventricular tachycardia at 177 bpm, ventricular fibrillation at 193 bpm and sequential AV stimulation were simulated at flow rates of 2.5, 3.0, 3.5 and 4 l/min and supported with pulsatile flow and R-wave synchronization at ratios of 1:1, 1:2 und 1:3. The gain in surplus hemodynamic energy (SHE) was highest for 1:1 synchronization under ventricular salvos. For all other arrhythmias, the 1:2 ratio of support generated flow curves of physiological quality and, with values of around 20,000 ergs/cm³, a substantially higher SHE than the 1:1 and 1:3 support. The authors confirmed that the i-COR® diagonal pump can provide adequate circulatory support in cases of life-threatening arrhythmias.

1.3 Description of prior research in humans (literature)

The main indication for use of veno-arterial circulatory support and extracorporeal gas exchange is combined heart-lung failure. In most cases, femoral veins and arteries are cannulated, and deoxygenated venous blood is oxygenated extracorporeally and reperfused arterially. The extracorporeal gas exchange part of the i-COR device and the pump form a parallel circulatory system to each patient's own heart and lungs. the addition of the i-COR device almost completely replaces left ventricular pumping function, thereby providing both relief to the pump function of the injured heart and support of the gas exchange function of the injured or compromised lungs (Hecker *et al.*, 2012). To date, there have been no prospective, randomized, multi-center studies of the application of veno-arterial ECMO in the setting of cardiogenic shock. In a small analysis with a historical control group, the ECMO group was found to have a significantly improved survival rate (Sheu *et al.*, 2010). The purpose of the Synchritude Registry to provide additional information on the performance characteristics and optimization of pulsatile synchronized cardiac assist in the setting of cardiogenic shock.

When ECMO is used the flow of blood returned to the arterial system (distal aorta) is retrograde against the normal, physiologically appropriate flow direction and this flow, opposed to the normal direction of flow, can an increase ventricular afterload when the retrograde flow occurs during systole. Patients who require ECMO can ill afford and increased afterload, which further reduces the cardiac output (The effect of retrograde flow is minimized in the i-COR device by delivering flow only during diastole). Ideally, blood should be returned to the arterial system in a pulsed flow, but this has not been possible using previously available pumps (Hecker *et al.*, 2012). The i-COR® Synchronized Cardiac Assist device overcomes this limitation and permits pulsed flow during diastole only (thereby avoiding increased afterload on the left ventricle during systole).

The putative benefits of pulsatile flow, demonstrated in vitro and in animal studies have been confirmed in human trails. Agirbasli et al. (2014) investigated the fibrinolytic equilibrium in blood plasma as a modulator of neurophysiological and pathological processes that can cause periventricular leukomalacia, injury to the white matter, in 40 infants, who underwent pulsatile (101±7 min) or non-pulsatile (108±8 min) extracorporeal circulation during open heart surgery. They measured the tissue plasminogen activator, tPA, and the plasminogen activator inhibitor-1, PAI-1, before the incision, 1h after starting extracorporeal circulation and 24h after surgery. Compared with the initial values, both values in both groups were three times higher after 1h of extracorporeal circulation and dropped off again significantly after 24h. PAI-1 levels in the non-pulsatile group decreased more and dropped below the initial level. This resulted in a significant deterioration in the PAI-1 to tPA ratio in the non-pulsatile group (median 4.63±0.83 to 1.98±0.48, p=0.03), but not in the pulsatile group (median 4.50±0.92 to 3.56±1.28, p=0.2). In a study of the sublingual microcirculation using side stream dark field imaging in prospectively randomized adult patients undergoing CABG, one group received non-pulsatile perfusion (n=17) and the other group received pulsatile perfusion at a frequency of 60 bpm (n=16) during clamping time (Koning *et al.*, 2012). The O_2 extraction rate increased significantly during pulsatile perfusion from 70±14 ml/min/m² at the start to 82±16 ml/min/m² at the end of clamping time. The density of the perfused vessels was reduced peri-operatively in both groups. In the non-pulsatile group, it remained low for 1h after surgery, while the density of perfused vessels returned to the initial value in the pulsatile group. The post-operative microvascular flow index was significantly higher in the pulsatile group than in the non-pulsatile group (2.5-2.9 vs. 1.7-2.5; p=0.001).

Gu et al. (2011) randomly allocated 32 adult patients, who were required to undergo elective CABG under hypothermic extracorporeal circulation, to two groups, of which one group was given pulsatile perfusion at 60 bpm at a pump minute volume of 2.4 l/min·m² BSA over the course of the X-clamp time, which lasted 47±11 min. The pressure pulse was 22±7 mmHg, which resulted in a clear increase in SHE in the arterial tubing of the extracorporeal circulation system. In the radial artery however, SHE was only a tenth of the value it had been in the extracorporeal tubing downstream from the oxygenator and a quarter of the value in the aortic cannula. There were no significant postoperative differences between treatment groups among fHb, vWF, NO and MCP-1 (markers of endothelial activation), IL-6 and CRP (markers of a systemic inflammation), or NAG and NGAL (markers of acute renal injury). Thus, much of the surplus energy generated by pulsatile flow can be lost in the extracorporeal circulatory elements. In a pilot study, Alkan et al. (2006) randomly allocated 50 consecutive patients aged between two days and six years, who had required surgical correction of a congenital heart defect using hypothermic extracorporeal circulation, into two groups receiving pulsatile or non-pulsatile perfusion. Soon after surgery in the pulsatile group, they found significantly lower catecholamine requirements both in number (1.5±1.1 vs. 2.4±1.0) and dosage, significantly higher urine production (659±211 vs. 528±225 ml/d) and a significantly shorter intubation time (20.4±17.0 vs. 35.4±30.7 h), time in ICU (2.2±1.1 vs. 4.3±4.2 d) and time in hospital (7.6±2.5 vs. 11.8±6.8 d). In a second outcome study, Alkan et al. (2007) allocated 215 consecutive patients aged two days to sixteen years to a group with pulsatile (n=151) and a group with non-pulsatile (n=64) during hypothermic perfusion. Not only were fewer inotropic drugs required during pulsatile compared to nonpulsatile extracorporeal circulation (1.4±0.1 vs. 2.0±0.1, p=0.0012), urine production was also higher

(603±22 vs. 506±34 ml/d, p=0.016). Moreover, intubation time (10.3±1.0 vs. 18.6±2.0 h) and time in ICU (1.5±0.1 vs. 2.8±1.2 d) and time in hospital (6.7±0.2 vs. 11.1±0.6 d) were significantly shorter. They found no differences for CRP, ALT and AST, but significantly lower lactate values (16.3±2.0 vs. 24.7±3.0 mg/dl) and higher albumin values (3.15±0.03 vs. 2.95±0.06 mg/dl) in the pulsatile flow treatment group. Finally, in a meta-analysis carried out on 298 clinical trials, Sievert and Sistino (2012) identified ten studies, of which three were in children, that investigated the effects of pulsatile perfusion on renal function after cardiac surgery during cardiopulmonary bypass. The pulse was generated using a roller pump in six studies (three pediatric studies) and generated using IABP in four studies. Overall, 708 patients (384 children) received pulsatile and 477 (170 children) patients received non-pulsatile extracorporeal circulatory support. No differences were found in creatinine and creatinine clearance before surgery or during bypass. However, creatinine clearance was significantly higher and serum lactate significantly lower after surgery in those patients who received pulsatile perfusion compared to the non-pulsatile perfusion group.

The foregoing studies confirm that at the level of the microcirculation, at the level of activation of the coagulation cascade and at a more macroscopic level of blood pressure support and organ perfusion, pulsatile flow offers significant advantages over stable, invariant patterns of flow. Moreover, the diagonal pump used in the i-COR® Synchronized Cardiac Assist device is capable of delivering adequate flow in a pulsatile manner so as to sustain effective synchronized cardiac assist during diastole.

2 Purpose of the Study

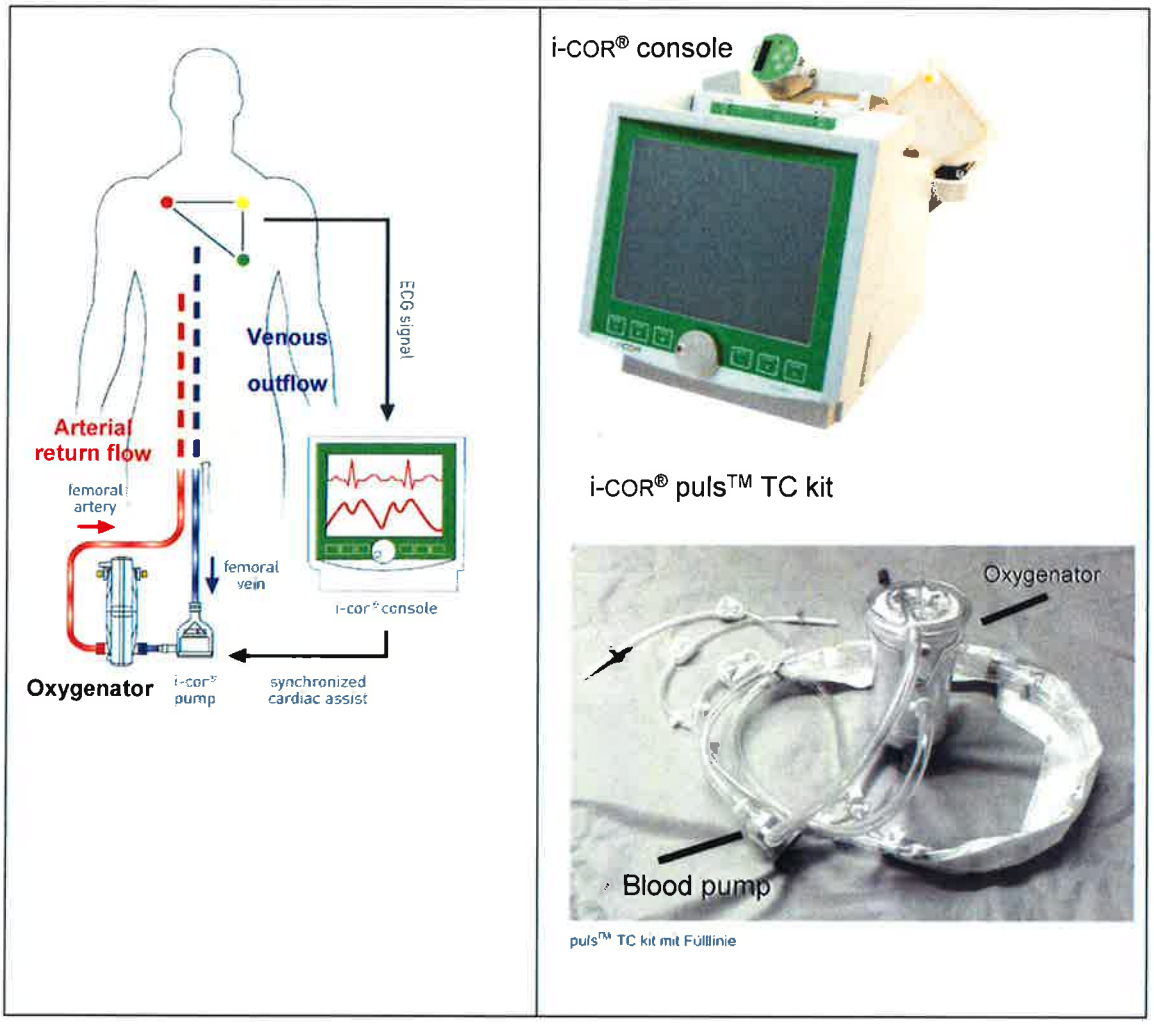
The purpose of the Synchritude Registry is to gather clinical data that describes the clinical outcomes of patients in whom the i-COR® Synchronized Cardiac Assist device is used to treat either cardiogenic shock or high risk percutaneous coronary intervention (PCI) procedures in the cardiac catheterization lab. Data will be collected that describes the best process to optimize synchronization of the i-COR® Synchronized Cardiac Assist device with each patient's electrocardiogram.

2.1 Study device

The i-COR® Synchronized Cardiac Assist device consists of two parts: the i-COR ®puls™ TC and the I-COR® console (as shown below). The i-COR® console operates, powers, controls, regulates and monitors the operation of the i-COR® blood pump and permits synchronization of the pump function with each patient's ECG rhythm. The i-COR® console consists of the following components: an i-COR® drive unit (drive motor for the pump module, with a control panel for emergency operation); the i-COR® sensor box (central control unit with connectors for various sensors); the i-COR® power supply; and the i-COR® console control panel, which is the user interface with a touchscreen display.

The i-COR console offers the following additional functions:

- Recording each patient's ECG and heart rate
- Representation of the recorded R wave as a spike above the ECG wave. The spike is the trigger point for synchronized cardiac assist therapy delivered mainly during diastole.
- Graphical presentation of the ECG
- Numerical presentation of the heart rate
- Cardiac synchronous pulsatile circulatory support
- User interface which accommodates the functionality



2.2 *Disposables*

The following items are disposable parts of the i-COR® system:

- Venous cannula – Standard cannula sizes should be 21-25 French diameter with a length of 55 cm with side holes. Alternatively, self-expanding 17 Fr catheters 630 to 680 mm long (Eurosets Smart Drainage Device) may also be used.
- Arterial cannula - For arterial cannulation, the Medos cannula with a diameter of 16 or 18 French and a length of 38 cm is designated.
- The i-COR® puls™ TC kit contains both a membrane oxygenator and a blood pump capable of generating pulsatile blood flow. The function of the i-COR® puls™ TC kit is controlled through the i-COR® console.

2.3 *Intended use of study device*

Synchronized Cardiac Assist delivers blood flow during diastole synchronized to the ECG of the patient. Synchronized Cardiac Assist is meant to be used in adult patients only, and the main indications are cardiovascular support for high-risk cardiological interventions or treatment of cardiogenic shock.

The i-COR® Synchronized Cardiac Assist device is indicated for treatment of cardiogenic shock and use in high risk coronary revascularization procedures.

2.4 Objectives of the study

The purpose of the Synchritude Registry is to provide additional information on the performance characteristics and optimization of synchronized cardiac assist in the setting of cardiogenic shock and in high risk coronary revascularization procedures.

2.4.1 Outcomes to be collected

Device Performance Outcomes: Technical success (defined as the ability to successfully deliver the i-COR® SYNCHRONIZED CARDIAC ASSIST device without serious adverse events).

Clinical Effectiveness Outcomes: Device performance success (defined as the ability to establish synchronized cardiac assist assessed immediately post-procedure in each patient.

3 Study protocol

3.1 Study Design

This is a prospective, non-randomized, open-label, multi-center observational study of the performance and clinical effectiveness of the i-COR® SYNCHRONIZED CARDIAC ASSIST device in patients with cardiogenic shock or undergoing high risk PCI procedures.

3.1.1 Study patients

Patients who the treating physician has elected to use the i-COR® SYNCHRONIZED CARDIAC ASSIST device in the setting of cardiogenic shock or undergoing high risk PCI may be enrolled in the Synchritude Registry.

3.1.2 Sample size

Up to three hundred (300) patients will be enrolled in the Synchritude Registry.

3.1.3 Inclusion Criteria

Patients treated with the iCOR® SYNCHRONIZED CARDIAC ASSIST device will have one of the following two medical problems:

- Patients in cardiogenic shock

  or

- Patients undergoing high risk coronary revascularization procedures (e.g., multi-vessel disease, unprotected left main, or last patent conduit interventions) in the catheterization lab.

- Cardiogenic shock is defined as
  - Systolic blood pressure < 90 mmHg for at least 30 min **OR**
  - Inotropes are needed to maintain blood pressure > 90 mmHg **OR**
  - Clinical signs of cardiac insufficiency with pulmonary congestion **OR**
  - Signs of end organ hypoperfusion with at least one of the following criteria:
    - Altered mental status
    - cold, damp skin or extremities
    - oliguria (≤ 30 mL/h)

- serum lactate > 2.0 mmol/L

- Patient or legal caregiver has provided written consent prior to data collection.

3.1.4 Exclusion criteria:

- Coma with fixed pupils not induced by drugs
- Mechanical causes for cardiogenic shock (ventricular septal defect of papillary muscle rupture)
- Severe peripheral arterial occlusive disease precluding insertion of femoral arterial or venous catheters
- Previous known aortic regurgitation greater than grade II
- Contra-indications for anticoagulation
- Severe hemolysis of any cause
- Use of radio frequency surgical instruments
- Use of a reservoir is prohibited

3.1.5 Patient consent and participation

Patients in whom the treating physician has decided to use the i-COR® Synchronized Cardiac Assist device are eligible to be enrolled in the Synchritude Registry. Patients will be provided a copy of the Informed Consent Form which will be verbally reviewed by the study site personnel, allowing adequate time for questions. Once the patient has read and understands the Informed Consent, he / she will indicate his / her willingness to participate in the study by signing the consent form. If the patient is unable to give consent, his / her legally authorized representative may do so. The study will be explained to the patient in lay terms. If a patient is unable to give consent, and a legal guardian is not available, consent may be obtained after the i-cor® Synchronized Cardiac Assist is used and the patient becomes capable of consent. In all cases the Patient Informed Consent (PIC), approved by the site Ethics Committee (EC), must be signed by the potential study participant before any patient data are recorded in the study database. A copy of the signed and dated PIC should be provided to the subject. Patients who expire prior to regaining the ability to consent may be included in the database. All patients or legal guardians must be informed that they may withdraw consent at any time, and for any reason, and will continue to receive therapy as indicated by their physician.

3.1.6 Patient enrollment

A patient is eligible for enrollment at the time the procedure to place the i-COR® Synchronized Cardiac Assist device and one or both of the cannulae are inserted or any time thereafter.

Enrolled patients will be followed until the completion of synchronized cardiac assist or until the termination of the study by Sponsor.

3.1.7 Withdrawals

Study participation is voluntary, and patients may choose to withdraw consent for this study at any time for any reason without effect on subsequent medical treatment or relationship with treating physician. Additionally, the Investigator may choose to withdraw patients from the study at any time if he feels that it is in the patient's best interest to discontinue the study. Reasons affecting the Investigator's decision to withdraw a patient may include, but are not limited to, the following:

- Lost-to-Follow-up: if patient fails to return or becomes lost to follow-up (i.e., patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw) for visits for any reason, the patient will be designated an early termination. The clinical site Primary Investigator should show "due diligence" by documenting in the source documents, all steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. Vital status for those lost-to-follow-up may be obtained using outside records/ death registries;
- Non-compliance to study treatment, protocol deviations and violations should not lead to early termination unless they indicate a significant risk to the patient's safety;
- Other Investigator determination;
- Early study closure; and
- Adverse event.

Patients with an ongoing adverse event (AE) at the time of withdrawal should be followed in the trial until the event has been resolved or stabilized. Withdrawn patients will be included in the outcome data analysis.

The study can be terminated by the Sponsor at any time and for any reason. Should this be necessary, patients currently receiving synchronized cardiac assist within the Synchritude Registry will be withdrawn from the study early. The clinical site Primary Investigator (PI) will be responsible for informing the appropriate Ethics Committee (EC), and/or other applicable regulatory authority of the early study termination.

3.2 Clinical sites

Up to 30 centers will take part, and up to 300 patients receiving the i-COR® SYNCHRONIZED CARDIAC ASSIST device with cardiogenic shock or undergoing high risk PCI procedures will be included in the study.

3.3 Study Overview

Each consented patient's medical record will be reviewed and relevant medical history and demographics will be recorded on the study Case Report Form (CRF; age, gender, weight, height). The indication for use of the i-COR® SYNCHRONIZED CARDIAC ASSIST device should also be noted: cardiogenic shock or high risk PCI procedure. The cause of cardiac shock and the nature of the risk in the PCI should be recorded.

Regardless of indication for treatment (cardiogenic shock or high risk PCI), three sets of measurements will be made as shown in the table below.

Indication:	**Cardiogenic shock**	**High risk PCI**
Measurements	Time:	Time:
Baseline assessment	Before initiation of synchronized cardiac assist	Before initiation of synchronized cardiac assist
Assessment after initiation of treatment	Within one hour after initiation of cardiac assist when the patient is stable	Immediately after initiation of cardiac assist and prior to PCI procedure
Interval assessment	24 hours after patient has been on cardiac assist or prior to termination of therapy, whichever comes first	Immediately post-PCI procedure and prior to termination of therapy

3.3.1 Baseline assessment

Each subject's vital signs (heart rate, blood pressure, respiratory rate and body temperature and SaO_2) will be recorded.

The most recent arterial blood gasses should be recorded along with the serum lactate level.

Baseline laboratory values, including a complete blood count, electrolytes, ionized calcium, BUN, creatinine, lactate dehydrogenase, haptoglobin and free hemoglobin should be recorded. In addition, the ACT or aPTT, INR, AT III, D-Dimers and fibrinogen should be recorded and standard indices of liver function should be recorded.

The occurrence and nature of the patient's myocardial event precipitating cardiogenic shock will be collected (EKG, CK-MB, Troponin and other relevant studies).

The medications and doses should be recorded. This is especially true of intravenous medications given to support blood pressure in the setting of shock.

3.3.2 Assessment of the procedure.

Arterial and venous cannulae will be placed. It is recommended that the location of the arterial and venous cannulae be confirmed with an abdominal x-ray, as per the standard of care for any circulatory support device or according to medical necessity.

Antegrade perfusion of the access arterial vessel, if used, will be noted and described.

The settings of the i-cor Synchronized Cardiac Assist device will be recorded, and the effectiveness of EKG capture and he ratio of assist will be noted. The flow rate, the adequacy of synchronization, the synchronization ratio and other values provided by the i-COR® CONSOLE should be recorded.

3.3.3 Assessment after initiation of treatment

The i-COR® SYNCHRONIZED CARDIAC ASSIST device should be placed according to the Instructions for Use. After the device is in place, each patient should be placed on cardiac assist and the device synchronized to each patient's ECG as quickly as possible. The i-COR® SYNCHRONIZED CARDIAC ASSIST device should be used initially in 1:1 heart beat: synchronized assist ratio. The flow rate should be adjusted to achieve a stable mean arterial blood pressure greater than 65 mm Hg and stable cardiac function.

Once stable vital signs have been obtained, data should be recorded on the following variables.

Each subject's vital signs (heart rate, blood pressure, respiratory rate and body temperature and SaO_2) will be recorded.

The most recent arterial blood gasses should be recorded along with the serum lactate level.

The settings of the i-COR® SYNCHRONIZED CARDIAC ASSIST device should be noted. The flow rate, the adequacy of synchronization, the synchronization ratio and other values provided by the i-COR® CONSOLE should be recorded.

The medications and doses should be recorded. This is especially true of intravenous medications given to support blood pressure in the setting of shock and true of any anticoagulants administered.

Whenever possible, the level of catecholaminergic cardiac support should be weaned to the minimum required dose(s).

Anticoagulation therapy should be performed and controlled according to the hospital standards for extracorporeal therapies requiring Unfractionated Heparin (UFH). If the Activated Clotting Time (ACT) is used to assess anticoagulation, the value should be kept above 180 seconds, at a minimum, and should be recorded before and after administering the heparin and assessed approximately every 20 minutes in the initial phase of anticoagulation. After stabilization, ACT should be assessed at 2 hour intervals the first day and at 6 intervals on the following days, plus additional measurements 20 minutes after each change in heparin dosage. If the Activated Partial Thromboplastin Time (aPTT) is used for routine clinical monitoring of anticoagulation therapy using UFH, the value should be kept at the recommended level according to the hospital standards, approximately 1.5 – 2.0 times greater than the baseline value and should be recorded approximately every 20 minutes in the initial phase of anticoagulation and, after stabilization, at 2 hour intervals the first day and at 6 hour intervals for the following days, plus additional measurements of the aPTT 20 minutes after each change in heparin dosage.

The adequacy of perfusion of the legs should be noted.

3.3.4 Interval assessment after initiation of synchronized cardiac assist

Each subject's vital signs (heart rate, blood pressure, respiratory rate and body temperature and SaO_2) will be recorded.

The most recent arterial blood gasses should be recorded along with the serum lactate level.

The settings of the i-COR® SYNCHRONIZED CARDIAC ASSIST device should be noted. The flow rate, the adequacy of synchronization, the synchronization ratio and other values provided by the i-COR® CONSOLE should be recorded.

The medications and doses should be recorded. This is especially true of intravenous medications given to support blood pressure in the setting of shock and true of any anticoagulants administered.

Whenever possible, the level of catecholaminergic cardiac support should be weaned to the minimum required dose(s) before the interval assessment if conducted.

Anticoagulation therapy should be performed and controlled according to the hospital standards for extracorporeal therapies requiring Unfractionated Heparin (UFH). It is recommended that the ACT be kept above 200 seconds and/or the aPTT be kept at values 1.5 times the baseline level. Whichever method is used, the level of anticoagulation should be carefully controlled and documented by measuring the ACT or aPTT at regular intervals not longer than 6 hours, plus additional measurements not later than 20 minutes after each change in heparin dosage. Additional measurements may be made whenever needed to achieve these recommended levels of anticoagulation.

The adequacy of perfusion of the legs should be noted.

3.4 Study Outcomes to be Collected

The objective of the Synchritude Registry is to collect prospective performance and effectiveness information for the i-COR® SYNCHRONIZED CARDIAC ASSIST when used in the setting of cardiogenic shock or in patients undergoing high risk PCI procedures.

3.4.1 Device Performance

i-COR® SYNCHRONIZED CARDIAC ASSIST device performance outcomes include Technical Success, defined as the ability to successfully deliver the i-COR® SYNCHRONIZED CARDIAC ASSIST device without serious adverse events.

3.4.2 Clinical Effectiveness

Clinical effectiveness outcomes to be collected include the incidence rates of blood hemolysis, bleeding, thromboembolic events, infections, other adverse events, serious adverse events and death of any cause occurring following the i-COR® SYNCHRONIZED CARDIAC ASSIST procedures. Composite incidence rates of these events and death of any cause will also be calculated.

3.5 Outcome Data Compilation and Analysis

Information from enrolled patients will be collected on the case report forms. Data will be compiled and summarized at interim periods throughout the study period by i-COR and its designated research partner.

4 Risk analysis

The intended indications for use of the i-COR® SYNCHRONIZED CARDIAC ASSIST are to provide Synchronized Cardiac Assist to enhance perfusion and oxygenation with pulsatile blood flow in the setting of combined heart-lung failure or in high risk percutaneous intervention procedures in the cardiac catheterization lab. These patients are, by definition, severely ill. Synchronized Cardiac Assist will often be provided as a 'rescue' therapy when supportive medical care is inadequate to sustain oxygenation and perfusion of tissues. This group of patients has a high mortality in even when optimal medical therapy is provided.

4.1 Anticipated risks

The i-COR® SYNCHRONIZED CARDIAC ASSIST DEVICE risk analysis and review was conducted as part of the CE Marking in accordance with ISO 14971:2012. Please reference i-COR® SYNCHRONIZED CARDIAC ASSIST Product Labeling for a complete listing of potential risks related to the use of the i-COR® SYNCHRONIZED CARDIAC ASSIST device.

Since this is an observational registry of patients being treated with the i-cor® SYNCHRONIZED CARDIAC ASSIST device, the only potential risk of study participation is the risk of loss of privacy during the collection of data on each subject's procedure and follow-up while participating in the study.

4.2 Manner in Which the Potential Risks Have Been Minimized

The Sponsor has implemented a risk management program to analyze, monitor, and mitigate risk identified in preclinical testing, during the clinical study, and in the commercial device. The program is based on ISO 14971:2012 and has been reviewed during both the ISO 13485 certification and CE Marking processes.

To protect against a subject's risk of participating in the study, all data collected will be made pseudonymous and the subject's name will not be recorded in the study. Any information obtained in connection with this study that may be identified with a specific subject will remain confidential.

4.3 Anticipated benefits

The i-COR® SYNCHRONIZED CARDIAC ASSIST is expected to increase cardiac output, stabilize the vital signs and reduce the manifestations of cardiogenic shock. After a period of synchronized cardiac assist, it is expected that patients will be weaned from i-COR® SYNCHRONIZED CARDIAC ASSIST with improved and stabilized cardiac function. In those patients receiving i-COR® SYNCHRONIZED CARDIAC ASSIST during high risk PCI procedures, it is expected that myocardial tissue will be preserved and cardiac function protected by the i-COR® SYNCHRONIZED CARDIAC ASSIST device. The benefits of using the i-COR® SYNCHRONIZED CARDIAC ASSIST device include the benefits of pulsatile flow in terms of surplus hemodynamic energy achievable at lower mean arterial pressures and the benefits of

improved endothelial function associated with pulsatile flow. The benefits of synchronized cardiac assist are likely to be greater than the benefits of intra-aortic balloon counterpulsatioon (IABP), since improved blood oxygenation is part of the i-COR® SYNCHRONIZED CARDIAC ASSIST device. Similarly, the benefits of synchronized cardiac assist are likely to be greater than the benefits of an LVAD device because the i-COR® SYNCHRONIZED CARDIAC ASSIST device does not place a load on the left ventricle during systole and incorporates improved blood oxygenation as well. Last, the benefits of synchronized cardiac assist are likely to be greater than the benefits of an ECMO because the i-COR® SYNCHRONIZED CARDIAC ASSIST device provides pulsatile, synchronized cardiac assistance during diastole in addition to the improved oxygenation associated with ECMO. Nevertheless, patients may not experience any direct benefits from participating in the study; however, patients may benefit from being more closely monitored by their physician. The information gathered from the Synchritude Registry may further inform physicians on the treatment options for cardiogenic shock and prevention of myocardial infarction during high risk PCI procedures. This knowledge may advance medical science and have a benefit on other patients.

4.4 Risk-to-benefit assessment

On the basis of the laboratory evaluations and the initial clinical experience to date, the i-COR® SYNCHRONIZED CARDIAC ASSIST device has a high success rate augmenting cardiac output and improving oxygenation in the setting of cardiogenic shock and a low risk of complications. The potential benefits are expected to match or exceed the benefits associated with IAPB use and with extracorporeal membrane oxygenation since the i-COR® SYNCHRONIZED CARDIAC ASSIST device provides both synchronized cardiac assist without increasing the work of the heart and improved oxygenation and carbon dioxide removal.

The i-COR® SYNCHRONIZED CARDIAC ASSIST device was determined to present acceptable potential risks and benefits by the EU Notified Body during the conformity assessment procedures resulting in achievement of the CE Marking.

5 Device accountability

The Investigator will maintain a Device Log and monitor the use of devices used for this study. The log will be kept with the study documents and will be available for review during sponsor monitoring visits. Documentation on the log will at a minimum include:

- Device lot/ serial number
- Date used on the patient along with the patient ID (if applicable)
- Date of return along with the reason for return (if applicable)
- Device failure or malfunctions will be documented; any failure will be reported on the appropriate CRF.

In case of a device failure or malfunction related to the study device, a description of the malfunction should be reported to XENIOS AG for analysis. Depending on the analysis of the device failure or malfunction, the i-COR® SYNCHRONIZED CARDIAC ASSIST device may be restored to proper functioning at the study site, or the device may be returned to XENIOS AG for analysis. If the Investigator thinks that an SAE during the procedure may be related to the device malfunction, then the device must be returned to XENIOS AG.

6 Monitoring procedures

6.1 Study monitoring

XENIOS AG and/or its designated representative will be responsible for monitoring procedures related to study conduct and data collection/reporting to ensure the quality and integrity of the outcomes registry data. Before commencement of enrollment at each clinical site, a site initiation visit will be conducted. During the duration of the study, a trained field

monitor will visit each clinical site periodically, to check the completeness of patient records, the accuracy of entries on the case report forms (CRFs), the adherence to the protocol and to Good Clinical Practice (GCP), per the Monitoring Guidelines. Monitoring procedures will include verification of a completed informed consent for each patient, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the accurate collection of the objective outcomes data. Upon completion of the study (i.e., all patients at the clinical site have completed follow-ups and/or been closed-out), a final site close-out visit will be conducted to ensure that all protocol and data management issues have been resolved.

Key trial personnel at the site must be available to assist the study monitor during these visits. The investigator must give the monitor access to relevant hospital or clinical records, to confirm consistency with reported CRF data. No identifier data from these records will be recorded or removed from the clinical site.

6.2 Audits and inspections

The PI will allow representatives of the governing EC and other applicable regulatory agencies to inspect all study records, CRFs, and corresponding portions of the PI's office and/or hospital medical records as necessary. These inspections are intended to verify protocol adherence, data completeness and accuracy, and compliance with all applicable regulations.

The investigator and/or his designee should contact XENIOS AG, Im Zukunftspark 1, 74076 Heilbronn, Germany within 24 hours upon being notified of an impending regulatory body inspection. A clinical monitor may assist and review study documentation with the investigator and/or designee to prepare for the audit.

An investigator shall permit authorized regulatory body employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where the investigational study devices are used and to inspect and copy all records relating to the study.

An investigator shall permit authorized regulatory body employees to inspect and copy records that identify patients, upon notice that the regulatory authority has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or EC or other applicable regulatory authority have not been submitted or are incomplete, inaccurate, false or misleading.

7 Statistics

7.1 Power and Determination of Sample Size

This is a single-arm observational study. No power calculation was performed.

7.2 Statistical Hypotheses and Level of Significance

This is not a hypothesis testing study; this is a descriptive performance study.

7.3 Evaluability of Data

Summaries of the study results will include all available data from enrolled subjects.

7.4 General Statistical Considerations

Summaries of continuous data will include the number of subjects, mean and standard deviation. The median and range may also be provided as appropriate. Categorical data will be displayed as the mean and percent.

7.5 Missing Data

Unless otherwise noted, denominators for the computation of percentages will exclude subjects with missing data. Missing results will be identified, but no imputation of missing values will be performed. This also applies to withdrawn subjects.

7.6 Data Pooling

Data will be pooled from all trial sites. The basis for pooling is that all sites used the same protocol, the Sponsor monitored the sites to assure protocol compliance, and the sites all used the same data gathering mechanism (CRFs and data entry methods).

7.7 Subject Demographic and Baseline Characteristics

The baseline characteristics of the trial population observed at baseline will be presented descriptively. For continuous variables, such as subject age, the mean, standard deviation (SD), median and range will be presented. For categorical variables, such as presence of conditions observed under medical history, the number of subjects experiencing the condition over the total number of subjects completing the trial, the percentage and the exact 95% confidence interval on the percentage will be presented.

7.8 Adverse Events

The number of subjects experiencing one or more Device Related Serious Adverse Events (DR-SAE) including: death; myocardial infarction; bleeding, hemolysis or thromboembolic events at discharge and 30-days post-procedure, the percentage, and the exact 95% confidence limit will be provided.

7.9 Primary Performance Summary

The rate of technical success (defined as the ability to successfully deliver i-COR® SYNCHRONIZED CARDIAC ASSIST support without serious adverse events) will be tabulated. The number of subjects with technical success, the percentage of all subjects and the exact 95% confidence limit will be provided.

Device performance success (defined as the ability to establish synchronized pulsatile cardiac assist, enhancement of cardiac function – blood pressure and cardiac output - and improve tissue oxygenation) assessed immediately post-procedure (acute) and serially as device remains in place in each patient will be tabulated. The number of subjects with performance success and the magnitude of performance success, the percentage of all subjects and the exact 95% confidence limit will be tabulated for each of the variable collected.

8 Data management

Standardized CRFs will be provided to all participating sites for reporting the results of the trial. All data from the trial will be entered from the CRFs into a central database. Incoming data will be frequently reviewed to identify inconsistent or missing data and any adverse events. Any data issues are to be promptly addressed with the Investigator. Quality assurance procedures will be established to ensure that complete accurate, and timely data are submitted, that protocol requirements are followed and that adverse events are correctly reported and investigated as appropriate. Investigators are to maintain all source documents as required by the protocol, including laboratory results, supporting medical records, and signed patient informed consent forms (PICs). The source documents will be used during regular monitoring visits to verify data contained on the completed CRFs.

8.1 Data handling and confidentiality

Information about study patients will be kept confidential and managed according to the requirements of the Bundesdatenschutzgesetz. Those regulations require a signed patient authorization informing the patient of the following:

- What protected health information (PHI) will be collected from patients in this study.
- Who will have access to that information and why.
- Who will use or disclose that information.
- The rights of a research patient to revoke his/her authorization for use of his/her PHI.

In the event that a patient revokes authorization to collect or use PHI, the PI, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients 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 patient is alive) at the end of their study follow-ups.

9 Investigator responsibilities

The Investigator is responsible for ensuring that the study is conducted according to this protocol and all applicable regulations. It is the PI's responsibility to ensure that all staff assisting with the study have the appropriate qualifications and are fully instructed on the study procedures and respect patient confidentiality, as specified by the Investigator Agreement with the Sponsor. The PI and study staff should make every possible effort to ensure that complete and accurate data is obtained for each study patient.

The Investigator is responsible for ensuring that the conduct of this study conforms to the EC or other applicable regulatory authority requirements and provides all necessary communication with the EC or other applicable regulatory authority including, but not limited to, annual study reports and required AE notifications.

9.1 Clinical progress reports

The Investigator is responsible for required site study progress reports including, but not limited to, annual and final study reports. Copies of the reports will be submitted by the Investigator to the Sponsor and reviewing EC or other applicable regulatory authority at the required times.

9.2 Reportable adverse events

The Investigator is required to report any SAEs and device-related adverse effects (DR-AEs) within 24 hours of the Investigator becoming aware of the event to the Sponsor or their designated representative. Copies of each report must be kept on file at the clinical site and sent to XENIOS AG. Information about the SAEs relationship to study device or procedure will be recorded on the CRF. Sites are required to report all SAEs related (per clinical site PI determination at the time of report) to the study device/ accessories or to the study procedure, occurring in a patient during the procedure and until 30 days after ending study visits/ participation.

9.3 Withdrawal of approval

In the event of EC or other applicable regulatory authority withdrawal of study approval for any reason, the Investigator is required to notify the Sponsor and/or their designated representative as soon as possible, but not later than 5 working days after the withdrawal of approval.

9.4 Deviations from the protocol

In the event of deviation from the protocol, the Investigator is required to document the reason for the deviation and to notify the Sponsor and/or their designated representative.

The Investigator is required to notify the Sponsor and/or their designated representative of any deviation from the protocol. Such notice shall be given as soon as possible, but no later than 5 working days after the occurrence of deviation. Prior approval by the Sponsor is required for changes in or deviations from the protocol. If the changes and deviations may affect the soundness of the protocol and the rights, safety, and welfare of the patients, prior approval from the reviewing EC and applicable regulatory authorities are also required.

10 Ethical consideration

This study will be performed in accordance with the relevant part of the ICH Guidelines for GCPs, the Declaration of Helsinki, and any other applicable regional and/or national regulations.

10.1 Ethics committee Approval

The primary EC's approval for the protocol and PIC is required before any patient can be enrolled in the study.

The Investigator is required to submit protocol amendments and renewals as necessary. Primary EC approval of amendments/renewals is required prior to implementation/continuation at the clinical site.

Approval letters from the primary EC and confirmations of consultation by the local EC, along with the approved PIC and any correspondence between the site and the EC, should be submitted to the Sponsor and/or their designated representative.

10.2 Informed consent

The PIC must be approved by the primary EC and the Sponsor before any patient shall be asked to sign the PIC. An informed consent template will be provided to all of the clinical sites for their use. Any changes to the template consent form suggested by the Investigator must be agreed to by XENIOS AG before submission to the EC. A copy of the approved version must be provided to XENIOS AG after EC approval.

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP and any applicable regional and local regulations. At a minimum, patients must be informed that study participation is voluntary and he/she may withdraw from the study at any time for any reason. The nature of the study including, but not limited to, the purpose, study procedures/measures, follow-ups, and the potential risks and benefits, will be disclosed to the patient. The patient must read and understand the PIC and be given ample opportunity to inquire about the details of the study prior to signing the PIC. A signed PIC is required before a patient can be entered into the study and any study specific data collection can be completed. In cases where the patient is not able to consent to inclusion of his/her data in the study, a separate PIC for a legal guardian will be provided.

The Investigator is required to keep the signed PIC and to provide a copy to the patient.

10.3 Coverage of expenses

Patients will not be directly reimbursed for their participation in this study.

10.4 Confidentiality

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission

from the Sponsor. Authorized regulatory officials and Sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. Subjects should be identified only by unique alphanumeric codes on the CRF's. If necessary, their full names may be made known to a regulatory agency or other authorized officials. All patient data will be de-identified and made anonymous for scientific publications.

In the event that a patient or his/her legal guardian withdraws authorization to collect or use Personal Health Information (PHI), the Investigator retains the ability to use all information collected prior to the withdrawal of authorization. Additionally, the Investigator should attempt to obtain permission to collect at least the vital (i.e., mortality) status at the end of the patient's study follow-ups.

11 Data handling and record keeping

11.1 Source documents

The investigator is required to maintain detailed source documents on all patients who are screened and/or enrolled in the study. Source documents include patient medical records, hospital charts, clinic charts, investigator patient trial files, as well as the results of diagnostic tests (e.g., laboratory tests, hemodynamic studies).

The following minimum information should be entered into the patient's medical record:

- The date the patient entered the trial and the patient number;
- The trial protocol number and the name of the Sponsor;
- The date that Informed Consent was obtained;
- Evidence that the patient met the trial eligibility requirements (e.g., medical history, trial procedures and/or evaluations);
- The dates of all trial related patient visits;
- Evidence that required procedures and/or evaluations were completed;
- Use of any concurrent medications;
- Documentation of specific device used;
- Occurrence and status of any adverse events; and
- The date the patient exited the trial and a notation as to whether the patient completed the trial or was discontinued, including the reason for discontinuation.

Some data pertinent and specific to the study procedure will be collected on the Procedure CRF, thus the Procedure CRF will be considered source document.

11.2 Data collection

Data for screened and enrolled patients will be transcribed onto CRFs approved by the Sponsor. All required data should be transcribed promptly, completely, and legibly. Corrections should be made in a manner that does not obscure (i.e., render the writing illegible) or eliminate the error, and the correction should be initialed and dated along with the reason for change if the change is non-obvious.

11.3 Data retention

All records relating to the study will be retained for a minimum of ten (10) years after the date on which the study was completed or when the records are no longer required as determined by the Sponsor, whichever is the later date. Before any record transfer or destruction, the Investigator must have approval from the Sponsor.

12 Quality control and Quality assurance

12.1 Site training

To ensure ethical study conduct and quality data collection, the Sponsor or its representatives will train the Sites on the protocol, study measures, and data collection, submission, and retention.

12.2 Device operator training

To maximize patient safety, the Sponsor will train the Investigators on the study device. Device training will be completed by the Investigator and any Co-Investigators prior to any enrolled patient's i-COR® Synchronized Cardiac Assist procedure.

12.3 Training documents

All training will be documented in the Training Log.

13 Adverse Events

An adverse event (AE) is any untoward sign, symptoms, or medical condition occurring after the informed consent is signed. Adverse events will be assessed for seriousness. A serious AE (SAE) is an event that:

- Is life threatening or fatal;
- Results in permanent impairment of a body structure or function;
- Requires or prolongs hospitalization;
- Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure; or
- Results in a congenital anomaly/birth defect.

Adverse events will also be assessed for relatedness to the procedure or device as follows:

- Not Related: The event is due to an underlying or concurrent illness or effect of another device, drug or intervention and is not related to the device or procedure.
- Possible: The event has a strong temporal relationship to the use of the device or procedure, and an alternative etiology is equally or more likely.
- Probable: The event has a strong temporal relationship to the use of the device or procedure and another etiology is unlikely or significantly less likely.
- Definite: An event that can only be attributed to the use of the device or procedure.

If a SAE is determined to be possibly, probably, or definitely related to the device and has not been previously anticipated, the clinical finding would be classified as an unanticipated adverse device effect (UADE). An UADE is any SAE caused by or is associated with a device that was not previously identified in nature, severity, or degree of incidence in the Protocol, application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of patients.

13.1 Adverse Event Reporting

All AEs will be monitored from study enrollment through completion of this study. All AEs will be recorded in the database. A description of the event, including the start date, resolution

date, action taken and the outcome should be provided, along with the Investigator's assessment of the relationship between the AE and the study treatment.

All AEs should be followed until the event is resolved or judged to be chronically stable. The Site will provide relevant follow-up information to the Sponsor and/or their designated representative.

All Serious Adverse Events should be reported to the Sponsor on the Adverse Event CRF. The Investigator should report SAEs immediately upon being made aware of the event. The Sponsor will review the AE/SAE according to their Vigilance System as reviewed during the Sponsor's conformity assessment. The Sponsor will determine whether a Field Safety Notice or a Field Corrective Action Report is required and notify the Competent Authorities accordingly.

14 Publication policy

The data generated by this clinical trial are the property of the Sponsor and should not be disclosed without the prior written permission of XENIOS AG. Information pertaining to this clinical trial is confidential, and it should not be discussed with persons outside of the trial. The information in this document and regarding this trial may contain trade secrets and commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by regional or national law or regulations. In general, information pertaining to this trial may be disclosed only to those persons involved in the trial who have a need to know, but all such persons must be instructed not to further disseminate this information to others. These restrictions of disclosure will apply equally to all future information supplied to you that is indicated as confidential.

The Sponsor and the Investigators are committed to the publication and widespread dissemination of the results of the study. This study represents a joint effort between Sponsor and Investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or text shall be taken into consideration in the preparation of final scientific documents for publication or presentation. Subject to the terms of Confidentiality, the Sponsor and/or the Investigator shall be free to publish, present or use any results arising out of the performance of the study at their centers for their own instructional, study or publication objectives, provided that such Publication does not disclose any Confidential Information other than the results of the Study performed. At least one hundred and eighty (180) days prior to submission for publication, presentation or use, the Principal Investigator shall submit to Sponsor for review and comment any proposed oral or written Publication, which period may be extended for an additional thirty (30) days if requested in writing by Sponsor in the event that Sponsor provides reasonable need for such extension. Expedited reviews for abstracts or poster presentations may be arranged if mutually agreeable to by Sponsor and the Principal Investigator.

XENIOS AG has the right to review all proposed publications and presentation materials for scientific integrity, effect on clinical activities, and relevance to patent protection and partnership agreements. XENIOS AG will not suppress publications or presentations, but reserves the right to delay publications to avoid compromising intellectual property. Additionally, XENIOS AG reserves to right to delay publications of sub-analyses until after the publication of the main study results.

Authorship and accountability: Per ICMJE recommendations, an author is generally considered to be anyone who provides substantive intellectual contributions to a published study. Specifically, authorship credit should be based on 1. Substantial contributions to study conception and design, or acquisition, analysis and interpretation of data, *and* 2. Drafting the article or revising it critically for important intellectual content, *and* 3. Final approval of the version to be published, *and* 4. Agreement to be accountable for all aspects of the work to ensure its accuracy and integrity. *All four conditions should be met.* Conversely, individuals

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