Purpose

This document is the Clinical Investigation Protocol of the First in Human study of The FineHeart Icoms® FlowMaker ® System.

Record traceability

Version number	Cause	Modification location	Date
1.0	Creation	All pages	20241219
2	Update to ANSM feedback (06/FEB/2025) - §17 : MDR 2017/745 , article 80 was specified. - Update annexe J with ANSM template	 Page 50-56/101 Page 101/101	2025/FEB/06
3	Following Ethic Committee request of 24 Feb 2025: -Secondary objective updated -Study duration updated -Following sections were updated: § 6.1; §6.2; §6.3.2; §6.3.2; §8; §8.18; §8.19; §10	-See page 3 ; page 6 ; page 7 and § 3.2 secondary objectives page 25 -See Synopsis: § study duration and § 6.1 study design page 27 - See page 27 to page 50	2025/MAR/03
4	Following ANSM request on 11.04.2025 following changes were made. § synopsis , § 7.1 inclusion Criteria and 7.2 exclusion criteria § synopsis and §6.1 study design § 8.17 anticoagulation procedure § 8.20 management of patient with pacing device § 19 was created – submission of the clinical investigation Report	-Inclusion criteria N° 5, 7 and 10 were updated and N° 13 was added see page 5, 33 and 34 -Investigator site in France was reduced to 3 sites and patient Recruitment plan was added , see page 29 -Anticoagulation procedure is mandatory as requested by ANSM, see page 53 See page 59 See page 69	23/ 04/2025
5	Following ANSM request on 06 May 2025 following modifications were added: - Inclusion criteria N°13 was corrected - § 8.20 ICD management was corrected Following CPP request On 11 April: - § 8 Study Procedure was corrected : TTE was added	See cause column	06/05/2025

	at D0 in the study exams table - §10 statistical consideration: the location of the analysis has been specified - Annex I : DSMB members List was added		
6	"In the study approval letter dated May 6, 2025, the ANSM requested the removal of the word 'Especially' from inclusion criterion No. 13."	See §7.1	07 May 2025
7	Following CPP request of 26 April 2025: Assess the safety of the device was added as secondary objectives - The list of the investigation sites was updated Clarifications have been provided on the technical and proctors support provided by FineHeart - Clarifications on FineHeart technical including in-depth maintenance after 2 years of use and medical support.	See § synopsis- Objectives and § 5.2 Secondary objectives See page 72 See § 8.9 page 46 and § 6.1 page 30 See §8.8 page 45 and § 18 page 68	26 Aug.2025
8	- Clarification on the inform consent process patient reflexion delay: 3 days minimum - Expected Events : pyrexia deleted	See page 60 See Synopsis and page 64	23 MAY 2025
9	Submission for change of May 2026 following study temporary hold due to subject 003 thromboembolic event occurred on 23 Oct.2025: 1- Exclusion criteria N°12 reinforced + unstable INRs 2- Risk of thromboembolic event was added as risk associated with participation to this study. 3- Corrective and Preventive actions to mitigate the thromboembolic risks were added 4- An anticoagulation protocol has been implemented to ensure adequate	See Synopsis and § 7.2 Exclusion criteria page 35 See § 4.1 page 27 See §4.3 page 28-29 See § 8.17 page 52 Annex K	05 MAY 2026

	anticoagulation in study participants. 5- A core laboratory to investigate on issue related to thromboembolic events related to the device was added 6- The Study Examinations Flowchart has been updated. In addition, a table detailing specific blood tests and a table outlining echocardiography assessments have been created. 7- A more comprehensive biological assessment and a detailed review of the patient's medical history have been added at the screening stage to investigate thromboembolic risk.	 See § 8.17 page 52 and Annex K See § 8.1; 8.1.1; 8.1.2 page 36-Page 41 See § 8.2 page 41	

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Title Page

A prospective, single arm, multicentric, First in Human Study to evaluate the safety and performance at 30 days of the FineHeart Icoms® FlowMaker® in subjects with advanced heart failure.

Short Title: First in Man Study of the FineHeart Icoms® FlowMaker®

Study Code: FAIR (FineheArt fIrst in human tRial)

Protocol version no: 9 **Date: 05 May 2026**

Eudamed Number: CIV-23-08-043854.
IDRCB number: 2024-A02072-45

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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Signature of the sponsor's medically responsible person:

The signee agrees to the content of the final clinical study protocol as presented.

Name: Dr. Stéphane Garrigue Role: Chief Medical Officer

Date: Signature:

Signature of the Principal Investigator or the Coordinating investigator if appointed:

The signee agrees to the content of the final clinical study protocol as presented.

Name : Pr. Pascal Leprince Role: Coordinator Investigator

Date: Signature:

Synopsis

PROTOCOL SYNOPSIS	
TITLE	First in Human (FIH) Study for the FineHeart Icoms® FlowMaker®.
SPONSOR	FineHeart S.A, 28 Av. Gustave Eiffel, 33600 Pessac, Bordeaux, France.
INVESTIGATIONAL DEVICE	Implantable Cardiac Output Management System Icoms® FlowMaker®.
INTENDED USE OF THE DEVICE	Severe heart failure, resistant to the optimal medical treatment.
OBJECTIVES	**Primary objective: Evaluation of the Icoms® FlowMaker® Safety and Performance at 30 days on device.** **Secondary objectives:** • **Assess the hemodynamic and clinical status of the patient.** • **Assess the safety of the device** • **Assess the operating mode of the device according to his technical specifications**.
REGULATORY STATUS	Approved by the CA on _____ and the Ethical Committee on_____
STUDY DESIGN	Non-randomized, prospective, single arm, multicentric.
SAMPLE SIZE	Implantation in 10 patients. Competitive recruitment between investigation sites. Implantation of the 2 first subjects, followed by a pause in enrollment until the primary endpoint is analyzed at one month and the DSMB provides its opinion
COUNTRIES & SITES	Czeck Republic: 1 investigational site. France: 3 investigational sites with a sequential activation of the centers; the 2 first sites will be activated for the enrollment of the first 2 patients. The third site will be activated starting from the third patient.
STUDY DURATION AND TIMELINES	Approximately 44 months based on a 20 -month recruitment period and 24 months of follow up . Estimated First Enrollment: oct 2025. Estimated Last Enrollment: Jun 2027 Estimated Last patient visit for primary endpoint: July 2027. Estimated last patient last visit: Jun 2029. The study will continue as long as one of the patients is still under the device and the study insurance validity will be extended consequently.
Subjects Selection Committee	An international selection committee composed of independent experts will assess the clinical and anatomical eligibility of subjects identified by the investigator centers based on the inclusion and exclusion criteria. The patient's clinical data, collected by the investigator center during the selection visit, will be reviewed and evaluated by the selection committee. The committee is composed of the following members:

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	The principal investigators from the investigator centers. Four independent experts with extensive experience in the field of advanced heart failure, particularly in imaging, cardiac assist devices, and surgical therapy. The four experts will be appointed for the duration of the study to ensure continuity in the assessment of patient eligibility. The details regarding the operation of the selection committee are described in the selection committee charter.-.
INCLUSION CRITERIA	1- Age 18 and 80 years included. 2- Written inform consent. 3- Females of child-bearing age must agree to use adequate contraception. 4- Suitable neurocognitive status. 5- Distance between the aortic valve and the LV endocardial apex ≥ 95mm and the Left Ventricular (LV) volume > 200 mL 6- Body Surface Area (BSA) ≥ 1.2 m². 7- LVEF ≤ 35 % and assessed Intermacs ≤ 4 8- Advanced heart failure patients symptomatic despite optimal medical management (OMM) based on the European Cardiology Society guidelines[15] otherwise meeting standard best practice indications for implantable LVAD AND fulfilling at least one of the following criteria approved by the International multidisciplinary expert selection committee: **9- Contraindication or excessively heightened risk of a conventional LVAD implant due to factors such as:** ○ **CVP/PCWP ≤ 0.6** ○ **anatomical or surgical factors constituting excessive perioperative implant risks.** (*Duly recorded in the source document during the patient Inform consent process)* **OR** **10- Patient with high risk of percutaneous driveline-induced morbidity such as:** ○ **patient with recurrent infections / severe diabetes mellitus / immunodeficiency / cachexia** ○ **psychological factors limiting percutaneous driveline acceptance and / or management duly recorded in the Psychological evaluation report at screening.** **11- Temporary ineligibility to heart transplant (active or remission of cancer / highly sensitized PRA…)** *(Duly recorded in the source document during the patient Inform consent process)*

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12- Patient's affiliation to health care insurance, if local requirement
13- Patient implanted with a cardioverter defibrillator from Medtronic and Boston .
or patient requiring implantation of a cardiac defibrillator due to a risk of ventricular arrhythmia

EXCLUSION CRITERIA

1- Body Mass Index (BMI) > 40.
2- TAPSE ≤10 mm
3- Pulmonary VTI ≤ 6cm
4- Patients not eligible to transplant due to surgical risks
5- Existence of any ongoing mechanical circulatory support (MCS) other than an intra-aortic balloon pump (IABP)
6- History of left thoracotomy.
7- History of confirmed untreated abdominal or thoracic aortic aneurysm > 5 cm.
8- Cardiothoracic surgery within 30 days of implant.
9- Acute myocardial infarction within 14 days of implant.
10- On ventilator support for > 72 hours within the four days immediately prior to implant.
11- Pulmonary embolus within three weeks of implant.
12- Presence of current atrial or ventricular thrombus or free trabeculae, preferably confirmed by contrast-enhanced cardiac MRI, or, if that is not feasible Thoracic CT-SCAN with contrast or Trans-Esophageal Echocardiography.
13- Symptomatic cerebrovascular disease, stroke within 180 days of screening or > 80% stenosis of carotid, vertebral or cranial vessels.
14- Unstable INRs: at least four consecutive INRs out of [2-3] range, if patient under conventional anticoagulation.
15- Moderate to severe aortic regurgitation, defined as > 50% regurgitant fraction.
16- Moderate - Severe aortic stenosis, defined as an aortic valve area (AVA) ≤ 1.5 cm2.
17- Active, uncontrolled infections, history of hyperleukocytosis with Leucocytes > 10.000/mm3, CRP >10mg/l, PCT > 0,2ng/ml, positive hemocultures < 48 hours, positive urine cultures, positive sputum cultures, any abnormalities identified by CT scan of brain-thorax and abdomino-pelvic region.
18- Uncorrected thrombocytopenia or generalized coagulopathy (e.g., platelet count < 100,000 / INR > 2.0 in the absence of anticoagulation therapy).
19- Hepatic insufficiency: a total bilirubin > 3 mg/dL within 72 hours before implant, or biopsy proven liver cirrhosis or portal hypertension.
20- Pulmonary vascular resistance (PVR) demonstrated to be unresponsive to pharmacological manipulation and the PVR > 6 Wood units.
21- Patients with a mechanical heart valve.

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	22- Etiology of heart failure due to, or associated with, uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis, active myocarditis, or restrictive cardiomyopathy, ventricular septal defect 23- History of severe Chronic Obstructive Pulmonary Disease (COPD) or severe restrictive lung disease. GOLD (Global Initiative for Chronic Obstructive Lung Disease) score < 3. 24- Participation in any other study involving investigational drugs, devices, or biologics. 25- Severe illness, other than heart disease, which would limit survival to a maximum of 1 year. 26- Peripheral vascular disease with rest pain or ischemic ulcers of the extremities. 27- Pregnancy. 28- Patient unwilling or unable to comply with study requirements. 29- Patients unable or unwilling to sign the written informed consent. 30- Technical obstacles, which pose an inordinately high surgical risk, in the judgment of the investigator. 31- Intolerance to anticoagulant or antiplatelet therapies or any other peri- or postoperative therapy that the investigator may administer based upon the patient's health status. 32- Specific liver enzymes [AST (SGOT) and ALT (SGPT)] > 3 times upper limit of normal within 72 hours before implant. 33- Patient living alone (without an accompanying person). 34- Rapid AF, unless nodo-hissian junction ablation is considered. 35- Mid-septal end-systolic LV diameter ≤ 25mm. 36- Sequential Organ Failure Assessment Score (SOFA score > 8) 37- Minor subjects, persons deprived of liberty, protected adults, or those unable to consent 38- Subjects who have participated in a clinical trial within 12 months 39- Patient implanted with an Implantable Cardioverter Defibrillator (ICD) other than Medtronic and Boston.
PRIMARY ENDPOINTS	- **Survival free from stroke with MRS > 3 at 30 days after implant.** - **Device related reoperation and device related infection at 30 days after implant.**
SECONDARY ENDPOINTS	**1) Improvement of the clinical condition by measuring:** - NYHA functional status improvement - Quality of Life Change (EQ-5D-5L). - Withdrawal of intravenous inotropic drugs. - Blood chemistry (LDH, Free Hemoglobin, Von Willebrand Factor). - Improvement in 6-minute walking test **2) Safety of the investigational device:**

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- Incidence of adverse events, neurological status, and unanticipated adverse device effects (bleeding, stroke, device malfunction, major infection, renal failure, respiratory failure or heart failure).
- Incidence of disabling stroke with MRS > 3.

3) **Proper operating mode of the device**:
   - Hemodynamic improvement (assessed by CO, aortic VTI, LAP, inotropic drugs weaning).
   - Assessment of the external coil of the Transdermal Energy Transfer (TET) System.
   - Patient's ability to manage device alarms and the external controller, based on the device usability tests and device deficiencies reported during the study.
   - Proper operating conditions of the implanted battery.

ANTICIPATED ADVERSE EVENTS

1- Acute myocardial infarction.
2- Allergic reaction (anesthetic, contrast media, heparin, latex, implant materials, other).
3- Angina.
4- Annulus (damage, dissection, tear).
5- Aortic valve injury (trauma, clots, stenosis, regurgitation).
6- Arrhythmias, requiring cardioversion.
7- Atelectasis.
8- Atrial Fibrillation, new onset.
9- Bleeding (necessitating RBC transfusion and /or not Loss of > 3 mg/dl of Hgb)
10- Blood hemolysis, coagulopathy.
11- Cardiac arrest.
12- Cardiac Failure.
13- Chest pain/discomfort.
14- Damage to heart tissue.
15- Damage to vessels near the heart.
16- Death.
17- Drug reaction.
18- Dyspnea.
19- Edema.
20- Endocarditis.
21- Esophageal irritation.
22- Fever.
23- Heart Block.
24- Hematoma.
25- Hemodynamic complications.
26- Hemothorax.
27- Hypertension.
28- Hypotension.
29- Infection, local or systemic.
30- Leukopenia.
31- Nausea/vomiting.

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32- Neurological Event.
33- Permanent pacemaker.
34- Pericardial effusion.
35- Pneumonia.
36- Pneumothorax.

37- Renal Failure.
38- Reoperation/Removal/Replacement.
39- Respiratory Failure.
40- Stroke.
41- Systemic hypotension requiring medical intervention.
42- Thrombosis (cardiac or venous).
43- Transfusion.
44- Vasovagal reaction.
45- Worsening heart failure.
46- Wound dehiscence.
47- Wound infection.
48- Wound pain or swelling.

List of Abbreviations.

ACE	Angiotensin Converting Enzyme
ACT	Activated Clotting Time
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
ALAT	Alanine Amino Transferase
ASADE	Anticipated Serious Adverse Device Effect
ASAT	Aspartate Amino Transferase
BMI	Body Mass Index
CO	Cardiac Output
COPD	Chronic Obstructive Pulmonary Disease
CPB	Cardio-Pulmonary Bypass
CRP	C-reactive Protein
PCT	Procalcitonin
CRF	Case Report Form
CT-Scan	Computed Tomography Scan
CVP	Central Venous Pressure
EC	Ethic Committee
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECO	External Controller
EMD	Electro-Mechanical Delay
Fup	Follow up
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HCP	Health Care Practitioner
HR	Heart Rate
ICD	Intra Cardiac Defibrillator
ICU	Intensive Care Unit
INR	International Normalized Ratio
INTERMACS	Interagency Registry for Mechanicals Circulatory Support
ITC	Implantable Therapy Controller
I.U.	International Unit
KCT	Kaolin Clotting Time
LAP	Left Atrial Pressure
LDH	Lactate Dehydrogenase
LMWH	Low Molecular Weight Heparin
LV	Left Ventricle
LVAD	Left Ventricular Assist Device
LVDS	Left Ventricle Depolarization Signal
LVEF	Left Ventricular Ejection Fraction
LV EDD	Left Ventricular End Diastolic Diameter
LV EDV	Left Ventricular End Diastolic Volume
LV ESV	Left Ventricular End Systolic Volume

MCS	Mechanical Circulatory Support
MELD score	Model for End Stage Liver Disease
MRS	Modified Rankin Scale
NYHA	New York Heart Association
QOL	Quality of Life
PAP	Pulmonary Arterial Pressure
Pt1;Pt2	Patient 1; Patient 2
PCWP	Pulmonary Capillary Wedge Pressure
PFA	Platelet Function Analyzer
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TAPSE	Tricuspid Annular Plane Systolic Excursion
TEE	Transesophageal echocardiography
TET	Transcutaneous Energy Transfer
USADE	Unanticipated Serious Adverse Device Effect
VAD	Ventricular Assist Device
6MWT	6-Minute Walking Test

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Figures

1. Rationale.

The role of mechanical circulatory support (MCS) in the current landscape of heart failure (HF) therapies can only be appreciated by knowing the potential number of candidates for advanced HF treatment. HF prevalence is 2.6% in the over 300 million US population[1-4]. Approximately half of all patients with HF have reduced, versus preserved ejection fraction (3.5 million). Only 10-15% of those belong to the New York Heart Association (NYHA) class IIIB–IV[2-3] (annex D).
These data suggest that there are as many as 500,000 patients in whom either LVAD or cardiac transplantation could be indicated following current national guidelines[3-4]. However, taking into account important limitations based on age, comorbidities, social and financial constraints, the actual number might be less, but nevertheless 125,000 to 250,000 patients remain as potential candidates for this advanced therapy.
The INTERMACS Class 4-7 (annex D). population presents an incidence of at least 100,000 patients per year in the USA, Canada and Europe[8,13-14]. The main indications for the use of implantable LVADs in patients with end-stage HF are either as a bridge to candidacy (BTC), or as long-term option for those who do not qualify for cardiac transplantation, previously referred to as destination therapy (DT)[5-7]. Only 7.000 to 9.000 MCS devices are implanted worldwide every year, which represents a significant lack of treatment in such sick and mostly not elderly patients[8-9].
Consequently, there is a huge discrepancy between the need for MCS treatment (up to 250,000 patients) and the real proportion of patients implanted, due to known, much feared current LVAD-induced complications[6,8,10]

Yet, the greatest increase in LVAD volume has not been in those considered candidates for bridge to heart transplantation (BTT) but for DT, which requires technical improvements to expand MCS devices implants in less severe patients[5-6]. The overall survival with LVAD therapy is ≈ 80% at 1 year, and 60% at 5 years, with survival for DT indication lower than other indications at all time points, because of higher incidence of comorbidities and LVAD complications [10]. Presently, the use of the terms BTT or DT to define the indication for LVAD implantation is being replaced by whether the support is intended for temporary or chronic use[10].
The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database now includes 25,000 patients:

- 97% benefit from a non-physiological continuous-flow VAD[11].
- The average age at implant is 57 years and 80% are male.
- Overall, 1- and 2-year survival is 80% and 70%, respectively.
- Most implanted patients are INTERMACS Class 1-3 (80-85%).
- Patients with ambulatory HF still account for only 16% of durable device implants to date, due to the fear for LVAD-induced complications.
- Today, nearly 41% are implanted with an intent for long-term DT.
- With the HeartMate 3, neither survival rate, nor infection rate did improve compared to the Intermacs registry cohort (Jorde UP, et al. The Society of Thoracic Surgeons Intermacs 2023 Annual Report. Ann Thorac Surg 2024;117:33-44) only thrombosis and disabling stroke were significantly reduced at 2-year follow-up[12].

All these precious epidemiological data highlight the crucial need for a new type of MCS device, being more physiological and pulsatile, without a percutaneous driveline (i.e. “fully implantable”). It needs to be easier to implant and/or replace, with less invasive surgery without CPB and thus, finally able to address the most important population of severe HF patients. 8[13-14].

2. Identification and description of the investigational device.

2.1. Description of the investigational device.

The Icoms® FlowMaker® is a cardiac assist system in the true sense of the word. As assisting means to help or rescue, its function is providing assistance to the heart, which will continue to have its own hemodynamic pump function. The effect of the Icoms® FlowMaker® is to add an additional quantity of blood flow on top of the native blood flow, during each systole. The heart continues to have its own contribution, but a more satisfactory blood flow is restored by the complementary action of the Icoms® FlowMaker®.

It presents with the following properties:

- A significant increase in cardiac output
- Small size.
- No external driveline.
- Equipped with an internal battery providing a minimum of 30 minutes of autonomy up to > 4 hours.
- Lateral thoracotomy approach on a beating heart, without the use of CPB or ECMO.
- Short surgical procedure (less than 2 hours).
- Easy replacement with a specific dedicated delivery system.
- It delivers a physiological blood flow thanks to its unique intra-ventricular design, eliminating the need for an outflow graft in the aorta, unlike traditional LVADs.

Like other LVAD, the Icoms® FlowMaker® needs an electrical energy source for its functioning. It is Intended to be used for long term. It is composed of 2 parts, the Internal Components which are implanted during a surgical intervention and the External Equipment.

The patient can be completely free of the external equipment and energy supply with a guaranteed minimum autonomy time of 30 minutes up to 4 hours of time, under normal conditions. This will allow you to perform physical activities, such as showering, etc. with complete freedom of movement.

2.1.1 Internal Components

1-The Pump

The pump is placed in the left ventricle and implanted through the apex, without the use of CPB. The pump inflow is going through the pump inlet located at its base near the LV apex, and the blood is ejected through the open aortic valve via the pump outlet. To obtain an optimal effect, that is profitable in terms of energy consumption, hemodynamic effect and physiological flow, the pump is synchronized to the cardiac systole by capturing the left ventricular depolarization signal (LVDS), as a physiological sensor of the beginning of systole. The pump will cycle through several phases, much like the native cardiac cycle:
- Detection of the LVDS triggers the acceleration of its rotational speed during the electromechanical delay period (EMD; delay between LVDS detection and opening of the aortic valve).
-Followed by the ejection phase at a chosen systolic speed.
- And finally followed by the deceleration phase at the end of systole from the high systolic speed to the chosen diastolic pump speed.
Then, during the entire diastole, a phase of low rotational pump speed is maintained for two reasons: first to avoid LV filling speeds disturbances and second, to avoid diastolic opening of the aortic valve. The phases mentioned above (EMD, systolic time duration and deceleration time), are all calculated though trans-

thoracic echocardiography and subsequently entered the pump synchronization algorithm with the Clinical Programmer. It is currently recommended for the patients to have a pacemaker/implantable cardioverter defibrillator (ICD). The Icoms® FlowMaker® operating mode takes into account arrhythmias that may occur, such as premature atrial and/or ventricular complexes, as well as atrial and/or ventricular tachycardias, and finally asystolic episodes.

2-The Implantable Therapy Controller (ITC)

The Implantable Therapy Controller (ITC) is implanted in an abdominal position in a submuscular pocket in a traditional manner. It receives the LVDS signal via an epicardial sensing lead. The internal battery is integrated within the implantable therapy controller (ITC). The ITC controls the charge of the internal battery and controls also the energy delivered to powering the pump motor. The ITC is connected with two separate subcutaneous cables (power and communication) to the pump and is also connected to the internal coil of the Transcutaneous Energy Transfer system (TET) and the epicardial pacing lead.

3-The Epicardial Pacing Lead

The epicardial lead is fixed onto the surface of the left ventricle. Upon being tunneled up to the ITC pocket, the epicardial lead which detects the LVDS signal is directly connected to the ITC to which it transfers the signal.

4-The internal TET coil to receive energy wirelessly from the external batteries

The Internal TET Coil is implanted in a submuscular pocket. After tunneling to the ITC pocket, it is connected to the ITC to recharge the implanted battery continuously by induction via Transcutaneous Energy Transfer with the power being supplied by the external batteries. It also allows communication between the external controller and the ITC via Bluetooth.

5-The fixation system is comprised of:

- A fixation ring which will be sutured to the apex. There are four different rings available with inclinations of 0°, 3°, 5° and 7°
- A fixation tube and its clamping nut, which will be screwed into the fixation ring.

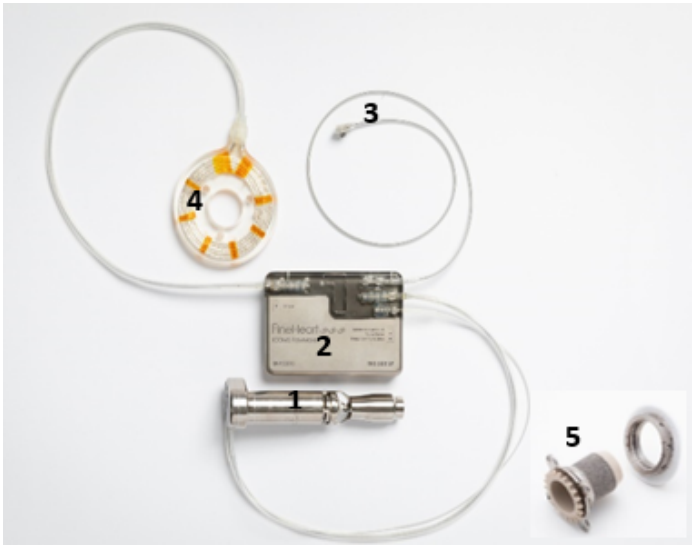

figure 1- Implantable Components

The pump, the epicardial pacing lead and the internal TET Coil are all connected with tunneled cables to the ITC. The fixation ring is sutured to the apex and the fixation tube is inserted through the fixation ring into the LV and fixed in place by screwing the fixation tube onto the fixation ring.

2.1.2. External Components.

6-The external TET coil:
The External TET coil is connected to the external controller (ECO) and transfers power transcutaneous from the ECO to the ITC. The power is provided by the external batteries, which are connected to the ECO**.**

7-The External Controller:
The ECO communicates with the ITC via Bluetooth connection. It is powered by external batteries and/or the power supply unit. It allows monitoring of the status of various elements of the system, the power consumption, the status of the internal battery, and the charge status of the external batteries.

8-External Batteries.
The external batteries power the whole system.

9-The Programmer.
The Clinical Programmer consists of a tablet computer with proprietary software. It is used by the HCP for monitoring the patient and monitoring the system's operation. It allows for control and adjustment of the pump settings timing, ITC adjustments, and reading of logged alarms and information stored by the ITC.

The clinical programmer will be used during the surgery and follow-up by the physician. This clinical programmer is a CE marked digital tablet. It is connected by a cable to the external controller.

10-The Carry System.
The external controller and the batteries have a special carry bag. The carry bag has dedicated slots to hold the ECO and the batteries, and an exit for the TET coil cable and power supply unit cable, ensuring safe handling of the system while the patient is mobilizing or at rest. The controller bag has a shoulder strap and a waist band to assure good fixation of the system and to maximize comfort for the patient.

- **The Battery Charger.**

The battery charger is used to recharge the external batteries.

Figure 2 – The external components

The system has several specific implantation tools to facilitate the surgical intervention and accessories (bags, shoulder strap and waist band) to facilitate its transport . See the Investigator Brochure for more details on device specific tools and accessories.

The Pump is implanted via a left thoracotomy, through the LV apex in the left ventricle. Details regarding the surgical intervention procedure, patient management, device storage and handling instructions can be found in the Clinician Manual of the Investigator Brochure.

Detailed description of the Icoms® FlowMaker® system is provided in the Investigator's Brochure. The Icoms® FlowMaker® does not contain any medicinal substances or human animal tissues or their derivatives or other biologically active substances.

2.1.3 Implantation tools not provided by the sponsor.

The following tools should be available at the investigation site:

- Sterile 6 Fr introducer set. Ex: Adalante ASG05010
- Floppy guidewire. Ex: Terumo Radifocus RF*GA35153M L:150cm, angled, Flex L: 3cm, diameter: 0.035"
- A pigtail catheter 5 Fr Ex : Cordis 532-598-A
- A super-stiff guidewire. Ex: Cordis Amplatz Length 260cm, 3mm, atraumatic end
- Thoracic catheter with trocar. Redax 21128
- A table with a non-metal surface for pump testing.
- 10 ml of sterile IV propofol solution.
- Small bowl to hold the propofol.
- Surgical scalpel nr 11.
- Long surgical/vascular clamp
- Bone wax.
- Sterile Ultrasound sleeve for the external TET coil and cable.

2.2. Details concerning the manufacturer.

The components of FlowMaker® are manufactured by FineHeart or its sub-contractors. Final assembling takes place at FineHeart.

FineHeart is ISO 13485 certified for its design and development activities, related to Implantable Cardiac Output Management System.
The components of the prosthesis are assembled by FineHeart in an atmospheric controlled room. The entire Icoms® FlowMaker® device, including mechanical parts, electronical parts and the specific implantation tools are sterilized with ethylene oxide.

2.3. Device Identification.

The Icoms® FlowMaker® system is identified and tracked by internal and visible serial numbers. The identification number of the model used for this study is Icoms® FlowMaker® 02690. The identification number of each device components including software version is specified in the investigator's brochure.

2.4. Device traceability during the clinical Investigation.

Once a patient is selected and accepted for surgery, the investigational devices with the corresponding order form, which lists serial numbers of all device components, will be shipped to the investigational site. Upon receipt of the investigational device supplies, an inventory shall be performed at the investigational site and a device receipt log shall be filled out and signed by the site referent person. Any damaged or unusable investigational devices in each shipment will be documented in the study files. The investigator or the site staff shall notify the sponsor of any damaged or unusable investigation devices.

To ensure traceability throughout the study, batch number and/or serial number and expiry date are assigned to the devices. From implant until return to FineHeart or destruction, their use will be controlled and documented in the appropriate log. “Device allocation, return and destruction forms” will be provided to the investigator site, to document the allocation per patient of device components, including any replacement, return or destruction. The site may also follow its local procedure to ensure traceability of the investigational medical device (IMD). At the completion of the study, a final reconciliation of investigational devices shipped, devices used or destroyed and the remaining devices will be done and documented. Any discrepancies noted will be investigated, resolved, and documented.

2.5. Intended Purpose of the Investigational Device.

The Icoms® FlowMaker® is intended to treat and support patients suffering from advanced heart failure.

2.6. Intended Population and Indication.

The Icoms® FlowMaker® should be suitable for patients suffering from severe heart failure and resistant to the optimal medical treatment.

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2.7. Training and experience needed to use the investigational device.

FineHeart will provide training to investigators and clinical personnel on the use of the Icoms® FlowMaker® system, with special attention on the surgical implant procedure and device management. Cardiovascular surgeons from study centers with experience in mechanical circulatory support will be trained to implant the device. Medical staff involved in the clinical study will be trained in device management. See the section 8.11 of this protocol for more details on the HCP training procedure.

In addition, the sponsor will provide technical support to the clinical staff during all phases of the treatment as follows:

- Before the implant procedure to check the equipment and to perform a refresher training if required.
- During the implant procedure and while the patient is in the ICU.
- For each selected center, a training curriculum with a support graph must be provided since the device and the pump operating is entirely new.
- During the post-operative follow-up by phone (24 hour/7 days hotline) and on-site if required

Clinical proctors experienced with the FlowMaker® will be also present during implantations at each site and are available during the follow-up to provide advice on medical management of patients supported by the device if needed.

A manual containing instructions for use is provided to the investigator and the clinical team. The patient and relative/caregiver will be trained by the clinical staff to have a complete understanding of the device management, especially regarding potential alarms and how to respond to these. The patient must have adequate social support (i.e. friends or family) to ensure a successful outcome. A patient manual in local language will be provided. See the section 8.10 of this protocol for more details on patient/ caregiver training procedure.

3 Justification for the design of the clinical investigation.

Pre-clinical data have been used to evaluate the First in Human study design. The details of the pre-clinical tests as well as their results are indicated in the Investigator Brochure. The purpose of this First in Human study is to collect the first clinical data and more specifically the feasibility of the device implant surgical procedure, the device safety and hemodynamic performances for its intended function.

3.1 Pre-clinical data.

Pre-clinical tests have been carried out to demonstrate device safety and performance before the use in human subjects.
The tests included:

- Biocompatibility testing: according to ISO 10993 standard requirements to demonstrate the compatibility of the device materials with patient's tissues.
- System Validation testing:
  - Functional testing on the complete system and on the sub-systems.

  - Environmental testing according to applied normative requirements for example: mechanical tests, electrical tests, and electromagnetic compatibility tests.
- Reliability testing: endurances tests were performed to demonstrate the reliability and robustness of the FlowMaker®.
- Animal testing: animal tests were carried out to monitor device performances and demonstrate its safety.

Detailed results of the pre-clinical testing are available in the Investigator's Brochure.

3.2 Anatomical compatibility.

The patient anatomic fit with the Icoms® FlowMaker ® is assessed during the screening period.
The following data, will be collected from the patient's Trans-Thoracic Echocardiography (TTE) or a CT-scan and will be provided by the investigator site to sponsor for validation, after the inform consent process was completed by the subject:

- Left Ventricle Transverse Diameter, end systolic diameter > 25 mm.
- Distance from the aortic valve to the apical endocardium ≥ 95mm.

4 Myocardial left ventricular Apex Thickness ≥ 6 mm.

3.3 Anticipated clinical benefits.

The FlowMaker® is an investigational device which has not yet been approved by regulatory authorities. The device has been tested in the laboratory in animal studies.

The anticipated clinical benefits include:

Potential benefits of the investigational device	**Icoms® FlowMaker ® Features**
Improves survival of patient with heart failure.	• CO improvement and hospitalizations number decrease over time.
bleeding events reduction and/or thrombo-embolic events	• Pulsatile synchronized operating device, providing physiological, fully pulsatile flow. • Wireless system reducing the infection rate. which maintains a stable anticoagulation level.
Reduces risk of hemolysis and thrombosis, compared to current approved MCS	Wireless system.
Provides minimal shear stress.	• Pump-induced flow in the same direction as the native aortic flow.
Reduces Infection risk.	• Wireless transcutaneous power transfer.
Improves functional status and quality of life.	• Wireless device with an internal battery offering several hours of full autonomy with no external component.
Allows cardiac transplant if eligible.	• Device easily removable without atria damages and sternum-free for transplantation or any additional conventional surgery

3.4 Potential risks.

The potential risks, including anticipated adverse events and anticipated adverse device effects, are expected to be similar or less to those seen with existing LVADs (See the 17.2 section anticipated adverse events of this study protocol).

The implantation of the Icoms® FlowMaker® is a mini-invasive procedure requiring anesthesia, mini-lateral left thoracotomy, mechanical ventilation, and can be performed without the need for cardiopulmonary bypass, (CPB). Mini left lateral thoracotomy procedures are associated with lower morbidity and mortality, compared with mid-sternal thoracotomy procedures, as currently used for LVAD implantation.

3.5 Risk to benefits rationale.

The risk management procedure is driven by the sponsor's quality management system, compliant to the ISO 14971 standard and conducted by a multidisciplinary team.
During the development phase and the lifecycle of the device, risk management activities are maintained on the device and on the sub-systems.
The risk management process includes 4 principal steps:

- Risk analysis: identification of potential risks.
- Risk evaluation: for each identified dangerous situation, a risk level is evaluated according to the following criteria: severity, occurrence, and detectability. Then, an acceptability assessment of the risk is identified as acceptable, potentially acceptable, undesirable or unacceptable.
- Risk control: Risk analysis is done for each control measure to determine if it's appropriate to reduce the risk to an acceptable level and ensuring the device evolution doesn't induce new risks with an unacceptable level.
- Evaluation of global residual risk: the final step evaluates risks of device use with all its known residual risks and guarantees absence of unacceptable risks for the expected use.

The risk management aim is to identify the potential hazards of the system during the device lifecycle and improve the device design to mitigate this risk. These activities include:

- For the system:
  - Preliminary hazard analysis: identify all potential hazards of the system that may lead to potential danger sources.

- For the sub-systems or components:
  - Functional FMEA (Failure Modes, Effects Analysis) on the subsystems: identify weakness of the design (oriented functional).
  - Product/Electronic FMEA: identify weakness of the design (oriented to hardware).
  - Software risk management: Software-FMEA (identify weakness of the software design), check coherence and completeness of software activities (specification, design, integration, and testing) and evaluation of residual risks of software.
  - Process FMEA: identify weakness of the manufacturing process.
  - Reliability data on critical components.

The risk management plan includes usability testing according to the ISO 62366 standard. It identifies all potential danger sources during its intended use and guarantees the device use is safe for the patient or for intended users during the pre-implantation phase, implantation phase and post-implantation phase. After usability testing, risk reduction actions should be eventually implemented, and recommendations shall be provided to reduce the usability risk to its lowest level.

Risk analysis is a continuous process during the clinical investigation. Clinical data, including adverse events, and information related to device performance and usability will be evaluated to assess the impact on the benefits/risk ratio.

4. Residual risks associated with the investigational device.

The risk analysis activities have identified residual risks concerning Icoms® FlowMaker®, the sub-systems and the software. There are no unacceptable risks identified.

The residual risks identified on the current configuration of the device are classified as acceptable or potentially acceptable. Examples of clinical acceptable residual risks are:

- The risk of the subject's death or the occurrence of any serious adverse device effects due to device malfunction was assessed as acceptable in reason of the device operation, which is to support the activity of the native heart. Therefore, the patient is not dependent of the device, since the native heart will continue to spontaneously contract and maintain an ejected blood flow, despite a device stop, until replacement of the defected device by another assist device or by a donor heart.
- The risk of patients' death or the occurrence of any serious adverse events, during the surgical re-intervention to replace a defected device, was assessed as acceptable, because of the fairly easy replacement of the Icoms® FlowMaker®.

Residual risks associated with the device are indicated in the Investigator Brochure.

4.1. Risks associated with participation to the clinical investigation.

The main risks associated with participation to this study are:

- Patient mis-selection due to non-respect of the inclusion/exclusion criteria
- Misuse of the investigational medical device by the users (HCP, Patients, caregivers)
- Anticipated adverse events / adverse device effects similar or less to those seen with existing LVADs (See the 17.2 section anticipated adverse events of this study protocol).
- Unanticipated adverse events / adverse device effects similar or less to those seen with existing LVADs.
- Investigational device malfunctions in post-operative period
- The risk of thromboembolic events

4.2. Risks control and mitigation in the clinical investigation.

The risks for study patients will be minimized through a thorough selection process of study sites including investigators, HCP training, patients' selection and patient/caregiver training procedures.

Risk mitigation will be accomplished by:

- Selection of study sites/hospitals that are experienced with heart transplant, mechanical circulatory support (MCS), clinical study conduct and site staff with demonstrated proficiency in the patients selection and management following MCS surgery. The records of the study sites on patients' selection and outcome will be documented.
- Clearly define and communicate to investigators the inclusion/exclusion criteria to ensure only appropriate patients are enrolled.
- Set up of a patient selection committee to ensure that selected patients are recruited according to the study inclusion and exclusion criteria
- Providing investigators and clinical personnel with extensive training on the device implantation procedure, the use of the device and device trouble shooting by certified sponsor training personnel. Competencies will be tested, and training must be completed and documented prior to the first enrollment.
- Providing technical support to the clinical staff during all phases of the treatment with clinical support hotline 24 hours a day,7 days a week (see section 2.7 of this protocol)
- Troubleshooting procedures with actions required in the event of device malfunctions and the management of alarms are clearly described in the user manual (Clinician manual & patient manual) and integrated to HCP and patients/caregivers training modules.
- Ensuring that patients and caregivers/relatives undergo an extensive hospital training program with focus on battery power management, daily living with the device and device troubles shooting. They will be tested for competency prior to the hospital discharge.
- Close monitoring of sites and oversight of patient selection, data acquisition, and general conduct of the trial according to the sponsor Trial Monitoring Plan.
- Critical safety issues will be evaluated by the sponsor's risk management according to the sponsor risks management procedure and taken into consideration by an independent Data Safety Monitoring Board for the study assessment.
- Patients and family/caregivers will be supported throughout the entire study and after the completion of the study. Regular home visits by a trained nurse will take place to provide support and additional training if needed.

4.3 Corrective and preventive actions to mitigate the risk of thromboembolic event

Following the thromboembolic events observed in previously implanted subjects (see the Investigator's Brochure for further details), both the device design and the device management process have been improved in order to reduce the risk of thrombogenicity, particularly in situations of insufficient anticoagulation.

Implanted subject anticoagulation management:
A reinforced anticoagulation protocol is now recommended to the medical team; refer to Annex K of this document for further details.

Design improvement:

- Update of flush functioning: The cleaning sequence(flush) consists of an ejection cycle at 6000 rpm's each 5 seconds. The ejection cleaning cycle is performed in synchrony with the native heart. During safety mode a 50 ms 6000 rpm ejection is performed each 30 seconds, this function could be turned off. The objective of the cleaning sequence is to reduce the neo-thrombus formation inside the FlowMaker.

Manufacturing process improvement:

- Device polishing process controls are reinforced to improve the way the device's surface roughness is implemented and controlled

Patient management:

The table below described the recommended patient management protocol in case of FlowMaker alarm consumption and suspicion of thromboembolic events

Initiating Event Descriptions / Biomarkers / Alarms	Criteria for biological suspicion to consider	Preventive actions
ALM 214 ; ALM 215 : significant consumption increase	• **Anticoagulation efficiency with, when applicable:** ○ INR ○ rAPTT (if Heparin) ○ Anti Xa (if Heparin) ○ Factor VIII • **CRP** • **ASAT** • **ALAT** • **Complete blood count** • **Procalcitonine** • **LDH** • **haptoglobin** • **D-Dimers :** Significant increase over 2 consecutive check-ups 24 hours apart Or > 10,000, check on a second assessment in the hours that follow • **Hemolysis index :** Increase between 2 consecutive blood samples • Or >20, check on a second assessment in the hours that follow • **Plasma Free Hbg :** >20 and increase on 2 consecutive assessments 24 hours apart or > 50, check on a second assessment in the following hours	1-Adjust anti-coagulation treatment according to the results and consider anti-coagulation increase 2-Add treatment if infection **3-Adjust Heparin to reach rAPTT 1,8-2 (consider cerebral and thoracic CT-scan result and INR value to adapt the treatment according to each patient)** **4-If cardiac decompensation, consider inotropic therapy.** **5-If the consumption issue is not resolved, consider a pump change.**

5 Objectives and hypotheses of clinical investigation.

The objective of this clinical investigation is to evaluate the clinical safety and performance of the Icoms® FlowMaker® in subjects with severe heart failure

5.3 Primary objective.

The primary objective of the study is to evaluate the clinical safety and survival rate of the Icoms® FlowMaker® at 30 days post-implantation.

5.4 Secondary objectives.

The secondary objectives are to:

1) Assess the hemodynamic and the subject's clinical status.
2) Evaluate the safety profile of the device
3) Assess device performance according to technical specifications.

5.5 Primary endpoints .

The primary endpoints at 30-days post implantation are:

1) Survival free from stroke with MRS ≥ 3
2) Freedom from device-related reoperation[1]
3) Freedom from device-related infection

[1]Nota Bene: In case of device replacement or heart transplantation if the patient becomes eligible to transplant during the study, the time of induction of anesthesia must be considered as the success of the bridge to transplant.

5.6 Secondary endpoints .

Secondary endpoints will be assessed at 30 days, 2 months, 3 months, and 6 months post-implantation.

1) Clinical improvements:
   - NYHA functional status improvement
   - Quality of Life Change (EQ-5D-5L).
   - Successful withdrawal of intravenous inotropic drugs.
   - Hemolysis markers (LDH, Free Hemoglobin, Factor of Von Willebrand).
   - 6-minute walk test (6MWT) distance

2) Safety of the investigational device.
   - Incidence of adverse events, neurological status, and unanticipated adverse device effects (bleeding, stroke, device malfunction, major infection, renal failure, respiratory failure or heart failure).
   - Incidence of disabling strokes with MRS > 3.

3) Proper functioning of the device.
   - Hemodynamic improvement (assessed by CO, aortic VTI, LAP, inotropic drugs weaning).
   - Assessment of the external coil of the Transdermal Energy Transfer (TET) System.

- Patient's ability to manage device alarms and the external controller, based on the device usability tests and device deficiencies reported during the study.
- Proper functioning of the implanted battery

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6 . Design of the clinical investigation.

6.1 Study Design

This study is a non-randomized, prospective, single-arm study (Fig. 3). A total of 10 subjects are planned to be enrolled. The Icoms® FlowMaker® will be implanted in these subjects during a surgical procedure. Subjects will be followed for up to 24 months. Implantation of the first two subjects will be followed by a pause in enrollment until the primary endpoint is analyzed at one month and the DSMB has issued its recommendation (fig.4).
Each subject must give his/her written consent to participate to the study and must sign the study informed consent form before any study procedure can be started. The subjects will be enrolled if they meet the clinical and anatomic criteria described in section 7 of this protocol.

A screening form, duly completed by investigators with the subject clinical data related to inclusion and exclusion criteria, will be sent to the sponsor's medical expert (Selection Committee) for validation of the clinical eligibility.
The subject's anatomic compatibility to receive the device will be assessed as described in section 3.2 of this protocol by the investigator site and the Selection Committee. The study primary endpoints will be assessed at 30 days (M1) post-implant. Secondary endpoints will be assessed at 60 days (M2), 90 days (M3) and 180 days (M6) post -implant.
Patient still under the device after 6 months post-implant will be followed in terms of safety surveillance at M9, M12, M18, M24. Safety data will continuously be recorded (see section 8.8 for more details).

a) <u>Study conduct overview</u>

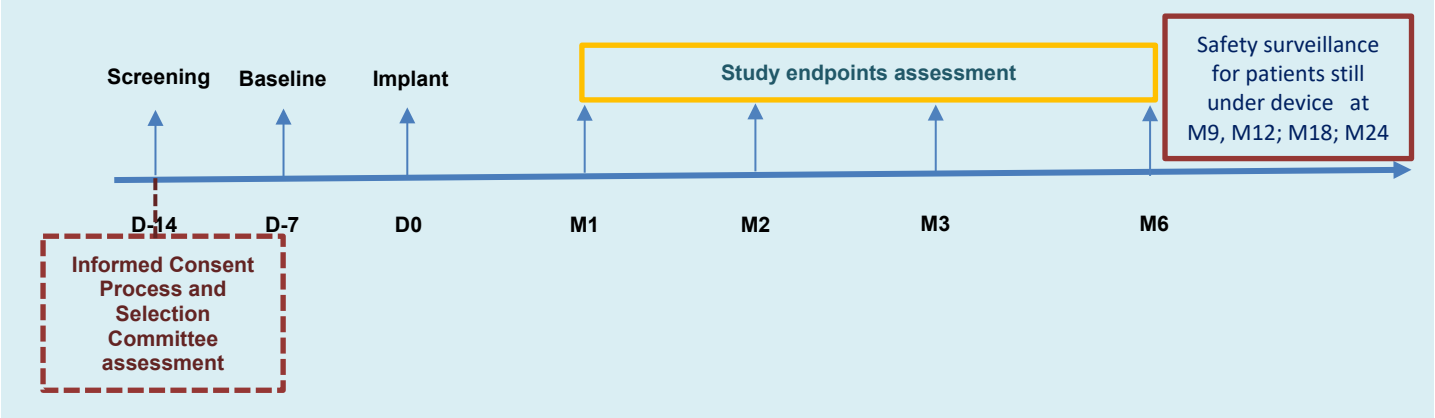

Fig 3. Study Scheme

The screening visit must take place within 14 days prior to the date of implantation.The study is estimated to last approximately 44 months, with a recruitment period of 20 months and 24 months of follow up. All subjects will be followed for primary endpoints.

Subjects remaining on the FlowMaker® after M6 post-implant assessment will be followed according to the section 8.8 of this protocole. Safety data will continue to be collected by the sponsor as part as device safety surveillance. FineHeart's technical teams and proctors will continue to support the medical team for the duration of the device use. FineHeart will provide free service and components necessary for the operation and replacement of device components for the entire time it is implanted in patients, even after the end of the study. The FlowMaker® system will be provided free of charge to the study site for patients enrolled in the clinical trial.

In the event of negative results and ultimately non-commercialization of the device or in the event of bankruptcy or cessation of payment of the company FineHeart, the device will be explanted from the patient upon the decision of the medical team, who will then ensure the patient's follow up in accordance with standard practice. The device may be replaced by a conventional commercially available LVAD or by a graft if the subject becomes eligible.

b) Subjects recruitment plan

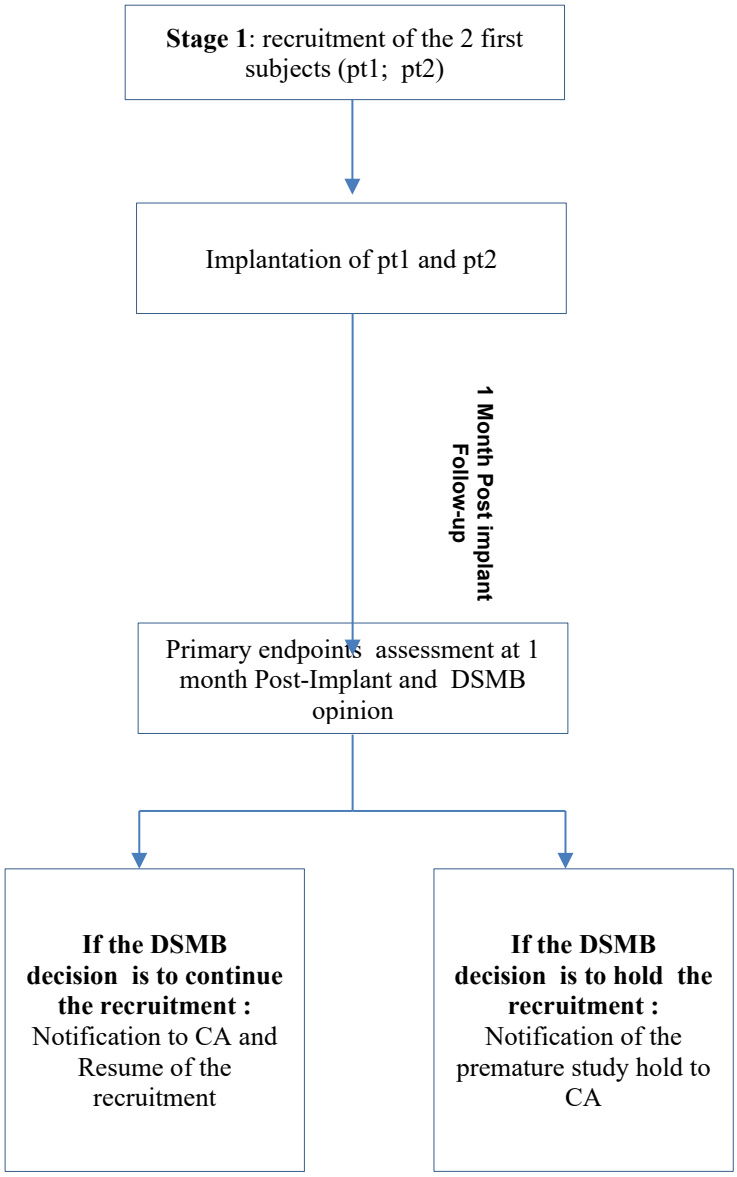

Fig 3. Subjects recruitment plan

6.2 Financing of the study

The study is fully funded by the company Fineheart, located at 28 Av. Gustave Eiffel, 33600 Pessac, France

Fineheart is the manufacturer of the Icoms FlowMaker and the sponsor of this study. All costs related to the specific procedures of the study described in section 8 of this document, will be the subject of a contract between Fineheart and the investigating center for their reimbursement. Meal, travel, and accommodation expenses related to the subject's participation in the study will be reimbursed by the sponsor via its subcontractor upon presentation of an invoice. The device under investigation as well as all its components and Fineheart's technical team will be made available free of charge to the centre for as long as a patient is implanted with the device. The patient's travel costs to and from the hospital as part of the specific visits will also be reimbursed.

For the French centers participating in the study, the financial agreement with the sponsor Fineheart will be established according to the Decree of July 29, 2024, Establishing the Standard Agreement Model Provided for in Article R. 1121-3-1 of the French Public Health Code.

6.3 Study Committees

6.3.1 Subjects Selection Committee

An international selection committee composed of independent experts will assess the clinical and anatomical eligibility of subjects identified by the investigator centers based on the inclusion and exclusion criteria. The patient's clinical data, collected by the investigator center during the selection visit, will be reviewed and evaluated by the selection committee. The committee is composed of the following members:

The principal investigators from the investigator centers.
Four independent experts with extensive experience in the field of advanced heart failure, particularly in imaging, cardiac assistance devices, and surgical therapy.
The four experts will be appointed for the duration of the study to ensure continuity in the assessment of patient eligibility.

The details regarding the operation of the selection committee are described in the selection committee charter. The four experts will be appointed for the duration of the study to ensure continuity in the assessment of patient eligibility for the study. The quorum is reached if 2 experts and one principal investigator are available to assess the eligibility of a patient and the decision should be unanimous among the committee.

6.3.2 Data Safety Monitoring Board

The role of the Data Safety Monitoring Board (DSMB) is to guarantee patients' safety, provide expertise and give potential recommendations to the Sponsor during the study. The DSMB will review study data, including adverse events, SAE adjudication and any updated risk analysis, Every 3 month, but an ad hoc meeting may be held earlier if necessary depending on the seriousness of device-related events observed during the study . The frequency of meetings is described in the DSMB charter and may vary depending on

the recruitment rate or the occurrence of unexpected events, findings, or risk analysis. The minutes of DSMB meetings could be forwarded to the competent authority if needed.
The DSMB committee is composed of 3 independents experts in the field of cardiac assist device implantation and patient management in post-device implantation period.
The details regarding the operation of the DSMB are described in the DSMB charter.

7 Study Population.

The study population consists of patients with severe heart failure who are at **high risk for a conventional LVAD and at high risk for a percutaneous driveline.** Ten patients will be recruited and implanted during the study.

7.1 Inclusion Criteria for subject selection.

Patients followed for severe heart failure and fulfilling the following inclusion criteria.

1-Age 18 and 80 years included.
2- Written inform consent.
3- Females of child-bearing age must agree to use adequate contraception.
4- Suitable neurocognitive status.
5- Distance between the aortic valve and the LV endocardial apex ≥ 95mm and the End-Diastolic Left Ventricular (LV) volume > 200 mL
6- Body Surface Area (BSA) ≥ 1.2 m².
7- LVEF ≤ 35 % and assessed Intermacs ≤ 4
8- Advanced heart failure patients symptomatic despite optimal medical management (OMM) based on the European Cardiology Society guidelines[15] otherwise meeting standard best practice indications for implantable LVAD

AND fulfilling following criteria approved by the International multidisciplinary expert selection committee:

9- Contraindication or excessively heightened risk of a conventional LVAD implant due to factors such as:

- **CVP/PCWP ≤ 0.6**
- **anatomical or surgical factors constituting excessive perioperative implant risks etc.**

(*Duly recorded in the source document during the patient Inform consent process)*

OR

10- Patient with High Risk of the percutaneous driveline such as:

- **Such as patient with severe diabetes mellitus / immunodeficiency / cachexia**
- **psychological factors limiting driveline acceptance and / or management duly recorded in the psychological evaluation report at screening.**

11- Temporary ineligibility to the heart transplant
(active or remission of cancer / highly sensitized PRA…)
(Duly recorded in the source document during the patient Inform consent process)

12- Patient's affiliation to health care insurance, if local requirement.
13- Patient implanted with an implantable cardioverter defibrillator Medtronic and Boston ICD.
or patient requiring implantation of a cardiac defibrillator due to a risk of ventricular arrhythmia.

7.2 Exclusion criteria for subject selection.

1- Body Mass Index (BMI) > 40.
2- TAPSE ≤ 10 mm
3- Pulmonary VTI ≤ 6cm
4- Patients not eligible to transplant due to surgical risks
5- Existence of any ongoing mechanical circulatory support (MCS) other than an intra-aortic balloon pump (IABP)
6- History of left thoracotomy.
7- History of confirmed untreated abdominal or thoracic aortic aneurysm > 5 cm.
8- Cardiothoracic surgery within 30 days of implant.
9- Acute myocardial infarction within 14 days of implant.
10- On ventilator support for > 72 hours within the four days immediately prior to implant.
11- Pulmonary embolus within three weeks of implant.
12- Presence of current atrial or ventricular thrombus or free trabeculae, preferably confirmed by contrast-enhanced MRI, or, if that is not feasible CT-SCAN or Trans-Esophageal Echocardiography.
13- Symptomatic cerebrovascular disease, stroke within 180 days of screening or > 80% stenosis of carotid, vertebral or cranial vessels.
14- Unstable INRs: at least four consecutive INRs out of [2-3] range, if patient under conventional anticoagulation.
15- Moderate to severe aortic regurgitation, defined as > 50% regurgitant fraction.
16- Moderate - Severe aortic stenosis, defined as an aortic valve area (AVA) ≤ 1.5 cm2.
17- Active, uncontrolled infections, history of hyperleukocytosis with Leucocytes > 10.000/mm3, CRP >10mg/l, PCT > 0,2ng/ml, positive hemocultures < 48 hours, positive urine cultures, positive sputum cultures, any abnormalities identified by CT scan of brain-thorax and abdomino-pelvic region.
18- Uncorrected thrombocytopenia or generalized coagulopathy (e.g., platelet count < 100,000 / INR > 2.0 in the absence of anticoagulation therapy).
19- Hepatic insufficiency: a total bilirubin > 3 mg/dL within 72 hours of implant, or biopsy proven liver cirrhosis or portal hypertension.
20- Pulmonary vascular resistance (PVR) demonstrated to be unresponsive to pharmacological manipulation and the PVR > 6 Wood units.
21- Patients with a mechanical heart valve.
22- Etiology of heart failure is due to, or associated with, uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis, active myocarditis, or restrictive cardiomyopathy, ventricular septal defect
23- History of severe Chronic Obstructive Pulmonary Disease (COPD) or severe restrictive lung disease. GOLD (Global Initiative for Chronic Obstructive Lung Disease) score < 3.
24- Participation in any other study involving investigational drugs, devices, or biologics.
25- Severe illness, other than heart disease, which would limit survival to a maximum of 1 year.
26- Peripheral vascular disease with rest pain or ischemic ulcers of the extremities.
27- Pregnancy.
28- Patient unwilling or unable to comply with study requirements.

29- Patients unable or unwilling to sign the written informed consent.
30- Technical obstacles, which pose an inordinately high surgical risk, in the judgment of the investigator.
31- Intolerance to anticoagulant or antiplatelet therapies or any other peri- or postoperative therapy that the investigator may administer based upon the patient's health status.
32- Specific liver enzymes [AST (SGOT) and ALT (SGPT)] > 3 times upper limit of normal within 72 hours before implant.
33- Patient living alone (without an accompanying person).
34- Rapid AF, unless nodo-hissian junction ablation is considered.
35- Mid-septal end-systolic LV diameter ≤ 25mm.
36- Sequential Organ Failure Assessment Score (SOFA score) > 8
37- Minor subjects, persons deprived of liberty, protected adults, or those unable to consent
38- Subjects who have participated in a clinical trial within 12 months
39- Patient implanted with an Implantable Cardioverter Defibrillator (ICD) other than Medtronic and Boston.

8. Study Procedures.

8.1 Study Exams Flowchart

The table below describes the study procedures. All examinations carried out from D-14 before implantation of the device and up to 6 months after implantation are specific to the evaluation of the experimental device. These examinations do not correspond to the routine management of patients and must therefore only be carried out as part of the study. Every effort should be made to carry out the assessments at the designated times or within the defined window. The maximum duration of a visit is 24 hours.

Table 1- Study Exams.

	Screening	Baseline	implant	Visit 1-7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12***	Discharge (if last visit > 14 days)****
Days (±2)	D-14	D-7 to D-1	D0	D1 to D7	D15	D30 M1	D60 M2	D90 M3	D180 M6	
Informed Consent	X									
Screening form	X									
Subject interview-thrombotic risks	X									
Intermacs class	X	X			X	X	X	X	X	X
NYHA class	X	X			X	X	X	X	X	X
Cerebral CT scan	X					X				
Psychological assessment	X								X	
Clinical exams (Weight, T°, BP , gender, age)	X	X	X	X	X	X	X	X	X	X
Heart Rate	X	X	X	X	X	X	X	X	X	X
Echo-TTE see table 3 for more details	x	x		TTE or TEE	TTE or TEE	X	X	X	X	X
Echo-TEE see table 3 for more details			x	TTE or TEE	TTE or TEE					

	Screening	Baseline	implant	Visit 1-7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12***	Discharge (if last visit > 14 days)****
Days (±2)	D-14	D-7 to D-1	D0	D1 to D7	D15	D30 M1	D60 M2	D90 M3	D180 M6	
Electrocardiogram	X		X							
Blood culture	X									
6MWT & EQ-5D-5L		X			X	X	X	X	X	X
Blood Tests see Table 2 for more details	X	X	X	X	X	X	X	X	X	X
Urine Culture	X									
Previous Medication	X									
Intubation & extubation time			X	X						
Medical History & medication	X									
Device Data Export			X	X	X	X	X	X	X	X
Patient Diary				X	X	X	X	X	X	X
Subject Training on Device				X	X	X	X	X		
AE, SAE, DD report		X	X	X	X	X	X	X	X	X
Implant Device Checklist			X							
Cardiac Catheterization	If available (CO; CI; Oxygen Saturation)		If available (CO; CI; Oxygen Saturation)	If available (CO; CI; Oxygen Saturation)	If available (CO; CI; Oxygen Saturation)	If available (CO; CI; Oxygen Saturation)				
Device Usability Test						X		X	X	
Device settings			X	X	X	X	X	X	X	X
Thoraco CT-Scan with contrast	X			D4		X				

**The echocardiography should be performed with the pump in safety mode, if possible, see the clinician manual for more detail.*
*** In case these data are missing at baseline, they should be collected at the Implant date (D0) during the pre-operative period (before starting the surgical intervention)Per-op: Per-operative*

**** Patients still under the investigational medical device after D180 post device implantation will be follow up according to section 8.8 of this document*

*****The patient can be discharged at any time after 1 month post-implantation on the decision of the medical team according to his/her clinical condition and the ability to use the device alone by using the patient user manual requirements.*

All visits and all exams, not carried out within defined windows, will be considered as a deviation from the study protocol. The reason and justification for any protocol deviations should be clearly documented in the patient's medical record.

8.1. Blood Tests details

Results of the monitoring workup should be made available **within 3 hours after sampling whenever possible**, **7 days a week including weekends**

Table 2- Blood tests details

PARAMETERS	Samples requirements	500 µL aliquot to be frozen at −80 °C for the Core Lab	Testing Frequency :
Complete blood count (CBC) **Platelet count by fluorimetry** **Immature Platelet Fraction (IPF%) (if available)** **Reticulocytes / schistocytes**	1 lavender EDTA tube, 5 mL PET		Baseline; Day 0 before device implantation; Day 0 after device implantation; daily post-implantation while the patient is in the ICU (one panel/day); twice weekly after ICU discharge (windows of 3 days); then at Month 1, Month 2, Month 3, and Month 6 ,M9, M12, M18, M24 post-implantation.
Anticorps anti-PF4	1 red serum tube, 5 mL PET	**Hemostasis serum bank**	Day 0 before implantation, Day 1, Day 4, Day 7, Day 15, then stop unless required by routine care
PT/INR, aPTT, factor II, factor V, fibrinogen, D-dimers, fibrin monomers, Anti-Xa activity, antithrombin	1 blue citrate tube, 3 mL PET (empty)		Baseline; Day 0 before device implantation; Day 0 after device implantation; daily post-implantation while the patient is in the ICU (one panel/day); twice weekly after ICU discharge (windows of 3 days); then at Month 1, Month 2, Month 3, and Month 6 , M9, M12, M18, M24 post-implantation.
Coagulation Factors VII X VIII IX XI	2 blue citrate tube , 3 mL PET	**Hemostasis plasma bank**	**Factor VIII only**: Baseline; Day 0 before device implantation; Day 0 after device implantation; daily post-implantation while the patient is in the ICU (one panel/day); twice weekly after ICU discharge (windows of 3 days); then at Month 1, Month 2, Month 3, and Month 6, M9, M12, M18, M24 post-implantation. **Factors VII, X IX and XI**: To be done if needed according subject clinical condition
Thrombin Generation Test (TGT) **P-selectin**		**hemostasis plasma bank**	Day 0 post-implantation, Day 4, Day 7; Then if needed in case of suspected platelet activation
VWF:Ag, VWF:RCo **VWF multimers**	2 blue citrate tubes 3 mL, PET	**hemostasis plasma bank**	Day 0 before implantation (VWF:Ag and VWF:RCo only) Day 1, Day 3 Once weekly during the first month Once monthly at Month 1, Month 2, Month 3,and Month 6, M9, M12,M18, M24 post-implantation Hemostasis plasma bank

CRP **Procalcitonin** **Ferritin** **Total bilirubin** **LDH, ALP, AST, ALT** **Haptoglobin** **Creatinine, urea** **Hemolysis index**	1 light green heparinized tube, 7 mL		Baseline; Day 0 before device implantation; Day 0 after device implantation; daily post-implantation while the patient is in the ICU (one panel/day); twice weekly after ICU discharge (windows of 3 days); then at Month 1, Month 2, Month 3, and Month 6, M9, M12, M18, M24 post-implantation. **Ferritine** : Baseline, M1, M2, M3, M6 , M9, M12, M18, M24 post-implantation
Plasma free hemoglobin	1 dark green heparinized tube, 7 mL		Baseline; Day 0 before device implantation; Day 0 after device implantation; daily post-implantation while the patient is in the ICU (one panel/day); twice weekly after ICU discharge (windows of 3 days); then at Month 1, Month 2, Month 3, and Month 6, M9, M12, M18, M24 post-implantation.
Total proteins **Prealbumin** **Albumin** **Triglycerides**	1 yellow serum tube, 7 mL		once weekly (1/week) till M6 post-implantation

8.1.2 Echocardiography details

Table 3- Echocardiography details

Parameters	**Selection D-14**	**Baseline D-7**	**Pre-implant & Per-implant D0**	**D1-D15 (daily)**	**M1; M2; M3**	**M6; M9 M12; M18; M24**
Type of Echocardiography (TTE or TEE)	TTE**	TTE	TEE*	TTE orTEE	TTE	TTE
LV diameter in diastole and systole: mid-septal level (mm)	x	x	x	x	x	x
Distance between the left apical endocardium and the aortic valve sigmoids in end of diastole (mm)	x	x	x			
Distance between the aortic valve and the pump tip (mm)				x	x	x
LV apical wall thickness (i.e. left apical myocardial thickness in 2D imaging via left parasternal or left apical approach, 4-chamber view) (mm)	x	x	x			
Ventricular ejection time (ET) (ms)	x	x	x	x	x	x
LVEF (%)	x	x	x	x	x	x
LV outflow tract diameter (LVOT diameter) (mm)	x	x	x	x	x	x
Subaortic Velocity Time Integral (VTI) without pump (cm)	x	x	x			
Subaortic Velocity Time Integral (VTI) with pump (cm)				x	x	x
Sub-pulmonary Velocity Time Integral (VTI) without pump (cm)	x	x	x			

Sub-pulmonary Velocity Time Integral (VTI) with pump (cm)				x	x	x
CO (L/min)	x	x	x	x	x	x
HR (bpm)	x	x	x	x	x	x
Electromechanical delay (EMD) (ms)	x	x	x	x	x	x
E wave (m/s)			x	x	x	x
A wave (m/s)			x	x	x	x
RVEF (%)	x	x	x	x	x	x
TAPSE (mm)	x	x	x	x	x	x
Mitral Valve diameter (mm)	x	x	x	x	x	x
Aortic Valve diameter (mm)	x	x	x	x	x	x
PAP (mmHg)	x	x	x	x	x	x
Triscupid Regurgitation grade (1, 2, 3, 4)	x	x	x	x	x	x
Mitral Regurgitation grade (1,2 3,4)	x	x	x	x	x	x
TEE*= Transesophageal echocardiography TTE**=transthoracic echocardiography						

8.2 Screening visit (Day -14 ± 2, within 2 weeks before device implantation).

The Following procedures and assessments will be performed within 14 days, prior device implantation:

- Confirm signed informed consent is available.
- Complete the study screening form via the e-CRF and send it to the sponsor for review and approval.
- Complete the subject interview on thromboembolic and hemorrhagic Risks (see Annex-K-Anticogulation Protocol-appendix1)
- and previous pertinent medications and history related to subject anticoagulation therapy according to Annex-K-Anticoagulation protocol.
- Previous pertinent medications and medical history, related to cardiac diseases including inotropic treatment, coagulopathies, renal failure and hepatic dysfunction , smoking history, within 6 months.
- Demographic data including, sex, year of birth, age.
- Clinical exams including Weight, BSA, Temperature, Systolic Blood Pressure and Diastolic Blood Pressure and Pulse Oximetry (SpO_2).
- Heart Rate.
- Intermacs class see annex D.
- NYHA class see annex D
- A cerebral CT-scan, done within 14 days
- Cardiothoracic-Scanner (CT-Scan) or cardiac MRI with contrast product injection, done within 14 days.
- A psychological assessment to ensure that the subject can comply with study requirements, especially the training on the device management and to adhere to medical instructions.
- Electrocardiogram (ECG).
- Blood Culture
- Urine Culture
- **A Trans-Thoracic Echocardiography (TTE),** refer to *Table 3- Echocardiography details.*
- Subject information on the investigational device management.
- **Cardiac Catheterization data if available** : Blood Pressure (SBP, DBP, MBP), Pulmonary Artery Pressure (PASP, PADP¨, MPAP, PAP index), Central Venous Pressure (CVP), Pulmonary Capillary

Wedge Pressure (PCWP), Pulmonary Gradient, Right Ventricular Stroke Work index (RVSWI), ratio CVP/PCWP, Cardiac Output, Cardiac Index, Systemic Vascular Resistance (SVR), Pulmonary Vascular Resistance (PVR),Venous Oxygen Saturation (SVO2)

Screening Blood Tests according to the anticoagulation protocol (see annex- K)

A comprehensive pre-operative biological work-up must be performed to screen for coagulation disorders, anemia, hemolysis, thrombocytopenia, infection…

Main Parameters assessed	Local laboratory / Core Laboratory
Complete blood count (CBC / NFS)	local
Platelet count by fluorimetry	local
Immature Platelet Fraction (IPF %)	local
Anti-PF4 antibodies	Local
Reticulocytes	local
Schistocytes	local
Plasma free hemoglobin	Local
Total bilirubin	local
LDH	local
Haptoglobin	local
PT / INR	local
aPTT	local
Coagulation factors (II, V, VII, VIII, IX, X, XI)	Local
Fibrinogen (Clauss method)	Local
D-dimers	Local
Fibrin monomers	local
Anti-Xa activity (if UFH or LMWH)	local
Antithrombin	Loca
Von Willebrand Factor antigen	Local
Von Willebrand Factor activity	Local
Von Willebrand Factor Multimers	Local
Thrombin Generation Test (TGT)	Core Laboratory
C- Reactive Protein (CRP)	Local
Procalcitonin	Local
Creatinine	Local
Urea	Local
Total Proteins	Local
Pre-albumin et albumin	Local
AST- ALT	Local
ALT (Alkaline Phosphatase)	Local
ferritin	Local
Triglycerides	Local

8.3 Baseline Visit (Day -7 ± 2, within 1 week before device implantation).

The Following procedures and assessments will be performed within 7 days prior to device implantation:

- Clinical exams including Weight, BSA, Temperature, Systolic Blood Pressure and Diastolic Blood Pressure and Pulse Oximetry (SpO_2).

- Heart Rate.
- Intermacs class see annex D
- NYHA class see annex D
- 6 Minutes Walking Test (6MWT) if possible (if not, the value of the last one performed).
- EQ-5D-5L questionary.
- **A Trans-Thoracic Echocardiography (TTE)** refer to *Table 3- Echocardiography details*

Blood tests: refer to *Table 2- Blood tests details*
Arterial Blood gas: PaO2 ,PaCO2, pH ,HCO3- ;SaO2; Lactate

8.4 Implant Visit - Day 0.

The Following procedures and assessments will be performed the day of implant:

1) Before starting the surgical intervention.
- Clinical exams including weight, BSA, temperature, systolic and diastolic blood pressure, pulse oximetry (SpO_2)
- Heart rate.
- An Electrocardiogram.
- **A Transesophageal Echocardiography (TEE)** refer to *Table 3- Echocardiography details*
- **Cardiac Catheterization data (Swan Ganz):** Blood Pressure (SBP, DBP, MBP), Pulmonary Artery Pressure (PASP, PADP¨, MPAP, PAP index), Central Venous Pressure (CVP), Pulmonary Capillary Wedge Pressure (PCWP), Pulmonary Gradient, Right Ventricular Stroke Work index (RVSWI), ratio CVP/PCWP, Cardiac Output, Cardiac Index, Systemic Vascular Resistance (SVR), Pulmonary Vascular Resistance (PVR),Venous Oxygen Saturation (SVO2)

Blood tests: refer to *Table 2- Blood tests details*
Arterial Blood gas: PaO2 ,PaCO2, pH ,HCO3- ;SaO2; Lactate

2) During Surgical intervention.
- Complete the implanted device components tracking form.
- Complete the Implant Device Checklist, to ensure that the surgical procedure is performed according to Sponsor requirements and collect surgical procedure specific data indicated therein, see the Clinician User Manual.
- **A Trans-Esophageal Echocardiography (TEE) is required during the whole surgical procedure** refer to *Table 3- Echocardiography details*
- A screen shot of the device programmer to collect the total flow rate with pump.
- **Cardiac Catheterization data (Swan Ganz):** Blood Pressure (SBP, DBP, MBP), Pulmonary Artery Pressure (PASP, PADP¨, MPAP, PAP index), Central Venous Pressure (CVP), Pulmonary Capillary Wedge Pressure (PCWP), Pulmonary Gradient, Right Ventricular Stroke Work index (RVSWI), ratio CVP/PCWP, Cardiac Output, Cardiac Index, Systemic Vascular Resistance (SVR), Pulmonary Vascular Resistance (PVR),Venous Oxygen Saturation (SVO2)

3) After Surgical intervention.
- Complete the allocated device external components tracking form.
- Export of the device technical data.
- Adverse Events and Device Deficiencies reports if needed.

- Relevant concomitant medications related to Adverse Event, cardiac disease, renal failure, hepatic dysfunction and other relevant diseases.
- Print device settings
- Perform a manual LIM monitoring
- **Cardiac Catheterization data (Swan Ganz):** Blood Pressure (SBP, DBP, MBP), Pulmonary Artery Pressure (PASP, PADP¨, MPAP, PAP index), Central Venous Pressure (CVP), Pulmonary Capillary Wedge Pressure (PCWP), Pulmonary Gradient, Right Ventricular Stroke Work index (RVSWI), ratio CVP/PCWP, Cardiac Output, Cardiac Index, Systemic Vascular Resistance (SVR), Pulmonary Vascular Resistance (PVR),Venous Oxygen Saturation (SVO2)

  Blood tests: refer to *Table 2- Blood tests details*
  Arterial Blood gas: PaO2 ,PaCO2, pH ,HCO3- ;SaO2; Lactate

8.5 Post-implant Visits – Visit 1 to Visit 7, From Day 1 to Day 7 post-implant.

The Following procedures and assessments will be performed during post implant visit 1 to visit 7 from D1 post device implantation to Day 7, on a daily basis :

- Clinical exams including weight, temperature, systolic blood pressure and diastolic blood pressure and pulse oximetry (SpO_2)
- Heart Rate
- **A Trans-thoracic echocardiography (TTE) or a Transesophageal echocardiography (TEE)** refer to *Table 3- Echocardiography details*
- A screen shot of the device programmer to collect the total flow rate with pump.
- Export of the device technical data see section 8.12 of this study protocol.
- Complete the patient diary see Annex G.
- Complete the patient training booklets if needed
- Adverse events and device deficiencies reports if needed.
- Relevant concomitant medications related to adverse events, cardiac disease, renal failure, hepatic dysfunction and ongoing other relevant diseases.
- Complete the device external components exchange tracking form and specify the reason of each device component replacement.
- Print device settings
- Perfom a manual LIM monitoring within 48 hours post -implant
- Thoraco CT-scan with contrast at Day 04 post-implant

- **Cardiac Catheterization data (Swan Ganz):** Blood Pressure (SBP, DBP, MBP), Pulmonary Artery Pressure (PASP, PADP¨, MPAP, PAP index), Central Venous Pressure (CVP), Pulmonary Capillary Wedge Pressure (PCWP), Pulmonary Gradient, Right Ventricular Stroke Work index (RVSWI), ratio CVP/PCWP, Cardiac Output, Cardiac Index, Systemic Vascular Resistance (SVR), Pulmonary Vascular Resistance (PVR),Venous Oxygen Saturation (SVO2)

  Blood tests: refer to *Table 2- Blood tests details*
  Arterial Blood gas: PaO2 ,PaCO2, pH ,HCO3- ;SaO2; Lactate

8.6 Post-implant Visits - Visit 8, Day 15 post -implant.

The Following procedures and assessments will be performed during post implant visit 1 at D15 post device implantation:

- Clinical exams including weight, temperature, Systolic Blood Pressure and Diastolic Blood Pressure and Pulse Oximetry (SpO_2).
- NYHA class , see Annex D.
- Intermacs Class, see Annex D.
- Heart Rate.
- **A Trans-thoracic echocardiography (TTE) or a Transesophageal echocardiography (TEE)** refer to *Table 3- Echocardiography details*
- A screen shot of the device programmer to collect the total flow rate with pump.
- Quality of life questionnaires, EQ-5D-5L
- 6MWT see annex C.
- Export of the device technical data see section 8.12 of this study protocol
- Complete the patient diary see Annex G
- Complete the patient training booklets if needed
- Adverse events and device deficiencies reports if needed.
- Relevant concomitant medications related to adverse events, cardiac disease, renal failure, hepatic dysfunction and ongoing other relevant diseases.
- Complete the device external components exchange tracking form and specify the reason of each device component replacement.
- Print device settings

- **Cardiac Catheterization data (till the Swan Ganz is implanted) :** Blood Pressure (SBP, DBP, MBP), Pulmonary Artery Pressure (PASP, PADP¨, MPAP, PAP index), Central Venous Pressure (CVP), Pulmonary Capillary Wedge Pressure (PCWP), Pulmonary Gradient, Right Ventricular Stroke Work index (RVSWI), ratio CVP/PCWP, Cardiac Output, Cardiac Index, Systemic Vascular Resistance (SVR), Pulmonary Vascular Resistance (PVR),Venous Oxygen Saturation (SVO2)

  Blood tests: refer to *Table 2- Blood tests details*
  Arterial Blood gas: PaO2 ,PaCO2, pH ,HCO3- ;SaO2; Lactate

8.7 Post -implant Visits – Visits 9,10,11 at Day 30, Day 60 and Day 90 post-implant.

The Following procedures and assessments will be performed during post implant visit 2, 3 and 4 respectively at D30, D60 and D90 post device implantation :

- Clinical exams including weight, temperature, Systolic Blood Pressure and Diastolic Blood Pressure and Pulse Oximetry (SpO_2).
- NYHA class , see Annex D.
- Intermacs Class, see Annex D.
- Heart Rate.
- Cerebral CT scan only at D30 post implant.
- **A trans-thoracic echocardiography (TTE)** refer to *Table 3- Echocardiography details*
- A screen shot of the device programmer to collect the total flow rate with pump.
- Quality of life questionnaires, EQ-5D-5L.
- 6MWT see annex C.
- Export of the device technical data see section 8.12 of this study protocol.
- Complete the patient diary see Annex G

- Adverse events and device deficiencies reports if needed.
- Relevant concomitant medications related to adverse events, cardiac disease, renal failure, hepatic dysfunction and ongoing other relevant diseases.
- Complete the device external components exchange tracking form and specify the reason of each device component replacement.
- Device Usability Test , see Annex H.
- **At Day 30 only, Cardiac Catheterization data (Swan Ganz) if available** : Blood Pressure (SBP, DBP, MBP), Pulmonary Artery Pressure (PASP, PADP¨, MPAP, PAP index), Central Venous Pressure (CVP), Pulmonary Capillary Wedge Pressure (PCWP), Pulmonary Gradient, Right Ventricular Stroke Work index (RVSWI), ratio CVP/PCWP, Cardiac Output, Cardiac Index, Systemic Vascular Resistance (SVR), Pulmonary Vascular Resistance (PVR),Venous Oxygen Saturation (SVO2)
- Print device settings.
- Thoraco CT-Scan with contrast at M1 post implant

Blood tests: refer to *Table 2- Blood tests details*
Arterial Blood gas: PaO2 ,PaCO2, pH ,HCO3- ;SaO2; Lactate

8.8 End of Study Follow up – Visit 12, D180 Post-implant.

The Following procedures and assessments will be performed during the end of study follow up visit at Day 180 post device implantation:

- Clinical exams including weight, temperature, systolic blood pressure and diastolic blood pressure and pulse oximetry (SpO_2).
- NYHA class, see Annex D.
- Intermacs Class, see Annex D.
- Heart Rate.
- Psychological assessment
- **A trans-thoracic echocardiography (TTE)** refer to *Table 3- Echocardiography details*
  A screen shot of the device programmer to collect the total flow rate with pump.
- Quality of life questionnaires, EQ-5D-5L.
- 6MWT see annex C.
- Export of the device technical data see section 8.12 of this study protocol.
- Complete the patient diary see Annex G.
- Adverse events and device deficiencies reports if needed.
- Relevant concomitant medications related to adverse events, cardiac disease, renal failure, hepatic dysfunction, and ongoing other relevant diseases.
- Complete the device external components exchange tracking form and specify the reason of each device component replacement.
- Print device settings

Blood tests: refer to *Table 2- Blood tests details*
Arterial Blood gas: PaO2 ,PaCO2, pH ,HCO3- ;SaO2; Lactate

8.9 Follow up of Subjects still under the Investigational Medical Device after D180 post-implant

After Day 180 post -implant, the subjects still on the investigational medical device should be monitored for safety until the device is explanted.
The follow up visits should be performed at 9 months (9M), 12 M, 18 M and 24 M post-implantation, in accordance with current practice, and the following examinations described above, which are not specific to the evaluation of the investigational device should be performed in accordance with current practice:

The maximum duration of the visit is 24 hours, after which the visit must be considered as a hospitalization and reported as an adverse event.

- Clinical exams: Weight , Blood Pressure , Temperature

- _**Blood tests:** refer to *Table 2- Blood tests details*
- **Arterial Blood gas:** PaO2 ,PaCO2, pH ,HCO3- ;SaO2; Lactate

- **A trans-thoracic echocardiography (TTE)** refer to *Table 3- Echocardiography details*
- A screen shot of the device programmer to collect the adjustable device parameters, lead impedance and electrical signals amplitude.

- Follow up visits at 9M, 12M, 18M and 24 months post-implantation will be the subject of a contract between FineHeart and the investigating center for their reimbursement.

- The device has been designed for an average estimated lifespan of approximately 2 years. After 2 years of use, more in-depth maintenance will be performed on the equipment and defective components will be replaced.

8.10 Withdrawal and Study Termination.

- **Withdrawal.**

Any enrolled subject can withdraw his consent at any time throughout the duration of the study. In the event of withdrawal of consent, the subject will be considered as withdrawn from the study. All data collected before its withdrawal of consent will be kept by the sponsor and used within the framework of the study. The study protocol procedure cannot be applied to him after his withdrawal of consent. In accordance with GDPR, the patient may at any time contact the sponsor for the deletion of all his personal data, collected as part of this study.

Should the medical team decide to maintain the subject on the device after consent withdrawal, FineHeart's technical teams and proctors will continue to provide support to the medical team for as long as the device remains in use. FineHeart will supply, free of charge, the services and components required for the functioning and replacement of device parts throughout the entire period the device is implanted in the subject, even beyond the end of the study.

- **Study Termination.**

All subjects implanted will be considered as being at the end of the study follow up according to the following conditions:
- Replacement of the implanted device by another device.
- Replacement of the implanted device by a graft (transplantation) if the patient becomes eligible to transplant.

- Death of the subject during the device support period.

The clinical investigation will be considered complete when the 24-month follow-up of the subjects is completed.

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8.11 Discharge Visit.

The discharge visit should be performed at the date of discharge from the hospital to home or rehabilitation center. Only the technical data export and the clinical exams must be collected at each discharge visit. All other procedures and assessments should be performed, if not already done within 14 days before discharge date:

- Clinical exams including weight, temperature, systolic and diastolic blood pressure, pulse oximetry (SpO_2).
- NYHA class, see Annex D.
- Intermacs Class, see Annex D.
- Heart Rate.
- **A trans-thoracic echocardiography (TTE)** including, the ventricular ejection time duration, the upper LV outflow diameter, LVEF %, LAP and PAP, the native VTI with ump (cm), the maximum pump induced flow diameter above aortic valve . The distance from the Aortic Valve to the pump outlet (cm).
- A screen shot of the device programmer to collect the Total Flow Rate with Pump.
- Quality of life questionnaires, EQ-5D-5L.
- 6MWT see annex C.
- Export of the device technical data see section 8.12 of this study protocol.
- Complete the patient diary see Annex G.
- Adverse events and device deficiencies reports if needed.
- Relevant concomitant medications related to adverse events, cardiac disease, renal failure, hepatic dysfunction, and ongoing other relevant diseases.
- Complete the device external components exchange tracking form and specify the reason of each device component replacement.
- Visit the patient home according to the local current practice to ensure that there is no critical issues for using the medical device in conformity with the device IFU.

- **Blood tests:** refer to *Table 2- Blood tests details*
  Arterial Blood gas: PaO2 ,PaCO2, pH ,HCO3- ;SaO2; Lactate

8.12 Subject training on Device Management.

The subject will be trained by the medical staff, a dedicated hospital referent, appropriately trained by the FineHeart team. A psychological assessment on the patient ability to manage the device will be performed during the screening procedure.

The subject training includes 3 phases as described in the patient and healthcare training schedule (Fig 4):

• Phase 1 - Patient information: This stage starts within 2 weeks before implant during the patient screening procedure, after the signature of the inform consent. It is focused on the presentation of the device to the patient, the implantable and the external components.

• Phase 2 - Patient training: This stage starts in post device implantation period, depending on the patient's clinical condition. The subject is trained on the external components management, daily living with the FlowMaker®, alarms and trouble shooting in accordance with the patient's instruction for use manual.

Phase 3 - Caregiver/Relatives Training: Patient relatives /caregiver training is mandatory before home discharge. This training is focused on the external components management, alarms and trouble shooting.

A specific training log with the list of the delivered training sessions and modules will be filled and signed by the trainer and the trainee. In case of incorrect device management, re-training of the patient shall be done. Demonstration of correct device management by the patient is imperative to allow hospital discharge. A patient instruction for use manual in local language will be provided.

8.13 Healthcare training on device management and sponsor support activities.

FineHeart will provide training to investigators and clinical staff on the surgical implant procedure and the FlowMaker® management. Cardiovascular surgeons with experience in mechanical circulatory support will be trained to implant the device.

A core team composed of Cardiovascular Surgeons, Cardiologists, Intensivists, Anesthesiologists, OR Nurses, Echocardiographist and MCS/VAD coordinators will be identified at each investigation center during the site qualification procedure and documented in the site delegation log. The core team members will be trained by the sponsor on the surgical implant procedure, device preparation, device management, post-operative care and patient management, according to the training schedule below (Fig 4).

The Core team is the medical staff responsible for:
-The device implantation
-The training of other members of the medical team
-The use of the device at the site while the study is being conducted.
In addition, the sponsor will provide technical support to the clinical team during the duration of the study and as long as the patient is on device support:

- On-site support:
  - Before the implant procedure to perform a refresher training, if required.
  - During the implant procedure and immediate post-operative period at the ICU.

- During the post-operative follow-up at each study assessment visits, according to the study flowchart described in section 8 of this study protocol and by phone (24 hour/7 days hotline).

Clinical Proctors trained and validated by the sponsor will be present at all implantation at the investigation site .They will remain available during the follow-up period to provide advice on medical management of patients supported by the device, if needed.

A clinician manual containing instructions for use is provided to the investigator and the clinical team.

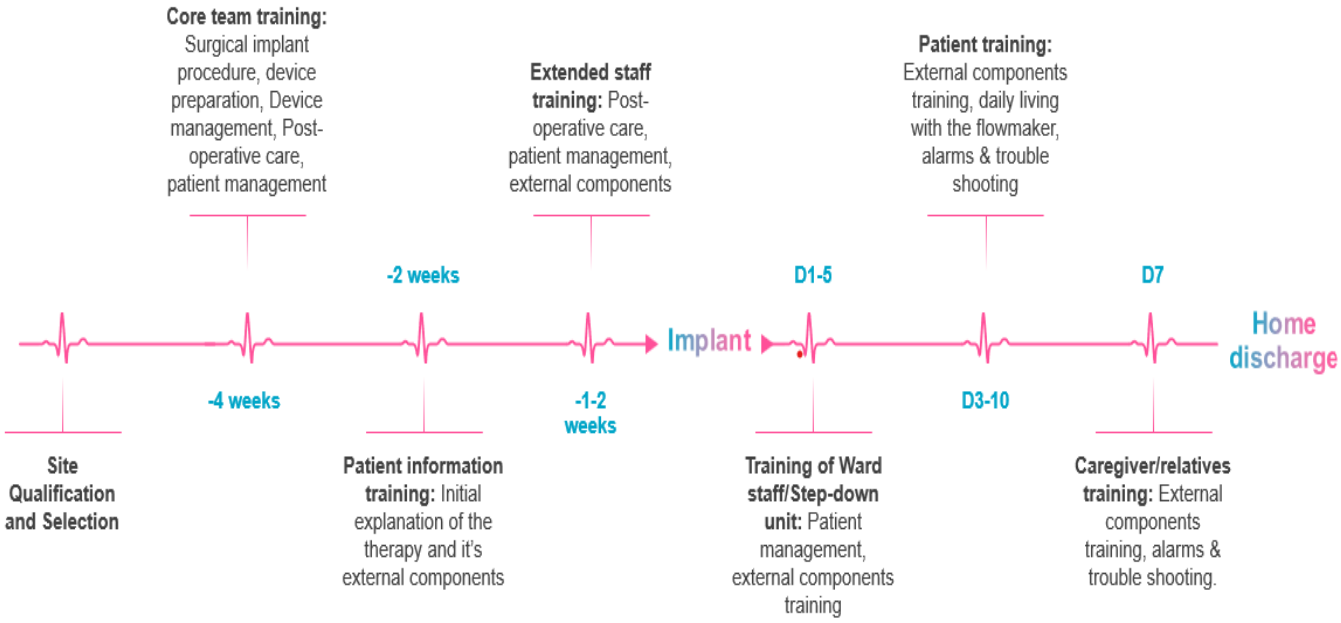

Figure 4 - Patient and Healthcare Training Schedule.

8.14 Recommendations for device management and patient management.

Clinical status	Echo parameters to check	Possible medications	Pump programming	Other parameters to check
Just after pump implant	LV and LA RV VTI pulmonary E and A waves	dobutamine / milrinone /adrénaline -Impaired Inotropes dosage should be reduced progressively over 3 days and do not stop for pump speed increase. -Stabilize the patient according to the Cardiac Index > 2.4 L/min/m² and satisfactory hemodynamic right ventricular improvement function (no further diameter increase, VTI > 6 cm, TAPSE > 14 mm). -Extubate when the patient is hemodynamically stable and progressive weaning of NO up to 6 to 8 hours if NO is applicable.	Start the pump with a moderate systolic speed not higher than 5500 rpm and adjusted according to the patient's hemodynamic parameters, accompanied by inotropic medications drugs.	Swan Ganz parameters PVC<12mmHg
Impaired LV / normal RV	LV and LA diameter RV diameter VTI pulmonary E and A waves	dobutamine / milrinone /adrenaline	2000-4000rpm Ejection time following echos	Swan Ganz parameters PVC<12mmHg
Impaired LV /moderate impaired RV	LV and LA diameter RV diameter VTI pulmonary E and A waves Intraventricular septum position	dobutamine / milrinone /adrenaline Noi / sildenafil optimize RV by using No in non-invasive solution	2000-4000rpm Ejection time following echos	Swan Ganz parameters PVC ASAT and ALAT
Impaired LV / impaired RV	LV and LA diameter RV diameter VTI pulmonary E and A waves	dobutamine / milrinone /adrenaline Noi / sildenafil optimize RV by using No in non-invasive solution	2000-4000rpm Ejection time following echos	Swan Ganz parameters PVC ASAT and ALAT
Tachycardia	LV and LA diameter RV diameter VTI pulmonary E and A waves	ivabradine : 1st recommendation if the patient has a sinusal rhythm esmolol cordarone : 300-600mg/24h IVSE	>120bpm use mode 2:1 Reduce the ejection time	Swan Ganz parameters
High LV preload: PCWP ≥20mmHg without aortic stenosis	LV and LA diameter RV diameter VTI pulmonary E and A waves	Adaptation of furosemide dose according to echos parameters	If LV with important volume ->increase the systolic pump speed If LV with difficult filling during diastole ->go to mode 2:1 If there is still issue ->reduce the ejection time If there is still issue ->decrease the pump systole speed	Swan Ganz parameters Blood gas Lactate SVO2
Sepsis/ vasomotor paralysis	LV and LA diameter RV diameter VTI pulmonary E and A waves	noradrénaline / vasopressine optimize coagulation	If LV with important volume ->increase the systolic pump speed If LV with difficult filling during diastole ->go to mode 2:1 If there is still issue ->reduce the ejection time	Swan Ganz parameters LDH Free hemoglobin CRP Anti-Xa Anti-thrombine

			If there is still issue ->decrease the pump systole speed	

8.15 Device Technical Data export.

During the conduct of the study, sponsor clinical support team will proceed with the export of data recorded by the implanted Icoms® FlowMaker® system in the external controller. Export of the technical device data will be performed at each study visits as described in the table 1 above, from the end of the device implant procedure (D0) to the end of the study visit (V12).
Following data will be exported:

- Pump current.
- Pump power / Programmed min-max pump speed.
- QRS amplitude.
- Therapy mode.
- Mean heart rate.
- Implant temperature.
- Internal battery temperature.
- Internal battery remaining capacity.
- Internal battery current and voltage.
- Pump humidity.
- ITC power status
- Power Fault
- Other pertinent data needed.

8.16 Device usability test

The objective of the device usability test is to gather additional information on the actual and daily use of the device by the patient. The subjects should fill-in the survey attached in the annex H at 1, 3, 6 months post implant. Only the period of use since the last survey completion should be assessed at 3 and 6 Month Post implant.

8.17 Device Explant

In the event that the device should be explanted for any reason (e.g. death, device exchange), the HCP team should follow the device explant procedure described in the Clinician Manual.
Following information should be documented in the study CRF:

- The device explant date
- The reason of the explant
- All pertinent observations

The explanted prosthesis shall be returned to the sponsor for analysis. In case of death of patients under device support, an autopsy should be performed according to the local procedure to determine the cause of death. An anonymized copy of the autopsy report shall be submitted to the sponsor.

8.18 Recommendation for anticoagulation management and centralized laboratory Protocol (Core Lab)

The anticoagulation procedure is described in Annex K. It is mandatory unless strong justification provided for the proper management of the implanted subjects; it can be adjusted according to local practice and the patient clinical condition:

A centralized laboratory (core laboratory) will be established at CHU Nantes. The objective of this core laboratory is to perform additional hemostasis testing required to investigate the root cause of any potential serious adverse events related to the pump.

Sampling will be limited to residual citrated plasma obtained from blood tests performed as part of the patient monitoring schedule (*see Table 2- Blood Tests details*). Samples will be prepared as 500 µL aliquots and stored at −80 °C.

All samples will be destroyed at the end of the study in accordance with applicable regulations.

8.19 Anesthesia and Surgery Procedures

8.19.1 Recommendation of Anesthesia Protocol

This Anesthesia protocol is not specific to the investigational device. It is conventional and practiced in the context of open-chest surgery without extracorporeal circulation. It could be adjusted by the medical team according to the patient clinical condition.

The main anaesthesia risks are included in the anticipated adverse events listed in the section 17.2 of this protocol.

Premedication the day before the intervention:
-Patient fasting within 6 hours before surgery.
-Nasal decontamination with 2% mupirocin
-At bedtime if needed: Xanax or Atarax

At 1 hour before the surgical intervention : Depending on the patient clinical condition:
-Nothing
-Xanax: 0.25 mg to 0.5 mg
-Atarax: 25 mg to 50 mg

On arrival at the operating room:
-Placement of a 5-lead ECG monitor
-SpO2 and respiratory rate monitoring
-Placement of a peripheral venous line (16 or 18 GA), of good caliber, placement of the arterial catheter at the level of the right or left radial artery under local anesthesia
-Pre-oxygenation with a mask with FiO2 at 100%

Anesthesia induction :

-Analgesia with Sufentanil or Remifentanil in TCI (target-controlled intravenous anesthesia)
-Sedation according to the patient's hemodynamic state either with a bolus of etomidate or with propofol
-Neuromuscular blockade with a bolus of Cisatracurium or Atracurium

Antibiotic prophylaxis with:
-2nd or 3rd generation cephalosporin
-In case of resistant staphylococcus:
-Daptomycin or Vancomycin

Anesthesia Maintenance
-Sufentanil or Remifentanil TCI
-Propofol TCI
-Possibility of using Halogenated agents: Sevoflurane

Intraoperative monitoring and Equipment: After induction and oropharyngeal intubation:
-Placement of a 2nd peripheral venous line (14-18GA) allowing effective filling if needed
-Central venous line with 3 lumens / in the right or left internal jugular vein
-Swan-Ganz catheter
-Urinary catheter with bladder temperature sensor
-TEE probe
-NIRS and BIS if available (cerebral oxygenation sensors and electroencephalogram)

Hemodynamic objective :
-MAP between 60-70mmHg
-CVP between 8 and 10mmHg
-In case of hypovolemia, filling with crystalloids (250mL according to hemodynamic response)

Optimization of perfusion pressure:
-Ephedrine bolus
-Norepinephrine bolus and/or IV infusion
-Vasopressin IV infusion

Optimization of Cardiac Inotropy
-Milrinone IV infusion
-Dobutamine IV infusion
-Adrenaline IV infusion
-Levosimendan IV infusion

Optimization of right ventricular function:
-Inhaled NO (between 10 and 20 ppm)

Arrhythmia prevention:
-Magnesium sulfate bolus or IV infusion
-Lidocaine bolus or IV infusion
-Amiodarone bolus or IV infusion

Ionic and blood gas monitoring:
-Arterial Blood Gas every 30 min

-Supplementation: Potassium, calcium, and bicarbonates if needed
-Optimization of ventilatory parameters

Anticoagulation:
-5 min before the placement of the left ventricular guide
-Heparin bolus 300IU/kg
-Monitoring of anticoagulation efficacy by measuring ACT 3 to 5 minutes after the bolus then every 30 minutes preoperatively
-Objectives: perioperative ACT 400-450s

Analgesia:
-Morphine
-Infiltration of the surgical site by the surgeon with Ropivacaine

8.19.2 The surgery procedure:

The Device implant surgery procedure is entirely described in the Clinician Manual in the Section 7.2 to 7.3 . Refer to the Clinician Manual for more details.

8.19.3 Anaesthesiological and Post-Operative Risks

Anesthetic and post-operative risks are not specific to the Icoms FlowMaker . Risks are Identical to those of all general anesthesia in the context of cardiac surgery:

-Allergic anaphylactic reaction : neuromuscular blocking agents, antibiotics..)
- Hypotension due to vasoplegia
- Hypovolemia
- Arterial hypertension
- Atelectasis of the lower ipsilateral lung lobe due to thoracotomy
- Anemia
- Atrial or ventricular arrhythmia
- Right ventricular failure
- Cardiac tamponade
- Stroke (CVA)
- Respiratory failure (Prolonged mechanical ventilation)
- Renal failure

These risks are included in the expected events described in Section17. 2 of this Document

8.20 Warnings and Contraindications :

Warning and contraindication are described in the clinician manual section 8 and the exclusion criteria of this first in human study include contra-indications to the use of the device. Refer to the Clinician manual section 8 for more details on warnings and Contraindications.

8.21 Management of patients with cardiac pacing, resynchronization, or defibrillation device.

During the surgical procedure for FlowMaker implantation and before activation of the FlowMaker:

1-Equip the patient with external defibrillator pads, as is done for any conventional cardiac surgery
2-If the patient is equipped with an ICD, place a magnet over the ICD onto the skin.
3-If a ventricular arrhythmia occurs, remove the magnet and the ICD will operate as intended or an external shock will be delivered (depending on the clinical center habits).
4-If the patient is equipped with a pacemaker, program it in DDD or VVI mode at 70 ppm

9. Monitoring Plan.

The investigator is required to perform the clinical investigation in accordance with the clinical investigation plan and good clinical practice (ISO 14155). He agrees to provide reliable data and all information requested by the clinical investigation plan. The investigator will provide the monitor, its representative, or other compliance or quality assurance reviewer access to all of the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and adequate space to conduct the monitoring visit. The sponsor trial monitoring plan describes the monitoring activities and defines the frequency of monitoring visit, depending on the enrollment status and the patient study flowchart.

10 Statistical Considerations.

10.1 Statistical design, method and analytical procedures

Standard summary statistics will be calculated for all study variables (demographic data, baseline data and outcome data). The categorical parameters (e.g. gender) will be summarized by frequencies and percentages. For continuous variables, statistics will include means, Standard Deviation, median, quartiles and range values. Continuous data subject to censoring (i.e. time to event data) will be summarized by the minimum, median and maximum values, when available from the KaplanMeier estimates. Statistical analysis will be conducted by FineHeart's Scientific Affairs team in collaboration with expert biostatisticians.

10.2 Sample Size

The sample size requirement for this First in Human study has been fixed at 10 patients. As the study is only collecting data, no assumption to calculate the sample size was considered. The number of patients to screen in order to recruit 10 eligible patients, may need to be at least 15 patients according to the sponsor's data on anatomic compatibility.

10.3 Level of significance and Power

As the study is a feasibility study and only collecting data, no level of significance for the primary endpoint was defined.

10.4 Expected Dop-out rates

Expected drop-out rate is considered around 0% given the profile of the investigational medical device, without considering accidental death as, for example, from a car crash.

10.5 Specification of analysis sets

- **Protocol deviations :**
  Deviations from the Clinical Investigation Plan are not authorized .Protocol deviations occurring during the study will be assessed before the statistical analysis.
- **Populations** :
  The enrolled population will include all patients fulfilling the selection committee criteria and signed their informed consent to participate in the study. The Intention-To-Treat (ITT) population will consist of enrolled patients for whom the study device implant procedure started. A Full Analysis Set (FAS patients are ITT patients with a value for the primary criteria) and a Per Protocol population (FAS patients without major protocol deviations) may be built up.
- **Outcomes**:
  For the primary and secondary objectives, except from adverse events, the primary analysis population will be the ITT population. In case a FAS population is needed, it will be the primary population, and analysis on the ITT population will be considered as secondary.
  The serious adverse events analysis will be performed on the overall population participating in the screening process and/or in the implant procedure.
- **Procedures for reporting any deviation(s) from the original statistical plan:** Any relevant change to the statistical plan requested after protocol approval must be defined and approved through a protocol amendment or must be clearly mentioned in the statistical plan of the study including the rationale of changes. Deviations from the original statistical plan would be reported in the final report, if applicable.
- **Treatment of missing data**:
  The number of missing data will be assessed for the outcomes. For the statistical analysis, the missing data for prematurely withdrawal purpose could be replaced by an appropriate method (for example, Last Observation Carried Forward). These statistical analyses with an estimation of missing data could be performed as additional supportive analyses and could be conducted on some endpoints if relevant to assess the effect of missing data on the endpoint.
- **Interim analysis**:
  Interim analysis will be performed: • 30 days post-implantation on the first 5 patients, 90 days post-implantation on the first 5 patients. The analysis will be performed on an audited frozen data base and will be conducted without interruption of patient recruitment. The reports will be presented with case narratives focusing on the overall functioning of the device both in terms of safety and performance; Patients' clinical condition, including Quality Of Life, 6MWT ; device operating mode and Adverse events reported .
  Study results will be shared with the DSMB members and forwarded to the Competent Authorities.

- **Primary endpoint analysis**: A clinical study report, based on a frozen data base, will be issued when all patients will have achieved their primary endpoint. This report will include:
  - Presentation of population with medical history,
  - Patient survival, at 1 month post-implant expressed as a success rate,
  - Patients' clinical condition: Quality of Life, 6MWT
  - Adverse events reported.

- **Secondary endpoints:** Secondary objectives will be evaluated upon primary objective achievement. This report will include:
  -Survival on device without disabling stroke (MRS score > 3) until
  -The change from baseline for the NYHA classification will be described at each applicable post-baseline timepoint using shift-tables

- The change from baseline for the 6MWT will be described at each applicable post-baseline timepoint
.-The change from baseline for the EQ-5D-5L health index score and Visual Analogue Scale (VAS) score will be described at each applicable post-baseline timepoint.
- Device proper operating will be analyzed based on hemodynamic improvement (assessed by CO, aortic VTI, LAP or PCWP, inotropic drugs weaning), device deficiencies, proper operating conditions of the implanted battery and device specifics data such as energy consumption.

Adverse events : Adverse events will be classified according to the INTERMACS® registry adverse events definitions The number of each type of adverse event will be computed as well as the number and proportion of patients that presented the Event.

11. Data Management.

11.1 Data recording and confidentiality.

.
In accordance with good clinical practices, this study received authorization from the regulatory authorities and the favorable opinion of an Ethic Committee. It is published on the clinicaltrials.gov website.
The subject personal data will be recorded in his medical file and collected from his medical file after signature of the study inform consent. Only anonymized data will be provided to the sponsor for analysis and study reports.

This study is conducted in accordance with the European Union (EU) data protection legislation updated on May 25, 2018, with the introduction of a new General Data Protection Regulation (GDPR).
The processing of subjects medical data will be carried out confidentially, to allow analysis of the results of the research. These data are identified by a code number.

The data will remain strictly confidential and will not be made public. At any time during or after the study, the authorized sponsor representatives, and the health authorities, unless the subject objects, may have direct access to the subjects medical file in order to check the accuracy of the data collected. In these circumstances the subject identity may be revealed.

Any enrolled subjects have the right to access (article 15 of the GDPR), via the study physician investigator, to all this collected data and request corrections (article 16 of the GDPR) if needed it.
They also have the right to object (article 21 of the GDPR) to the transmission or to request the deletion (article 17 of the GDPR) of their data without justification. They can also exercise their right to limit collected data in the situations provided for by law (Article 18 of the GDPR).

If case the subjects have any questions or complaints about the processing of data during this study, they can contact the investigator who will be able to direct the subjects request to the sponsor or, if necessary, to the sponsor data protection officer (DPO) specified in the inform consent form.

Throughout the study and after, measures will be taken to prevent accidental or premature destruction of study documentation. Study documentation will be filed and archived at the investigator and sponsor sites. Data will be retained at least 15 years after study closure, starting from the signature date of the clinical study report.

These documents may 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.

11.2 Data Monitoring, audit, and inspection.

Data integrity will be verified by sponsor representatives during the study conduct according to the Study Data Monitoring Plan. At any time, during or after the study, the authorized sponsor representatives and the health authorities can perform audits and inspections, to check the accuracy of the data collected.

11.3 Data Processing.

The subjects anonymized data will be collected via an e-CRF developed by the sponsor. Site staff representatives will be trained on the e-CRF management during the site initiation procedure. The data collected will be processed by the study data manager, according to the study data management plan.
FineHeart, as the Sponsor of the research, ensures the protection of the data of individuals participating in the study through technical and organizational measures, in accordance with the state of the art.

FineHeart has committed to the French data protection authority (CNIL: Commission Nationale Informatique et Libertés) to comply with a reference methodology “MR001” concerning "data processing carried out in the context of health research with the collection of the individual's consent." This methodology includes a set of security measures to protect your personal data.
Data Processing will be managed according MR001 methodology to comply with the European General Data Protection Regulation (GDPR)..

No transfer of personal data outside the European Union or to a country that does not ensure an adequate level of data protection is planned. FineHeart's headquarters are located in France, and its subcontractors for this study, IQVIA and Pharmaspecific, are also based in France. The hosting of data is also carried out within the territory of the European Union.

12. Amendment to the Clinical Investigation Plan .

Any amendment to the protocol will be submitted to appropriate authorities for authorization or information depending on the nature of the change. Moreover, any administrative update not requiring a submission to competent authorities will be documented in the study master file.

13. Deviation from the Clinical Investigation Plan.

The investigator is required to ensure compliance with this study protocol in accordance with good clinical practices requirements, especially the ISO 14155 – 2020. Except under emergency circumstances, the investigator is not allowed to deviate from the clinical investigation plan. Deviations to investigational plan that are decided by the investigators to protect the rights, safety and well-being of human patients shall be documented and reported to the sponsor as soon as possible.

It is recommended to make every effort to avoid deviations from the protocol including, but not limited to the following:

- Inclusion of a patient who does not meet inclusion criteria,
- Inclusion of a patient who meets the non-inclusion criteria,
- Missing any data related to primary and secondary objectives

Major protocol deviations are defined as changes in the conduct of the trial from that specified in the clinical investigation plan, compromising the subject's rights, safety, or welfare or the integrity of the study efficacy and/or safety results. Study deviations will be reported to the sponsor through a deviation form as soon as possible. Date, type of deviation and reason will be specified. If relevant, the sponsor will inform regulatory authorities. Corrective and preventive actions will be taken to avoid new deviations. All deviations will be included in the final report

All protocol deviations related to inclusion and exclusion criteria should be submitted to the regulatory authorities and ethic committees for approval.

14. Investigational device allocation and accountability.

Devices under investigation will be used only in this clinical investigation, according to the study protocol and device instructions for use. One complete Icoms® FlowMaker® system will be allocated to each patient eligible for implantation and one other complete system will be available at the investigation site as a backup system. At discharge from hospital, the subject will also receive a backup system composed of the External Batteries, External Controller and the Battery Charger.
Once a patient is selected and planned for surgery, investigational devices with corresponding delivery forms will be shipped to the investigation site. Upon receipt of the device components supplies, an inventory shall be performed at the investigational site and a device receipt log filled out and signed by the site's representative. The designated study staff should verify that the shipment contains all the items noted in the shipment form. Any damaged or unusable investigational devices in each shipment will be documented in the device receipt form. The investigator or the site staff shall notify the sponsor of any damaged or unusable investigational devices that were supplied to the investigator's site.
To ensure traceability throughout the study, batch number and/or serial number and expiry date are assigned to the devices. From implant until return or disposal, their access and use will be controlled and documented. The "Device dispensing and allocation" forms will be provided to the site to document the allocation of device components per patient, including any replacement. At the completion of the study, a final reconciliation of investigational devices shipped, devices used, and devices remaining will be done and documented. Any discrepancies noted will be investigated, resolved, and documented prior to return investigational devices to the sponsor.
Following device components, will be subject to traceability during the study conduct:

- ITC.
- ECO.
- Internal TET coil.
- External TET coil.
- The Epicardial Pacing Lead.
- The Programmer.
- The Pump.
- External batteries.
- Battery charger.
- The Carry System.

- Delivery System

15. Statements of compliance.

The Icoms® FlowMaker® conforms to the general safety and performance requirements apart from the aspects covered by the clinical investigation and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the subject. See the signed statement of compliance in annex J.

16. Informed consent process.

The Investigator must give to the subject a complete information on the conduct of the study under circumstances that minimize the possibility of coercion or undue influence. The subject must be given the opportunity to ask questions and ample time (3 days minimum) to take a decision. The consent form must be signed and dated by the subject and the investigator obtaining the consent before starting any study procedure.

The information given by investigator to the patient must explain the purpose of the study, including the screening process and the study design must, the risks/benefits assessment of participation to the study, the possibility for the patient to stop participating in the study at any time and to receive an alternative treatment, without any change in his medical care.

A copy of the signed consent form is given to the patient and the original is filed at the investigational site. vulnerable persons are not allowed to be recruited in this study.

17. Adverse Events, Adverse Device Effects and Device Deficiencies Recording and Reporting.

Safety reporting (adverse events and device deficiencies -Fig. 5) in this study shall be performed in line with the requirements of the Regulation (EU) 2017/745 – Medical Device Regulation (MDR) Article 80(2) and the guideline MDCG 2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745.

The sponsor shall report, without delay to all Member States in which the clinical investigation is being conducted, all of the following by means of the safety report tabular format md_mdcg_2020-10-2 or the Eudamed web form when it will be available.

a) any serious adverse event that has a causal relationship with the investigational device, or the investigation procedure or where such causal relationship is reasonably possible;

b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;

c) any new findings in relation to any event referred to in points a) and b).

The period for reporting shall take account of the severity of the event. Where necessary to ensure timely reporting, the sponsor may submit an initial report that is incomplete followed up by a complete report.

Upon request by any Member State in which the clinical investigation is being conducted, the sponsor shall provide all available information.

17.1 Definitions.

The Adverse events and device deficiency definitions are derived from MDCG 2020-10/1 Safety Reporting in Clinical Investigations of Medical Device under regulation (EU) 2017/745.

In addition to that, in this study, Clinician will refer to the INTERMACS Adverse Events Definition, the (version of the 10 Nov 2021, see Annex B of this protocol) for the clinical assessment and diagnosis of each events, including device malfunction issues.

- **Adverse event (AE):**

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device (MDR Article 2(57)).
Note:
a. This definition includes events that are anticipated as well as unanticipated events.
b. This definition includes events occurring in the context of a clinical investigation related to the investigational device or the procedures[2] involved.

[2]*Nota Bene: For the purpose of safety reporting all activities related to the use of a medical device may be considered procedures.*

- **Serious Adverse Event (SAE).**

Any adverse event that led to any of the following:
a) Death.
b) serious deterioration in the health of the subject, that resulted in any of the following:
i. Life-threatening illness or injury.
ii. Permanent impairment of a body structure or a body function.
iii. Hospitalization or prolongation of patient hospitalization.
iv. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
v. Chronic disease.
c) Foetal distress, foetal death or a congenital physical or mental impairment or birth defect

- **Specific Events not to be reported as adverse event.**

Hospital admission required to replace external equipment for a curative and/or a preventive maintenance linked to a known reported event with no signs of health deterioration will be not reported as AE/SAE. The replacement of external material and its reason will be documented at site on the patient "device allocation form".
Hospital admission for surveillance during the conduct of the study linked to a known reported event with no signs of health deterioration will not be reported as AE/SAE but documented in patient medical record. These hospital admissions will be notified as hospitalization with reason in eCRF.

- **Adverse Device Effect (ADE).**

Adverse event related to the use of an investigational medical device.
NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

- **Serious Adverse Device Effect (SADE).**

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

- **Unanticipated Serious Adverse Device Effect (USADE).**

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

- **Device deficiency.**

Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

<table>
<tr><th>Adverse events</th><th>Non-device-related</th><th colspan="2">Device- or investigational procedure-related</th></tr>
<tr><td>Non-serious</td><td>Adverse event (AE)[a]
(3.2)</td><td colspan="2">Adverse device effect (ADE)[c]
(3.1)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious adverse event (SAE)[b]
(3.45)</td><td colspan="2">Serious adverse device effect (SADE)
(3.44)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated serious adverse device effect (ASADE)[c]
(3.1, Note 1 to entry)</td><td>Unanticipated serious adverse device effect (USADE)
(3.51)</td></tr>
<tr><td colspan="4">[a] Includes all categories.
[b] Includes all categories that are serious.
[c] Includes all categories that are related to the device or the investigational procedure.</td></tr>
</table>

Figure 3- Categories of Adverse Events.

The Flowchart below on device deficiencies should only be used in case the device deficiency is not associated to an adverse event.

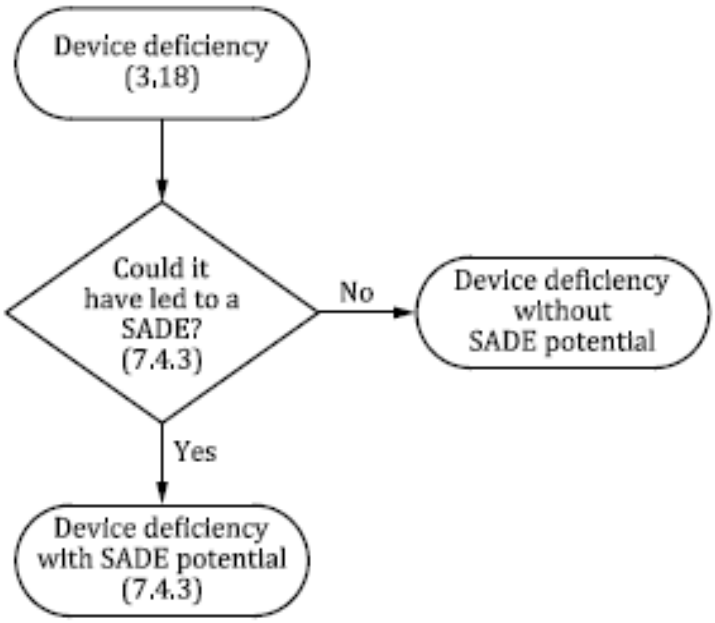

Figure 4 - Adverse Events Categorization Chart.

17.2 Anticipated adverse events and adverse device effects.

Foreseeable adverse events in patients supported with the FlowMaker® that are reasonably expected to occur include those in association with any cardiac surgery, and as a result of implanting a mechanical circulatory device.

- **The anticipated AEs that may occur are the following:**

1- Acute myocardial infarction.
2- Allergic reaction (anesthetic, contrast media, heparin, latex, implant materials, other).
3- Angina.
4- Annulus (damage, dissection, tear).
5- Aortic valve injury (trauma, clots, stenosis, regurgitation).
6- Arrhythmias, requiring cardioversion.
7- Atelectasis.
8- Atrial Fibrillation, new onset.
9- Bleeding (necessitating RBC transfusion and /or not Loss of > 3 mg/dl of Hgb)
10- Blood hemolysis, coagulopathy.
11- Cardiac arrest.
12- Cardiac Failure.
13- Chest pain/discomfort.
14- Damage to heart tissue.
15- Damage to vessels near the heart.
16- Death.
17- Drug reaction.
18- Dyspnea.
19- Edema.

20- Endocarditis.
21- Esophageal irritation.
22- Fever.
23- Heart Block.
24- Hematoma.
25- Hemodynamic complications.
26- Hemothorax.
27- Hypertension.
28- Hypotension.
29- Infection, local or systemic.
30- Leukopenia.
31- Nausea/vomiting.
32- Neurological Event.
33- Permanent pacemaker.
34- Pericardial effusion.
35- Pneumonia.
36- Pneumothorax.

37- Renal Failure.
38- Reoperation/Removal/Replacement.
39- Respiratory Failure.
40- Stroke.
41- Systemic hypotension requiring medical intervention.
42- Thrombosis (cardiac or venous).
43- Transfusion.
44- Vasovagal reaction.
45- Worsening heart failure.
46- Wound dehiscence.
47- Wound infection.
48- Wound pain or swelling

- **Anticipated adverse device effects (ADE) that may occur are:**

- Device malfunction which could lead to a re-intervention to replace the device or to death.
- Device deficiencies related to external components.
- Thrombosis risk as well as a device-induced platelets decrease.
- Tissue heating due to the transdermal energy transfer system due to the surgical intervention (insufficient pocket depth of the internal coil).
- Device malfunction due to incorrect programming.
- infection.
- Device-induced anemia caused by an excessive hemolysis phenomenon.

17.3 Reporting Process.

Information about adverse events, carried out by the patient, discovered by the investigator or detected by a diagnostic examination, should be recorded in the appropriate section of the Case Report Form. The report shall include a full description, including the nature, date of start and resolution of the adverse event, the

action and the corrective treatment. All Adverse Events will be recorded from the time of signature of the informed consent for screening until the patient participation in the clinical investigation is considered complete; i.e. at screening failure, completion of study participation, or when a patient is. All Adverse Event should be followed until complete resolution, or until an adequate level of stabilization effects, or until to be no longer clinically significant as considered by the investigator.
The investigator will assess the seriousness of the event and the causal relationship between the event and the investigational device or related procedure.

- **The following reportable Serious Adverse Events and Device Deficiencies:**

a) Any serious adverse event that has a causal relationship with the investigational device, the investigation procedure or where such causal relationship is reasonably possible.
b) Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate,
c) Any new findings in relation to any event referred to in points a) and b).
must be reported immediately to the sponsor, using e-CRF application and applicable study SAE and device deficiencies reporting form or in emergency case, by a call to the study manager or other sponsor representative.

Any reportable SAE and device deficiencies that might have led to an SAE will be reported by the sponsor to the competent authorities using the summary tabulation MDCG 2020-10/2 - clinical investigation summary safety report Form v1.0.
Separate reporting to the ethics committee(s) will be done**.** Upon request by any Member State in which the clinical investigation is being conducted, the sponsor shall provide all available information.

The sponsor's risk analysis report is updated with any new adverse event during the medical device lifecycle in order to re-evaluate the benefits/risks balance.

- **Causality assessment:**

The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized. During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Investigation Plan or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

For the purpose of harmonizing reports, each SAE will be classified according to four different levels of causality:
1. Not related
2. Possible
3. Probable
4. Causal relationship

The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational device or the investigation procedure.

1. Not related: Relationship to the device or procedures can be excluded when:
- the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
- the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
- the event involves a body-site or an organ that cannot be affected by the device or procedure.
- the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis9, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time.

2. Possible: The relationship with the use of the investigational device, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

3. Probable: The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
4. Causal relationship: the serious adverse event is associated with the investigational device or with procedures beyond reasonable doubt when:
- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
    - o the investigational device or procedures are applied to;
    - o the investigational device or procedures have an effect on;

- the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;

In order to establish the relatedness, not all the criteria listed above might be met at the same time.

The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device.

Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are applied

to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.

In some particular cases the event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where an investigator assessment is not available and/or the sponsor remains uncertain about classifying the serious adverse event, the sponsor should not exclude the relatedness; the event should be classified as "possible" and the reporting not be delayed. Particular attention shall be given to the causality evaluation of unanticipated serious adverse events. The occurrence of unanticipated events related could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

18. Suspension or premature termination of the Study.

The sponsor, a principal investigator or regulatory authorities/EC may decide to suspend or prematurely terminate the study. In this case, the sponsor shall promptly inform the clinical investigators, the competent authorities and EC's of the termination or suspension, the reason(s) why and the management (including a description of what measures were or will be taken to ensure the safety and the rights and welfare of currently enrolled patients).
If any deleterious effect due to the implementation of the protocol (AE, SAE device related or not) is observed, the study can be suspended at any time by the DSMB and the sponsor. In case no satisfactory solution to the problem can be found, the study can be discontinued permanently.
A sponsor committee, including medical director and risk analysis manager or their designee, appraises the risks/benefits of the investigational device once a week by reviewing all events occurring in the study (clinical data, AE/SAE/IMD deficiencies), and may suspend or prematurely discontinue the study:

- if serious adverse events occur and are caused by a mechanical or electronic origin requiring a review of the product safety profile, and according to the DSMB evaluation on benefits/risks.
- In case of new findings on the medical device that changes the risk/benefit ratio where the risk for study subject is unacceptable.

In case of premature termination of the study or withdrawal of consent, implanted patients should be followed according to the site local procedure related to patients under mechanical circulatory support in agreement with the therapeutic strategy decided by the investigators. However, the sponsor will continue to provide technical support to the medical team until the patient is explanted from the device and free service and components necessary for the operation and replacement of device components for the entire time it is implanted in patient

In case of the temporary halt of the study, new patients' selection must be stopped till study resumption. The follow-up of patients already implanted before, will be adjusted by the investigators, based on the analysis of the study suspension roots cause and the assessment of the risk/benefit of the need or not to continue the requested study exams (see section 8 of this protocol) in patient care. The sponsor will continue to provide technical support to the medical team and free service and components necessary for the operation and replacement of the device components till study resumption.

The device has been designed for an average estimated lifespan of approximately 2 years. After 2 years of use, more in-depth maintenance will be performed on the equipment and defective components will be replaced.

- event (incidence)

19. Submission of the clinical investigation report and Publication of the results, suspension or premature termination of the Study.

In accordance with the requirements of EU Regulation 2017/745 Article 77, paragraphs 5 and 7 , If the study was temporarily halted or was terminated early, FineHeart will inform within 15 days the Member State in which that clinical investigation has been temporarily halted or terminated early, through the EUDAMED electronic system of the temporary halt or early termination, providing a justification.

If the study was temporarily halted or terminated early on safety grounds, FineHeart will inform all Member States in which that clinical investigation is being conducted thereof within 24 hours.

The end of the clinical investigation is the last visit of the last subject implanted with the device. within 15 days of the end of the clinical, FineHeart will notify each Member State in which a clinical investigation was being conducted of the end of that clinical investigation in that Member State.

Irrespective of the outcome of the clinical investigation, within one year of the end of the clinical investigation or
within three months of the early termination or temporary halt, FineHeart will submit to the Member States in which a clinical investigation was conducted a clinical investigation report accompanied by a clinical investigation summary understandable to the intended user.

Both the report and summary will be submitted by FineHeart by means of the EUDAMED electronic system.

Where, for scientific reasons, it is not possible to submit the clinical investigation report within one year of the end of the investigation, it will be submitted as soon as it is available with a justification.

The summary and the clinical investigation report shall become publicly accessible through the EUDAMED electronic system at the latest when the device is registered in and before it is placed on the market. In cases of early termination or temporary halt, the summary and the report shall become publicly accessible immediately after submission.

If the device is not registered within one year of the summary and the report having been entered into the EUDAMED electronic system, they shall become publicly accessible at that point in time.

The sponsor will propose a plan for communications and publications regarding study primary and secondary objectives and ancillary analysis if any. The plan may be regularly updated according to the study advancement.

Apart from the EU Regulation 2017/745 Article 77, paragraphs 5 and 7 requirements described above, neither the complete nor any part of the results of the study carried out under this clinical investigation plan, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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21. Annexes.

Annex A. Investigators list.
Annex B. Adverse events per INTERMACS definitions.
Annex C. 6 Minutes Walking Test.
Annex D. NYHA Classification. And INTERMACS Classification
Annex E. EQ-5D-5L questionnaire.
Annex F. Modified Rankin scale.
Annex G. Patient diary.
Annex H. Device usability tests
Annex I. Composition of the patient Selection Committee
Annex J. Statement of compliance
Annex K. Anticoagulation Protocol

21.1Annex A - Investigator Lists.

List of Principal Investigators

Site code	Principal Investigator	Site Address
001_CZ	Pr. Ivan NETUKA	Institute for Clinical and Experimental Medicine Videnska 1958/9, 140 21 Prague 4 – Krc, CZECH REPUBLIC
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003_FR	Dr Mathieu Pernot	Bordeaux - Haut Levêque
002_FR	Dr. Charles-Henri David	Nantes- Hôpital Laennec

List of expert Hematologist in charge of subject anticoagulation surveillance and Core laboratory tests:

Site code	Principal Investigator	Site Address
003_FR	Dr Brett Victor-Emmanuel	Pharmacist -BiologistBordeaux - Haut Levêque -
002_FR	Dr Elodie Boissier	Pharmacist -Biologist -Nantes- Hôpital Laennec

21.2 Annex B - Adverse Events per INTERMACS Definition (Version of 10 Nov 2021).

This document contains the following adverse event definitions:

1. Hemolysis.
2. Right Heart Failure.
3. Device Malfunction.
4. Major Bleeding .
5. Major Infection.
6. Neurological Dysfunction.
7. Renal Dysfunction.
8. Cardiac Arrhythmias.
9. Respiratory Failure.
10. Venous Thromboembolism.
11. Wound Dehiscence.
12. Arterial Non-CNS Thromboembolism.
13. Hepatic Dysfunction.
14. Hypertension.
15. Pericardial Fluid Collection.
16. Myocardial Infarction.

1-Hemolysis Adverse Event

Minor Hemolysis

A plasma-free hemoglobin value greater than 20 mg/dl or a serum LDH level greater than two and one-half times (2.5 x) the upper limits of the normal range at the implanting center occurring after the first 72 hours post-implant **in the absence of** clinical symptoms or findings of hemolysis or abnormal pump function (see Major Hemolysis for a list of symptoms and findings) and thought not attributable to laboratory error.

Major Hemolysis

A plasma-free hemoglobin value greater than 20 mg/dl or a serum LDH level greater than two and one-half times (2.5 x) the upper limits of the normal range at the implanting center occurring after the first 72 hours post-implant **and associated with** clinical symptoms or findings of hemolysis or abnormal pump function.

Major Hemolysis requires the presence of at least one of the following conditions:

- Hemoglobinuria ("tea-colored urine")
- Anemia (decrease in hematocrit or hemoglobin level that is out of proportion to levels explainable by chronic illness or usual post- VAD state)
- Hyperbilirubinemia (total bilirubin above 2 mg/dl, with predominately indirect component)
- Pump malfunction and/or abnormal pump parameters as per section on device malfunction

Note:

- Isolated LDH elevations should not be reported as hemolysis if attributable to laboratory error, hepatic or pulmonary dysfunction. If suspected, confirmatory testing of LDH, LDH isoenzymes and plasma-free hemoglobin within 24 hours should be obtained to rule out laboratory error.
- All causes of hemolysis should be reported regardless of whether they are thought attributable to the device or not.

The association of the hemolysis event should be classified as:

- **Patient related:** (i.e., hematologic abnormalities)
- **Management related:** (i.e., drug related, secondary pump or IABP related, pump malposition)
- **Device related:** (i.e., related to pump thrombosis or device malfunction)

2-Right Heart Failure Adverse Event

Early Acute Right Heart Failure (RHF)

- Need for implantation of a temporary or durable RVAD (including ECMO) concomitant with LVAD implantation (RVAD implanted before the patient leaving the operating room).

Early post-implant Right Heart Failure

- Need for implantation of a temporary or durable RVAD (including ECMO) within 30 days following LVAD implantation for any duration of time
- Failure to wean from inotropic or vasopressor support or inhaled nitric oxide within 14 days following LVAD implantation or having to initiate this support within 30 days of implant for a duration of at least 14 days.

  The primary diagnosis of right heart failure is made by the presence of at least two of the following clinical findings:
  - Ascites
  - Functionally limiting peripheral edema (> 2+)
  - Elevated estimated jugular venous pressure at least halfway up the neck in an upright patient.
  - Elevated measured central venous pressure or right atrial pressure (≥16 mm Hg)

  Or is associated with at least one of the following manifestations:
  - Renal failure with serum creatinine > 2 baseline values.
  - Liver injury with an elevation of at least 2 upper limit normal in AST/ALT or total bilirubin > 2.0.
  - SVO2 < 50%.
  - Cardiac index < 2.2 liter/min/m2.
  - Reduction in pump flow of > 30% from the previous baseline in the absence of mechanical causes such as cardiac tamponade or tension pneumothorax.
  - Elevated lactate >3.0 mmol/liter.
- Death occurring in patients within 14 days of LVAD implant who have not received an RVAD but who remain on inotropes or vasopressors at the time of death and meet criteria for the diagnosis of Right Heart Failure on the basis of the above **clinical findings (2 criteria) or manifestations (1 criterion)** will be considered to have early post-implant right heart failure at the time of death. The contribution of early post-implant right heart failure to the death (primary or secondary) will be made by the clinical care team.

Late Right Heart Faillure

- Need for implantation of an RVAD (including ECMO) greater than 30 days after an LVAD implantation. This may occur within the index hospitalization for LVAD implant or during subsequent rehospitalization for any diagnosis which resulted in a need for temporary or permanent right-sided mechanical assist devices.
- Hospitalization that occurs greater than 30 days post-implant and which requires intravenous diuretics or inotropic support for at least 72 hours and is associated with:

  The diagnosis of right heart failure is made by the presence of at least two of the following clinical findings:
  - Ascites
  - Functionally limiting peripheral edema (>2+).
  - Elevated estimated jugular venous pressure at least halfway up the neck in an upright patient.
  - Elevated measured central venous pressure (>16 mm Hg).

  Or is associated with at least one of the following manifestations:
  - Renal failure with serum creatinine > 2 baseline value
  - Liver injury with an elevation of at least 2 upper limit normal in AST/ALT or total bilirubin > 2.0
  - A reduction in pump flow of > 30% from the previous baseline in the absence of tamponade
  - SVO2 < 50%
  - Cardiac index < 2.2 liter/min/m2
  - Elevated lactate >3.0 mmol/liter

The association of the RHF event should be classified as:

- **Patient-related:** (e.g., pre-implant right heart failure, volume overload secondary to non-adherence with medical management, severe aortic regurgitation, cardiorenal syndrome, arrhythmia induced, pulmonary disease, elevated pulmonary vascular resistance).
- **Management-related:** (e.g., related to implant surgery, volume overload, inotropic agent withdrawal).
- **Device-related:** (e.g., associated with Pump malfunction, outflow graft compromise).

3-Device Malfunction Adverse Event

Device Malfunction

A device malfunction occurs when any component of the MCSD system ceases to operate to its designed performance specifications or otherwise fails to perform as intended. Performance specifications include all claims made in the instructions for use. Device malfunctions are further defined as major or minor.

Major Device Malfunction

Major device malfunction, otherwise known as failure, occurs when of one or more of the components of the MCSD system either directly causes or could potentially induce a state of inadequate circulatory support (low cardiac output state) or death. A failure that was iatrogenic or recipient-induced will be classified as an Iatrogenic/Recipient- Induced Failure.

A device malfunction or failure is categorized as major when one of the following conditions occurs:

- Death.
- Hospitalization, emergency room visit or prolongation of hospitalization, or escalation of the level of care in an ongoing hospitalization (i.e., transfer to the intensive care unit).
- Life-threatening event (i.e., stroke or TIA, cardiac arrest, heart failure, syncope or near syncopal event, arrhythmia, etc.).
- Results in significant disability or incapacity.
- Requires an intervention to prevent impairment/injury including:
    - Urgent transplantation listing (immediate urgent listing for the transplant).
    - Pump replacement.
    - Pump explant.
    - Pump deactivation without explant or partial explant of components.
    - Breach of integrity of percutaneous lead requiring repair.
    - Operation to repair or replace any internal component of the circulatory support system.
    - Procedure to repair or stent an outflow graft.

Note: Replacement or external controller that is done in an inpatient setting for logistical reasons, in an otherwise stable patient, should be considered a minor device malfunction rather than major.

Minor Device Malfunction

Minor device malfunction includes inadequately functioning external components that require repair or replacement but do not result in 1a to g. Device malfunction does not apply to routine maintenance including replacement of external controller, pneumatic drive unit, electric power supplies, batteries, and interconnecting cables that are not related to a failed component.

Device Thrombus

Intracorporeal device thrombus represents a special case of major device malfunction and can be categorized as a suspected device thrombus or confirmed device thrombus. Device thrombus will be classified as suspected (see definition below) on the basis of clinical, biochemical, or hemodynamic findings or confirmed (see definition below) on the basis of device inspection or incontrovertible radiologic studies or absence of appropriate Doppler flow signals that confirm thrombus within the device or its conduits that results in or could potentially induce circulatory failure.

Suspected Device Thrombus

Suspected device thrombus is a device-related malfunction in which clinical or MCSD (Minimal Clinically Significant Difference) parameters suggest thrombus on the blood-contacting components of the pump, cannula, or grafts.

Suspected device thrombosis will be defined as signs and symptoms to include at least 1 of the 3 following criteria:

- Presence of major hemolysis (including elevation of biochemical markers of hemolysis; i.e., lactate dehydrogenase or plasma-free hemoglobin, or clinical evidence of hemolysis; i.e., hemoglobinuria).
- Presence of heart failure not explained by structural heart disease.
- Abnormal pump parameters consistent with diminished pump output/pump efficiency/pump performance.

AND

Suspected device thrombus will be accompanied by 1 or more of the following events or interventions:

- Death
- Stroke or TIA.
- Arterial non-CNS thromboembolism.
- De-novo need for inotrope therapy.
- Treatment with intravenous anti-coagulation (i.e., heparin), intravenous thrombolytics (i.e., tPA), or intravenous anti-platelet therapy (i.e., eptifibatide, tirofiban).
- Pump replacement.
- Pump explantation with or without exchange.
- Pump deactivation without pump removal.
- Operation to repair or replace any internal component of the circulatory support system.
- Urgent transplantation listing (immediate urgent listing for transplant).

Confirmed device thrombus

Confirmed device thrombus is a major device-related malfunction in which thrombus is confirmed within the blood-contacting surfaces of device inflow cannula or outflow conduit or grafts. This can be reported through direct visual inspection or by incontrovertible contrast radiographic evidence or by the absence of

an appropriate Doppler flow signal that results in or could potentially induce circulatory failure or result in thromboembolism.

Note:

- Para conduit device thrombus represents a special case of device malfunction whereby thrombus obstructs the outflow graft from the pump. This should be classified as major if the thrombus directly interferes with pump function by obstructing flow and if the pump is replaced because of the thrombus. The event should be classified as minor if there is visible thrombus with the preserved function of the pump but requires surgical intervention (difficult to define minor when it requires surgical intervention). In all instances, visual confirmation of the thrombus is sufficient for confirmation.
- If a suspected device thrombus event is ultimately confirmed through visual inspection following pump replacement, urgent transplantation or on autopsy following death, the event will be maybe reclassified to confirmed device thrombus.

The association of the device malfunction event should be classified as:

- **Patient-related:** (i.e., non-adherence with care of device or Instructions for Use, or its peripheral components, non-adherence with the anti-coagulation regimen, pro- coagulation abnormalities)
- **Management-related** (i.e., surgical protocol deviation, sub-optimal anti-coagulation)
- **Device-related:** (i.e., detected in a device at explant or on contrast studies or associated with hemolysis or other controller data consistent with device malfunction.

4-Bleeding Adverse Event

Type 1

Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional. This type is not relevant during a hospitalization.

Type 2

Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that *does not fit the criteria for Type 3, 4, or 5* but does meet at least one of the following criteria:

- Requiring non-surgical, medical intervention by a healthcare professional
- Leading to hospitalization or increased level of care
- Prompting evaluation

Type 3

- **Type 3a**
  - Overt bleeding accompanied by hemoglobin drop of 3 to < 5 g/dl or (1.86−3.1 mmol/liter SI units) (provided hemoglobin drop is related to bleed)

    OR
  - Any transfusion with overt bleeding
- **Type 3b**
  - Overt bleeding plus hemoglobin drop 5 g/dl ((3.1 mmol/liter) or greater (provided hemoglobin drop is related to bleed)

    OR
  - Cardiac tamponade

    OR
  - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)

    OR
  - Bleeding requiring intravenous vasoactive agents

Type 4: VAD implantation-related bleeding (includes concomitant cardiac or non-cardiac surgical procedures)

- Reoperation after the closure of incision or incisions used to implant the VAD to control bleeding
- ≥ 50 kg: ≥ 4U PRBC within any 48 hours during the first 7 days post-implant.
- < 50 kg: ≥ 20 cm3/kg PRBC within any 24 hours during the first 7 days post-implant.
- Chest tube output > 2 liters within 24 hours.

Type 5: Fatal bleeding

- **Type 5a:** Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
- **Type 5b.** Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

The association of the bleeding event should be classified as follows:

- **Patient-related:** (e.g., coagulopathy unrelated to surgical technique such as non-adherence with anti-coagulation medication resulting in an inappropriately high level of anti-coagulation, hepatic failure)
- **Management-related:** (e.g., related to surgical technique; hypertension; bleeding in the setting of inappropriate levels of anticoagulation) or to mismanagement of anti-coagulants.
- **Pump related:** (e.g., bleeding from the outflow graft, apical connector, or other internal components)

5-Infection Adverse Event

MCS Related infections

- **Percutaneous lead site infections**
  - **Superficial percutaneous lead infection:** A positive culture from the skin surrounding the percutaneous lead when there is clinical evidence of infection such as pain, fever, drainage, erythema, or leukocytosis coupled with the need to treat with anti-microbial therapy. The percutaneous lead exit site may have drainage and/or the surrounding skin may have erythema. The epithelialization of the percutaneous lead exit site is pre- served. The gram stain of the skin specimen at the driveline exit site will contain white blood cells (i.e., positive sign for inflammation).
  - **Deep percutaneous lead infection:** A positive culture from the driveline exit site deep to the epithelium, when there is clinical evidence of infection such as pain, fever, drainage, erythema, or leukocytosis coupled with the need to treat with anti-microbial therapy. The epithelialization of the percutaneous lead exit site is disrupted and no longer preserved or intact, or there is radiographic evidence of findings consistent with infection along the path of the percutaneous lead outside the mediastinum.
- **Infection of external surfaces of an implantable component.** A positive culture from the tissue surrounding the external housing of a pump or one of its components implanted within the body (including device components such as controllers, batteries, etc.), when there is clinical evidence of infection such as pain, fever, drainage, erythema, or leukocytosis coupled with the need to treat with anti-microbial therapy.
- **Infection of blood-contacting surfaces of an implantable component (device endocarditis):** Infection of blood-contacting internal surfaces of the MCS device including inflow/outflow grafts: documented by positive blood cultures or radiographic or echocardiographic evidence of vegetation in blood flow path of the pump coupled with the need to treat with anti-microbial therapy.

Non−MCS-related infections.

- **Infective Endocarditis:** Non−MCS related Positive blood cultures and echocardiography findings for mass or vegetation only on native valves, ICD, or pacemaker leads.
- **BSI**
  - Positive blood cultures with no other source identified
  - Bloodstream infection: non-VAD site or central venous catheter-related (definition from the Centers for Disease Control/National Healthcare Safety Network)
  - Should be coupled with the need to treat with anti-microbial therapy.
- **Mediastinitis**
  - **Procedure-related mediastinitis**
    - Deep sternal wound infection (isolated)

        - Deep sternal wound infection involving MCS device components (continuous with mediastinum or already situated in the mediastinum). Maybe contiguous with implanted components of the MCS device
    - **Non−MCS-related mediastinitis:**
        - Mediastinitis definitively owing to another cause (e.g., esophageal perforation during endoscopy, contiguous with empyema).
    - **Superficial mediastinal or thoracotomy wound infection**
        - Infection involving only skin, sub-cutaneous fat, and muscle of implant incision.
        - Should be coupled with the need to treat with anti-microbial therapy.
- **Sepsis**
    - Life-threatening organ dysfunction caused by a dysregulated host response to infection with:
        - Evidence of systemic involvement by infection, manifested by need to treat with anti-microbial therapy
        - Positive blood cultures and/or two of the following:
            - PaO2/FIO2 < 400 or respiratory rate ≥ 22/min or ventilated respiratory support
            - Hypotension with systolic BP < 100 mm Hg or MAP ≤ 65 mm Hg.
            - Platelet count < 150 or elevated prothrombin time or fibrinogen degradation products
            - Bilirubin (serum) > 50% above baseline
            - Altered mental status (Glasgow score < 15)
            - Creatinine (serum) > 50% above baseline
            - Need for intravenous vasoconstricting agents
- **Localized non-MCS device infection:** Infection localized to a site not involving the MCS device or components (e.g., pneumonia, urinary tract infection, cholecystitis, diverticulitis, dental abscess) coupled with the need to treat with anti-microbial therapy

The association of the infection event should be classified as:

- **Patient-related:** (e.g., non-adherence or poor management of driveline exit site or indwelling catheters, IV drug abuse, aspiration)
- **Management-related:** (e.g., improper tunneling, contamination of the intraoperative site, prolonged intubation)
- **Device-related:** (e.g., Device endocarditis diagnosed by radiological examination or detection of pannus within the conduits or device)

6-Neurologic Dysfunction Adverse Event

Type 1: Overt CNS injury: acutely symptomatic brain or spinal cord injury

- **Type 1a - Ischemic stroke:** Sudden onset of neurologic signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina, that:
  - Persist for ≥ 24 hours or until death, with pathology or neuroimaging evidence that demonstrates either:
    - CNS infarction in the corresponding vascular territory (with or without hemorrhage); or
    - Absence of other apparent causes (including hemorrhage), even if no evidence of acute ischemia in the corresponding vascular territory is detected.

    OR
  - Symptoms lasting < 24 hours with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory. Note: when CNS infarction location does not match the transient symptoms, the event would be classified as covert CNS infarction (Type 2a) and a TIA (Type 3a), but not an ischemic stroke.

  Note: Signs and symptoms consistent with stroke typically include an acute onset of one of the following: focal weakness and/or numbness, impaired language production or comprehension, homonymous hemianopia or quadrantanopia, diplopia, altitudinal monocular blindness, hemispatial neglect, dysarthria, vertigo, or ataxia.

- **Type 1aH - Ischemic stroke with hemorrhagic conversion:** Ischemic stroke includes hemorrhagic conversions. These should be sub-classified as Class A or B when an ischemic stroke is the primary mechanism and pathology, or neuroimaging confirms a hemorrhagic conversion.
  - **Class A- Petechial (non−space-occupying) hemorrhage:** Petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect.
  - **Class B – confluent (space-occupying) hemorrhage:** Confluent hemorrhage or hematoma originating from within the infarcted area with space-occupying effect.
- **Type 1b - Symptomatic intracerebral hemorrhage:** Rapidly developing neurologic signs or symptoms (focal or global) caused by an intraparenchymal, intraventricular, spinal cord, or retinal collection of blood, not caused by trauma.
- **Type 1c - Symptomatic Sub-arachnoid hemorrhage:** Rapidly developing neurologic signs or symptoms (focal or global) and/or headache caused by bleeding into the sub-arachnoid space, not caused by trauma.
- **Type 1d - Stroke, not otherwise specified:** An episode of acute focal neurologic signs or symptoms and/or headache presumed to be caused by CNS ischemia or CNS hemorrhage, persisting 24 hours or until death, but without sufficient evidence to be classified as one of the above (i.e., no neuroimaging performed).

- **Type 1e - Symptomatic hypoxic-ischemic injury:** Non-focal (global) neurologic signs or symptoms due to diffuse brain, spinal cord, or retinal cell death (confirmed by pathology or neuroimaging) in a non-vascular distribution, attributable to hypotension and/or hypoxia.
- **Type 1f - Symptomatic sub-dural hemorrhage:** An episode of acute focal neurologic signs or symptoms and/or headache accompanied by evidence of bleeding into the sub-dural space.

Type 2: Covert CNS injury: Acutely asymptomatic brain or spinal cord injury detected by neuroimaging

- **Type 2a - Covert CNS infarction:** Brain, spinal cord, or retinal cell death attributable to focal or multifocal ischemia on the basis of neuroimaging or pathologic evidence of CNS infarction, without a history of acute neurologic symptoms consistent with the lesion location.
- **Type 2aH - Covert CNS infarction with hemorrhagic conversion:** Covert CNS infarction includes hemorrhagic conversions. These should be sub-classified as Class A or B when CNS infarction is the primary mechanism and neuroimaging, or pathology confirms a hemorrhagic conversion.
    - **Class A - Petechial (non−space-occupying) hemorrhage:** Petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect
    - **Class B - Confluent (space-occupying) hemorrhage:** Confluent hemorrhage originating from within the infarcted area with space-occupying effect
- **Type 2b - Covert CNS hemorrhage:** Neuroimaging or pathologic evidence of CNS hemorrhage within the brain parenchyma, sub-arachnoid space, sub-dural space, ventricular system, spinal cord or retina on neuroimaging that is not caused by trauma, without a history of acute neurologic symptoms consistent with the bleeding location

Type 3: Neurologic dysfunction (acutely symptomatic) without CNS injury

- **Type 3a - TIA:** Transient focal neurologic signs or symptoms (lasting < 24 hours) presumed to be owing to the focal brain, spinal cord, or retinal ischemia, but without evidence of acute infarction by neuroimaging or pathology (or in the absence of imaging)
- **Type 3b - Delirium without CNS injury:** Transient non-focal (global) neurologic signs or symptoms (variable duration) without evidence of cell death by neuroimaging or pathology
- **Seizures** – (abstraction form places seizures under the sub-types for Type 3)

Classification of Acute Severity, Recovery and Long-Term Disability

- **Acute Severity**
    - **Mild neurologic dysfunction:** NIHSS 0-5
    - **Moderate neurologic dysfunction:** NIHSS 6-14
    - **Severe neurologic dysfunction:** NIHSS ≥15

Note: Severity assessment should be performed at the time of diagnosis of any overt CNS injury (Types 1) to ensure accurate classification

- **Stroke Recovery**
  - **Stroke with complete recovery:** A modified Rankin Score (MRS) at 30-90 days of 0 OR a return to the patient's pre- stroke baseline MRS, in the absence of any ongoing new symptoms due to the stroke.
- **Stroke Disability**
  - **Fatal Stroke**: Death resulting from a stroke where the cause of death is attributable to the stroke.
  - **Disabling stroke:** An MRS ≥2 at 30-90 days with an increase of at least 1 point compared to the pre-stroke baseline.
  - **Non-disabling stroke:** An MRS <2 at 30-90 days, or ≥2 without an increase of at least 1 compared to the pre- stroke baseline.

Note: Disability assessment applies only to subjects with overt CNS injury (Type 1) and should be performed at 90±14 days after the stroke event.

The association of the neurologic event should be classified as:

- **Patient-related:** (e.g., documentation of previous carotid or cerebrovascular disease, coagulopathy unrelated to surgical technique such as non-adherence with anti-coagulation medication resulting in an inappropriately high level of anti-coagulation, related to illicit drug use, non-adherence with other medications, trauma, associated with sepsis)
- **Management-related:** (e.g., over anti-coagulation or associated with the use of accessory assist device, hypotension or hypertension-related to surgical procedure
- **Device-related:** (e.g. secondary to pump thrombosis or device malfunction)

7-Renal Dysfunction Adverse Event

Acute Renal Dysfunction

- **Stage 1**
  - Increase in serum creatinine to 150% to 199% (1.5−1.99 x increase compared with baseline) or increase of > 0.3 mg/dl (> 26.4 mmol/liter) or
  - Urine output < 0.5 ml/kg/h for > 6 but < 12 hours.
- **Stage 2**
  - Increase in serum creatinine to 200% to 299% (2.0 x −2.99 x increase compared with baseline) or
  - Urine output < 0.5 ml/kg/h for > 12 but < 24 hours.
- **Stage 3**
  - Increase in serum creatinine to >300% (>3 x increase compared with baseline) or
  - Serum creatinine of > 4.0 mg/dl (>354 mmol/liter) with an acute increase of at least 0.5 mg/dl (44 mmol/liter) or
  - Urine output <0.3 ml/kg/h for >24 hours or
  - Anuria for >12 hours or
  - Need for renal replacement therapy (includes dialysis or ultrafiltration) regardless of above criteria.

Chronic Renal Dysfunction

An increase in serum creatinine of 2 mg/dl or greater above baseline, or requirement for renal replacement therapy, either of which is sustained for at least 90 days.

The association of the renal dysfunction event should be classified as follows:

- **Patient-related:** (e.g., non-adherence to medical therapy resulting in renal dysfunction).
- **Management-related:** (e.g., overprescribing of diuretic therapy or administration of renal toxic drugs or contrast agents that result in renal dysfunction).
- **Device-related:** (e.g., device failure resulting in renal dysfunction).

8-Cardiac Arrhythmias

Any documented arrhythmia that results in clinical compromise (e.g., abnormal VAD function [e.g., diminished VAD flow or suction events], oliguria, pre-syncope or syncope, angina, dyspnea), or requires hospitalization or treatment (drug therapy, defibrillation, cardioversion, ICD therapy (e.g., shock or anti-tachycardia pacing) or arrhythmia ablation procedure).

Cardiac arrhythmias are classified as 1 of 2 types:

- **Sustained ventricular arrhythmia** resulting in clinical compromise, or requiring hospitalization or drug treatment, defibrillation, cardioversion, ICD therapy, or arrhythmia ablation procedure.
- **Sustained supraventricular arrhythmia** resulting in clinical compromise, or requiring hospitalization or drug treatment, cardioversion, ICD therapy, or arrhythmia ablation procedure.

The association of the cardiac arrythmia event should be classified as:

- **Patient-related:** (e.g., recurrence of pre-operative arrhythmia non-adherence with medications).
- **Management-related:** (e.g., related to uncorrected electrolyte imbalance, Swan Ganz malposition, secondary to cardiac tamponade).
- **Device-related:** (e.g., Pump malfunction, malposition of pump, or inflow cannula).

9-Respiratory Failure

Impairment of respiratory function requiring reintubation, tracheostomy, or the inability to discontinue ventilatory support within 6 days (144 hours) post-VAD implant. This excludes intubation for reoperation or temporary intubation for diagnostic or therapeutic procedures.

The association of the respiratory failure event should be classified as follows:

- **Patient-related:** (e.g., non-adherence to medical therapy resulting in respiratory failure).
- **Management-related:** (e.g., inadequate diuretic therapy resulting in respiratory dysfunction).
- **Device-related:** (e.g., device failure resulting in respiratory dysfunction).

10-Venous Thromboembolism

Evidence of venous thromboembolic event (e.g., deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

11-Wound Dehiscence

Disruption of the apposed surfaces of a surgical incision, excluding infectious etiology, and requiring surgical repair.

MCS-ARC Arterial non-CNS Thromboembolism

An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by 1 or more of the following:

- Standard clinical and laboratory testing
- Operative findings
- Autopsy findings

Note: This definition excludes neurologic events.

12-Hepatic Dysfunction

An increase in any two of the following hepatic laboratory values (total bilirubin, AST, and ALT) to a level greater than 3 times the upper limit of normal for the hospital, beyond 14 days post-implant (or if hepatic dysfunction is the primary cause of death).

13-Hypertension: Adult

New-onset blood pressure elevation greater than or equal to 140 mm Hg systolic or 90 mm Hg diastolic (pulsatile pump) or 110 mm Hg mean pressure (rotary pump).

14-Psychiatric Episode:

Disturbance in thinking, emotion or behavior that causes substantial impairment in functioning or marked subjective distress and requires intervention. Intervention is the addition of new psychiatric medication, hospitalization, or referral to a mental health professional for treatment. Suicide is included in this definition.

The psychiatric event should be classified according to the DSM 5 classification:

- **Axis I:** Clinical disorders, including anxiety disorders, mood disorders, schizophrenia and other psychotic disorders.
- **Axis II:** Personality disorders and mental retardation.
- **Axis III:** General medical conditions.
- **Axis IV:** Psychosocial and environmental problems.

15-Pericardial Fluid Collection:

Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac/VAD output) and those without signs of tamponade.

16-Myocardial Infarction:

Two categories of myocardial infarction will be identified:
Peri-Operative Myocardial Infarction: The clinical suspicion of myocardial infarction together with CK-MB or Troponin > 10 times the local hospital upper limits of normal, found within 7 days following VAD implant together with ECG findings consistent with acute myocardial infarction. (This definition uses the higher suggested limit for serum markers due to apical coring at the time of VAD placement and does not use wall motion changes because the apical sewing ring inherently creates new wall motion abnormalities.)
Non-Perioperative Myocardial Infarction: The presence at > 7 days post-implant of two of the following three criteria:
Chest pain which is characteristic of myocardial ischemia,
ECG with a pattern or changes consistent with a myocardial infarction, and
Troponin or CK (measured by standard clinical pathology/laboratory medicine methods) greater than the normal range for the local hospital with positive MB fraction (≥ 3% total CK). This should be accompanied by a new regional LV or RV wall motion abnormality on a myocardial imaging study.

21.3 Annex C - 6 Minutes Walking Test

Location

The 6 Minutes Walking Test (6MWT) should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be 30 m in length. A 100-foot The 6MWT is a self-paced test of walking capacity. Patients are asked to walk as far as possible in 6 minutes along a flat corridor. The distance in meters is recorded. Standardized instructions and encouragement are commonly given during the test. According to the American Thoracic Society: *"ATS Statement: Guidelines for the Six-Minute Walk Test", Am J Respir Crit Care Med Vol 166: 111-117, 2002*, the guidelines to follow are the following:

hallway is, therefore, required. The length of the corridor should be marked every 3 meters. The turnaround points should be marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-meter lap, should be marked on the floor using brightly colored tape.

Patient Preparation

1. Comfortable clothing should be worn.

2. Appropriate shoes for walking should be worn.

3. Patients should use their usual walking aids during the test (cane, walker, etc.).

4. The patient's usual medical regimen should be continued.

5. A light meal is acceptable before early morning or early afternoon tests.

6. Patients should not have exercised vigorously within 2 hours of beginning the test.

Measurements

1. Repeat testing should be performed about the same time of day to minimize intraday variability.

2. A "warm-up" period before the test should not be performed.

3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate.

4. If Pulse oximetry is performed, measure and record oxygen saturation (SpO2) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact. Make sure the readings are stable before recording.

5. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale*.

6. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale*, worksheet) and move to the starting point.

7. Instruct the patient as follows: *"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able. You*

will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. Start now, or whenever you are ready."

8. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.

9. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it.

Each minute, use the standardized encouragement and tell the patient the following:

1 min	You are doing well. You have 5 minutes to go.
2 min	Keep up the good work. You have 4 minutes to go.
3 min	You are doing well. You are halfway.
4 min	Keep up the good work. You have only 2 minutes left.
5 min	You are doing well. You have only 1 minute to go.
15 sec from completion	In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you

When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor

10. Record the number of laps from the counter and calculate the total distance in meters walked by the patient.

11. Record the postwalk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"

12. If using a pulse oximeter, measure SpO2 and pulse rate from the oximeter and then remove the sensor.

13. Congratulate the patient on good effort and offer a drink of water.

*Borg scale:

Scale	Signification
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

The following elements should be present on the 6MWT worksheet and report:

Patient ID: _____

Date: _____

Baseline Value:

Blood Pressure (mmHg): _____/_____

Medications taken before the test (dose and time): _____

Predicted distance: _____ meters

Test: Done Not Done

If not done specify the reason: _____

Not done for Clinical reason not done for Logistic reason

Comment: _____

	Baseline **Start time (T0°)**	**End of test**
Time (consider time of controller)	____:____	____:____
Heart Rate	_____	_____
Dyspnea [Borg Scale]	_____	_____
Fatigue [Borg Scale]	_____	_____
SpO_2 (%)	_____	_____

Supplemental oxygen during the test: No Yes , flow _____ L/min, type _____

Stopped or paused before 6 minutes: No Yes , reason: _____

Total distance walked in 6 minutes: _____meters; Percent predicted: _____%

Other symptoms at end of exercise:

Other relevant comment? Yes No

If yes, specify_____

21.4 Annex D - NYHA Classification & INTERMACS Classification

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

ADULT PROFILES	Current CMS - DT Functional Indication	IV INO*	Official Shorthand	NYHA CLASS Assumed	Modifier option
INTERMACS LEVEL 1	Met	X	"Crash and burn"	IV	TCS A
INTERMACS LEVEL 2	Met	X	"Sliding fast" on inotropes	IV	TCS A
INTERMACS LEVEL 3	Met	X	"Stable" continuous inotrope dependent * Can be in hospital or at home	IV	TCA if hosp FF if home A
INTERMACS LEVEL 4	+ Peak $VO_2 \leq 12$		Resting symptoms on oral therapy at home	AMB IV	FF A
INTERMACS LEVEL 5	+ Peak $VO_2 \leq 12$		"Housebound", Comfortable at rest, symptoms with minimum activity ADL	AMB IV	FF A
INTERMACS LEVEL 6			"Walking wounded"-ADL possible but meaningful activity limited	IIIB	FF A
INTERMACS LEVEL 7			Advanced Class III	III	A only

** Intravenous inotropic therapy only approved for refractory Class IV symptoms*
INTERMACS. www.intermacs.org. Accessed October 2010

Functional Capacity

Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels.
*9th ed. Boston, Mass: Little, Brown & Co; **1994**:253-6*

21.5 Annex E – EQ-5D-5L Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

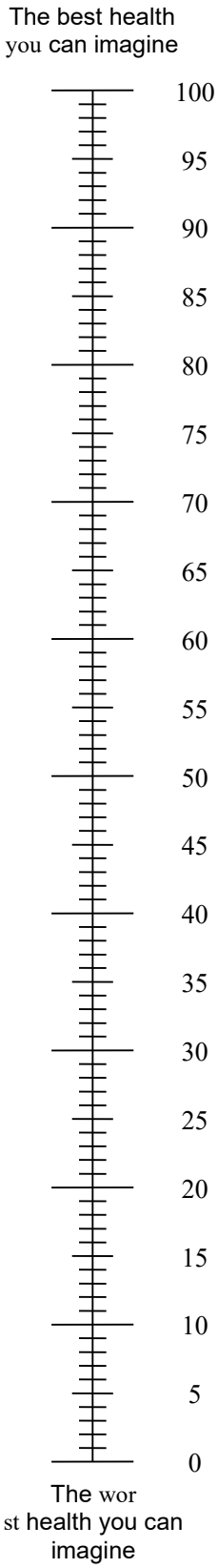
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



21.6 Annex F - Modified Ranking Score

Score	
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and Activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability requiring some help, but able to walk without assistance
4	Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

References:

-Rankin J. “Cerebral vascular accidents in patients over the age of 60.”
Scott Med J 1957;2:200-15
-Bonita R, Beaglehole R. “Modification of Rankin Scale: Recovery of motor function after stroke.”
***Stroke* 1988;19:1497-1500**
-Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. “Interobserver agreement for the assessment of handicap in stroke patients.”
***Stroke* 1988;19:604-7**
-Vidula H, et al. Hospitalization patterns and impact of a magnetically-levitated left ventricular assist device in the MOMENTUM 3 trial.
Heart Fail 2022;10:470-81

21.7 Annex G - Patient Diary

The Patient Diary should be filled by the implanted subject / the caregiver / the relatives from the Day 1 post-implantation of the device till the end of the study (see section 8 – study procedures – of this study protocol). The purpose of this Diary is to reinforce the patient surveillance and safety on the following key device specifications to monitor the proper functioning of the entire system allocated to the patient.

Patient ID:
Date (DD/MM/YYYY):
Day Post - implant:

BATTERY EXCHANGE	**Comments**
Time of Exchange :	
New Battery ID Number:	
New battery Charge %:	
Former Battery ID Number:	
Former battery Charge % :	
Transcutaneous Energy Transfert COIL CONNECTION	**Comments**
Time of Disconnection:	
Time of Reconnection:	
External Controller and Implantable Therapy Controller Communication	**Comments**
Time of Disconnection:	
Time of Reconnection:	

ALARMS # 1		
Alarms Triggering?	Yes☐	No☐
If yes, Alarm ID Number:		
Alarm Start time:		
Alarm Stop time :		
Event Description:		
Event Resolved	Yes☐	No☐
Event Resolution time:		
Event Resolution Action:		

ALARMS # 2		
Alarms Triggering?	Yes☐	No☐
If yes, Alarm ID Number:		
Alarm Start time:		
Alarm Stop time :		
Event Description:		

Event Resolved	Yes☐	No☐
Event Resolution time:		
Event Resolution Action:		

ALARMS # 3		
Alarms Triggering?	Yes☐	No☐
If yes, Alarm ID Number:		
Alarm Start time:		
Alarm Stop time :		
Event Description:		
Event Resolved	Yes☐	No☐
Event Resolution time:		
Event Resolution Action:		

ALARMS # 4		
Alarms Triggering?	Yes☐	No☐
If yes, Alarm ID Number:		
Alarm Start time:		
Alarm Stop time :		
Event Description:		
Event Resolved	Yes☐	No☐
Event Resolution time:		
Event Resolution Action:		

ALARMS # 5		
Alarms Triggering?	Yes☐	No☐
If yes, Alarm ID Number:		
Alarm Start time:		
Alarm Stop time :		
Event Description:		
Event Resolved	Yes☐	No☐
Event Resolution time:		
Event Resolution Action:		

ALARMS # 6

Alarms Triggering?	Yes☐	No☐
If yes, Alarm ID Number:		
Alarm Start time:		
Alarm Stop time :		
Event Description:		
Event Resolved	Yes☐	No☐
Event Resolution time:		
Event Resolution Action:		

21.8 Annex H – Device Usability Tests

Objective :

This survey is given to you as part of the study in which you are currently participating concerning the FlowMaker®. The objective of this survey is to gather additional information on your actual and daily use of the device. To be noted that there is no good or bad answer, the objective is to have yours feedbacks to make the device as safe, pleasant, and easy to use as possible.
Questions could be part of different categories such as :

- Your feedbacks after the use of the device
- The positive points of the device making it easier to use
- Elements to improve
- Possible errors related to use

You will be asked to fill-in this survey 1, 3 and 6 months after the implant. In this survey, you will find questions that require to indicate the frequency of apparition. If you fill the survery after 3 or 6 months, please only consider the period of use since the last survey completion.

Information	
Patient number in the study :	
Implant date :	
Patient age :	
Date of the day :	
Post-implant survey :	☐ 1 month ☐ 3 months ☐ 6 months

All data will be processed in compliance with the "Informatique et Libertés" laws of 1978 and the General Data Protection Regulation (GDPR) of May 2018.

1-External Controller (ECO°)

1) Do you find all the symbols/indicators of the external controller easy to understand ?

- ☐ Yes
- ☐ No

If no, which one(s) are not clear enough ? Why ?

2) Are you using the “mute” button when alarms appear ?

- ☐ Yes
- ☐ No

If yes, in which cases ?

Please fill the table below indicating your level of agreement with the different proposals.

Items	Not satisfactory at all	Not satisfactory	Neutral	Satisfactory	Very satisfactory
Read information on the external controller					
Read the information through the carrying system	☐	☐	☐	☐	☐
Display time of information on the screen	☐	☐	☐	☐	☐
Understanding screen text	☐	☐	☐	☐	☐
Number of lines of text on screen	☐	☐	☐	☐	☐
Screen brightness during the day	☐	☐	☐	☐	☐
Screen brightness during the night	☐	☐	☐	☐	☐
Visibility of LEDs indicators during the day	☐	☐	☐	☐	☐
Visibility of LEDs indicators during the night	☐	☐	☐	☐	☐
Buttons					
Button size	☐	☐	☐	☐	☐
Easiness to press buttons	☐	☐	☐	☐	☐
Alarms					
Alarm sound level when being at home	☐	☐	☐	☐	☐
Alarm sound level when being outside (garden, stores, street)	☐	☐	☐	☐	☐
Alarm sound level when being under the shower	☐	☐	☐	☐	☐
Understand the alarm level	☐	☐	☐	☐	☐
Read the alarm number	☐	☐	☐	☐	☐
Comments : justifications, ideas for improvement, other comments:					

3) Do you have positive elements to indicate regarding the external controller ?

Description

2- Carrying system

1) Is the carrying system a nuisance in everyday life ?

- ☐ Yes
- ☐ No

If yes, could you explain why?

2) Is wearing the External Controlleron the front of the body and not on the back a problem?

- ☐ Yes
- ☐ No

If yes, could you comment ?

3) What do you think of the carrying system's aesthetics?

4) What aesthetic design ideas would suit you best?

5) Do you have positive elements to indicate regarding the carrying system ?

Description

Items	Not satisfactory at all	Not satisfactory	Neutral	Satisfactory	Very satisfactory

Insert the external controller and the batteries in the carrying system	☐	☐	☐	☐	☐
Manage TET coil and batteries with the carrying system	☐	☐	☐	☐	☐
Equip yourself with the carrying system	☐	☐	☐	☐	☐
Weight of the carrying system (with the external controller and the batteries)	☐	☐	☐	☐	☐
Carrying system bulkiness	☐	☐	☐	☐	☐
Interact with the external controller through the carrying system	☐	☐	☐	☐	☐
Perform activities with the carrying system	☐	☐	☐	☐	☐
Comments : justifications, ideas for improvement, other comments…					

3-Batteries

1) How often do you replace external batteries ?

   ☐ Every 8 hours

   ☐ Every 15 hours

   ☐ Other :

2) What do you think of the weight of external batteries ?

3) Is battery charging complicated? If so, can you explain why?

4) Would it bother you to verify the state of charge of external batteries back-up and charge them if necessary?

   ☐ Yes
   ☐ No

If yes, could you comment?

5) you have positive elements to indicate regarding the external batteries and the internal battery ?

Description

Items	Not satisfactory at all	Not satisfactory	Neutral	Satisfactory	Very satisfactory
External batteries					
Check the external batteries load level from the external controller	☐	☐	☐	☐	☐
Check the external batteries load level on the batteries	☐	☐	☐	☐	☐
Connect a battery to the external controller	☐	☐	☐	☐	☐
Disconnect a battery from the external controller	☐	☐	☐	☐	☐
Charge an external battery with the battery charger	☐	☐	☐	☐	☐
Understand that the charge of the battery is complete	☐	☐	☐	☐	☐
Understand external battery alarms	☐	☐	☐	☐	☐
Frequency of external batteries replacement	☐	☐	☐	☐	☐
Charging time of external batteries	☐	☐	☐	☐	☐
Internal battery					
Understand internal battery charge level	☐	☐	☐	☐	☐
Comments : justifications, ideas for improvement, other comments…					

4-External Transcutaneous Energy T ransfert coil and Trancutaneous Energy Transfert coil holder

4.1External TET coil

1) Does the visual indicator on the external controller allow to obtain the ideal placement of the external Trancutaneous Energy Transfert coil on top of the internal Trancutaneous Energy Transfert coil ?

☐ Yes

☐ No

If no, why ?

2) To perform the Trancutaneous Energy Transfert coil replacement, do you need to consult the patient manual ?

- ☐ Yes
- ☐ No

If yes, for which reason(s) ? For which specific step(s) ?

Do you have positive elements to indicate regarding the external Transcutaneous Energy Transfert coil ?

Description

4.2 TET coil holder

1) How often do you change the Transcutaneous Energy Ttransfert coil holder adhesive? ……..
2) How often do you change the Trancutaneous Energy Transfert coil holder bra? ……..
3) Which Transcutaneous Energy Transfert coil holder option do you prefer to wear?

- ☐ Adhesive
- ☐ Bra

Could you explain this choice?

4) Does the Transcutaneous Energy Transfert coil holder cause any inconvenience like irritation, redness, sense of discomfort? If yes, could you precise the inconvenience and the Transcutaneous Energy

Transfert coil holder option ?

5) Does the TET coil holder disturb you in your daily life ?

☐ Yes

☐ No

If yes, which option (bra or adhesive) and for which reason(s)/actions/activities ?

6) Does the adhesive hold properly during the night ?

☐ Yes

☐ No

If no, could you provide more details ?

7) Does the bra hold properly during the night ?

☐ Yes

☐ No

If no, could you provide more details ?

8) Do you have positive elements to indicate regarding the external Transcutaneous Energy Transfert coil holder ?

Description

Items	Not satisfactory at all	Not satisfactory	Neutral	Satisfactory	Very satisfactory
Position the external Transcutaneous Energy Transfert (TET) coil on the TET holder	☐	☐	☐	☐	☐
Position the adhesive on the skin	☐	☐	☐	☐	☐
Remove the adhesive	☐	☐	☐	☐	☐

Position the bra on the skin	☐	☐	☐	☐	☐
Remove the bra	☐	☐	☐	☐	☐
Find the good position for the external TET coil in front of the internal TET coil	☐	☐	☐	☐	☐
Disconnect the external TET coil	☐	☐	☐	☐	☐
Verify the external TET coil alignment on the external controller	☐	☐	☐	☐	☐
Comments : justifications, ideas for improvement, other comments…					

5 Perform activities

Items	**Not satisfactory at all**	**Not satisfactory**	**Neutral**	**Satisfactory**	**Very satisfactory**	*Not concerned*
Sleep with the device	☐	☐	☐	☐	☐	
Take a shower	☐	☐	☐	☐	☐	
Go to the toilet	☐	☐	☒	☐	☐	
Perform household activities with the device	☐	☒	☐	☐	☒	☐
Going out (supermarket, etc)	☐	☐	☐	☐	☐	☐
Perform physical activities	☐	☐	☐	☐	☐	☐
Drive with the device	☐	☐	☐	☐	☐	☐
Using public transport	☐	☐	☐	☐	☐	☐
Other:	☐	☐	☐	☐	☐	☐
Other:	☐	☐	☐	☐	☐	☐

Other:	☐	☐	☐	☐	☐	☐
Comments : justifications, ideas for improvement, other comments…						

1) According to you, which activity(ies) is/are the hardest to perform with the system and why ?

2) Do you prevent yourself from performing some activities due to the device because of difficulties (not contraindicated activities but activities you are allowed to perform) ?

6 Other

Here you can add any feedbacks you want to (positive points, negative points, ideas for improvement).

Description

21.9 Annex I – Composition of the patient selection committee and the Data Safety Monitoring Board

1- Patient Selection Committee Members

Title	Name	Function	Professional Address
MD, PhD	**Lars H. Lund**	Cardiologist with a focus on Heart Failure	Karolinska Institutet and Karolinska University Hospital Heart, Vascular and Neuro Theme, Research Unit Solna site: S1:02, Norrbacka, 171 64 Stockholm, Sweden Huddinge site: Hälsovägen 13, 141 57 Huddinge, Sweden
MD, PhD	**Linda W. Van Laake**	Cardiologist with a focus on Heart Failure	Department of Cardiology, University Medical Center Utrecht International, Netherlands
MD, PhD	**Jan Gummert**	Cardiothoracic Surgeon	Director of the Clinic for Thoracic and Cardiovascular Surgery Heart and Diabetes Center North Rhine-Westphalia Ruhr-University Bochum Georgstr. 11, 32545 Bad Oeynhausen
MD, PhD	**Carlo Banfi**	Cardiothoracic Surgeon	IRCCS Ospedale Galeazzi-Sant'Ambrogio, Gruppo San Donato, Department of Cardio-Thoracic Surgery, Chair of Cardiac Surgery, University of Milan Via Cristina Belgioioso 17 Milano, Italy

2- Data Safety Monitoring Board Members

Title	Name	Function	Professional Address

MD, PhD	**Bart Meyns**	Cardiothoracic Surgeon	University Hospital UZ Leuven Belgium, Herestraat 49, 3000 Leuven, Belgium
MD	**Nicolas Clementy**	Cardiologist- Interventional Rythmologist	Millénaire Medical Center , 220 Bd Pénélope, 34000 Montpellier, France
MD, PhD	**Carlo Banfi**	Cardiothoracic Surgeon	IRCCS Ospedale Galeazzi-Sant'Ambrogio, Gruppo San Donato, Department of Cardio-Thoracic Surgery, Chair of Cardiac Surgery, University of Milan Via Cristina Belgioioso 17 Milano, Italy

21.10 Annex J – Statement of Compliance

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ansm	**Annexe 4 :** **Modèle de déclaration de conformité aux exigences générales en matière de sécurité et de performances**

Je soussigné **Arnaud Mascarell**, de la société **FineHeart au 28 Av. Gustave Eiffel, 33600 Pessac, France** certifie que le dispositif médical **Icoms® FlowMaker®** fabriqué par **FineHeart au 28 Av. Gustave Eiffel, 33600 Pessac** utilisé dans l'étude **"A prospective, single arm, multicentric, First in Human Study to evaluate the safety and performance at 30 days of the FineHeart Icoms® FlowMaker® in subjects with advanced heart failure"** est conforme aux exigences générales en matière de sécurité et de performances définies à l'annexe I du règlement européen 2017/745, à l'exception des aspects devant faire l'objet de l'investigation sus-mentionnée, pour lesquels je certifie que toutes les précautions ont été prises pour protéger la santé et la sécurité des patients.

Fait à **Pessac**

Date **12 Mai 2026**

Titre **Chief Executive Officer (Directeur General)**

Signature

DocuSigned by:
Arnaud Mascarell
[illegible]

21.11 Annex K – Anticoagulation Protocol

List of Abbreviations

Anticoagulation / Hémostase

- **ACT** : Activated Clotting Time
- **AA** : Arachidonic Acid
- **aPTT (TCA in French)** : Activated Partial Tromboplastin Time
- **AVK** : Anti Vitamine K
- **AXa / Anti-Xa** : Anti-Xa activity
- **DIC:** Dissaminated Intravascular Coagulation
- **CRP** : C-Reactive Protein
- **DDI** : D-Dimers
- **EDTA** : Ethylene-Diamin-Tetra-Acid
- **Fib** : Fibrinogen
- **FV, FII, FVII, FVIII, FIX, FX, FXI** : Coagulation Factors
- **LMWH** : **LMWH** Low Molecular Weight Heparin
- **UFH** : UnFraction Heparin
- **INR** : International Normalized Ratio
- **IPF %** : Immature Platelet Fraction
- **LDH** : Lactate Deshydrogenase
- **CBC** : Complete Blood Count
- **PF4** : Platelet Factor 4
- **aPTT:** activated Partial Tromboplastin Time
- **TGT** : Thrombin Generation Test
- **PT :** Protrombin Time
- **TT** : Thrombin Time
- **VASP** : Vasodilator-Stimulated Phosphoprotein
- **vWF** : von Willebrand Factor
- **vWF:Ag** : von Willebrand Factor/ Antigen
- **vWF:Rco** : von Willebrand factor : Ristocitine cofactor activity

Cardiologie / Réanimation / Dispositif

- **ALM** : Alarme
- **ICU** : Intensive Care Unit (Soins intensifs)
- **LV** : Left Ventricle (Ventricule gauche)
- **RV** : Right Ventricle (Ventricule droit)
- **LA** : Left Atrium (Oreillette gauche)
- **PCWP** : Pulmonary Capillary Wedge Pressure
- **CVP** : Central Venous Pressure
- **rpm** : Rotation per Minute
- **VTI** : Velocity Time Integral

- **TAPSE** : Tricuspid Annular Plane Systolic Excursion
- **NO / iNO** : Nitrous Oxide

Biologie / Métabolisme / Infection

- **ALAT** : Alanine Aminotransferase
- **ASAT** : Aspartate Transaminase
- **Hb / Hbg** : Hemoglobin
- **LAP** : leukocyte Alkaline Phosphatase
- **sVO2**: Venous Oxygen Saturation
- **IU** : International Unit

Thrombose / Évènements cliniques

- **PE** : Pulmonary Emboly
- **DVT** : Deep Vein Thrombosis
- **SVT:** Superficial Vein Thrombosis

Autres

- **Core Lab** : Centralized Laboratory
- **IV / IVSE:** Intravenous / Intravenous via electric syringe pump
- **J, J0, J1… J30** : **Day, Day 0, Day1…Day 30** Day (protol chronology)
- **M1–M6** : Month 1 to Month 6
- **PV**: Plasma Volume

1- Objective of the anticoagulation protocol:

This protocol is intended to guide the management and monitoring of anticoagulation for medical teams involved in the care of patients implanted with a FlowMaker device.

2- Screening visit (J-14) and Baselin visit (J-7)

The objective is to evaluate thromboembolic and bleeding risks, and to establish baseline reference values for parameters used during patient follow-up.

2.1- Biological assessment at screening visit

A comprehensive pre-operative biological work-up must be performed to screen for coagulation disorders, anemia, hemolysis, thrombocytopenia, infection…

Main Parameters assessed	Labo Local (L) / Core Lab (C)
Complete blood count (CBC / NFS)	local
Platelet count by fluorimetry	local
Immature Platelet Fraction (IPF %)	local
Anti-PF4 antibodies	Local

Reticulocytes	local
Schistocytes	local
Plasma free hemoglobin	Local
Total bilirubin	local
LDH	local
Haptoglobin	local
PT / INR	local
aPTT	local
Coagulation factors (II, V, VII, VIII, IX, X, XI)	Local
Fibrinogen (Clauss method)	Local
D-dimers	Local
Fibrin monomers	local
Anti-Xa activity (if UFH or LMWH)	local
Antithrombin	Loca
Von Willebrand Factor antigen	Local
Von Willebrand Factor activity	Local
Von Willebrand Factor Multimers	Local
Thrombin Generation Test (TGT)	Core Lab (frozen)
C- Reactive Protein (CRP)	Local
Procalcitonin	Local
Creatinine	Local
Urea	Local
Total Proteins	Local
Pre-albumin et albumin	Local
AST- ALT	Local
ALT (Alkaline Phosphatase)	Local
ferritin	Local
Triglycerides	Local

2.2- Patient Interview – Thromboembolic and Bleeding Risks

The patient interview must be conducted by the **Principal Investigator**, in the presence of the **local hematologist**, using the questionnaire provided in **Appendix 1**.

The interview will focus on:

- personal and family bleeding history,
- personal and first-degree family thrombotic history,
- history of anemia or thrombocytopenia,
- comprehensive review of all concomitant medications.

If the patient is receiving **anticoagulant therapy** (apixaban, rivaroxaban, dabigatran, VKAs, LMWH, etc.), treatment must be discontinued **according to standard clinical practice** prior to device implantation.

2.3- Advisory Opinion of the Expert Biologists Committee

The committee will review laboratory findings from Day –14 and recommend additional investigations at Baseline (Day –7), with specific attention to:

- bleeding risk,

- thrombotic risk,
- inflammatory status,
- anticoagulant and antiplatelet management,
- anemia or hemolysis,
- thrombocytopenia,
- renal and hepatic function,
- iron stores.

Antithrombotic Therapy An American College of Chest Physicians Clinical Practice Guideline 2022)
Reactualisation-GIHP_AOD_actes-programmes_Septembre-2015
Perioperative management of antithrombotic therapy Chest 2022

2.4- Day before device implantation (Day-1)

Verification of the absence of clinical or biological signs of infection, which would contraindicate implantation according to the exclusion criteria.

2.5- Per-operative management (Day 0)

ACT monitoring every 30 Min

- Baseline ACT before anticoagulation
- UFH bolus: **100 IU/kg** immediately before LV puncture
- Target ACT ≥ **300 seconds**, 5 minutes after bolus
- Additional bolus (25–50 IU/kg) if ACT<300s
- Discontinuation of heparin (while ACT monitoring is maintained) once the pump is operational
- End-of-procedure testing: ACT, PT, aPTT, fibrinogen, TT, Anti-Xa
- **No routine protamine administration**

2.6- Immediate Post-operative Bleeding (Operative Room - Day 0)

In case of bleeding:

- Emergency Anti-Xa measurement
- Protamine dose calculation:

Protamine dose (IU) = Body weight (kg) × Plasma volume (mL/kg) × Anti-Xa activity (IU/mL)

If Anti-Xa activity is unavailable:

- ACT 180–250 s → 500 IU protamine
- ACT > 250 s → 1,000 IU protamine

Other bleeding events must be managed according to local institutional procedures.

2.7- Post- Operative Management (ICU at Day 0)

- Check **PT, aPTT, fibrinogen, thrombin time, anti-Xa**
- Resume anticoagulation with **unfractionated heparin (UFH)** at **H + 6** if drainage from both pleural drains is **< 50 mL/hour**
    - **Heparin dosage:** 100 to 200 IU/kg
- **Hemostasis assessment at H + 6 after initiation of heparin therapy:**
    - Anti-Xa activity: **target 0.2–0.3 IU/mL**
    - aPTT: **target > 1.5**
    - PT
    - Fibrinogen
    - Antithrombin
    - In case of discrepancy, **refer to the opinion of a hematologist**
- Repeat the hemostasis workup **6 hours after any dosage change**
- In case of bleeding: PT (plus factors II, V, VII, X if PT is decreased), aPTT, fibrinogen, complete blood count, and thromboelastometry (if available and if the team is trained)

Resumption of heparin may be delayed **up to a maximum of H24**.

- **Daily meeting** to assess the effectiveness of anticoagulation between the **principal investigator**, the **local hematologist**, and the **expert biology committee**

2.8- Post-Operative period from Day 1 to Day 4.

- **Day 1:** Initiate **aspirin** between **75 and 100 mg** in aspirin-naïve patients (if the patient is already on aspirin, continue the initial dose).
- **Hemostasis assessment 6 hours after any change in UFH dosage** and **at least once daily**:
    - Anti-Xa activity: **target 0.35–0.55 IU/mL**
    - aPTT: **target > 2**
    - PT
    - Fibrinogen
    - In case of discrepancy, **refer to the opinion of a hematologist**
- **Daily meeting** to assess the effectiveness of anticoagulation between the **principal investigator**, the **local hematologist**, and the **expert biology committee**.
- **Day 3 – Removal of drains:**
  Discontinue heparin **2 to 4 hours before** drain removal, then **resume heparin without a bolus 2 hours after** removal.
- **Day 3 – Initiation of vitamin K antagonists (VKAs):**
  If there are **no hemorrhagic complications**, initiate VKAs **after pharmacist consultation** to assess potential drug interactions.
  Start **Coumadin at a dose of 4 mg**.
  Refer to the appendix for the main medications that interfere with VKAs.

If initiation of VKAs is not feasible after drain removal:

- Continue **UFH**, with hemostasis assessment **at least once daily** or **6 hours after any dosage change**:
  - Anti-Xa activity: **target 0.4–0.6 IU/mL**
  - aPTT: **target > 2**
  - PT
  - Fibrinogen
- In case of discrepancy, **refer to the opinion of a hematologist**
- **Daily meeting** to assess the effectiveness of anticoagulation between the **principal investigator**, the **local hematologist**, and the **expert biology committee**.

2.9- From Day 5 until pump explantation.

Continue Coumadin at a dose of 4 mg.

- **Day 5:**
  Check **INR** to screen for hypersensitivity to vitamin K antagonists (VKAs).
  - If **INR > 2**, reduce to **3 mg/day**
  - If **INR < 2**, continue **4 mg/day**
- **Day 6:**
  Check **INR**
  - If **INR < 1.5**, increase to **5 mg/day**
  - If **INR > 1.5**, continue **4 mg/day**

Discontinue heparin after **two consecutive INRs**, measured **24 hours apart**, within the **target range of 2–3**.

In accordance with local practices, INR monitoring should be performed twice weekly whenever feasible, with a maximum interval of four days between measurements.

<u>Aspirin and/or Clopidogrel monitoring from Day 5 to Day 30:</u>

- Screen for **aspirin resistance** using a **platelet aggregation test** at least **once per week**; reassess if **platelet count > 600 G/L**.
  - **Target:** arachidonic acid (AA)–induced aggregation **< 20%**
  - If the target is not achieved, a **systematic meeting with the expert biology committee** is required

Table 4- Biological monitoring of clopidogrel :

Cloipidogrel Monitoring*	Hemorragic risk zone	Intermediate zone	throimbotic risk zone
VN PRU	< 95	95 -208	> 208
Multiplate AU.min	< 190	190 -390	➢ 390
VASP (non-urgent)	<20	20-50	➢ >50

*Tests and results must be interpreted in collaboration with the biologist due to limitations, particularly for VN and Multiplate tests (platelet count, hematocrit).

Frequency of anticoagulation efficacy assessment meetings with the expert biology committee:

- **From Day 5 to Day 15:** one meeting per day
- **From Day 15 to Day 30:** one meeting every 2 days
- **From Day 30 until pump explantation:** one meeting per month

3- Criteria for anticoagulation efficacy in the presence of an inflammatory syndrome

Adjustment of anticoagulation during patient management should be **discussed on a case-by-case basis** by the **expert biology committee**. The objective is to achieve a **minimum r-aPTT (rTCA) value > 2**.

4- Monitoring of Heparin Dose Changes

To be completed by the investigational center in the event of any change in heparin dosage:

Date	Start time or time of heparin dose change	heparin dose (IU/kg)	rTCA	AXa UI/ml	TP	Fib	End Time
JO							
J1 J2…Explant							

5- Centralized Laboratory Protocol (Core Lab)

Objective: To perform additional hemostasis tests required to determine the root cause of any potential serious adverse events related to the pump.

Sampling concerns only the remaining citrated plasma from blood tests specified in the patient monitoring workup (see Table 2), prepared as 500 µL aliquots and stored at −80 °C. Samples will be destroyed at the end of the study**.**

.

Appendix 1- Patient Interview on Thromboembolic and Hemorrhagic Risks .

Personal Thrombotic History:

Patient Screening Number: _____

Antécédents de TVP/EP/TVS/T artérielle : History of DVT/PE/SVT/Arterial Thrombosis

- **Date** :
- **Type** (deep, superficial, others…) :
- **Localization** :
- **Diagnostic Method**:
- **Contributing clinical factors :**

	Yes	NO	UNK
Major transient risk factors			
- Surgery with general anesthesia > 30 minutes within the last 3 months	☐	☐	☐
- Lower-limb fracture within the last 3 months	☐	☐	☐
- Immobilization > 3 days for an acute medical condition within the last 3 months	☐	☐	☐
- Estrogen–progestin contraceptive use	☐	☐	☐
- Pregnancy, postpartum period	☐	☐	☐
- Menopausal hormone therapy	☐	☐	☐
Major persistent risk factor			
- Active cancer	☐	☐	☐
Minor transient risk factors			
- Surgery with general anesthesia < 30 minutes within the last 2 months	☐	☐	☐
- Lower-limb trauma without casting, with reduced mobility for ≥ 3 days	☐	☐	☐
- Immobilization < 3 days for an acute medical condition within the last 2 months	☐	☐	☐
- Travel duration > 6 hours	☐	☐	☐
Minor persistent risk factors			
- Chronic inflammatory bowel or joint disease			
- (Crohn's disease, ulcerative colitis)	☐	☐	☐

- Preventive anticoagulation during these situations: Yes/ No ……
- **Others Events** (Specify the date) :

……

……

- **Obstetric conditions:**

……
……

-Personal Medical History
For each episode of DVT / PE, indicate the date, location, any associated risk factors, and management (including treatment duration):
……
……
……

- **First-degree family history of venous thromboembolism (VTE)**
  Description for each family member: venous or arterial thrombosis, dates of events, degree of relationship, location, risk situations at the time of the event, etiological workup performed and results, management.

……
……

Date of interview: _____
Name and surname of the Principal Investigator: _____
Signature of the Principal Investigator: _____
Name and surname of the hematologist: _____
Signature of the hematologist: _____

Bibliography :

<u>Drugs that potentiate warfarin (Coumadin) and increase INR</u>

- ***Major interactions***

5-fluoro-uracil, tegafur, capecitabine, defibrotide
Amiodarone
Fluconazole, voriconazole, econazole (including topical formulations)
Cefazolin, imatinib

- ***Moderate interactions***

Azathioprine
Itraconazole
Allopurinol
Colchicine
Cephalosporins, tetracyclines, fluoroquinolones, macrolides, sulfonamides
Fibrates
Thyroid hormones
Statins (atorvastatin, fluvastatin, rosuvastatin, simvastatin)
Paracetamol (acetaminophen) at doses of 4 g/day
Tramadol
SSRIs, imipramines

Valproate

- ***Contraindication***

Miconazole (all routes of administration

Drugs that induce metabolism and decrease INR
Rifampicin
Carbamazepine
Phenobarbital
St John's wort (herbal medicine)

Reference:
https://www.drugs.com/drug_interactions.html