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EasyCross™ Device

VIVHEART Transcatheter Aortic Valve Replacement (TAVR) Self-centering Catheter first-in-human feasibility trial (VIV-FIH)


Clinical Investigation Plan

Title of the clinical investigation	Study Code	Revision	Date
VIVHEART Transcatheter Aortic Valve Replacement (TAVR) Self-centering Catheter first-in-human feasibility trial (VIV-FIH)	CIP01	3	14/09/2023

REVISIONS HISTORY

Revision	Description of Changes	Date
1	First Issue	16/12/2022
2	Cap 18 point f	09/08/2023
3	Cap 18 points c, d and f	14/09/2023

	<i>name</i>	<i>function</i>	<i>date</i>	<i>signature</i>

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Principal Investigator (IRCCS, San Raffaele, Milanl (Italy)

Name	Signature	Date (dd/mm/year)
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ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
AESI	Adverse Event of Special Interest
CA	Competent Authority
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRO	Clinical Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
EU	European Union
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IFU	Instructions For Use
MDCG	Medical Device Coordination Group
PI	Principal Investigator
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SOP	Standard Operating Procedure
SVT	Superficial Venous Thrombosis
TAVR	Transcatheter Aortic Valve Replacement
USADE	Unanticipated Serious Adverse Device Effect

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1. GENERAL

1.1. SPONSOR

Manufacturer	VIVHEART s.r.l.
Address	Via Senato, 15 20121 Milano (MI) – Italy
PRRC	Dott. Alessandro Stella
E-mail	alessandro.stella84@gmail.com
Phone	+39 353 4259930


1.2. PRINCIPAL INVESTIGATOR

Name: Marco Bruno Maria Ancona

Address: IRCCS San Raffaele (Milan, Italy)


Professional Position: Interventional Cardiologist

Investigation site: IRCCS San Raffaele (Milan, Italy)


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1.3. OVERALL SYNOPSIS


1. STUDY NAME	VIVHEART Transcatheter Aortic Valve Replacement (TAVR) Self-centering Catheter first-in-human feasibility trial (VIV-FIH)
2. INVESTIGATORS	Marco Bruno Maria Ancona
3. CLINICAL / SCIENTIFIC BOARD	Not available/Not applicable
4. INVESTIGATION CENTERS	San Raffaele IRCCS, Milano, Italy
5. SPONSOR	VIVHEART s.r.l., Milano, Italy
6. STUDY DEVICE	VIVHEART EasyCross™ is a self-centering device for inserting a guidewire through a heart valve. It consists in a temporary catheter inserted into an artery with a terminal part able to expand a distal structure with 6 arms ("basket") to allow distancing of the catheter from the vessels walls and thus facilitating the passage of the guide wire through the aortic valve. The device is expected to reduce the attempts and the time needed to cross the valve and improves the safety of TAVR procedure.
7. STUDY DESIGN	The VIVHEART EasyCross™ fist-in human (VIV-FIH) study is a single-center, prospective, open-label, non-randomized, single-group assignment, first-in-human feasibility trial of the VIVHEART EasyCross™ catheter used according to the indication of use. The experimental part of the trial which differs from the traditional TAVR procedure is the use of the self-centering catheter from its insertion in an artery and up to its removal from the patient body (henceforth "investigational procedure").

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8. PATIENT POPULATION INDICATION /	<p>VIVHEART EasyCross™ catheter is intended for patients candidate to transcatheter aortic valve replacement in:</p> <ul style="list-style-type: none"> - native aortic valve - surgical aortic prosthesis (valve-in-valve procedure) - transcatheter aortic prosthesis (TAVR in TAVR) - recrossing and balloon post-dilation of a transcatheter aortic prosthesis
9. NUMBER OF PATIENTS	The total minimum number of patients is 20 up to a maximum of 25.
10. STUDY OBJECTIVE	The primary objective of this clinical study is to confirm the safety and performances of VIVHEART EasyCross™ device when used in accordance with the Instructions for Use.
11. PRIMARY ENDPOINT	<p>The primary endpoint is the safety of VIVHEART EasyCross™ catheter, in term of adverse events (AE) and serious adverse events (SAE). Occurrence of any AE will be recorded, in particular the following AE will be coded and investigated as adverse events of special interest (AESI):</p> <ul style="list-style-type: none"> - Intra-operative death, - Any intra-operative complication due to device malfunction, - Any embolization event, - Any allergic reaction.
12. SECONDARY ENDPOINTS	<p>The secondary endpoints will evaluate the performances of the VIVHEART EasyCross™ catheter in terms of:</p> <ul style="list-style-type: none"> - Investigational device crossing procedure duration, - Correct valvular device placement after procedure.
13. ELIGIBILITY CRITERIA	<p>The subjects eligibility criteria will be:</p> <p><u>Inclusion Criteria</u></p> <ul style="list-style-type: none"> - Age: ≥18 years old - Candidate to TAVR of a native valve, recrossing and balloon post-dilation of a prosthetic aortic valve, or a valve-in-valve aortic valve replacement. - Willingness to undergo follow-up visits. - Ability to understand scope, content and risks of the study, and provide informed consent to participation. <p><u>Exclusion Criteria</u></p> <ul style="list-style-type: none"> - Contraindications for endovascular procedures - Pregnancy or breastfeeding females at screening and at time of investigational procedure - Hemodynamically unstable or other clinical conditions increasing the risk of transcatheter valve procedure failure - Needing emergent procedure

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	<ul style="list-style-type: none"> - Allergies to components of the device - Allergies to drugs or contrast material that may be used during the investigational procedure and all the TAVR procedure - Participation in another clinical trial
14. FOLLOW-UP	<p>After pre-procedure evaluation, including clinical examination, and baseline visit for the investigational procedure and TAVR with a post procedure evaluation, subsequent time-points will be:</p> <ul style="list-style-type: none"> - Short-term follow-up/hospital discharge (up to 7 days after the investigational procedure) - End of Study (EOS) (4 weeks after the investigational procedure) <p>At each time-point general examination, concomitant medications assessment, safety evaluation, blood tests and instrumental evaluation (as per clinical practice) will be assessed. In addition, after the investigational procedure, prosthetic valve will be evaluated with echography. During the investigational procedure the total investigational device procedure duration and the removal of the fully intact VIVHEART EasyCross™ device will be assessed.</p>
15. STUDY DURATION	<p>Expected duration of the study will be of 6 months: 4 months to complete the enrolment and an additional 2 months to complete the follow-up. The complete study duration per patient is expected to be of about 6 weeks including the screening period.</p>

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2. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

a. Summary description of the investigational device

VIVHEART EasyCross™ is a self-centering device for inserting a guidewire through a heart valve. It consists in a temporary catheter inserted into an artery with a terminal part able to expand a distal structure with 6 arms (“basket”) to allow distancing of the catheter from the vessels walls and thus facilitating the passage of the guide wire through the aortic valve. The device is expected to reduce the attempts and the time needed to cross the valve and improves the safety of TAVR procedure.

b. Details concerning the manufacturer of the investigational device

The legal manufacturer is VIVHEART s.r.l., Milano, Italy.

c. Name or number of the model/type

Only one model is available, identified as “EasyCross”.

d. Traceability

The device is identified by a serial number corresponding to the related production lot. All the serial number will be identical within each production lot.

e. Intended purpose of the investigational device in the proposed clinical investigation

The VIVHEART EasyCross™ device is a catheter is intended to allow a rapid and safe centering of a heart valve in order to direct and introduce a guidewire through it. The intended purpose is the use of the device during percutaneous TAVR procedures, including TAVR of a native valve, recrossing and balloon post-dilation of a prosthetic aortic valve, or a valve-in-valve aortic valve replacement within the scope of the CE mark.


f. Population and indications for which the investigational device is intended

The VIVHEART EasyCross™ device is intended for patients candidate to TAVR of a native valve, recrossing and balloon post-dilation of a prosthetic aortic valve, or a valve-in-valve aortic valve replacement. The suitability of the patient is to be verified case by case by the specialized physician, by means of proper physical examination and instrumental evaluation, according to clinical practice.

g. Description of the investigational device including any materials that will be in contact with tissues or body fluids

The device is a non-implantable catheter, designed to support the central positioning in the aortic lumen of a coronary guide, through a percutaneous access, to facilitate the passage of the prosthetic or native aortic valve, in the context of a TAVR surgical procedure.

The device is composed by an inner and an outer tube, the latter designed with an expandable distal structure with 6 arms (“basket”) to allow distancing of the catheter from the vessels walls

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and thus facilitating the passage of the guide wire through the aortic valve. Pushing / pulling the inner tube causes the outer tube to slide on the inner tube and concomitant closing / opening the arms of the basket without losing the catheter's position.

The catheter has a Y connector with haemostatic valve, for the flushing of the area between the inner and outer tubes. It is introduced percutaneously via the femoral artery using conventional catheterization techniques; the proximal luer, directly assembles to the inner tube, allows the introduction of 5F diagnostic catheters and 0.035" guide wires.

The device is single use and single patient and is supplied sterile to the final user.

The materials used for manufacturing the VIVHEART EasyCross™ device are already used in medical devices and include Pebax compound (rigid polyamide blocks and soft polyether blocks copolymers), barium dispersion in ethylene vinyl acetate copolymer, low-density polyethylene resin, high-density polyethylene, methyl methacrylate acrylonitrile butadiene styrene, polycarbonate, and silicone.

h. Summary of the necessary training and experience needed to use the investigational device

The necessary training and experience needed to use the investigational device is the formation as an Interventional Cardiologist, which is the intended user of the device. Before the trial initiation a training on the use of the device will be conducted by VIVHEART.


i. Description of the specific medical or surgical procedures involved in the use of the investigational device

Medical and surgical procedures involved in the use of the investigational device do not differ from the traditional TAVR procedure. The only difference consists in the use of the VIVHEART EasyCross™ catheter which would allow the centering of the aortic valve. Thus, since this is a first-in-human evaluation and no clinical data in human exist, the only expected difference from the standard TAVR procedure is a reduced number of attempts to center the aortic valve.

3. JUSTIFICATION FOR THE DESIGN OF THE CLINICAL STUDY

VIV-FIH is a single-center, prospective, open-label, non-randomized, single-group assignment, first-in-human feasibility clinical trial of the VIVHEART EasyCross™ catheter aimed at collecting clinical safety and performances data of the VIVHEART EasyCross™ catheter used in patients candidate to percutaneous transcatheter aortic valve replacement (TAVR) according to the indication of use within the scope of the CE mark. The experimental part of the trial which differs from the traditional TAVR procedure in use is the use of the self-centering catheter from its insertion in an artery and up to its removal from the patient body (henceforth "investigational procedure").

The study will enroll a minimum number of 20 patients and up to a maximum of 25 subjects at the center. All the subjects will be evaluated up to 2 weeks before the investigational procedure, the day of the procedure, at a short-term follow-up/hospital discharge (up to 7

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days after the investigational procedure), and at End of Study (EOS) (4 weeks after the investigational procedure).

The eligibility criteria are compliant with the indication of use within the scope of the CE mark.

a. Evaluation of the results of the relevant pre-clinical testing/assessment

Biocompatibility

The biocompatibility of the VIVHEART EasyCross™ device was evaluated in the Biological risk assessment report as described in the IB. Briefly, the device has been assessed for cytotoxicity, sensitization, irritation or intracutaneous reactivity, pyrogenicity, and hemocompatibility. Based on the biological evaluation carried out, it can therefore be declared that the EasyCross aortic catheter complies with the biocompatibility requirements according to the ISO 10993-1: 2018 reference standards and in accordance with the purpose of use for which it is designed.

Preclinical evaluation


Preclinical simulations have been performed in artificial models of aortic arc and aortic valve. Two models of aortic arc have been evaluated, including a model representative of the anatomy of the patient population in terms of age and pathologies starting from a CT scan of a typical patient and a case scenario of aortic arc conformation derived from literature data (Hütter 2016; Huetter 2015). Such simulated tests replaced in-vivo testing since animal models are not representative of human anatomy. The results showed that the device was compliant to specifications and requirements for its intended use. Further results on preclinical models are provided in the IB.

Evaluation of clinical data that are relevant to the proposed clinical investigation

At the moment, one of the main open issues of the traditional use of a catheter to introduce a guidewire through a prosthetic or native valve is the absence of tri-dimensional visualization during the procedure. Since the catheter and the guidewire are visualized by a two-dimensional imaging, the interventional cardiologist has to repeat several attempts to cross the valve. However, even if the guidewire seems to be positioned in the correct place, this may be only apparent. As a consequence, both during the valve crossing and the extraction of the guidewire a series of complication may occur and have been reported. While a prosthetic valve could seem correctly crossed, the guidewire could have been instead introduced between the valve and the aortic wall (Vella 2022).

Also, a catheter or a guidewire which seemed correctly positioned may be otherwise impinged in an already present valve during a postdilation or valve-in-valve procedure (Cubero-Gallego 2022; Piayda 2018). Albeit uncommon, these complications are potentially life-threatening and may require a prolongation of the procedural time and even surgery to be solved.

The VIVHEART device has been designed to overcome these complications. In particular, it has the possibility to be centred on the valve using the blood vessel wall, facilitating the crossing procedure. This could allow a reduction in the catheter misplacements and impingement

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events. Also, it might reduce the duration of the crossing procedure since with its self-centering capability it could reduce the attempts of the i to cross the valve.

b. Clinical development stage

This is an interventional study of a first-in-human use of an investigational device.

4. BENEFITS AND RISKS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

a. Anticipated clinical benefits

The anticipated clinical benefits resulting from the use of the VIVHEART EasyCross™ catheter are:

- reduction of the risk of complications during the crossing phase of the valve;
- reduction of the crossing procedure duration.

b. Anticipated adverse device effects

A risk analysis has been conducted according to ISO 14971:2019 Medical devices. Application of risk management to medical devices. Adverse events potentially associated with the VIVHEART EasyCross™ device are listed below:

- Bleeding
- Cardiac perforation
- Damage to vessel (bleeding, inflammation, hematoma)
- Damage to vessel walls
- Embolism
- **Inability to carry out the procedure / extension of procedural time**
- Post- procedure events (phlebitis, leg pain, local infection)
- Tissue damages
- Transient ischemic attack

c. Risks associated with participation in the clinical study

The possible risks associated with the use of the VIVHEART EasyCross™ catheter are common to all TAVR procedures and are reported in § 4.b.


The follow-up procedures planned in the study (clinical visits and eco color doppler) do not involve additional risks for the patients.

d. Possible interactions with concomitant medical treatments

VIVHEART EasyCross™ catheter does not interfere with concomitant medical treatment.

e. Steps that will be taken to control or mitigate the risks

Measure for controlling and mitigating the risks are described in the RMP annexed to IB.

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f. Risk-to-benefit rationale

The expected benefits from the use of the VIVHEART EasyCross™ catheter include all those obtained by the TAVR procedure with conventional catheters. Benefits of TAVR are recognized by the clinical practice and deemed favourably with respect to the corresponding risk of adverse events.

Since the technology of the VIVHEART EasyCross™ catheter may solve some limitations of the TAVR procedure:

- allowing the self-centering of the valve,
- overcoming the risk of incorrect crossing or impingement of the valve,
- possibly reducing the procedure duration,

it is reasonable to expect a more favorable risk/benefit profile and for this reason the device should be evaluated in a clinical trial.

5. OBJECTIVES OF THE CLINICAL STUDY

The primary objective of this clinical study is to confirm the safety and performances of VIVHEART EasyCross™ device when used in accordance with the Instructions for Use.

6. DESIGN OF THE CLINICAL STUDY

a. Type of clinical study

VIV-FIH is a single-center, prospective, open-label, non-randomized, single-group assignment, first-in-human feasibility study of the VIVHEART EasyCross™ catheter used according to the indication of use within the scope of the CE mark.


The experimental part of the trial which differs from the traditional TAVR procedure in use is the use of the self-centering catheter from its insertion in an artery and up to its removal from the patient body.

b. Primary and secondary endpoints

The primary endpoint is the safety of VIVHEART EasyCross™ catheter, in term of adverse events (AE) and serious adverse events (SAE). Occurrence of any AE will be recorded, in particular the following AE will be coded and investigated as adverse events of special interest (AESI):

- Intra-operative death,
- Any intra-operative complication due to device malfunction,
- Any embolization event,
- Sepsis or other systemic infections,
- Any allergic reaction.

AE will be coded using the Medica Dictionary for Regulatory Activities (MedDRA) and graded according to the Common Terminology for Adverse Events (CTCAE). AE will be classified as serious adverse events (SAE) if they caused death, were life threatening, required hospitalization or caused the prolongation of existing hospitalization, resulted in persistent or significant disability, may have caused a congenital anomaly/defect, required an intervention

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to prevent permanent impairment or damage, were considered clinically important by study investigator judgement or are present in the European Medicines Agency (EMA) Important Medical Events list (IME List).

The secondary endpoints will evaluate the performances of the VIVHEART EasyCross™ catheter in terms of:

- Investigational device crossing procedure duration. During the procedure, the total time of the procedure encompassing the use of the VIVHEART EasyCross™ catheter will be collected starting from the arterial insertion of the device and ending at the moment of the complete device extraction from the body.
- Complete removal of the fully intact device. The device will be inspected immediately after its removal from the body to verify its integrity.
- Correct valvular device placement after surgery performed with echocardiography as per clinical practice.

c. Methods and timing for assessing, recording and analysing variables

Variables are correct valvular placement, investigational device crossing procedure duration, complete removal of the fully intact device, any AE, concomitant medications, age, sex, type of TAVR procedure, medical history, medical evaluation, blood test, and instrumental evaluation according to clinical practice. The variables will be recorded in the CRFs.

d. Definition of completion of the clinical investigation

The completion of the study coincides with the last visit of the last subject and when follow-up is complete for the clinical investigation (according to ISO 14155:2020).

7. INVESTIGATIONAL DEVICE


a. Description to the exposure to the investigational device

The exposure to the investigational device consists in the sole duration of the device use, from the introduction in the blood vessel and up to the removal from the patient body after the guidewire is successfully placed across the aortic. No further exposure to the device is expected for the patient.

b. List of any other medical device or medication to be used during the clinical study if not already specified in the IFU

All the equipment and medication apart from the investigational device will be the same used during a standard TAVR procedure according to the clinical practice.

c. Number of devices to be used

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Only one device will be used for each patient. Another device will be readily available for the patient during the crossing procedure as a backup. For the study, a total of 50 devices will be provided. Further devices could be requested to the Sponsor, if needed.

8. SUBJECTS

VIVHEART EasyCross™ catheter is intended for patients candidate to transcatheter native aortic valve replacement, recrossing and balloon post-dilation of a prosthetic aortic valve, or valve-in-valve aortic valve replacement.

a. Inclusion criteria

- Age: ≥18 years old
- Candidate to TAVR of a native valve, recrossing and balloon post-dilation of a prosthetic aortic valve, or a valve-in-valve aortic valve replacement.
- Willingness to undergo follow-up visits.
- Ability to understand scope, content and risks of the study, and provide informed consent to participation.

b. Exclusion criteria

- Contraindications for endovascular procedures
- Pregnancy or breastfeeding females at screening and at time of investigational procedure
- Recent infarction or cerebrovascular accident (6 months before investigational procedure)
- Hemodynamically unstable or other clinical conditions increasing the risk of transcatheter valve procedure failure
- Needing emergency surgery
- Allergies to components of the device
- Allergies to drugs or contrast material that may be used during the investigational procedure and all the TAVR procedure
- Participation in another clinical trial


c. Criteria and procedure for subject withdrawal or lost to follow-up

Upon signing of the informed consent, the subject is considered enrolled and will be asked to undergo the scheduled follow-ups.

A patient is considered withdrawn from the study when:

- The subject chooses to end participation in the clinical study. Subjects may end their participation to the study at any time, without prejudice to further treatments.
- The subject is “lost to follow-up” when after three unsuccessful attempts to reach the patient by telephone and by letter, the site is unable to locate the patient. The lost subjects will be withdrawn from the study.

In all these cases a Withdrawal will be recorded and CRF study conclusion form must be completed.

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d. Point of enrolment

The point of enrolment is defined as the time at which, following recruitment, a patient has signed and dated the consent form.

e. Total expected duration of the clinical investigation

Expected duration of the study will be of 6 months: 4 months to complete the enrolment and an additional 2 months to complete the follow-up.

f. Expected duration of each subject's participation

The complete study duration per patient is expected to be of about 6 weeks including the screening period.

g. Number of subjects required to be included in the clinical investigation

The total minimum number of patients is 20 up to a maximum of 25.

h. Estimate time needed to select this number (enrolment period)


4 months.

9. PROCEDURES

a. Description of all the clinical investigation related procedure

Timeline of the procedures is the following table.

Procedure	Screening visit	Procedure day	After procedure	Follow-up	End Of Study
	T0 - 2w	T0	T0 (after procedure)	T0 + 7d	T0 + 4w
Informed consent	X				
Inclusion/exclusion criteria verification	X	X			
Procedure		X			
Case history	X				
Concomitant medications	X	X	X	X	X
Medical evaluation	X	X	X	X	X
Medical history	X				
Physical examination	X				
Emato-chemical analyses	X	X	X		
Angio-CT; coronary, and thoracic	X				

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abdominal aorta, with contrast enhancement					
Echocardiogram	X				
Valve correct placement check			X		
Crossing procedure duration		X			
Complete removal of the fully intact device		X			
Safety evaluations		X	X	X	X

Written informed consent must be obtained for all the patients who are potential study candidates before any specific test or procedure are performed.

The patients will undergo a clinical evaluation to review inclusion and exclusion criteria of the study. The following data will be recorded:

- Medical history
- Concomitant medications
- Medical evaluation
- Blood test (as per clinical practice or if needed due to any clinical reason)
- **In particular, the necessary pre-operative tests are:**
Emato-chemical analyses: blood count, creatinine, sodium, potassium, PT, aPTT, AST, ALT, blood urea nitrogen, LDH, troponin, blood group.
 - Echocardiogram (transthoracic or transesophageal) -
 - Coronary CT angiography and thoracic and abdominal aortic CT angiography with contrast medium**


Procedure

The procedure is fully detailed in the IFU.

A summary of the procedure is here reported.

At T0 the patient will undergo the TAVR procedure including the investigational procedure with the VIVHEART EasyCross™ catheter.

The interventional cardiologist will introduce the VIVHEART EasyCross™ catheter through the femoral artery with a percutaneous access according to the clinical practice through a vascular introducer on an already positioned guidewire. An operator in the procedure room will start a chronometer at this point to measure the investigational device crossing procedure duration. The VIVHEART EasyCross™ catheter will be progressed into the aorta and up to the aortic valve. At that time the external part of the VIVHEART EasyCross™ catheter will be opened to allow the self-centering of the catheter on the aortic valve. The guidewire will be introduced and once having crossed the valve the VIVHEART EasyCross™ catheter will be retracted by the physician and removed from the patient's body. At this time the chronometer will be stopped and the removed VIVHEART EasyCross™ catheter will be inspected to verify the complete

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removal of the fully intact device. Afterwards, the TAVR procedure will continue as per usual clinical practice. The access point is medicated as per standard protocols. Data collected during the procedure will be recorded on dedicated CRF.

Post – procedure / Follow-up

After pre-procedure evaluation, including clinical examination, and baseline visit for the investigational procedure and TAVR with a post procedure evaluation, subsequent time-points will be:

- Short-term follow-up/hospital discharge (up to 7 days after the investigational procedure)
- End of Study (EOS) (4 weeks after the investigational procedure)

The length of hospital stay may be different in-between patients; however, this is generally of about 2-3 days. In case of longer hospital stay, the short-term follow-up will be collected at 7 days of follow up after surgery even if the patient is still in hospital. If the length of stay is equal or exceeds the prespecified EoS time-point for any reason (e.g., adverse events, worsening of previously-existing or intercurrent new medical conditions) the EoS for that patient will coincide with the final discharge date.

At each time-point general examination, concomitant medications assessment, safety evaluation, blood tests and instrumental evaluation (as per clinical practice) will be assessed. In addition, after the investigational procedure and TAVR prosthetic valve placement will be evaluated with echography. During the investigational procedure the total investigational device procedure duration and the removal of the fully intact VIVHEART™ device will be assessed.

b. Description of those activities performed by sponsor representative

The Sponsor will provide a dedicated form verifying the comprehension of the IFU. The Investigators must fill and sign the form to confirm they read and understood the IFU.

c. Any known or foreseeable factors that may compromise the outcome of the clinical study or the interpretation of results


At the moment there is no known or foreseeable factor that may compromise the outcome or the results of the clinical study.

10. MONITORING PLAN

Monitoring will be conducted throughout the course of this study according to the Monitoring Plan.

Monitoring visits to the investigational centre will be made by personnel appointed by the Sponsor, prior to the start (site initiation visit) and close out visit.

The Investigator will provide direct access to source documents to the personnel appointed by the Sponsor. The Investigator will provide adequate collaboration in compiling and revising the

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CRFs. Data will be evaluated for accuracy and compliance with the CIP and in relation to source documents.

At the conclusion of the study, the personnel appointed by the Sponsor will conduct a site closeout visit, to implement the procedures for concluding the study, or will communicate remotely the instructions for the closeout.

11. STATISTICAL DESIGN AND ANALYSIS

The study is not designed to statistically test a prespecified hypothesis through a formal comparison. In this first phase of the VIVHEART EasyCross™ catheter clinical development the data collected are intended for generating a first-in-human description of the safety and feasibility of the use of the device for subsequent studies. Thus, a power study was not performed and the sample size was based on clinical consideration related to the availability of eligible patients in the clinical practice. Therefore, patients numerosity at this stage does not fulfill statistical requirements. Categorical values will be reported as counts and percentages; continuous variables will be reported as mean and standard difference and median with minimums and maximums.

12. DATA MANAGEMENT

a. Method for data entry and collection

All relevant data of the patients enrolled in the study will be recorded on dedicated CRFs provided by the Sponsor. The Investigator will assure the accuracy and completeness of the data reported to the Sponsor on the CRFs.

The data reported on the CRFs will be consistent with the source documents and any discrepancies will be explained in writing.

b. Procedure to maintain and protect subject privacy


CRFs pages will be identified only by the participant's unique study identifier to maintain the participant's confidentiality. The participant's name must not appear on the same document. The Principal Investigator will retain a confidential master list linking the participants' unique study numbers with participant names; this will be accessible only those working on study data retrieval.

Source documents will be identified by the participant's name or other personal identifiers (e.g. hospital record number) allowing the participant to be identified. Again, to maintain the participant's confidentiality the unique study identifier (assigned to the participant at study entry) must not be recorded on the source document.

c. Procedure for data retention

The Investigator will maintain in original format all essential clinical investigation and source documentation, in compliance with the EN ISO 14155:2019 standard. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed.

The Investigator is responsible for retention of the following records:

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- All correspondence pertaining to the study
- Subject records including, but not limited to, the following:
 - o signed ICF for each enrolled subject
 - o all relevant source documentation such as medical history, information on the condition of the subject during the investigation, the results of all applicable diagnostic tests
 - o observations of adverse device effects, whether anticipated or unanticipated
 - o CRFs.
- Copy of the CIP
- Copy of all the signed and dated Investigator Agreements
- EC approval documentation and correspondence

The Sponsor will maintain the following record:

- Correspondence and reports pertaining to the clinical study
- Signed and dated Investigator Agreements and curriculum vitae of each investigator
- Records concerning adverse device effects and complaints
- CRFs
- CIP, including all amendments
- Pre-study visit reports
- Monitoring visit follow up letters
- Copies of EC's approval and correspondence
- Copies of Competent Authorities correspondence

d. Specified retention period

The study documents shall be retained for at least 10 years after the end of the clinical study.

13. AMENDMENT TO THE CIP

The CIP and the ICF may be amended throughout the clinical investigation if needed. A justification statement will be included with each amended section of a document.

Amendments to the CIP will be agreed upon between the Sponsor and the Principal Investigator.


Any change that may require modification of the ICF must receive approval by the responsible personnel from the Sponsor.

The amendments to the CIP, and the ICF will be notified to, or approved by, the EC and the concerned Competent Authorities if required, prior to implementation.

Upon approval, the CIP amendments will be distributed to all CIP recipients, with instructions to attach them to the CIP.

The amendment of a document will be documented through change of version number of the concerned document, and it will be dated.

Administrative changes that do not affect the subject benefit/risk ratio (e.g., editorial changes for clarity) may be made without any particular approval.

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14. DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN

a. Statement specifying that the investigator is not allowed to deviate from the CIP

The Investigator is not allowed to deviate from the CIP without approval of the Sponsor and the EC. If the deviation affects subjects' rights, safety and well-being, or the scientific integrity of the clinical investigation, a Request For Deviations and a corresponding report shall be submitted to the EC and to the Competent Authorities, if required.

Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Sponsor and the EC. Such deviations will be documented and reported to the Sponsor and the EC as soon as possible, if report to the EC is required.

b. Procedures for recording, reporting and analysing CIP deviations

During each monitoring visit, the Monitor will record and report to the Sponsor CIP deviations, that will be analysed by the Sponsor.

c. Notification requirements and timeframes

The non-substantial changes to the approved CIP and the approved subject's informed consent form (for example minor logistical or administrative changes, change of monitor telephone number, renewal of insurance) which do not affect the safety and well-being of human subjects or not related the clinical investigation objectives or endpoints, will be notified to the EC and the competent authority where appropriate in a timely manner.

In case of substantial change, approval of the EC will be obtained before implementation, followed by a notification to the Competent Authority.

d. Corrective and preventive actions, and principal investigator disqualification criteria


If the monitoring visit identifies:

- serious and / or repeated deviations to the CIP on the part of an investigator
- that an investigator does not follow the ethical principles
- any issue of non-compliance

the Sponsor shall implement appropriate corrective and preventive actions which may include disqualification of the Investigator.

15. DEVICE ACCOUNTABILITY

All devices provided from the sponsor to the participating center will be checked at the time of the arrival. The devices will be counted and the serial lot number will be verified. A visual inspection of the sealed devices in their packages will be carried out at the time of the arrival and before its use in a patient. The device will be inspected for integrity before its introduction in the patient and after its removal from the patient body, as described in the protocol. All these procedures and the derived evaluation of integrity and conformity will be registered in the CRF. Afterwards the device will be disposed as a biohazard material according to the participating center procedures for the disposal of biological wastes.

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16. STATEMENTS OF COMPLIANCE

a. Compliance with the Ethical principles

The Sponsor ensures that this clinical study will be conducted in full conformity with the ethical principles described in the Declaration of Helsinki adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, as last amended by the World Medical Assembly (October 2013). The Sponsor will avoid improper influence on, or inducement of, the subject, the monitor, the investigators and other parties participating or contributing to this clinical investigation. The PI, the monitor, the Sponsor and all the parties involved in this clinical investigation share the responsibility for its ethical conduct in accordance with their respective role in the clinical investigation.

b. Compliance with ISO 14155 and any regional / national regulations

This clinical investigation, which will be conducted according to this CIP, is designed to meet the requirements of, and will be conducted in accordance with, the following regulations:

- EN ISO 14155:2020 standard: Clinical investigation of medical devices for human subjects – Good clinical practice
- MDR: REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
- Declaration of Helsinki

c. Approval of EC

The clinical study will not begin until approvals have been obtained from the Ethics Committee and from the Ministry of Health.

d. Insurance


Participation to this clinical study, under the conditions defined in this protocol, is covered by an insurance policy undertaken by the Sponsor.

e. Agreements

An agreement will be in place between the Sponsor and the Investigation site, which defines the responsibilities of each party in the clinical study. All the agreements will be recorded in writing, signed, and dated by all parties involved.

17. INFORMED CONSENT PROCESS

- ### a. Description of the general process for obtaining the informed consent, including the process for providing subjects with new information, as needed

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The subjects participating to this clinical investigation must personally date and sign the latest approved version of the ICF before any clinical investigation procedure is performed.

Verbal information and the written Informed Consent will be presented to the participants detailing as a minimum: the exact nature of the clinical investigation, the implications and constraints of the CIP, the known side effects and any other risk deriving from participating to the clinical investigation. It will be clearly stated that the participant is free to withdraw from the clinical investigation at any time and for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider this information, and the opportunity to ask questions to the Investigator, to his/her GP or other independent parties to decide whether to participate or not. The written Informed Consent will then be obtained by means of dated signature of both the participant and the person who has presented the Informed Consent. This person must be qualified and experienced, and have been authorized to exert this role by the PI. A copy of the signed ICF will be given to the participant, while the original will be retained at the clinical investigation site.

The principal investigator shall ensure that important new information is provided to new and existing subjects throughout the clinical investigation. If new information becomes available that can significantly affect a subject's future health and medical care, that information will be provided to the subject(s) affected in written form. If relevant, all affected subjects will be asked to confirm their continuing informed consent in writing.

b. Description of the informed consent process in circumstances where the subject is unable to give it

Vulnerable subjects must not participate to this clinical investigation.

Subjects unable to understand and sign the ICF in absence of legal protection must not be enrolled in the clinical trial.


Subjects unable to read or write must not be enrolled in this clinical investigation.

18. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

a. Definitions of Adverse Events (AE) and Adverse Device Effects

The AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational device and whether anticipated or unanticipated. This definition includes also events related to the investigational device and the involved procedures.

The Adverse Device Effect (ADE) is an AE related to the use of an investigational medical device. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation or any malfunction of the investigational medical device, and any event resulting from use error or from intentional misuse of the investigational medical device.

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b. Definition of Device Deficiencies

Device deficiency is inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Device Deficiencies include malfunctions, use errors, and inadequate labelling.

c. Definitions of Serious Adverse Events, Serious Adverse Device Effects and Unanticipated Serious Adverse Device Effects

Serious Adverse Event (SAE) is an AE that led to any of the following:

- death,
- serious deterioration in the health of the subject, that either resulted in
 - o a life-threatening illness or injury, or
 - o a permanent impairment of a body structure or a body function, or
 - o hospitalization or prolongation of patient hospitalization,
 - o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
 - o chronic disease
 - o foetal distress, foetal death or a congenital physical or mental impairment or birth defect

Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE.

Serious Adverse Device Effect (SADE) is any ADE that has resulted in any of the consequences characteristics of a SAE

Unanticipated Serious Adverse Device Effect (USADE) is any SADE the nature, severity or outcome of which is not consistent with the reference safety information.

d. Time period during which the PI shall report all AEs and Device Deficiencies to the Sponsor and to ECs and the Regulatory Authorities


The PI shall report all serious and non-serious adverse events to the Sponsor immediately, but not later than 24 hours from the awareness of each event or follow up of an already reported event. It is the responsibility of the PI to inform the EC of any SAE.

The sponsor will report to the competent authority any serious incident involving devices made available on the Union market, except expected side-effects which are clearly documented in the product information and quantified in the technical documentation. Serious incidents occurring in sites located in Third Countries will be reported by the Sponsor to the Competent Authority.

e. Details of the process for reporting AEs

Any AE shall be described in the dedicated CRF that includes the following information:

- Date of procedure

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- Date of the AE
- Action or treatment and subject outcome
- Resolution
- Assessment of relationship to the procedure
- Assessment of both the seriousness and the relationship to the investigational device
- The management/notification of adverse events to the CE and CA will take place in compliance with the provisions of EU Reg. 745/2017.


f. Details of the process for reporting

Device deficiencies that might have led to a SAE are handled under the SAE reporting system. As per regulation MDR 2017/745 ART. 80, and the European guideline MDCG 2020/10, *Safety reporting in clinical investigations of medical devices under the Regulation (EU)*, the Sponsor fully records all the following aspects:

- any AE of a type identified in the clinical investigation plan as being critical to the evaluation of the results of this clinical investigation
 - any SAE
 - any device deficiency that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate
 - any new conclusion relate to any of the events reported in the previous points.
1. The sponsor will report to all NCAs where the clinical investigation is authorised to start, without delay to the Member State in which the clinical investigation is being conducted (i.e., Italy), all of the following according to the provisions of MDCG 2020/10 guideline - Safety reporting in clinical investigations of medical devices under the EU Reg. 2017/745:
- any SAE that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible
 - any device deficiency that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate
 - any new findings in relation to any event referred to in the previous points.

The Sponsor shall report all reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.

Any other reportable event will be reported by the Sponsor immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

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Causality assessment will be performed by the Sponsor and Investigators according to the provisions of MDCG 2020/10 guideline - Safety reporting in clinical investigations of medical devices under the EU Reg. 2017/745.

Each SAE will be classified according to the following levels of causality:

- Not related
- Possible
- Probable
- Causal relationship

19. VULNERABLE POPULATION

This clinical study will not be conducted on vulnerable populations.

20. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

The clinical study may be suspended or prematurely terminated by the Sponsor, PI, EC or competent authority for significant and documented reasons.

The Sponsor will consider terminating or suspending the participation of an investigator if monitoring or auditing identifies serious or repeated deviations on the part of this investigator. If suspicion of an unacceptable risk to subjects arises during this clinical study, or when so instructed by the EC or the CA, the sponsor will suspend the clinical investigation while the risk is assessed. The Sponsor will terminate the clinical investigation if an unacceptable risk is confirmed.

The Sponsor will terminate or suspend this clinical investigation in the interest of safety.


In case of suspension or premature termination, the Sponsor will inform the CA if required and ensure that the EC is notified, either by the PI or by the Sponsor. The Sponsor will remain responsible for providing resources to fulfil the obligations of the CIP and existing agreements for following up the subjects enrolled in the clinical investigation. The PI will promptly inform the enrolled subjects.

The Sponsor will conclude an analysis of the reason(s) for the suspension, will implement the necessary corrective actions. If he decides to lift the temporary suspension, the sponsor will inform the PI, the EC and where appropriate the CA of the rationale and provide them with the relevant data supporting his decision.

The clinical investigation will not resume until prior approval from EC and where appropriate CA.

The PI or his/her authorized designee will inform the subjects of the reasons for resumption, if they have been informed of the suspension.

21. PUBLICATION POLICY

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In accordance with the Declaration of Helsinki, a description of the clinical study will be registered in a publicly accessible database before the start of recruitment activities and the content will be updated throughout the conduct of the clinical study and the results entered at completion of the clinical study.

The information concerning VIVHEART's device venous catheter and scientific data supplied by the Sponsor to the Investigator and not previously published is considered confidential and remains the sole property of the Sponsor. The investigator agrees to use this information only to accomplish this study and will not use it for other purposes without Sponsor written consent. The Investigator is obliged to provide the Sponsor all data obtained in the study.

The results of the study will be reported in a Study Report generated by the Sponsor or Designee and will contain CRF data about the study. The research data will be publicly disclosed and published independent of the outcome of the study in scientific, peer-reviewed, international journals and at international conferences. The Sponsor reserves the right to analyse data for development and intellectual property purposes before public disclosure.

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