The HOVER Study
Heterotopic Implantation Of the Sapien 3 Transcatheter Aortic Valve in the Inferior VEna cava for the treatment of severe tricuspid Regurgitation

This protocol represents an original investigational device exemption (IDE) for placement of a SAPIEN-XT or S3 Transcatheter Heart Valve in the inferior vena cava for treatment of severe tricuspid regurgitation.

Physician-led US Multi-Center IDE Pilot Study - IDE: G-140131-S2

Sponsor Investigator:

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LIST OF ABBREVIATIONS

AE	Adverse Event
ACC	American College of Cardiology
ACT	Activated Clotting Time
AHA	American Heart Association
AST	Alanine Transaminase
AST	Aspartate Transaminase
BIB	Balloon in Balloon
BNP	Brain Natriuretic Peptide
BUN	Blood Urea Nitrogen
CAVI	Caval Valve Implant
CBC	Complete Blood Count
CEC	Clinical Events Committee
CKMB	Creatinine Kinase MB
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
FDA	Food and Drug Administration
Gy	Gray
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IFU	Instructions for Use
IMA	Internal Mammary Artery
INR	International Normalized Ratio
IRB	Institutional Review Board
IVC	Inferior Vena Cava
IVUS	Intravascular Ultrasound
KAP	Kerma Air Product
KCCQ	Kansas City Cardiomyopathy Questionnaire
LE	Lower extremity
LLC	Limited Liability Corporation
LMW	Low molecular weight
MELD	Model for End Stage Liver Disease
mmHg	Millimeters of mercury
MRI	Magnetic resonance imaging
NYHA	New York Heart Association
PA	Pulmonary Artery
PAH	Pulmonary Arterial Hypertension
PFT	Pulmonary Function Testing
Plt	Platelets

PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RA	Right Atrium
RV	Right Ventricle
RVEF	Right ventricular ejection fraction
SAE	Serious Adverse Events
SD	Standard Deviation
SRDL	Substantial Radiation Dose Level
STS	Society of Thoracic Surgeons
SVC	Superior Vena Cava
TAPSE	Tricuspid Annular Plane Systolic Excursion
TAVR	Transcatheter Aortic Valve Replacement
TEE	Transesophageal Echocardiogram
THV	Transcatheter Heart Valve
TIA	Transient Ischemic Attack
TR	Tricuspid Regurgitation
TTE	Transthoracic echocardiogram
TVR	Tricuspid Valve Replacement
UADE	Unanticipated Adverse Device Event
UF	Unfractionated
US	Ultrasound
VARC	Valve Academic Research Consortium
WBC	White Blood Cell Count
WHO	World Health Organization
6MWT	6-Minute Walk Test

Statement of Investigator

This statement is required to comply with the Investigational Device Exemption regulations contained in the 21CFRR 812.43(c)

Study Title: The HOVER Study: Heterotopic Implantation Of the Sapien 3 Transcatheter Aortic Valve in the Inferior VEna cava for the treatment of severe tricuspid Regurgitation

Protocol Number: v2.3 24 Apr 2020

Investigator Name:

Institution Name:

Address:

Telephone Number:

Email:

I have read and understood the Clinical Investigational Plan and agree to participate in this trial and provide to the Sponsor the required information.

I certify that I am a(n) _____ __ (insert medical specialty) qualified by training and experience to conduct this trial. As evidence of my training and experience, I will provide the Sponsor with a signed and dated copy of my curriculum vitae.

I was ____/ I was not ____ involved in an investigation or other research in which my participation was terminated by a Sponsor, IRB/IEC or FDA. (If I was, an explanation of the circumstances that led to termination is attached to this Agreement.)

☐I agree to conduct the investigation in accordance with the agreement, the investigational plan, Code of Federal Regulations Title 21, Parts 50, 56 and 812, and the conditions of approval imposed by the reviewing IRB and FDA.

☐(For Principal Investigators only) I agree to supervise the handling of the device and its use involving human subjects;

☐N/A (not site Principal Investigator)

☐I agree to ensure that the requirements for obtaining informed consent are met.

☐I agree to allow the Sponsor (or approved representative) to monitor the progress of the clinical investigation through the review of subject source documentation and study records.

Signature:_____ Date:_____

HOVER PROTOCOL SUMMARY

Title:	The HOVER Study: Heterotopic Implantation Of the Sapien 3 Transcatheter Aortic Valve in the Inferior VEna cava for the treatment of severe tricuspid Regurgitation
Design:	This is a prospective multi-center, non-blinded (open label), non-randomized safety and feasibility study of the heterotopic implantation of the Sapien 3 valve in the inferior vena cava for the treatment of severe tricuspid regurgitation in patients who are inoperable or at a very high surgical risk for tricuspid valve replacement. A total of 15 patients will undergo implantation. Primary endpoints will be assessed at 30-days and 6-months. This study is an off-label use of an FDA-approved and commercially available medical device.
Study Objectives:	#1: Determine the short term safety (<30 days) of Caval Valve Implant (CAVI) #2: Determine the intermediate term (6 months) efficacy of CAVI on palliation of patient symptoms of right heart congestion.
Primary Endpoints:	#1: Safety as defined by successful vascular access without unplanned major vascular complication as defined by VARC-2, delivery and retrieval of the transcatheter valve delivery system, correct position of both the vascular stent(s) and transcatheter valve in the IVC, a single valve placed within the IVC, and no need for additional surgery or re-intervention (including drainage of pericardial effusion) with the patient being alive at 30-days. #2: Efficacy as defined by Improvement of KCCQ score >15, or improvement in 6-minute walk test (6MWT)>70 meters or improvement of greater than 6% of peak Vo2 in cardiopulmonary exercise testing.
Population:	Patients with severe symptoms (NYHA class III-IV) and signs of peripheral and venous congestion (specifically lower extremity edema and abdominal ascites requiring diuretics), resulting from documented severe tricuspid regurgitation. These patients may benefit from tricuspid valve repair or replacement, but are believed to be at high risk or are deemed inoperable for standard tricuspid valve surgery as assessed by at least one cardiac surgeon.
Phase:	1-2
Clinical Sites:	1. Henry Ford Hospital, Detroit, Michigan – site PI: Dr. Brian O'Neill (Coordinating Center) 2. Temple University Hospital, Philadelphia, Pennsylvania – site PI: Vladimir Lakhter, DO 3. University of California San Francisco, San Francisco, California – site PI: Dr. Vaikom Mahadevan 4. Baptist Hospital of Miami, Miami, FL – site PI: Dr. Ramon Quasada

Statement: This protocol represents an original investigational device exemption (IDE) for placement of a SAPIEN XT or S3 Transcatheter Aortic Heart Valve in the inferior vena cava for treatment of severe tricuspid regurgitation.

Study Duration: 84 months from start of enrollment to completion of follow up

Participant Duration: 60 months

Sponsor Investigator and overall PI:

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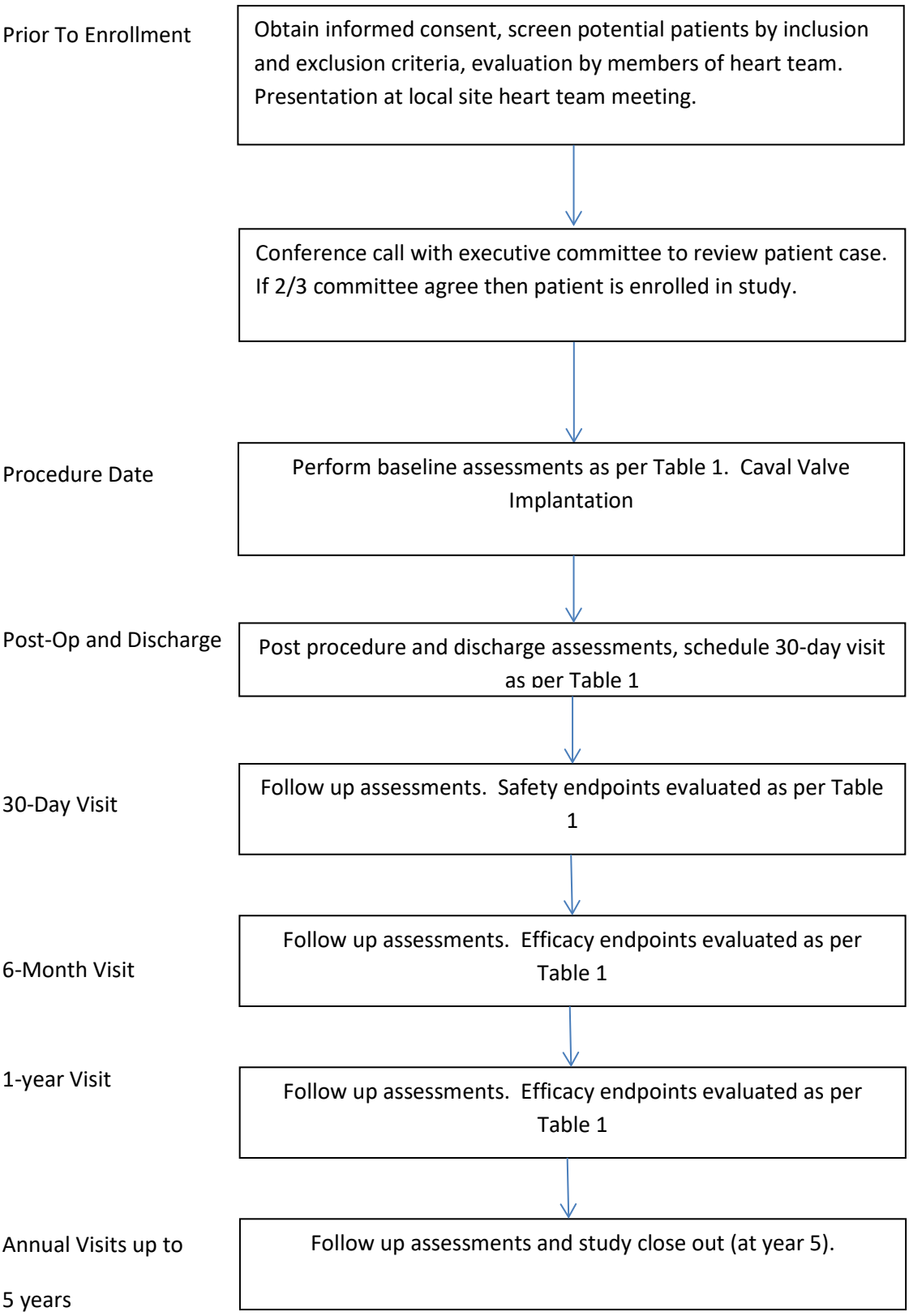
Pre-Submission Meetings: The concept of this study was initially proposed to the structural heart disease branch of the FDA in a conference call on 4/4/2014. After that call a preliminary protocol was submitted for review to Changfu Wu on 4/24/2014. Feedback for the initial protocol was provided on 4/28/2014 by the FDA. Additional correspondence was received and on January 08, 2016 the FDA approved the updated protocol to include: 1. The use of either the Sapien XT or the Sapien S3 valve and 2. Expansion of the study to the 4 additional sites.

SCHEMATIC OF STUDY DESIGN



1.0 BACKGROUND

Severe tricuspid regurgitation (TR) is an under treated disease state associated with significant morbidity and mortality. Nath and colleagues showed a 1-year mortality of 33.1% in patients diagnosed with severe tricuspid regurgitation[1]. In the United States alone, 1,600,000 patients are diagnosed with severe tricuspid regurgitation each year, while only 8,000 (less than 1%) are treated with tricuspid valve surgery[2]. The reasons for this are varied, however, many of these patients who are not treated go on to exhibit signs of central and peripheral venous congestion, including irreversible hepatic cirrhosis and chronic kidney disease. This creates a vicious spiral, in which those patients who are initially good operative candidates may become high risk or inoperable for conventional tricuspid valve surgery. Additional therapeutic options are therefore needed for these patients and their treating physicians.

Currently, there are no specifically designed devices for the transcatheter treatment of tricuspid valve disease. As a result, the treatment of these patients to date has relied on the off-label use of transcatheter aortic valve technology. Multiple case reports have shown the feasibility of percutaneous transcatheter aortic valve impantation within degenerated tricuspid valve bioprostheses or "valve-in-valve" [3,4]. The experience is less robust for transcatheter tricuspid replacement within a native tricuspid valve[5] and is likely limited in part to the annular dilatation which is present in patients with severe TR[6]. Despite this promising experience with transcatheter aortic valve placement directly within the tricuspid valve, long term data is lacking, and recent reports have demonstrated early valve failure in patients using this technique[7].

Recently, caval valve implant of the Edwards Sapien Transcatheter valve for treatment of severe tricuspid regurgitation has shown promise as an additional therapy for patients with severe TR who are high risk or inoperable. Placement of a valve in the right atrial (RA)/caval junction would in theory prevent the massive reflux of blood into the IVC, thereby protecting the hepatic, renal, and lower extremity veins from volume overload. Santhanakrishnan and colleagues evaluated the effects of placing a unidirectional valve in the IVC in a bench model simulating a Fontan procedure, in which the SVC and IVC are directly anastomosed to the right and left pulmonary artery in those patients with one ventricle. Although short term effects of this procedure are favorable, long term patients go on to develop elevation in the systemic venous pressure from retrograde flow in expiration, particularly to the hepatic veins. In their study, the authors created a flexible wall model to simulate the IVC/SVC/PA connections. Using a Medtronic melody valve placed in the IVC in a sub-diaphragmatic position, they demonstrated a significant decrease in hepatic venous pressure through 20% of the cardiac cycle, with minimal gradient across the valve. They concluded this therapy may have potential for lowering hepatic venous pressure by arresting retrograde flow occurring in the IVC [8].

The first in-vivo animal experience of this procedure was by Corno and colleagues in 2003[9]. In their study, bovine jugular xenografts were mounted on self-expanding nitinol stents and placed in the IVC of 5 adult pigs. Animals were anesthetized and the diameter and length of the IVC was measured using Intravascular ultrasound (IVUS). After placement of the valve, pressures were measured proximal and distal to assess for any gradients. IVUS showed partial opening and closing of the valve, with complete closure occurring during deep breaths. Autopsy showed adequate positioning of the valve stent without any deformation, with the proximal most portion of the valve 2cm proximal to the right atrial junction without any deformation of the valved stent. Sochmann et al performed twin valve caval stenting in a series of studies of three sheep and one swine. In their series, severe TR and reflux into the SVC and IVC was induced through papillary muscle avulsion in sheep, while the swine served as a control. Self-designed stents were placed in the caval veins through a 12-French sheath. 5-French pigtail catheters

were introduced into the femoral and jugular veins so that bicaval venography could be performed. In the swine, the valve functioned well for 3 hours without a position change and remained stable on necropsy. In 3 sheep, after placement of the stents, right ventricular (RV) angiography demonstrated retrograde filling of the SVC and IVC to the valves but not beyond[10]. At necropsy, the valve position remained stable.

Contemporary animal models have confirmed and expounded on these early results. Lauten and colleagues created acute severe TR in a sheep model via papillary muscle and chordae avulsion[11]. Successful creation of TR was verified by a prominent ventricular (v) wave which was present in the central venous pressure tracing. Self-expanding nitinol stents containing a porcine pulmonary valve were placed in the superior vena cava (SVC) and inferior vena cava (IVC). In both an acute group (n=9) and chronic group (n=4), a significant decrease in the v-wave was demonstrated post-implant with an accompanying increase in cardiac output. At autopsy in the chronic group, the stents were covered with fibrous tissue and adhered strongly to the vessel wall. In one animal in the acute group, the SVC valve embolized into the right atrium with resultant hemodynamic instability. This did not cause immediate death. Autopsy showed correct device position in all successfully treated animals.

The effectiveness of this therapy in animals has also translated to humans. In the first-in-man report, a 79 year old woman with a history of severe TR who was declined for traditional tricuspid valve surgery had been experiencing worsening symptoms of right ventricular (RV) congestion for several years. After institutional review board (IRB) approval the patient underwent the procedure. Reflux into the caval and hepatic veins were confirmed by angiography. After careful position guiding by fluoroscopy and echocardiography, the valve, a self-made nitinol stent frame porcine pericardial valve, was placed in the IVC. Transesophagehal echo (TEE) performed immediately after the procedure and repeated every 2 weeks demonstrated stable position and valve function. At 8 weeks of follow-up, CT-angiogram confirmed the absence of regurgitation into the IVC. The patient had clinical improvements in New York Heart Association Functional Class (NYHA), and improvement in both peripheral edema and ascites. Sadly, 3 months later, the patient was admitted with an intracranial hemorrhage and expired. Autopsy revealed stable position of the valve, with fibrous tissue covering the valve helping to anchor it in position [12]. The same authors describe a second case of an 83 year-old woman with severe TR also with symptoms of chronic right heart failure. Caval valve implant was performed as part of a compassionate treatment. Valves were again individually designed with the upper segment of the IVC valve to lay in the right atrium above the diaphragm to avoid backflow into the IVC, with a funnel shape to the SVC valve. After deployment of both valves, both the IVC and SVC mean pressures decreased with a stable mean right atrial (RA) pressure. Clinical follow up of the patient demonstrated complete resolution of ascites and peripheral edema, with normalization of synthetic liver function. Echo and CT confirmed stable valve position without paravalvular regurgitation[13]. In the largest series to date, Laule et al report on three patients who underwent caval valve implant for severe TR. Each of these patients had recurrent right heart failure despite optimal medical therapy. 2 of these patients underwent stenting to the IVC alone. These investigators employed a novel technique of pre-stenting the IVC with placement of an Edwards-Sapien XT (29mm) valve within the stent. Follow up at 30-days showed no adverse events according to valve academic research consortium criterium (VARC). In addition, all patients improved by at least 1 NYHA class, symptoms of right heart congestion, and improvements in indices of RV function. Longer term follow up of these patients is forthcoming.

An unanswered question with this technique is the effects of redirection of blood flow from the IVC to the right atrium, and the clinical impact on increased volume load do the right atrium and SVC.

The initial animal studies by Lauten demonstrated an increase in RA pressure with the creation of severe TR, with minimal increases in RA pressure after the implantation of the IVC valve [11]. In addition, there were increases in cardiac output noted. In the 12-Month follow up of a patient undergoing bicaval valve implant, RA pressure was noted to decrease from 21-16mmHG at 3-month follow up [13]. This suggests a chronic decrease in right ventricular volume load from effective diuresis of the patient, as demonstrated by a 9kg body weight loss the patient was noted to have at follow-up. These findings are also demonstrated in follow up from a patient in the HOVER trial. In this patient, mean RA pressure was noted to decrease from 12-10mmHG immediately post-implantation. At 6-month follow up there was a further decrease in mean RA pressure noted to 5mmHg[14]. These decreases in RA pressures were again accompanied by increasing cardiac output. Although these observations will require further study, these reports suggest that this re-directed flow is well tolerated by the right heart, and may improve overall hemodynamics through diuresis and augmentation of cardiac output. We hope to evaluate the effects of this, as well as clinical improvement in symptoms of right heart congestion with this study.

2.0 PROJECT PLAN

2.1 Rationale for Study

Severe TR is characterized by right heart congestion and volume overload[15]. Non-surgical treatment for TR relies on the administration of increasing doses of diuretic therapy to promote diuresis and volume contraction. However, many patients go on to become refractory to chronic diuretics over time. This is in part to the effects on chronic right heart congestion on the kidney. Based on previous studies, we believe that protection of the hepatic and renal veins with a one-way valve from the transmitted TR will allow for continued diuresis, and improvement in symptoms. Although CAVI has shown improvements in right heart congestion in a small series of patients, several questions remain. Previous studies have not clearly excluded TR that can occur with pulmonary arterial hypertension (PAH.) As 2/3 of the regurgitant flow from tricuspid regurgitation is directed to the IVC, the effects of redirection of this flow to the SVC are unknown. The degree of TR can be sensitive to changes in pre-load. It remains unclear if improvement in right heart congestion may therefore also affect degree of TR and indices of right ventricular (RV) function. Finally, the durability of the procedure beyond the intermediate term (6 months) is not well characterized. To help clarify these issues, we have created the Heterotopic Implantation Of the Edwards Sapien 3 Transcatheter Aortic Valve in the Inferior VEna cava for the treatment of severe Tricuspid Regurgitation study.

2.2 Design:

This is a prospective multi-center, non-blinded (open label), non-randomized safety and feasibility study of the heterotopic implantation of the Edwards Sapien 3 valve in the inferior vena cava for the treatment of severe tricuspid regurgitation in patients who are inoperable or at a very high surgical risk for tricuspid valve replacement. Patients enrolled will have severe TR and cardiac symptoms of right heart congestion in whom conventional tricuspid valve surgery (TVR) would be associated with high risk. Severe TR is defined by a vena contracta width > 7mm OR evidence of systolic hepatic vein flow reversal OR visible tricuspid valve coaptation defect + dense/triangular continuous wave with early peaking as assessed by continuous wave signal AND a very large central jet or eccentric wall impinging jet as assessed by color flow. [16]. All patients must be on diuretics with documented evidence of continued venous congestion, such as lower extremity or abdominal wall edema.

All patients will be evaluated by at least one cardiac surgeon. The cardiac surgeon must agree that based on his assessment the patient is high risk or inoperable for TVR as per the surgical office note and attached (appendix E). Most inoperable patients have elevated STS risk scores including one or more STS risk elements that exceed thresholds considered safe for operation. A common example is respiratory disease, for which the STS risk-scoring threshold usually signals increased risk in operable patients, but which may be severe enough in a given patient to explain inoperability. In trials of TAVR, oxygen dependency in particular, has been independently associated with increased one-year mortality [17]. Other "inoperable" patients, regardless of STS score, are rendered inoperable by severe co-morbidities of the low-prevalence, high-heterogeneity variety that are difficult to represent statistically and are not part of the STS risk model. Common examples include liver disease, porcelain aorta, chest wall abnormalities, and frailty. Chest wall abnormalities may include prior chest irradiation, a graft close to the sternum, or an absent or reconstructed sternum [18,19]. It must be acknowledged that "inoperable" is frequently an integration of multiple dimensions of an individual patient in whom no simple, single-factor quantifiable line can be drawn between operable and "inoperable." Factors which make a patient high risk or inoperable will be clearly de-lineated in the patient's surgical evaluation. The "operable" patient will have characteristics which include a normal RVEF, normal creatinine, no previous open heart surgeries, preserved left ventricular ejection fraction. As the STS is undefined for these patients, should a patient have no other characteristics which make them high risk, an STS score for a simulated mitral valve procedure of <5 can also be considered in declaring a patient operable.

2.2.1 Definition of the Heart Team

When a potential subject is identified in the clinical practice of a participating site, the subject will be referred to the site heart team. The goal of the heart team is to optimize patient selection and improve procedural success. Originally intended for transcatheter aortic valve replacement (TAVR) decision making, the concept of the heart team has expanded to involve patients with structural or complex coronary artery disease in whom the participation of multiple physicians from differing areas of expertise is beneficial [20 21]. Ideally, this team is comprised of an interventional cardiologist and cardiac surgeon at the core, with other expertise from advanced imaging, cardiac anesthesia, and heart failure as important adjuncts. Patients are seen individually by physicians, or, as part of a dedicated visit to multiple specialties in the form of a valve "clinic." After patients are evaluated, the members of the heart team will discuss the patient's case at a weekly conference. Here, a patient's clinical history and clinical data are reviewed, and a group recommendation is made. If after evaluation by an interventional cardiologist, heart failure specialist, and cardiac surgeon, as well as presentation at the local heart team conference, a patient is deemed a suitable candidate for the trial, they will be presented to the executive committee of the trial. The credentialing of heart team members will be the responsibility of the local heart team site.

2.2.2 Core Lab

Either concomitantly or after decision by the local heart site to presentation to the executive committee, baseline echocardiograms and CT scans will be reviewed by the coordinating center (Henry Ford Hospital) to confirm severe TR and anatomic suitability for implant.

2.2.3 The Executive Committee

The purpose of presentation of patients to the executive committee is to provide additional consultation from experts to further review and approve the selection prior to the patient being enrolled in the trial. The executive team will be comprised of the site PI from each site. The presentation will occur in the form of a conference call which is open to any member of the individual sites included in the HOVER trial. During the executive committee conference call, the local site will verify that the patient meets the

inclusion, and is free from exclusion criteria for the trial. The local site will present the patient's case for committee review. Any questions the executive committee may have regarding the case will be addressed during this call. If after the case presentation, 2/3 of the executive committee agree the patient is suitable for CAVI, the patient will be enrolled in the trial and an implantation date will be set. Documentation of approval for the trial of the patient by the executive committee will be added to the patient's chart. If all members of the executive committee are unable to convene on one conference call, the case will be presented individually to members of the committee in separate phone calls.

2.2.4 Use of Edwards-Sapien Transcatheter Valve

This trial represents the off-label use of an approved medical device. The on-label indications are as follows:

The Edwards SAPIEN 3 transcatheter heart valve (THV), model 9600TFX, and accessories are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy.

2.3 Statistical Analysis

A total of up to 15 patients will be enrolled. Due to the lack of preliminary data as well as exploratory nature of the study, no sample size and power analyses were performed. We expect to screen approximately 45 patients to enroll up to 15 eligible patients into this trial.

All clinically relevant baseline and follow-up data will be tabulated. Means (SDs), medians (ranges), and 95% confidence intervals will be reported for continuous variables and frequencies, percentages, and 95% confidence intervals for categorical variables. Specifically, each of the two primary endpoints (the procedural success at 30-days and the composite binary response variable at 6-months) will be summarized using both a point estimate and its exact confidence interval based on a binomial distribution. Other binary safety and efficacy secondary endpoints will be analyzed similarly. Continuous secondary endpoints (e.g., hemodynamics data) will be reported using descriptive summary statistics as well as a point estimate and its confidence interval based on a normal distribution assumption. The changes from baseline to each follow-up timepoint will additionally be evaluated using the McNemar matched pairs test for dichotomous variables and the t-test for continuous variables. In the presence of distributional non-normality, the Wilcoxon signed rank test will be used instead of the t-test. Data transformations such as log or square-root may also be considered. The analyses of NYHA functional classification will involve comparison of the baseline and post-operative (at each timepoint) functional class and determination of the percentages of patients improving, not changing, or worsening at each postoperative timepoint. The same principle will be applied to quality of life score (KCCQ) and 6-minute walk distance. Although this is an exploratory analysis, we anticipate 50% of patients will demonstrate improvement in one of the three pre-specified components of the primary efficacy outcome.

The time-to-event approach may be considered to analyze some of safety and efficacy endpoints (e.g., time to treatment failure, event-free survival, and overall survival) while taking censoring into account in data analyses. Such endpoints will be summarized using the Kaplan-Meier method. Confidence intervals for the medians and survival rates at different time points will be constructed, when appropriate. For a continuous endpoint measured repeatedly over time, a mixed-effects regression model may be employed to study its over-time trajectory or change patterns. All these results will be reported descriptively.

The intent-to-treat approach will be used for data analyses of this trial. That means all enrolled patients will be included in the interim and final data analyses regardless of their eligibility or subsequent events. Patients who are lost to follow-up or drop out of study prior to their scheduled follow-up evaluation time due to any reason will be treated as a treatment failure for response determination and censored for time-to-event type of endpoints at the time of their last follow-up if no relevant event has occurred by then. A secondary analysis that includes only all eligible patients may be conducted in addition to the primary analysis described above at the discretion of the trial PI and study biostatistician. However, such analysis may not serve as the basis for drawing conclusions concerning treatment safety or efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

All enrolled patients will be evaluable for adverse events from the time of their protocol treatment. Adverse events will be tabulated by type and severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

During the entire study period, adverse events will be closely monitored by the trial PI and clinical trial coordinator of this study, working along with the study DSMB. In particular, formal stopping rules on the 6-month mortality are stipulated in this protocol (please refer to section 4.1 "Efforts to minimize procedure risks"). In addition, in the event that other adverse events (e.g., surgical complications) are thought to be excessive for the study patient population at any point of the trial, the patient accrual to the trial will be suspended immediately, pending a review of all adverse events data. A final decision will be made by the trial PI and DSMB as to whether the trial should be amended, terminated or continue accrual. Such decision should be filed with and pre-approved by the institutional IRB.

2.4 Study Endpoints:

The primary safety endpoint is procedural success at 30-days. Procedural success will include:

- Successful vascular access without unplanned major vascular complication as defined by VARC-2, delivery and retrieval of the transcatheter valve delivery system, correct position of both the vascular stent(s) and transcatheter valve in the IVC, a single valve placed within the IVC, and no need for additional surgery or re-intervention (including drainage of pericardial effusion) with the patient being alive at 30-days.

The primary efficacy endpoint will be improvement in one of three variables assessed from baseline to 6-months.

- Improvement of KCCQ score >15. This has been shown to correlate with improvement in quality of life with heart failure patients[22].
- Improvement in 6-minute walk test (6MWT)>70 meters. This has been shown to provide prognostic information in patients with congestive heart failure after an intervention[23].
- Improvement of greater than 6% of peak Vo2 in cardiopulmonary exercise testing. In a heart failure population, this has been shown to help assess prognosis in patients who were instituted in an exercise program [24].

Secondary endpoints will be evaluated at several timepoints and will be divided into safety and efficacy: The first in the acute setting which will be out to 30 days or hospital discharge whichever being longer; additional time points will be at midterm (6 months post-procedure), long term (1 year and annually up to 5-years post-procedurally.)

Secondary safety endpoints include:

- All stroke and TIA (VARC-2)
- Mortality (VARC-2)
- Myocardial infarction (VARC-2)
- Acute Kidney Injury (VARC-2)
- Major Vascular Complication (VARC-2)

Secondary efficacy endpoints include:

- Assessment of improvement of LE edema by the Villalta Score[25]. A 3.1 point improvement in this scale was associated with improved quality of life[26].

Besides the above formal secondary endpoints, we will monitor for the following throughout the trial:

- Deep Vein/IVC thrombosis or pulmonary embolism
- Improvement in grades of tricuspid regurgitation as assessed by echocardiogram
- Changes in TAPSE by echocardiogram for RV function
- Pleural effusions
- Additional quality questionnaires to assess for changes in ascites (EORTC QLQ-C30 [27] and ESAS-AM [28]). A 10-point change in mean score in the QLQ-C30 has been shown to be a meaningful response (O'Connor R. Measuring Quality of Life in Health Churchill Livingstone: Philadelphia; 2004). A decrease of 1.25 points in the ESAS-AM has been shown to correlate with symptom improvement after paracentesis[28].

3.0 STUDY ENROLLMENT AND WITHDRAWAL

3.1. Baseline

The screening phase of the trial is designed to meet two objectives:

1. Patient Consent.
2. Determine study patient eligibility and access site for the procedure.

3.2. Informed Consent

Informed Consent will be obtained from all prospective subjects prior to beginning any study activities. All aspects of the trial including that participation is voluntary, will be explained and the patient will have the opportunity to have their questions answered before deciding whether to participate. Patients who agree to participate and sign the informed consent document will be given a copy of their signed consent to take home with them.

Upon completion of the screening process, the patient's case will be presented to the site heart team. If after presentation to the site heart team it is agreed by the members the patient is a suitable candidate, the patient will be presented to the executive committee of the trial. If after the conference call 2/3 of the executive committee members agree, the patient is enrolled in the trial.

3.3 Eligibility Process

All patients with severe tricuspid regurgitation and symptoms who are high risk or inoperable will be screened for study inclusion. Patients must have all inclusion criteria, and be free from all exclusion criteria. Screening and enrollment logs will be maintained. Reasons for screen failures will be documented. The full description and timing of screening tests can be found in Table 1.

3.4 Participant Inclusion Criteria:
In order to be eligible to participate in this study, an individual must meet all of the following criteria
1. Patients must be at least 21 years old.
2. The patient must have severe, symptomatic (ACC/AHA Stage D symptoms) tricuspid regurgitation (TR) as assessed by 2D echocardiogram with evidence of peripheral and central venous congestion (specifically lower extremity edema and abdominal ascites requiring diuretics.)
3. The patient must be evaluated by a "heart team" of physicians including an interventional cardiologist, cardiothoracic surgeon, heart failure specialist, and imaging specialist, and presented for review at a local multi-disciplinary conference. By consensus, the heart team must agree (and verify in the case review process) that valve implantation will likely benefit the patient.
4. The heart team must agree that medical factors preclude operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Also, other factors which may increase the patients perceived surgical risk for inclusion in the trial will be clearly delineated if they are present. These include, but are not limited to the following as defined by VARC 2: Frailty, Hostile chest, porcelain aorta, IMA or other critical conduit crossing the midline or adherent to the posterior table of sternum, severe right ventricular (RV) dysfunction. The surgeons' consultation notes shall specify the medical or anatomic factors leading to that conclusion. At least one of the cardiac surgeon assessors must have interviewed and examined the patient.
5. The study patient provides informed consent and agrees to comply with all required post-procedure follow-up visits, including annual visits up to 5 years.
6. Mean diameter of the IVC at the right atrial junction or superior most hepatic vein ≤30.5mm

3.5 Participant Exclusion Criteria:
Patient or Subject will be excluded from the study if any of the following conditions are present:
1. Heart Team assessment of operability (the heart team considers the patient to be a good surgical candidate).
2. Evidence of an acute myocardial infarction ≤ 1 month (30 days) before the intended treatment [defined as: Q wave MI, or non-Q wave MI with total CK elevation of CK-MB ≥ twice normal in the presence of MB elevation and/or troponin level elevation (WHO definition)].
3. Untreated, severe, left sided valvular heart disease including mitral regurgitation or stenosis, and aortic regurgitation or stenosis.
4. Mean pulmonary artery pressures ≥40mmHG and PVR >4 woods units as assessed by right heart catheterization.
5. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure. Examples of permanent implant would include any new heart valve. Implantation of a permanent pacemaker is excluded.
6. Patients with planned concomitant surgical or transcatheter ablation for Atrial Fibrillation.
7. Leukopenia (WBC < 3000 cell/mL), acute anemia (Hgb < 9 g/dL), Thrombocytopenia (Plt < 50,000 cell/mL).
8. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of screening evaluation.
9. Need for emergency surgery for any reason.
10. Left ventricular ejection fraction <40%.
11. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
12. Active upper GI bleeding within 3 months (90 days) prior to procedure.
13. A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure.

14. Recent CVA clinically confirmed (by neurologist) or neuroimaging confirmed stroke or transient ischemic attack (TIA) within 6 months (180 days) of the procedure.
15. Estimated life expectancy < 1 year from conditions other than TR.
16. Expectation that patient will not improve despite treatment of tricuspid regurgitation
17. Currently participating in another investigational cardiac device study or any other clinical trial, including drugs or biologics. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.
18. Active bacterial endocarditis within 6 months (180 days) of procedure.
19. Patients with signs or symptoms of SVC syndrome, or hepatic cirrhosis not felt due to passive congestion from TR.
20: Subject unable to personally provide informed consent
21. FEV1<30% of predicted[29]
22. Model for End State Liver Disease (MELD) score ≥21 (calculated per reference study [30]) for patients not on blood thinners

4.0 RISK AND BENEFIT ANALYSIS

There are potential risks associated with transcatheter heart valve implantation. There are risks related to the overall procedures (complications associated with standard cardiac catheterization which include bleeding, infection, stroke, death, cardiac arrest, pacemaker implantation, allergic reactions, emergency open heart surgery, and emergency blood transfusion, prolonged hospital stay, renal failure, groin lymphocele, limb ischemia, myocardial infarction, injury to adjacent structures including nerves, blood vessels, or other structures.) In addition, there are also risks associated with the valve itself which include valve embolization and/or migration and the emergent need for open heart surgery and possibly death, as well as valve thrombosis which can lead to death, stroke, pulmonary embolism, or venous thrombosis. Structural valve deterioration may also occur in the form of wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis.

There are risks associated with stenting of the IVC for valve implantation. These include migration of the stent and injury to the vessels of the heart or the heart itself, as well as venous thrombosis and stroke. Although these risks are present, the potential of a new therapy which improves the quality of life in those patients who are otherwise ineligible for surgery outweighs these potential risks.

Pleural effusions may occur either immediately post-operatively, or at follow up. It is recommended that a trial of diuretic therapy, as well as attempts at diagnosis of the effusion (exudative vs. transudative) be attempted if the patient becomes symptomatic. If diuretic therapy fails, a thoracentesis should be considered for symptomatic relief. If the effusion reoccurs, additional thoracenteses may be considered. Alternatively, the placement of a permanent drainage catheter, or pleuredesis may be another option in patients with continued fluid accumulation who remain symptomatic.

4.1 Efforts to minimize procedure risks

Efforts to minimize procedural risks will be addressed in the following manner.

4.1.1. Site Heart Team and Executive Committee Presentation

All possible patients will be presented at a site heart team conference. There the data will be reviewed, including any aspects which may or may not affect the possible success of the procedure. After this step, patients will be presented to a panel of experienced operators outside of the local heart team institution, the executive committee. There, the data will be reviewed a second time prior to enrollment in the trial.

4.1.2. Data Safety Monitoring Board (DSMB)

A DMSB will be established. The DSMB is independent from the Sponsor, the investigators, or anyone involved in the medical care of the study subjects. Members will not have scientific, financial, or other conflict of interest related to the Sponsor or the investigators. The committee will be selected by the overall Principal Investigator and managed independently.

The members must have the following characteristics:

- working professionally as physicians or statisticians;
- at least one member with specific expertise in cardiothoracic surgery clinical trials;
- no relevant conflicts of interest;
- they will not be involved in the conduct of this trial in any other capacity, such as principal investigators, sub-principal investigators;
- they will not be engaged in any simultaneously occurring competitive trials;
- they should not be on the NIDPOE or debarred list of investigators.

Members will not serve on the DSMB, Clinical Event Adjudication Committee (CEC) or Operating Committee of a competing device trial. Members will not have any affiliation with the core laboratories, the data coordinating center, or the principal investigator of the trial. The DSMB committee will review all safety data from the HOVER Trial and make recommendations based upon the safety analyses. The frequency of the DSMB meetings will be determined prior to study commencement; however, the DSMB may call a meeting at any time if there is reason to suspect safety is an issue. DSMB oversight for this trial is expected to be rigorous with frequent review of all essential safety data. The DSMB chairperson will notify the principal investigator of any safety or compliance issues. They will also provide confidential recommendations, when necessary, of study termination. All DSMB reports will remain strictly confidential, but will be made available to regulatory authorities. The principal investigator will notify the FDA if any member of the DSMB advises to terminate the study due to safety concerns.

4.1.3. Interim Monitoring and Stopping Rules

The interim monitoring and stopping rules will focus on the 6-month mortality. Based on current literature, it is reasonable to assume a 6-month mortality of at least 30% for the high risk patients targeted in this clinical trial [31]. For the purpose of this trial, we will focus on device-related mortality.

The interim monitoring will be implemented with stopping rules when 3, 6, and 9 patients have been enrolled and treated with the protocol device. The proposed stopping rules are:

Number of patients on trial:	When number of 6-month deaths $\geq$:	Probability of stopping the trial early when the true 6-month mortality is 30%:
3	2	0.216
6	3	0.105
9	4	0.064
15	6	0.064

As it can be seen from the above table, the probability of stopping the trial early is very small (≤10.5%) assuming the true 6-month mortality rate is no more than 30% when there are at least 6 patients

enrolled and treated on the clinical trial. When there are only 3 patients enrolled, we are only stopping the trial early when two (or more) out of the first three patients died within 6 months on trial due to a device-related death. This probability is reasonably small as well (21.6%).
In addition to mortality, should valve thrombosis occur in ≥30% of patients at 6-months, the trial will be paused to evaluate if any additional precautions are required.

The trial PI (Dr. Brian O'Neill, MD), working along with the study DSMB, will monitor other safety parameters such as significant surgery complications, one-year mortality, overall survival, and event-free survival at least biannually (every 6 months) as well in an effort to make certain that the patients on trial are not inadvertently harmed by the proposed protocol treatment.

4.2 Potential Benefits

Implantation of the transcatheter heart valve into the IVC may have immediate and long term benefits. In the immediate term, patients may notice stability to the amount of edema they have in their abdomen and legs. In the long term, with protection of the renal veins from the TR, patients may notice improvement in central and peripheral venous congestion, improvement in end organ function including liver and kidneys, and improvement in overall quality of life.

5.0 STUDY PROCEDURES AND SCHEDULE

The study procedures and schedule are listed below. If patients are unable to perform examinations for any reason, justification of this must be provided by the study site PI.

5.1 Pre-Procedure Assessments

The following will be collected in all patients at baseline (within 90 days of procedure, except for Informed Consent which will be obtained prior to beginning screening). Items in bold font are required to determine eligibility and must be performed prior to the Heart Team and Executive Committee meetings.

- **Informed Consent**
- **Medical history**. This will include past medical and surgical history, social history, family history.
- **Physical Exam**. This will include vital signs and weight, head, ears, eyes, nose and throat (HEENT), neck, lungs, cardiovascular, abdomen, genitourinary, gastrointestinal, musculoskeletal, neurological
- **NYHA functional Class** as per 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; 1994:253-256
- **Diuretic types and doses**
- Surgical note documenting high risk/inoperable status.

Laboratory Measurements

- CBC with differential (During 6 months of screening and within 21 days of procedure)
- Cardiac Enzymes (Troponin I and/or CK and CKMB) (≤72 hours before the procedure)
- **Comprehensive metabolic panel** (within 90 days of procedure)
- Lactate Dehydrogenase (LDH)
- ACT (within 21 days of procedure)
- aPTT (within 21 days of procedure)
- **PT/INR** (within 90 days of procedure)
- Brain Natriuretic Peptide (BNP) (within 21 days of procedure)

Non-Invasive Tests

- ECG (within 21 days of procedure)
- Chest X-ray (portable or PA and lateral) (within 21 days of procedure)
- **Echocardiogram** (Transthoracic) (within 90 days of procedure)
- **Chest and Abdominal CT** (within 90 days of procedure)
- Cardiopulmonary Exercise Stress test [32] (within 90 days of procedure)
- Venous Lower Extremity Duplex Study (within 21 days of procedure)
- **Pulmonary Function Testing** (PFT) (within 90 days of procedure)

Functional Assessments

- 6-minute walk test [33] (within 90 days of procedure)
- Villalta Scale [25,26] (within 21 days of procedure)
- EORTC QLQ-C30 [27] (within 21 days of procedure)
- ESAS-AM [28] (within 21 days of procedure)
- Kansas City Cardiomyopathy Questionnaire (KCCQ) [22] (within 21 days of procedure)

Invasive Tests

- **Left Heart Catheterization with or without LV gram and IVUS**. (Within one year of baseline)
- **Right Heart Catheterization** (within 90 days of procedure)

5.2 PROCEDURE Description

Procedure Assessments
The following tests and assessments will be performed on the day of or during the procedure:
Total procedure time is defined as the time from skin incision to the time of skin incision access closure.
The following invasive hemodynamic data must be collected pre and post implant:

- Echo assessments of severity of tricuspid regurgitation and RV function
- Fluoroscopic imaging of the implanted valve
- Medications given for cardiovascular effect including anti-platelet/anti-thrombins
- Event assessment

5.2.1 Placement of percutaneous aortic valve in the inferior vena cava

The procedure will be performed in the cath lab/ hybrid Cath Lab/OR under general anesthesia and transesophageal echocardiographic as well as fluoroscopic guidance.

Measurements obtained prior to the procedure
The diameter of the IVC at the RA/IVC junction will be measured prior to the procedure by contrast CT or rotational cine fluoroscopy to determine sizing of the stent which will be placed in the IVC. In order to avoid compromise of the hepatic veins with the valve skirt, distances from the RA/IVC junction to the hepatic veins will be measured by contrast CT.

Procedure
The procedure will be performed through the right or left femoral vein using standard technique. We will use fluoroscopic and ultrasonographic landmarks to locate the right femoral vein and using a micropuncture needle for initial access, and then will place an 8F sheath in the right Common Femoral vein. We will than perform a cavogram using a Omniflush catheter. The Edwards expandable sheath and delivery system will be placed into the right femoral vein. A 5-French sheath will be placed in the right or left radial femoral artery to monitor arterial pressure and secure arterial access throughout the procedure, and a catheter may or may not be placed in the right internal jugular vein. Heparin will be administered to achieve an activated clotting time (ACT) between 250-300s. To achieve stable position of the valve in the IVC, we will perform pre-stenting of the IVC with with either a balloon expandable or self-expandable stent according to standard technique. A repeat cavogram with an Omniflush catheter will be done to delineate the takeoff of the hepatic veins prior to valve implantation. When positioning is confirmed the Edwards or balloon in balloon (BIB) delivery system will be deployed into the suprahepatic segment of the IVC by standard technique. Right ventricular (RV) angiography from IJ access and echocardiogram will be performed to confirm intact valve function and any evidence of regurgitation. At the end of the procedure, the venous sheath will be removed and perclose devices will be deployed or a figure of 8 suture will be used to achieve adequate hemostasis. The arterial sheath will be removed with closure devices or with direct manual pressure.

Anticoagulation Regimen:
Pre-procedure: Patients in atrial fibrillation on warfarin may be bridged with LMW or UF heparin prior to the procedure. During the procedure: IV heparin will be given to maintain ACT > 250 sec. Patients may be bridged to a therapeutic INR with either heparin or Lovenox post-procedurally.

Recommended Antiplatelet/Anticoagulation Regimen
Aspirin 81 mg p.o. daily indefinitely plus warfarin therapy to maintain an INR between 2-3. In those patients with severe hepatic dysfunction whom have elevated INR at baseline, ASA 81mg will be continued and the level of additional anti-coagulation will be decided on a case by case basis.

Radiation precautions:
Radiation exposure will be documented at each study visit in the CRF, with options to record whether chest x-ray, including additional plain x-rays, CT scans and all fluoroscopy procedures were performed. In the event that a dose isn't recorded; such as a plain X-ray, an average dose will be assigned for each applicable test. A trigger will be applied in the database such that when the cumulative estimated radiation exposure calculation exceeds 150 to 250 Gy/cm2.
Additional precautions: for any study patient, the site coordinator and investigator will be notified and a follow-up visit advised to assess patient for skin reaction. Substantial radiation dose level (SRDL) - The operator should be notified promptly if SRDL was exceeded. The SRDL is a trigger level to initiate follow-up of a radiation dose that might produce a clinically relevant injury in an average patient. Some suggested values for the SRDL are a skin dose of 3 Gy, a KAP of 500 Gy/cm2, or an air kerma at the interventional reference point of 5 Gy (NCRP 2010). For cardiology procedures, a level greater than 2Gy will be noted and close follow up will be performed to evaluate for skin toxicity.
The operator should write an appropriate note in the patient's medical record, stating that a substantial radiation dose has been administered, and indicating the reason. This information may be included in the post procedure notes. Patients with reported KAP between 150 and 250 Gy/cm2 must be further evaluated for radiation injury and the event must be reported as a serious adverse event in the case report form.
Acute evaluation - When the SRDL has been exceeded, clinical follow-up essential for early detection and management of skin injuries. The patient should be advised of the possibility of a skin injury due to a tissue reaction, and should be told to examine the beam entrance site at 2-4 weeks after the procedure. The operator should be notified if any skin changes are seen. Patients who have not previously notified the operator should be contacted by telephone at approximately 30 days after the procedure, in order to ensure that a skin injury is not missed.
Long-term evaluation - If a skin injury is suspected, the interventionalist should see the patient at an office visit, and should arrange for appropriate follow-up care. The physician responsible for the patient's care should be informed of the possibility of radiation effects.

5.3 Post-Procedure assessments:
Study patients will be continuously monitored clinically, hemodynamically, and electrocardiographically during catheterization for all local, systemic side effects and complications. After completion of the procedure, patients will be admitted to the hospital for further monitoring.

- Physical Exam. This will include vital signs and weight, head, ears, eyes, nose and throat (HEENT), neck, lungs, cardiovascular, abdomen, genitourinary, gastrointestinal, musculoskeletal, neurological
- NYHA functional Class as per 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; 1994:253-256
- Diuretic types and doses
- Event assessment as per VARC-2 [19].

Laboratory Measurements

- CBC with differential
- Cardiac Enzymes (Troponin I and/or CK and CKMB) every 8 hours x3
- Comprehensive metabolic panel
- Lactate Dehydrogenase (LDH)
- ACT (optional)
- PT/INR
- Brain Natriuretic Peptide (BNP)

Non-Invasive Tests

- ECG
- Echocardiogram (Transthoracic)

5.4 Discharge Procedures

The following data will be collected for all study patients as close to the date of discharge as possible. A post-procedure echocardiogram will also be performed prior to discharge. If a patient is discharged over a weekend or holiday, the discharge tests may be completed on the last weekday prior to discharge.

Systems:

- Physical Exam. This will include vital signs and weight, head, ears, eyes, nose and throat (HEENT), neck, lungs, cardiovascular, abdomen, genitourinary, gastrointestinal, musculoskeletal, neurological
- NYHA functional Class as per 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; 1994:253-256
- Diuretic types and doses
- Event assessment as per VARC-2 [19].

Laboratory Measurements

- CBC with differential
- Comprehensive metabolic panel
- Brain Natriuretic Peptide (BNP)
- Haptoglobin
- Lactate dehydrogenase (LDH)

5.5 Follow-Up Procedures

Patients will follow up at 1, 6 and 12 months with a member of the study team. The following information will be collected at follow up visits.

Systems:

- Physical Exam. This will include vital signs and weight, head, ears, eyes, nose and throat (HEENT), neck, lungs, cardiovascular, abdomen, genitourinary, gastrointestinal, musculoskeletal, neurological
- NYHA functional Class as per 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; 1994:253-256
- Diuretic types and doses
- Event assessment as per VARC-2 [19].

Laboratory Measurements

- CBC with differential
- Comprehensive metabolic panel
- Brain Natriuretic Peptide (BNP)
- Haptoglobin
- Lactate Dehydrogenase (LDH)

Non-Invasive Tests

- ECG
- Chest X-ray (portable or PA and lateral)
- Echocardiogram (Transthoracic)
- Chest and Abdominal CT (6-months only)
- Cardiopulmonary Exercise Stress test [32] (6-months only)

Functional Assessments

- 6-minute walk test [33]
- Villalta Scale [25,26]
- EORTC QLQ-C30 [27]
- ESAS-AM [28]
- Kansas City Cardiomyopathy Questionnaire (KCCQ) [22]

Invasive studies

- Right heart catheterization (6-months only)

5.6 Annual Study Visit, Final Study Visit, premature discontinuation or unscheduled study visit
The following variables will be collected for the above parameters.

- Physical Exam. This will include vital signs and weight, head, ears, eyes, nose and throat (HEENT), neck, lungs, cardiovascular, abdomen, genitourinary, gastrointestinal, musculoskeletal, neurological
- NYHA functional Class as per 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; 1994:253-256
- Diuretic types and doses
- Event assessment as per VARC-2 [19].

Table 1: Summary Schedule of Procedure and Follow-Up

	Baseline	**During the procedure**	**24 hrs. after the procedure**	**7 days after procedure or at discharge**	**At 30 days (+/- 7 days)**	**At 6 months (+/- 14 days)**	**At 1 yr (+/- 21 days)**	**Annually up to 5 years (+/- 21 day)**	**Premature discontinuation or unscheduled visit**
Informed Consent	Xb†								
Medical History	Xb†								
Physical Exam (incl. Vital signs)	Xb†		X	X	X	X	X	X	X
NYHA Class	Xb†		X	X	X	X	X	X	X
Diuretic types and doses	Xb†		X	X	X	X	X	X	X
Event Assessment	Xb		X	X	X	X	X	X	X
Surgical note documenting high risk/inoperable status	Xb†								

Laboratory Measurements									
CBC with Differential	Xd		x	X		X	X		
Cardiac Enzymes (Troponin I and/or CK and CK-MB)	Xe		X (every 8 hours x 3)						
Comprehensive Metabolic Panel	Xb†		X	X	X	X	X		
LDH (to assess hemolysis)	Xc		X	X	X	X	X		
ACT^		X*	X*						
aPTT	Xc	X*							
PT/ INR	Xb†		X						
Brain Natriuretic Peptide (BNP)	Xc		x	X	X	X	X		
Haptoglobin	Xc			X	X	X	X		
Non-Invasive Tests									
ECG	Xc		X		X	X	X		
Chest X-ray	Xc				X	X	X		
Echocardiogram - TTE or TEE	Xb†	X	X		X	X	X		
Chest and/or Abdominal CT	Xa†					X			
Cardiopulmonary Exercise Stress test	Xb					X			
Venous Lower Extremity Duplex Study	Xc								
Pulmonary Function Test (PFT)	Xb†								
Functional Assessments									
6-Minute Walk Test	Xb				X	X	X		
Quality of Life (Kansas City Cardiomyopathy Questionnaire (KCCQ)	Xc				X	X	X		
Villalta Scale	Xc				X	X	X		
EORTC QLQ-C30	Xc				X	X	X		
ESAS-AM	Xc				X	X	X		
Invasive Tests									
Left Heart Catheterization w/wo LV gram and IVUS[a]	Xa†	X*							
Right Heart Catheterization	Xb†	X				X			

a. The following assessment will be collected within one year of procedure day.
b. The following assessments will be completed within 90 days before the procedure day
c. The following assessments will be completed within 21 days before the procedure.
d. The following assessment needs to be done during the 6 months screening and within 21 days before the procedure.
e. CK/CKMB and/or Troponins ≤ 72 hours before the procedure
f. Right heart catheterization only
* Optional
† Required prior to Heart Team and Executive Committee meetings to determine eligibility

5.7 Patient Withdrawal

All study patients are required to complete clinical follow-up for all designated study visits. A careful review of these requirements must be communicated to the patient and family members prior to obtaining the study consent. Patients who cannot make study visits due to physical or geographical constraints should be encouraged to complete as many assessments within the planned visit as possible. A study patient that has been withdrawn from the study will not be replaced and may impact the ITT analysis.

Every patient should be encouraged to remain in the study until they have completed the protocol required follow-up period. If the patient discontinues prematurely from the study, the reason for discontinuation must be documented. Possible reasons for premature discontinuation may include, but are not limited to the following:

• Withdrawal of consent: Patient decides to withdraw from the study.

• Lost to follow-up: All patients should be encouraged to return to the clinic for evaluation during long term follow-up. The patient will be considered lost to follow-up if this communication is unsuccessful. Patients who discontinue prematurely will be included in the analysis of results, and will not be replaced.

• Death registries: In the event of a patient withdrawal or lost to follow-up, the sponsor may opt to obtain the death certificate, search the Social Security Death Index and/or other death registries to obtain survival information.

6.0 ADMINISTRATIVE RESPONSIBILITIES

6.1 Institutional Review Board (IRB) Information

This protocol and the informed consent must be reviewed and approved by the appropriate IRB before enrollment of patients. All changes to the protocol must be approved in writing by the IRB before the change is implemented.

6.1.1 Institutional Review Board Approval Letter

Institutional Review Board (IRB) approval to participate in this trial is required from each institution participating in this investigation. Prior to patient enrollment, a signed copy of the IRB approval letter must be submitted to the sponsor investigator certifying trial approval. Investigators are responsible for submitting and obtaining initial and continuing review of the trial at least annually unless otherwise directed by their IRB.

6.2 Informed Consent

Informed consent is mandatory and must be obtained from all study patients prior to their participation in this trial. Any modifications to the Informed Consent Form must be approved by the IRB. A copy of the IRB approved Informed Consent Form along with a copy of each patient's signed consent form must be maintained by each investigator in a designated clinical trial administrative file. A signed copy of the consent form must be given to each patient.

6.3 Confidentiality

All information and data collected in this trial will be considered confidential. Only authorized data management center personnel will have access to these confidential files. Authorized personnel from the regulatory authorities have the right to inspect and copy all records pertinent to this trial. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the patient.

7.0 ADVERSE EVENT REPORTING

7.1 Adverse events:
An adverse event (AE) is any untoward medical event in a patient and does not necessarily have a causal relationship with the use of the device. Symptoms or medically significant laboratory or instrumental abnormalities of a preexisting disease, such as hypertension or other disease, should not be considered adverse events but must be documented in the medical history if clinically significant. New symptoms or laboratory abnormalities, however, as well as worsening of existing ones, are considered adverse events. Study device causality for adverse events will be graded as unlikely, possible or probably.

7.2 Serious Adverse Events
A serious adverse event (SAE) is any untoward medical occurrence that:
• results in death
• is life-threatening, i.e., an event that, in the view of the investigator, places the subject at immediate risk of death from the event as it occurred (it does not include an event that could have caused death if it had been more severe)
• requires inpatient hospitalization or prolongs the existing hospitalization
• results in persistent or significant disability or incapacity, where disability is defined as a substantial disruption of a person's ability to conduct normal life functions, either reported or defined as per clinical judgment
• is a congenital anomaly or birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child)

All investigators will be responsible for reporting serious adverse events to the sponsor and their reviewing IRBs in accordance with local guidelines. In addition, all SAEs will be reviewed by an independent Data Safety Monitoring Board (DSMB) in accordance with their charter. (An SAE will be reported to the Sponsor and DSMB Chair within 24 hours from when the event was discovered and the SAE CRF will be submitted no later than ten (10) days after the SAE was discovered) Study device causality for SAE's will be graded as unlikely, possible or probably.

7.3 Non-Serious Adverse Events
A non-serious adverse event is any AE that does not meet the criteria listed above for a serious adverse event, or the outcome (subject treatment, life-threatening condition, hospitalization, recovery) cannot be determined with the information provided. Non-serious AEs will be documented on the AE log and will be reported to IRB per local regulations.

7.4 Unanticipated Adverse Events
An unanticipated adverse event is an AE for which the nature or severity are not consistent with the applicable product information (refer to IFU and on-label use). Unanticipated adverse events are to be reported to the study sponsor, each reviewing IRB, and the FDA, no later than ten (10) days after the date the adverse event was discovered. The coordinating center will be responsible for the communication with the regulatory bodies.

7.5 Anticipated Adverse Events
An anticipated adverse event is an AE for which the nature and severity are consistent with the applicable product information (e.g. Package insert/summary of product characteristics for an approved product). This term relates only to the treatment, not the patient's underlying condition.

7.6 Unanticipated Adverse Device Effects

Unanticipated adverse device effects (UADE) are defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of study patients.

All UADEs must be reported to the FDA immediately upon the Investigator's awareness of the event. The AE Forms of the CRF must be completed with 7 working days for all UADEs. The Investigator is also responsible for notifying his/her IRB of all UADEs occurring at his/her site no later than 10 days after the investigator first learns of the effect (and any additional information as required by EC/IRB or local regulations). All UADE adverse events must be followed until resolution or until a stable clinical endpoint is reached. All required treatments and outcomes of the UADE adverse event must be recorded.

7.7 Adverse Event Follow-up

All adverse events occurring within the follow-up period (whether serious, non-serious, unanticipated, or anticipated) will be monitored and documented according to the follow-up. To be compliant with ethical and regulatory principles, treatment-related SAEs that occur after follow-up is completed (outside the protocol) and are assessed by the investigator as "unanticipated" must be updated to the FDA via the MAUDE reporting system in accordance with FDA regulations

8.0 DATA MONITORING AND QUALITY CONTROL

8.1 Case Report Forms (CRFs)

Case report forms (CRFs, see addendum) will be generated, based on the investigational plan. An electronic clinical trial management system (RedCap, Vanderbilt U, TN) will be used to collect all patient data during the trial by the data coordinators or their designee. Data will be collected in a paper form or in electronic format and entered into the electronic clinical trial management system. Paper forms will be kept in a secure location and only accessible to the data coordinator or investigator.

8.2 Data Reporting

The Investigator or his/her designee is responsible for recording all data from the trial onto the CRFs. Completed CRFs will be reviewed at regular intervals throughout the trial. To this end, the Investigator must permit inspection of the trial paper files and patient CRFs by such representatives and/or responsible government agencies including the FDA or DMSB.

8.3 Data Review

All CRFs will be thoroughly reviewed and all missing or unclear data will be adjudicated by the investigator or his designee throughout the study. Any data which has not been collected or is unavailable will also be noted. For purposes of safety review the DMSB will have access to all necessary safety and event data.

8.4 Records

Records to be maintained by the site investigator include:

- Correspondence
    - IRB Correspondence (incl. IRB approval)
    - Sponsor correspondence
    - General correspondence
- Study documents
    - Clinical protocol including all amendments
    - Informed consent and HIPAA authorization
    - Sample case report form (database)
    - Instruction for use (device)
    - Statement of investigator
    - Laboratory certifications
    - Laboratory reference ranges
- Study tracking logs
    - Subject logs
    - Adverse events and unanticipated adverse device effects log
    - Device accountability log
    - Monitoring log
- Research personnel
    - PI (site PI):
        - curriculum vitae
        - current medical license
        - human subject protection training document
        - conflict of interest or financial disclosure form(s)
    - Sub-PI:
        - curriculum vitae
        - current medical license
        - human subject protection training document
        - conflict of interest or financial disclosure form(s)
    - Signature and delegation of responsibility log
- For sites that are using a local IRB
    - IRB compliance document (FWA)
- Bi-annual reports to the FDA

The following records must be maintained for each patient enrolled in the trial:

- Signed Patient Informed Consent Form;
- All completed CRFs;
- Supporting documentation of any complications or serious adverse events.

Investigator's Final Report

Upon completion or termination of the HOVER study, the overall Principal Investigator must submit a final written report to the FDA and the IRB. The report must be submitted within 3 months (90 days) of completion or termination of the trial.

Protocol Deviations/Violations
The investigator will not deviate from the protocol without the prior written approval of the IRB except where necessary to eliminate an apparent immediate hazard.

9.0 ETHICAL AND REGULATORY CONSIDERATIONS

9.1 Role of the Sponsor investigator
The sponsor investigator has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the appropriate regulatory bodies. In this study, the sponsor will have certain direct responsibilities and may delegate other responsibilities to the study coordinator or other investigators.

9.2 General Duties
The Sponsor's general duties consist of submitting the appropriate regulatory applications, obtaining IRB or Ethics Committee approval, selecting investigators, ensuring proper clinical site monitoring and ensuring study patient informed consent is obtained. Based on data collected from the study, the sponsor will prepare written progress reports and a final report.

9.3 Selection of Investigators
The Sponsor will select qualified investigators, obtain a signed Investigator's Agreement and provide the investigators with the information necessary to conduct the study.

9.4 Monitoring (See also Monitoring Plan)
The Sponsor or its designee, will monitor the study to ensure compliance with the protocol and the Investigator's Agreement. The sponsor will evaluate circumstances where an investigator deviates from the clinical protocol and will retain the right to remove the investigator from the study. The Sponsor will review significant new information, including unanticipated adverse events and ensure that such information is provided to the DMSB, study investigators and to all reviewing IRB/ECs.

9.5 Supplemental Applications
As appropriate, the principal investigator will submit changes in the Investigational Plan to the regulatory authority. The principal investigator will submit all changes in the Investigational Plan to investigators to obtain IRB re-approval.

9.6 Maintaining Records
The Sponsor will maintain copies of correspondence, all data, adverse device effects and other records related to the clinical trial as appropriate.

9.7 Submitting Reports
The Sponsor will submit all reports required by the appropriate regulatory authorities, including unanticipated adverse device effects, withdrawal of IRB approval, current investigators list, annual progress reports, final reports protocol violations.

9.8 Informed Consent
All study patients must personally provide written informed consent. Copies of the informed consent form must be maintained for the duration of the study. One copy will reside in the medical chart, one copy will be provided to the patient, and the original resides in the regulatory binder on site. The IRB approval letter for the study will also be maintained. The study patient has been informed of the nature

of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.

10.0 STUDY DATA REPORTING AND PROCESSING

10.1 Data Processing and Quality Control
The online database will reside on a central server accessible through the Internet. It will be password protected and available only the investigators and study personnel. The database will be protected by whole disk encryption.

10.2 Data Entry
The data entry is performed by study personnel on a secured and dedicated website. All data entered is subjected to data type verification.

10.3 Data Cleaning
All CRFs will be subjected to initial inspection for omitted data, data inconsistencies, and deviations. The resolution of data inconsistencies will be done by the investigators or other data management specialists.

10.4 Data Editing
Corrections to the CRFs will be made by the research coordinator, and approved by the investigator or designee.

10.5 Confidentiality and Protection of Study Files
Passwords will be issued to appropriate data management personnel to ensure confidentiality and protection of the data by allowing variable levels of access to the computer system.

10.6 Coordinating Center
Henry Ford Hospital, Detroit, MI will serve as the coordinating center, providing administrative, regulatory, and statistical support for the trial. Henry Ford Hospital staff will coordinate activities across the HOVER sites and will perform the following functions:

- Participate in study start-up site inservicing and training;
- Ongoing site monitoring to assure compliance with federal regulations and GCP;
- Oversight of compliance with IRB requirements, including initial and continuing review approvals, modifications and Serious Adverse Event submissions;
- Coordination of DSMB meetings and communications;
- Registration and updates on clinicaltrials.gov;
- Oversee data collection and verification via RedCap;
- Perform statistical analyses;
- Perform study close out activities;
- Execute and administer contractual/financial agreements between Henry Ford Hospital and the other sites;
- Liaison between investigator, FDA, IRB, DSMB and study sites.

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		ADVERSE EVENTS						
#	Describe Event	Onset Date (mm/dd/yyyy) and Time (Military)	Outcome	Resolution Date (mm/dd/yyyy) and Time (Military)	Intensity	Expected Event?	Treatment Stopped?	Study Device Causality
		___/__/___ ___:___	☐1 Ongoing ☐2 Resolved ☐3 Pt. Died	___/__/___ ___:___	☐1 Mild ☐2 Moderate ☐3 Severe ☐4 SAE*	☐0 NO ☐1 YES**	☐0 NO ☐1 Stopped temporarily ☐2 Stopped Permanently	☐1 Unlikely ☐2 Possibly ☐3 Probably
		___/__/___ ___:___	☐1 Ongoing ☐2 Resolved ☐3 Pt. Died	___/__/___ ___:___	☐1 Mild ☐2 Moderate ☐3 Severe ☐4 SAE*	☐0 NO ☐1 YES**	☐0 NO ☐1 Stopped temporarily ☐2 Stopped Permanently	☐1 Unlikely ☐2 Possibly ☐3 Probably
		___/__/___ ___:___	☐1 Ongoing ☐2 Resolved ☐3 Pt. Died	___/__/___ ___:___	☐1 Mild ☐2 Moderate ☐3 Severe ☐4 SAE*	☐0 NO ☐1 YES**	☐0 NO ☐1 Stopped temporarily ☐2 Stopped Permanently	☐1 Unlikely ☐2 Possibly ☐3 Probably
		___/__/___ ___:___	☐1 Ongoing ☐2 Resolved ☐3 Pt. Died	___/__/___ ___:___	☐1 Mild ☐2 Moderate ☐3 Severe ☐4 SAE*	☐0 NO ☐1 YES**	☐0 NO ☐1 Stopped temporarily ☐2 Stopped Permanently	☐1 Unlikely ☐2 Possibly ☐3 Probably
Describe:								
If event is SAE then submit AE form to medical reviewer within 24 hours. **If YES and device related, complete UADE form								

UNANTICIPATED ADVERSE DEVICE EFFECT FORM

1. Date form completed __ __/__ __/__ __ __ __
MO DAY 4-Digit YEAR

2. Date and time of onset: __ __/__ __/__ __ __ __ __ __: __ __
MO DAY 4-Digit YEAR (Military time)

3. Has event resolved? ☐ YES ☐ NO f YES, Date/Time resolved: __ __/__ __/__ __ __ __ __ __: __ __
MO DAY 4-Digit YEAR (Military time)

4. Relationship to study device: *(choose one)*
☐ NOT related ☐ Probably related ☐ Unknown
☐ Possibly related ☐ Definitely related
If related, (1, 2 or 3) then specify Serial ID# for device _____

5. In your opinion, is this a UADE* ☐ YES ☐ NO

6. Action taken *(Check all that apply)*
☐ YES ☐ NO None
☐ YES ☐ NO Medication, specify:_____
☐ YES ☐ NO Surgery, specify _____
☐ YES ☐ NO Other, specify _____

7. Severity *(Check one)* ☐ Mild ☐ Moderate ☐ Severe ☐ Life threatening

8. Outcome *(Check all that apply)*

YES	NO		YES	NO	
☐	☐	A. Continuing WITHOUT treatment	☐	☐	E. Recovered WITHOUT treatment
☐	☐	B. Continuing WITH treatment	☐	☐	F. Recovered WITH treatment
☐	☐	C. Continuing with sequelae, specify: _____	☐	☐	G. Patient expired *(attach copy of autopsy or death summary)*
☐	☐	D. Temporary disability	☐	☐	H. Permanent disability

9. Description of adverse effect:_____

* An Unanticipated Adverse Device Effect (UADE) is any serious adverse effect on health or safety, or any life-threatening problem or death caused by or associated with this device, if that effect, problem, or death is not identified in nature, severity, or degree of incidence in this Investigational Study; or any other unanticipated serious problem associated with this device that relates to the rights, safety or welfare of the subjects. UADEs must be reported to the principal investigator and the IRB within 10 working days.

I verify that the form completed for this UADE is accurate and representative of the data available in source documentation.

_____ Date __ __/__ __/__ __ __ __
Investigator's signature MO DAY 4-Digit YEAR

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE OF RESEARCH STUDY: The HOVER Study: Heterotopic Implantation Of the Sapien 3 Transcatheter Aortic Valve in the Inferior VEna cava for the treatment of severe tricuspid Regurgitation.

PROTOCOL NO: Version 2.3
WIRB® Protocol #20161648

SPONSOR: Henry Ford Hospital

LEAD INVESTIGATOR and SITE:
Brian O'Neill, MD
Henry Ford Hospital
Center for Structural Heart Disease
2799 West Grand Blvd.
Clara Ford Pavilion # 440
Detroit, MI 48202
313-970-6483 (p)
313-916-2819 (f)

LOCAL INVESTIGATOR/study doctor: {First, Last Name, Degree}

LOCAL SITE: { Name, Department, and Address where patients will be seen}

LOCAL STUDY-RELATED PHONE NUMBER(S):
DAYTIME PHONE NUMBER:
24-HOUR EMERGENCY PHONE NUMBER:

Why you are being invited to take part in a research study
Your tricuspid valve is very leaky. This leakiness is causing symptoms, such as shortness of breath, and swelling in your legs or stomach. This leakiness may be affecting the other organs in your body. If the valve is not fixed, you will continue to have these problems.

The current standard treatment is to repair or replace the leaking valve with an artificial valve using open heart surgery. However, you are at a very high risk of experiencing serious complications from this treatment. Because of this, we invite you to take part in a research study investigating a way to replace the function of the tricuspid valve without using open heart surgery. Instead, the valve is replaced during a cardiac catheterization where an artificial valve is inserted through a large vein in your body. Your old tricuspid valve will not be replaced as is the normal practice with surgery. Instead, a valve will be inserted into your body which will assist your leaky valve with its function. The valve used in this research study is FDA-approved to replace the aortic valve. It is designed to replace the aortic valve, not the tricuspid valve. It is also designed to be inserted through an artery, not a vein. It is not FDA approved to use as a replacement for function of the tricuspid valve. Therefore, use of this valve in this research is experimental and investigational.

Who can I talk to?
{Non-Henry Ford sites replace information in bolded italics with site-specific information}
If you have questions, concerns, or complaints, or think the research has hurt you, contact the research team at Phone: ***313-970-6483*** or send a letter to

Brian O'Neill, MD
Henry Ford Hospital
Center for Structural Heart Disease
2799 West Grand Blvd.
Clara Ford Pavilion # 440
Detroit, MI 48202

This research has been reviewed and approved by Western Institutional Review Board. You may talk to them at 1-800-562-4789 or 360-252-2500, 1019 39th Avenue SE Suite 120, Puyallup Washington 98374-2115, or e-mail them at: **Help@wirb.com** for any of the following:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research subject.
- You want to get information or provide input about this research.

WIRB is a group of people who perform independent review of research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Disclosure Of Potential Conflict Of Interest

In addition to serving as the principal investigator (PI) on the study, Dr. Brian O'Neill also serves as a consultant for Edwards Lifesciences LLC. In this position he receives funding from Edwards for his expertise. Edwards is providing partial financial support for this study in form of a research grant. Involvement as a consultant is independent of this study and has no financial relationship to the enrollment or conduct of this study. Although none of the Henry Ford Health System doctors are supposed to let his/her financial interests affect the study, this may not always be possible.

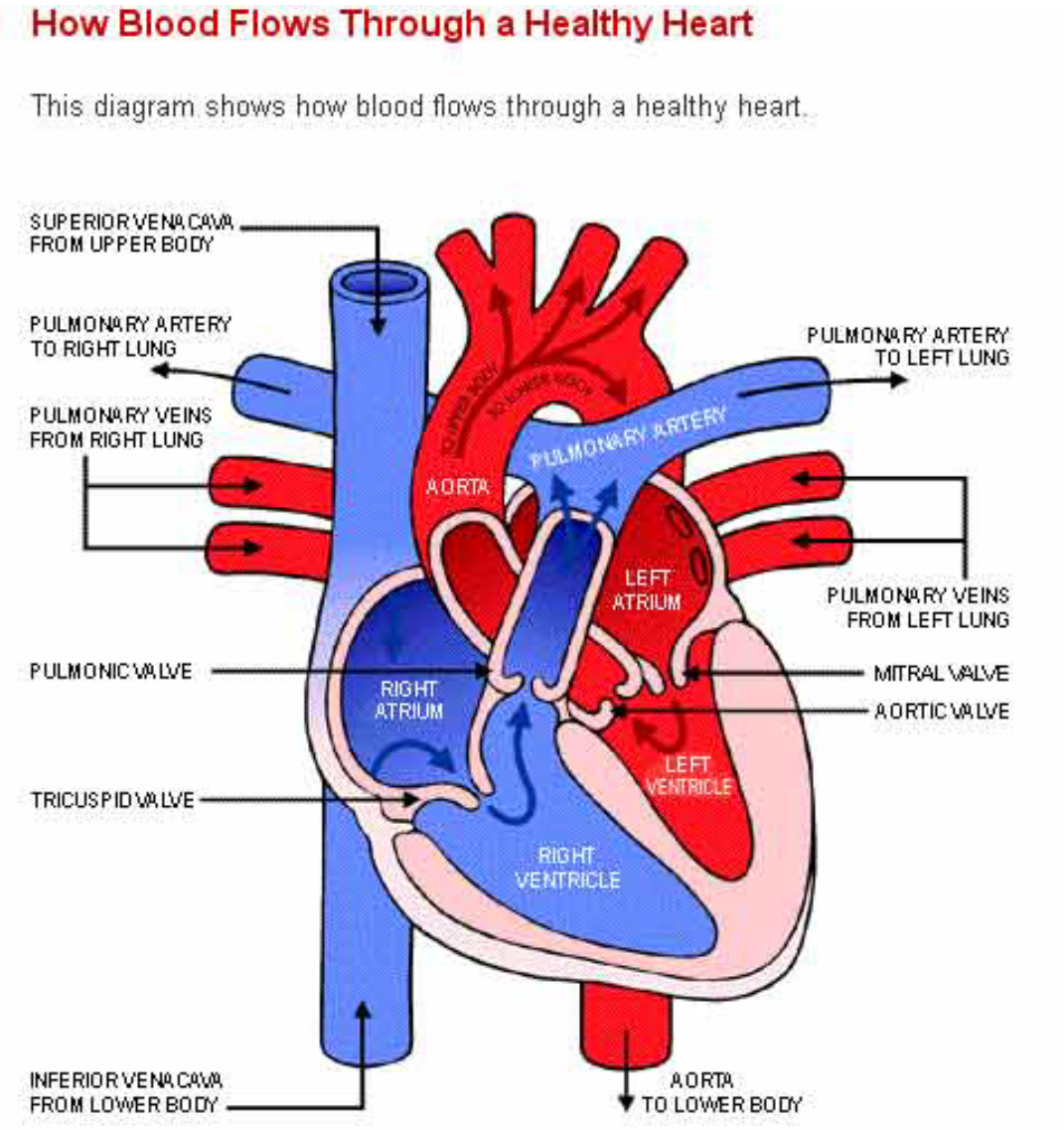
The investigator(s) in this study are also healthcare providers. They are interested in the knowledge to be gained from this study and are interested in your well-being. Henry Ford Health System receives funding from Edwards in form of a research grant to support this research study. However, investigators do not receive salary or other financial support from Edwards in exchange for conducting this study.

Why are we doing this research?

Blood that flows between different chambers of your heart must flow through a heart valve. These valves open up enough so that blood can flow through. They then close, keeping blood from flowing backward.

The tricuspid valve separates the right lower heart chamber (the right ventricle) from the right upper heart chamber (right atrium).

Tricuspid regurgitation is a disorder in which this valve does not close tightly enough. This problem causes blood to flow backward into the right upper heart chamber (atrium) when the right lower heart chamber (ventricle) contracts.



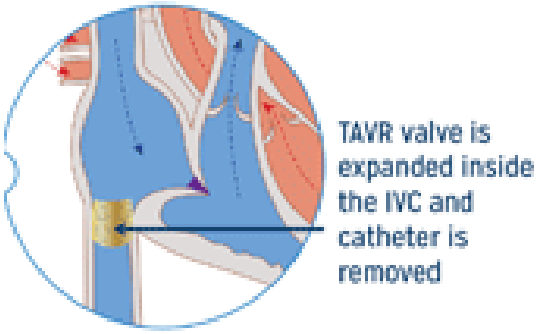
The current standard treatment is to repair or replace the leaking valve with an artificial value using open heart surgery. However, some patients are too sick to undergo surgery.

A few years ago, the FDA approved a new method to treat seriously diseased aortic valves. This procedure repairs the aortic valve without removing the old, damaged valve. Instead, it wedges a replacement valve into the aortic valve's place. The procedure is called a transcatheter aortic valve replacement (TAVR) or transcatheter aortic valve implantation (TAVI).

Transcatheter aortic valve replacement involves threading a catheter through an artery into the heart and then threading a collapsed replacement valve to the valve site through a catheter. Once the new valve is expanded, it pushes the old valve out of the way and the replacement valve takes over the job of regulating blood flow.

The Edwards SAPIEN 3™ (S3) Transcatheter Heart Valve are valves that are FDA-approved for transcatheter aortic valve replacement. The Edwards SAPIEN 3™ Transcatheter Heart Valve is not FDA approved to surgically implant to replace the function of the tricuspid valve. Therefore, use of the The Edwards SAPIEN 3™ Transcatheter Heart Valve in this research is experimental and investigational.

The purpose of this research is to try using the The Edwards SAPIEN 3™ Transcatheter Heart Valve as an implant to replace the function of the triscuspid valve. The Edwards SAPIEN 3™ Transcatheter Heart Valve is designed to replace the aortic valve, not the tricuspid valve. It is also designed to be inserted through an artery, not a vein. This research will place the valve at the junction of the inferior vena cava (large vein that drains the lower body) and the heart to prevent blood from the heart from flowing backwards to the lower body. This research will be the first time the safety and effectiveness of using the The Edwards SAPIEN 3™ Transcatheter Heart Valve as a replacement for the function of the tricuspid valve is tested in humans as part of a clinical trial.



There is very limited experience with surgically implanting the The Edwards SAPIEN 3™ (S3) Transcatheter Heart Valve to replace the function of the tricuspid valve with fewer than thirty patients reported in the literature. The research team at the lead investigative site has used this valve to replace the aortic valve. However, before starting this research study, Dr. O'Neill, who is also the lead principal investigator, has performed research into the field of transcatheter valve replacement. In preparation for this research protocol, Dr. O'Neill performed extensive research into the field including a review of all the literature available. He has spoken with physicians who are performing this procedure in Germany, and also participated in the first procedure which was performed in the United States. Dr. O'Neill has worked closely with your doctors participating in this study along with an excellent team of cardiothoracic surgeons who have performed hundreds of tricuspid valve replacements over the years, and who will be involved in all parts of your workup and procedure.

How long will the research last?
We expect that you will be in this research study for up to 5 years. You will have a visit with one of the doctors involved in the research study at 30-days, 6-months, and 1 year, and then annually after that for up to 5 years. In addition to scheduled visits, you may also be contacted via the telephone in-between visits to see how you are doing and schedule your follow–up visits.

How many people will be studied?
This study will take place at several institutions. We expect up to 15 people in total to be enrolled in the research study. Up to 10 patients will be enrolled at this institution.

Do I have to participate?
Your participation in this study is voluntary. You may decide not to participate or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent for any reason, including:

- if it is in your best interest;
- If you do not consent to continue in the study after being told of changes in the research that may affect you.

What happens if I say yes, I want to be in this research?
If you choose to be included in the study, you will have the following studies performed if they have not already been done as part of your regular clinical care, to determine if you would meet the criteria for inclusion in the study.

Prior to the Procedure

- Physical Exam including vital signs
- NYHA classification
- 12-Lead Electrocardiogram (EKG)
- Chest X-ray
- Echocardiogram (heart ultrasound)
- CT scan (computed axial tomography) of your chest, abdomen, and pelvis
- Cardiopulmonary exercise stress test (VO2)
- Lower extremity venous dopplers
- 6-minute walk test
- Right heart catheterization, intravascular ultrasound of the inferior vena cava and right ventriculogram
- Left heart catheterization
- Quality of Life Assessment (Kansas City Cardiomyopathy Questionnaire KCCQ)
- ESAS:AM and EORTC QLQ-C30 questionnaire
- Formal Frailty Assessment
- Villalta Scale

Clinical laboratory tests including

- Comprehensive metabolic panel
- CBC with differential and platelet count

- Liver panel including AST and ALT
- Albumin
- B-type natriuretic peptide (BNP)
- LDH
- Haptoglobin
- PTT or PT/INR
- CK/CKMB and/or Troponins ≤ 72 hours before the procedure

At your subsequent follow up visits

- NYHA classification
- Standard 12-lead ECG
- Comprehensive transthoracic echocardiogram (TTE)
- Clinical laboratory tests (see above)
- Functional Assessments:
- 6-minute walk test
- Quality of Life Assessment (Kansas City Cardiomyopathy Questionnaire KCCQ)
- Chest X-ray examination
- CT scan (at 6-month visit only)
- ESAS:AM and EORTC QLQ-C30 questionnaires

- Finally, you will have doctors' visits during enrollment with a heart failure specialist, an interventional cardiologist, and a cardiothoracic surgeon. You will see some, if not all of these doctors at subsequent follow up visits.
- During the procedure you will be put to sleep by the anesthesia team using medications that will make you sleep and prevent you from having any pain. You will also be given heparin which is a medication that will thin your blood during the procedure.
- A metal stent will be placed in the vein leading to your heart which will allow the heart valve to remain implanted. After the procedure you will remain in the hospital for several days while the doctors work to ensure that the valve is functioning properly.
- After you leave the hospital you will be seen at 30-days, 6 months, 1-year, and then annually up to 5 years. If you are not feeling well you may be seen on a more frequent basis by members of the study team or your primary care physician.
- These doctor visits should only take up to 1 hour based on how you are feeling.
- A total of up to 50mL of blood will be drawn from you at your follow up visits, but most likely less than this.
- At your visits you will speak with the members of the study team and research coordinator.
- It is important to understand that although studies have shown this is a safe procedure to perform in humans, it has not been studied extensively in a large trial which is why at this time the procedure is experimental. The valve which will be implanted has been studied in large scale clinical trials which have proved it is safe, although it has not been implanted in the position in which we plan for you.
- After the invasive procedure is performed there are no additional invasive planned procedures as part of the study protocol. You will undergo routine lab testing and ultrasound as part of the protocol. However, if any additional invasive procedures are required, they will be explained to you and your consent for them will be obtained on a different form.
- As there currently are no long term studies to tell us how you will improve with this procedure, as well as how the valve will function in the part of your body in which it will be placed, we will

be performing laboratory testing, ultrasound, and questionnaires to see how you are feeling, to see how your body responds to the valve, and to ensure the valve functions properly in its position.

- If you choose not to be included in the procedure, you will continue to have follow up appointments with your doctors which will likely include blood testing and ultrasound, although this will be decided between you and your doctor.

Once you decide to participate in this trial, and if you qualify, you will be treated with the valve. If there are any unexpected findings from this procedure, for example a change in the way the valve functions, you will be notified in a timely manner and counseled regarding any additional procedures which may or may not need to be performed.

What are my responsibilities if I take part in this research?

If you take part in this research:

1. You will need to follow up with the study doctors as outlined in the consent form.
2. You will need to agree to have the follow up blood testing and other follow up testing performed.
3. You will need to notify your study doctors if there is a change in how you feel to determine if this is due to the placement of the valve.
4. You will need to notify the doctors if you are admitted to the hospital for any reason.

This valve can form blood clots that can lead to serious life-threatening side effects. During the procedure you will be given drugs that will stop your blood from clotting. After the procedure you will need to take medicine to prevent blood clots for the rest of your life.

If you expire during study participation, your family/next-of-kin will be asked to allow an autopsy.

What happens if I say no, I do not want to be in this research?

You may decide not to take part in the research and it will not be held against you. It will in no way affect your relationship with the study doctor. Instead of being in this research study, your choices may include: The continuation of your medicines for your condition, finding a surgeon who would agree to valve surgery and re-consideration of valve surgery if your condition should improve in the future.

What happens if I say yes, but I change my mind later?

If you agree to take part in the research now and if you decide to stop at any time, it will not be held against you. Again, it will in no way affect your relationship with the study doctor.

If you decide to leave the research, then you may not undergo the recommended follow up to make sure that your body is functioning properly with the device in place. In addition, any changes in the valve that may affect your health may not be noticed.

If you decide to leave the research, contact the investigator so that the investigator can make note of this and notify the proper officials who are also involved with the monitoring of the trial.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care. If you agree, this data will be handled the same as research data.

Is there any way being in this study could be bad for me?
We have limited knowledge about the risks of using the SAPIEN 3 Transcatheter Valve for replacement of the tricuspid valve.

The known risks of the valve replacement procedures in general include bleeding, infection, stroke, death, cardiac arrest, pacemaker implantation, allergic reactions, emergency open heart surgery, emergency blood transfusion, prolonged hospital stay, renal failure, groin lymphocele, limb ischemia, myocardial infarction, and injury to adjacent structures including nerves, blood vessels, or other structures.

Pleural effusions (excess fluid that accumulates in the space that surrounds the lungs) may occur either immediately post-operatively, or at follow up.

There are risks associated with stenting of the vessel for valve implantation. These include migration of the stent and injury to the vessels of the heart or the heart itself, as well as venous thrombosis and stroke.

You may need surgery to remove the valve.

Although it is impossible to predict which, if any, of the above risks may occur with your procedure, based on our experience of using the Edwards SAPIEN 3™ Transcatheter Valve to replace the aortic valve, the likelihood of each of these risks can be best estimated as follows:

Occasional: Bleeding, infection, pacemaker implantation, allergic reactions, prolonged hospital stay, renal failure

Rare: Emergency blood transfusion, groin lymphocele, limb ischemia, myocardial infarction, injury to adjacent structures including nerves, blood vessels, stroke, death, cardiac arrest, emergency open heart surgery.

The risks of using the Edwards SAPIEN 3™ Transcatheter Valve to replace the tricuspid valve may be different than the risks of using the Edwards SAPIEN 3™ Transcatheter Valve to replace the aortic valve. Because of the extremely limited experience with this procedure, the exact side effects, their severity, and their frequency are essentially unknown.

There is a risk that the procedure may not work and may make your heart condition worse.

With any new procedure, physicians get better over time. Since the physicians have no prior experience in performing this procedure in humans to replace the tricuspid valve, risks may occur more often or be more severe than when physicians have more experience in performing this procedure.

Because this treatment is experimental, there may be risks that are currently unknown. These risks may be a minor inconvenience or severe enough to cause disability and death.

The tests that you undergo in preparation for the procedure may also have risks. The known risks associated with each test will be explained to you. . The risks may include but are not limited to: bleeding, infection, stroke, death, cardiac arrest, pacemaker implantation, allergic reactions, emergency open heart surgery, emergency blood transfusion, prolonged hospital stay, renal failure, groin

lymphocele, limb ischemia, myocardial infarction, injury to adjacent structures including nerves, blood vessels, or other structures.

In addition to the risks which may occur during the procedure, the following risks may be encountered during your workup for the procedure.

- CT scan: There is a small risk you may have an allergic reaction with the contrast which is given to you during this test. This reaction can be very serious in some cases and cause death. In addition, there is also a risk that the contrast given to you may cause problems to your kidneys and you may require dialysis.
- Cardiopulmonary exercise stress test: You will be monitored closely during this procedure. However, in rare circumstances you may suffer abnormal beating of the heart which may threaten your life and cause death or permanent disability.
- Echocardiogram: In certain circumstances, a contrast agent may be required to evaluate your heart function. In rare circumstances, you may develop an allergic reaction to this contrast which could cause death or permanent disability.
- Right and left heart catheterization: You may experience bleeding, infection, stroke, death, cardiac arrest, pacemaker implantation, allergic reactions, emergency open heart surgery, emergency blood transfusion, prolonged hospital stay, renal failure, groin lymphocele, limb ischemia, myocardial infarction, and injury to adjacent structures including nerves, blood vessels, or other structures.

Although it is impossible to predict which, if any, of the aforementioned risks may occur with your procedure, the likelihood of each of these risks can be best estimated as follows.

Being a part of this study while pregnant may expose the unborn child to significant risks as you will be exposed to radiation during the initial procedure, CT scan of the chest and body and chest x-ray. If you are a woman capable of having children, you must use a medically acceptable form of birth control. Medically acceptable contraceptives include: surgical sterilization (such as a tubal ligation or hysterectomy), approved hormonal contraceptives (such as birth control pills, patches, implants or injections), barrier methods (such as a condom or diaphragm) used with a spermicide, or an intrauterine device (IUD). Contraceptive measures such as Plan B sold for emergency use after unprotected sex is not an acceptable method for routine use. If you do become pregnant or have unprotected sex any time after signing the consent form, you must notify the study physician immediately.

If you take part in this research, you will be exposed to radiation from fluoroscopy needed for the implantation of the experimental Edwards SAPIEN 3™ Transcatheter Valve, 3 catheterization procedures to prepare for implantation, a ventriculography procedure if the physician is unable to adequately assess your condition by echocardiogram as well as radiation from 2 chest and abdomen CT scans and 4 chest x-rays for stent sizing and implant follow-up. Not all parts of your body receive the same amount of radiation from this experimental valve implant procedure and your heart and breast individually receive a larger amount. Based on current scientific understanding, there is a small risk of causing cancer from this amount of radiation exposure. The radiation dose we have discussed is what you will receive from this study only and does not include any exposure you may have received or will receive from other tests or treatments. The additional radiation exposure is a minimal risk except for the fluoroscopy guidance placement where skin injury could result.

Are there costs involved with participating in this research?

The investigational drug/device will not be provided by the sponsor. The cost of the device, the procedure to implant the device, and all supporting medical care will be billed to your insurance. Your insurance may not cover some or all of these procedures, in which case, the costs will be billed to you. Before you agree to be in the study, the research team will talk to your insurance provider and determine what costs are likely to be billed to you. In some cases, insurance will not pay for services ordinarily covered because these services were performed in a research study.

You and your insurance company will be charged for the health care services that you would ordinarily be responsible to pay. In some cases, insurance will not pay for services ordinarily covered because these services were performed in a research study. You should check with your insurance to see what services will be covered by your insurance and what you will be responsible to pay.

You will not be paid for being in this study.

Will being in this study help me anyway?
We cannot promise any benefits to you or others from taking part in this research. However, possible benefits include improvement in your level of energy, breathing, functioning of vital organs, functioning of your heart, and decreases in the amount of fluid that may have been built up in your stomach, legs, chest and lungs.

What happens to the information we collect?
Efforts will be made to limit your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. For example, though the study team has put in safeguards to protect your information, there is always a potential risk of loss of confidentiality.

Organizations that may inspect and copy your information include the *IRB, Henry Ford Hospital, Henry Ford Health System and its affiliates*, and other representatives of these organizations, and the Food and Drug Administration (FDA).

The, monitors, auditors, the IRB, and the Food and Drug Administration will be granted direct access to the portion of your medical records which are related to this research study for verification of the research procedures and date. You will need to sign a separate “Authorization to use and disclose your protected health information” to be a part of this research study.

We may publish the results of this research. However, we will keep your name and other identifying information confidential.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Federal law provides additional protections of your personal information. These are described in an attached Authorization document referred to above.

Can I be removed from the research without my permission?
The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include if the research being conducted is no longer in your best interest. The sponsor can also end the research study early.

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

What if I am injured because of taking part in this research?
{Non-Temple sites replace information in bolded italics with site-specific information}
If you are injured as a result of taking part in this research, *immediately* notify the research team and they will arrange for you to get immediate medical care. There is no commitment by *Henry Ford Hospital, Henry Ford Health System or its subsidiaries* to provide monetary compensation or free medical care to you in the event of a research-related injury. If you have a research-related injury, please contact *Dr. O'Neill at (313) 970-6483* during regular hours and at *(313) 916-2600* after hours and on weekends and holidays.

The study patient has been informed of the nature of the study, agrees to its provisions, and has provided consent as approved by the Institutional Review Board (IRB) of the respective clinical site.

Signature Block for Adult Subject Capable of Consent

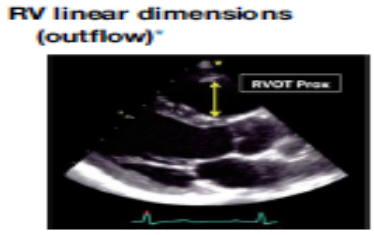
Your signature documents your permission to take part in this research.

Signature of subject	Date and Time
Printed name of subject	
Signature of person obtaining consent	Date and Time
Printed name of person obtaining consent	

APPENDIX A: HOVER ECHO PROTOCOL

-left parasternal long axis

-Coronary sinus dimension
-proximal RVOT dimension



-left parasternal RV inflow

-2D: distinguish functional vs. degenerative/rheumatic/carcinoid TR etiologies
-Color Doppler:
    -identify TR etiology
    -help identify TR severity
-Vena contracta: >7 mm is in favor of severe TR; <6mm - non-severe TR
-Continuous wave Doppler
    -assess density/contour of TR signal
    -measure RVSP

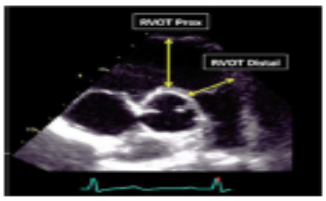
-left parasternal RV outflow

-distal RVOT dimension
-pulsed wave/continuous Doppler of RVOT (RVOT VTI)
-RV stroke volume

-left parasternal short axis

-2D: distinguish functional vs. degenerative/rheumatic/carcinoid TR etiologies

-2D: proximal/distal RVOT dimension



-Color Doppler:

-identify TR etiology

-help identify TR severity

-Continuous wave Doppler

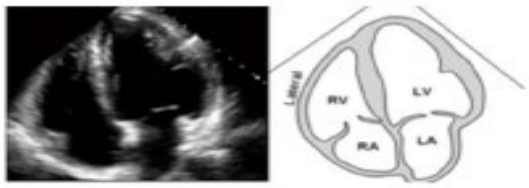
-assess density/contour of TR signal

-measure RVSP

- pulsed wave/continuous Doppler of RVOT (RVOT VTI)

-RV stroke volume

-Apical 4 chamber

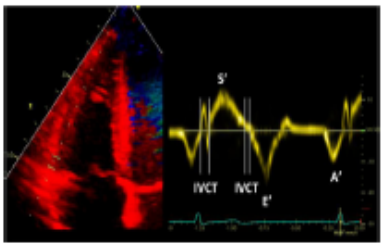


Apical 4-chamber

-2D: distinguish functional vs. degenerative/rheumatic/carcinoid TR etiologies
-2D: Measure tenting area and coaptation distance
-Coronary sinus dimension (apical 4 chamber tilted inferiorly)
-RV TAPSE (*obtained from whichever apical view with best alignment)
-Color Doppler:
    -identify TR etiology
    -help identify TR severity
-PISA:
    -lower Nyquist limit to 15-40 cm/s
    -EROA >= 40 mm2 or Regurgitant Volume >= 45 mL suggestive of severe TR
-Pulsed Doppler of TV inflow
    -get E/A with sample volume at TV tips; E >= 1 m/s suggests severe TR
-Continuous wave Doppler
    -assess density/contour of TR signal
    -measure RVSP
-RV dp/dt (from best TR signal)

-RV lateral tricuspid annulus tissue Doppler (*obtained from whichever apical view with best alignment)

Pulsed tissue Doppler S wave



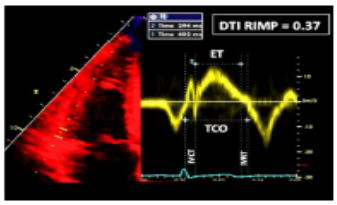
- Peak systolic velocity of tricuspid annulus by pulsed-wave DTI (cm/sec), obtained from the apical approach, in the view that achieves parallel alignment of Doppler beam with RV free wall longitudinal excursion

- Easy to perform
- Reproducible
- Validated against radionuclide EF
- Established prognostic value

- Angle dependent
- Not fully representative of RV global function, particularly after thoracotomy, pulmonary thromboendarterectomy or heart transplantation

-RV Tei index (tissue Doppler) (*obtained from whichever apical view with best alignment)

Tissue Doppler RIMP

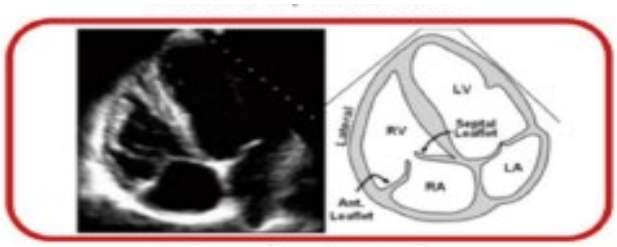


RIMP by tissue Doppler:
RIMP = (IVRT + IVCT)/ET = (TCO − ET)/ET

- Less affected by heart rate
- Single-beat recording with no need for R-R interval matching
- Unreliable when RA pressure is elevated

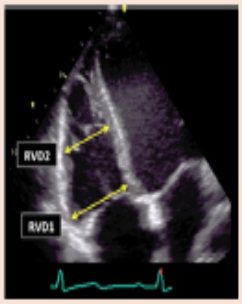
-RA volume index (via area-length or method of discs)

-RV-focused apical 4-chamber



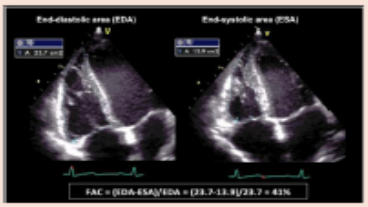
RV focused apical 4-chamber

-RV basal and mid dimensions

Echocardiographic imaging	Recommended methods	Advantages	Limitations
RV linear dimensions (inflow)* 	• Basal RV linear dimension (RVD1) = maximal transversal dimension in the basal one third of RV inflow at end-diastole in the *RV-focused view* • Mid-cavity RV linear dimension (RVD2) = transversal RV diameter in the middle third of RV inflow, approximately halfway between the maximal basal diameter and the apex, at the level of papillary muscles at end-diastole.	• Easily obtainable • Simple • Fast • Wealth of published data	• RV size may be underestimated due to the crescent RV shape • RV linear dimensions are dependent on probe rotation and different RV views; in order to permit inter-study comparison, the echocardiography report should state the window from which the measurement was performed.

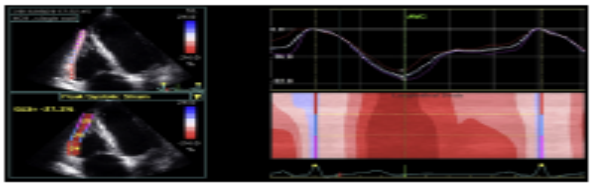
-RVEF (2D planimetry of end-sys and end-dias area) *consider contrast microbubble contrast

-

RV global systolic function FAC 	RV FAC in RV-focused apical four-chamber view: RV FAC (%) = 100 × (EDA − ESA)/EDA	• Established prognostic value • Reflects both longitudinal and radial components of RV contraction • Correlates with RV EF by CMR	• Neglects the contribution of RV outflow tract to overall systolic function • Only fair inter-observer reproducibility

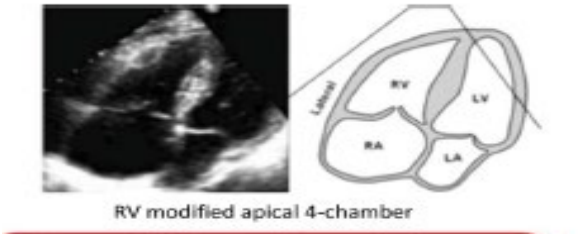
-RV global longitudinal strain

GLS



• Peak value of 2D longitudinal speckle tracking derived strain, averaged over the three segments of the RV free wall in RV-focused apical four-chamber view (%)

-RV modified apical 4-chamber



RV modified apical 4-chamber

-subcostal views with IVC/SVC and R/L hepatic vein visualization

-hepatic vein flow reversal
-Bubble study – looking at reflux in hepatic veins
-measure IVC flow and hepatic vein dimension
-measure SVC flow and dimensions
-measure distance between hepatic vein os and IVC-RA junction
-measure RV free wall thickness
-(post CAVI) identify position of Edwards-Sapien valve in relation to hepatic vein os and IVC-RA junction

-3D TTE of TV (obtained in any view with greatest TV visualization)

-distinguish functional vs. degenerative/rheumatic/carcinoid TR etiologies
-Measure tenting area and coaptation distance
-Color Doppler:
    -identify TR etiology
    -help identify TR severity
-Vena contracta: EROA > 75 mm2 by 3D Color – severe TR

-3D TTE of RV

-quantify RV volume with full volume acquisition

References:

Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, JASE Jan 2015; 28:1-39.

European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease) European Journal of Echocardiography (2010) 11, 307-332

APPENDIX B: VARC-2 ENDPOINT DEFINITIONS

TABLE 1. Risk factors not captured by traditional risk scores

Comorbidities	Definition/criteria	Diagnostic modalities
Porcelain aorta or severely atherosclerotic aorta	Heavy circumferential calcification or severe atheromatous plaques of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible	Noncontrast axial CT at levels: Sinotubular junction Tubular ascending aorta between the sinotubular junction and the innominate artery Innominate artery Entire transverse arch
Frailty	Slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity, loss of independence Criteria: 5 m walking time* Grip strength* BMI <20 kg/m^2 and/or weight loss 5 kg/year Serum albumin <3.5 g/dL Cognitive impairment or dementia	Medical history Physical examination Physical performance measures Cognitive assessments Laboratory tests
Severe liver disease/cirrhosis	Any of the following: Child-Pugh class C MELD score ≥10 Portal-caval, spleno-renal, or transjugular intrahepatic portal shunt Biopsy proven cirrhosis with portal hypertension or hepatocellular dysfunction	Medical history Physical examination Laboratory tests Child-Pugh classification MELD score Liver biopsy
Hostile chest	Any of the following or other reasons that make redo operation through sternotomy or right anterior thoracotomy prohibitively hazardous: Abnormal chest wall anatomy due to severe kyphoscoliosis or other skeletal abnormalities (including thoracoplasty, Potts' disease) Complications from prior surgery Evidence of severe radiation damage (eg, skin burns, bone destruction, muscle loss, lung fibrosis, or esophageal stricture) History of multiple recurrent pleural effusions causing internal adhesions	Medical history Physical examination Chest x-ray CT scan
IMA or other critical conduit(s) crossing midline and/or adherent to posterior table of sternum	A patent IMA graft that is adherent to the sternum such that injuring it during reoperation is likely. A patient may be considered at extreme risk if any of the following are present: The conduit(s) are radiographically indistinguishable from the posterior table of the sternum. The conduit(s) are radiographically distinguishable from the posterior table of the sternum but lie within 2–3 mm of the posterior table.	Axial CT scan images illustrating the graft crossing the midline so that the distance from sternum to graft can be measured. Angiogram from the lateral and PA projections and/or a CPR or VR (volume rendering) 3D reconstructed CT scan image showing relationships between the graft and the sternum
Severe pulmonary hypertension Severe right ventricular dysfunction	Primary or secondary pulmonary hypertension with PA systolic pressures greater than two-thirds of systemic pressure Criteria as defined by the guidelines (eg, TAPSE <15 mm, RV end-systolic area >20 cm^2, etc)†	Echocardiography, right and left-heart-catheterization documenting PA and systemic pressures Documentation of secondary causes of pulmonary hypertension

CT, Computed tomography; *BMI*, body mass index; *MELD*, Model for End-Stage Liver Disease; *CPR*, curved planar reformation; *RV*, right ventricular; *IMA*, internal mammary artery; *PA*, pulmonary artery; *TAPSE*, tricuspid annular plane systolic excursion. *Variable with respect to age and gender without validated scientific thresholds. †Rudski et al.[71]

TABLE 2. Mortality

All-cause mortality
Cardiovascular mortality
Any of the following criteria
Death due to proximate cardiac cause (eg, myocardial infarction, cardiac tamponade, worsening heart failure)
Death caused by noncoronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease
All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events
Sudden or unwitnessed death
Death of unknown cause
Noncardiovascular mortality
Any death in which the primary cause of death is clearly related to another condition (eg, trauma, cancer, suicide)

TABLE 3. Myocardial infarction

Periprocedural MI (≤72 h after the index procedure)
- New ischemic symptoms (eg, chest pain or shortness of breath), or new ischemic signs (eg, ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q-waves in at least 2 contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality) AND
- Elevated cardiac biomarkers (preferable CK-MB) within 72 h after the index procedure, consisting of at least 1 sample postprocedure with a peak value exceeding 15× as the upper reference limit for troponin or 5× for CK-MB.* If cardiac biomarkers are increased at baseline (>99th percentile), a further increase in at least 50% postprocedure is required AND the peak value must exceed the previously stated limit

Spontaneous MI (>72 h after the index procedure)
- Any 1 of the following criteria:
- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile URL, together with the evidence of myocardial ischemia with at least 1 of the following:
  - Symptoms of ischemia
  - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]
  - New pathological Q-waves in at least 2 contiguous leads
  - Imaging evidence of a new loss of viable myocardium or new wall motion abnormality
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- Pathological findings of an acute myocardial infarction

*Previously in the original VARC it was 10× and 5× for troponin and CK-MB, respectively.

=

TABLE 4. Stroke and TIA

Diagnostic criteria
Acute episode of a focal or global neurological deficit with at least 1 of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting 1 side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
Stroke: duration of a focal or global neurological deficit ≥24 h; OR <24 h if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death
TIA: duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct
No other readily identifiable nonstroke cause for the clinical presentation (eg, brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated neurologist*
Confirmation of the diagnosis by at least 1 of the following:
Neurologist or neurosurgical specialist
Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone
Stroke classification
Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue
Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage
A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic
Stroke definitions†
Disabling stroke: an mRS score of 2 or more at 90 days and an increase in at least 1 mRS category from an individual's prestroke baseline
Nondisabling stroke: an mRS score of <2 at 90 days or one that does not result in an increase in at least 1 mRS category from an individual's prestroke baseline

mRS, Modified Rankin Scale. *Patients with nonfocal global encephalopathy will not be reported as a stroke without unequivocal evidence of cerebral infarction-based upon neuroimaging studies (CT scan or Brain MRI). †Modified Rankin Scale assessments should be made by qualified individuals according to a certification process.[23-25]

TABLE 5. Bleeding

Life-threatening or disabling bleeding
Fatal bleeding *(BARC type 5)* OR
Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome *(BARC type 3b and 3c)* OR
Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery *(BARC type 3b)* OR
Overt source of bleeding with drop in hemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units* *(BARC type 3b)*
Major bleeding *(BARC type 3a)*
Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND
Does not meet criteria of life-threatening or disabling bleeding
Minor bleeding *(BARC type 2 or 3a, depending on the severity)*
Any bleeding worthy of clinical mention (eg, access site hematoma) that does not qualify as life-threatening, disabling, or major

BARC, Bleeding Academic Research Consortium[29]; *RBC*, red blood cell. *Given that 1 *unit* of packed RBC typically will raise the hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated.

TABLE 6. Acute kidney injury (AKIN classification*)

Stage 1
Increase in serum creatinine to 150%-199% (1.5-1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dL (≥26.4 mmol/L) OR
Urine output <0.5 mL/kg/h for >6 but <12 h
Stage 2
Increase in serum creatinine to 200%-299% (2.0%-2.99% increase compared with baseline) OR
Urine output <0.5 mL/kg/h for >12 but <24 h
Stage 3†
Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) OR
Urine output <0.3 ml/kg/h for ≥24 h OR
Anuria for ≥12 h

The increase in creatinine must occur within 48 h. *Mehta et al.[31] †Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.

TABLE 7. Vascular access site and access-related complications

Major vascular complications
Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudoaneurysm OR
Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) *leading to* death, life-threatening or major bleeding,* visceral ischemia, or neurological impairment OR
Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR
The use of unplanned endovascular or surgical intervention *associated* with death, major bleeding, visceral ischemia or neurological impairment OR
Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR
Surgery for access site-related nerve injury OR
Permanent access site-related nerve injury
Minor vascular complications
Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) *not leading to* death, life-threatening or major bleeding,* visceral ischemia, or neurological impairment OR
Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR
Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR
Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)
Percutaneous closure device failure
Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

*Refers to VARC bleeding definitions.

TABLE 8. Conduction disturbances and arrhythmias

Up to 72 h, continuous rhythm monitoring is recommended in order to maximize the detection of arrhythmias
Data elements to be collected should include
Baseline conduction abnormalities, paroxysmal or permanent atrial fibrillation (or flutter), and the presence of permanent pacemaker*
Implant-related new or worsened cardiac conduction disturbance (new or worsened first-degree atrioventricular (AV) block, second-degree AV block (Mobitz I or Mobitz II), third-degree AV block, incomplete right bundle branch block, right bundle branch block, intraventricular conduction delay, left bundle branch block, left anterior fascicular block, or left posterior fascicular block, including block requiring a permanent pacemaker implant
Persistent or transient high-degree AV block. High-grade AV block is persistent if it is present *every* time the underlying rhythm is checked
New permanent pacemaker implantation, with precision of the indication and the number of days postimplant of the placement of new permanent pacemaker
New-onset atrial fibrillation (or flutter)†
Any new arrhythmia resulting in hemodynamic instability or requiring therapy‡

*Type of permanent pacemaker should be recorded (eg, defibrillator, single vs dual chamber, biventricular). †New-onset atrial fibrillation (or flutter) is diagnosed as any arrhythmia within hospitalization that has the ECG characteristics of atrial fibrillation (or flutter) and lasts sufficiently long to be recorded on a 12-lead ECG, or at least 30 s on a rhythm strip. ‡Therapy includes electrical/medical cardioversion or initiation of a new medication (oral anticoagulation, rhythm, or rate controlling therapy).

TABLE 9. Other TAVI-related complications

Conversion to open surgery
Conversion to open sternotomy during the TAVI procedure secondary to any procedure-related complications
Unplanned use of cardiopulmonary bypass (CPB)
Unplanned use of CPB for hemodynamic support at any time during the TAVI procedure
Coronary obstruction
Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the valve prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVI procedure
Ventricular septal perforation
Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVI procedure
Mitral valve apparatus damage or dysfunction
Angiographic or echocardiographic evidence of new damage (chordae papillary muscle, or to the leaflet) to the mitral valve apparatus or dysfunction (eg, restrictions due to the THV) of the mitral valve during or after the TAVI procedure
Cardiac tamponade
Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the TAVI procedure
Endocarditis
Any 1 of the following:
Fulfilment of the Duke endocarditis criteria*
Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a reoperation
Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy
Valve thrombosis
Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related should not be reported as valve thrombosis
Valve malpositioning
Valve migration
After initial correct positioning, the valve prosthesis moves upwards or downwards, within the aortic annulus from its initial position, with or without consequences
Valve embolization
The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus
Ectopic valve deployment
Permanent deployment of the valve prosthesis in a location other than the aortic root
TAV-in-TAV deployment
An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and/or function, during or after the index procedure

TAVI, Transcatheter aortic valve implantation; *THV*, transcatheter heart valve. *Durack et al.[72]

TABLE 10. Prosthetic valve dysfunction

	Prosthetic aortic valve stenosis*		
	Normal	**Mild stenosis**	**Moderate/severe stenosis**
Quantitative parameters (flow-dependent)†			
Peak velocity (m/s)	<3 m/s	3-4 m/s	>4 m/s
Mean gradient (mm Hg)	<20 mm Hg	20-40 mm Hg	>40 mm Hg
Quantitative parameters (flow-independent)			
Doppler velocity index‡	>0.35	0.35-0.25	<0.25
Effective orifice area§	>1.1 cm^2	1.1-0.8 cm^2	<0.8 cm^2
Effective orifice area‖	>0.9 cm^2	0.9-0.6 cm^2	<0.6 cm^2
	Prosthesis–patient mismatch (PPM)		
	Insignificant	**Moderate**	**Severe**
Indexed effective orifice area¶ (cm^2/m^2)	>0.85 cm^2/m^2	0.85-0.65 cm^2/m^2	<0.65 cm^2/m^2
Indexed effective orifice area# (cm^2/m^2)	>0.70 cm^2/m^2	0.90-0.60 cm^2/m^2	<0.60 cm^2/m^2
	Prosthetic aortic valve regurgitation		
	Mild	**Moderate**	**Severe**
Semiquantitative parameters			
Diastolic flow reversal in the descending aorta—PW	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
Circumferential extent of prosthetic valve paravalvular regurgitation (%)**	<10%	10%-29%	≥30%
Quantitative parameters‡			
Regurgitant volume (mL/beat)	<30 mL	30-59 mL	≥60 mL
Regurgitant fraction (%)	<30%	30-49%	≥50%
EROA (cm^2)	0.10 cm^2	0.10-0.29 cm^2	≥0.30 cm^2

PW, Pulsed wave; *EROA*, effective regurgitant orifice area. *In conditions of normal or near normal stroke volume (50-70 mL). †These parameters are more affected by flow, including concomitant aortic regurgitation. ‡For LVOT >2.5 cm, significant stenosis criteria is <0.20. §Use in setting of BSA ≥1.6 cm^2 (note: dependent on the size of the valve and the size of the native annulus). ‖Use in setting of BSA <1.6 cm^2. ¶Use in setting of BMI <30 kg/cm^2. #Use in setting of BMI ≥30 kg/cm^2. **Not well-validated and may overestimate the severity compared with the quantitative Doppler.

APPENDIX C: HOVER CT PROTOCOL AND PATIENT DOSE ESTIMATION

Scanner: Philips iCT 256

Dose estimation for an average adult (BMI < 30 and equivalent to 32 cm. diameter water equivalent phantom)

I. CT Protocol:

Scan 1: Topogram

Dual projection – Cardiac chest and upper abdomen
Centered around the diaphragm

Scan 2: Spiral Retrospectively ECG Gated acquisition

Single Post-contrast phase
FOV: Z –Axis: Superior cardiac margin down to T12 vertebra (~10-12 cm)

kVp	- 100 kVp for BMI < 30; 120 kVp for BMI > 30
mAs (mA)	- 400(242) @ 100 kVp
Beam collimation	- 0.6 x 128 mm
Pitch	- 0.2
Gantry speed	- 0.27 s

Contrast: Omnipaque 350 IV, 60 cc @ 5 cc/s followed by saline 30 cc @ 5 cc/s.
Bolus track in MPA; 150 HU threshold; Minimum scan delay

Reconstruction:

Iterative reconstruction (iDose (L3) / IMR (L1) as required)
Phases: 20%, 30%, 40% R-R interval
Multiphase: 0 – 90%
Axial slice thickness/overlap – 0.8 mm/50%
COR & SAG Reconstruction 1 mm.
Axial slice thickness 3 mm (ST Kernel)

II. Patient Dose estimation:

Scan	mAs[2]	kV[2]	CTDI vol mGy	DLP mGy*cm.	Z axis FOV cm.
Topogram	30	120	0.01	1.5	30 cm.
Spiral	400	100	15.4	265	12 cm[1].

Total DLP (1.5 + 265) = 266.5 mGy-cm.
Estimated Effective Dose = 271.5 mGy-cm. x 0.015 = ~ 3.8 mSv (3.5 - 4.5 mSv)

1. Z axis FOV for spiral scanning will be superior cardiac margin down to T12 vertebra.
2. Exposure factors will be adjusted depending on the patient's BMI (i.e. smaller than normal BMI < 20 and larger than normal BMI > 30). Automatic Exposure Control (Cardiac DoseRight) will be utilized as appropriate.
3. Effective dose conversion factor based on European guidelines on quality criteria for computed tomography EUR 16262.

All studies are supervised by a Board certified Radiologist.

APPENDIX D: INCLUSION/EXCLUSION CHECKLIST

I. Study Information

Protocol Title:	**Heterotopic Implantation Of the Edwards-Sapien 3 Transcatheter Aortic Valve in the Inferior Vena cava for the treatment of severe tricuspid Regurgitation**
IRB Number:	
Principal Investigator:	**Brian O'Neill, MD**

II. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Patients must be at least 21 years old	☐	☐	
2. The patient must have severe, symptomatic (ACC/AHA Stage D symptoms) tricuspid regurgitation (TR) as assessed by 2D echocardiogram with evidence of peripheral and central venous congestion (specifically lower extremity edema and abdominal ascites requiring diuretics.)	☐	☐	
3. The patient must be evaluated by a "heart team" of physicians including an interventional cardiologist, cardiothoracic surgeon, heart failure specialist, and imaging specialist, and presented for review at a local multi-disciplinary conference. By consensus, the heart team must agree (and verify in the case review process) that valve implantation will likely benefit the patient.	☐	☐	

4. 4. The heart team must agree that medical factors preclude operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Also, other factors which may increase the patients perceived surgical risk for inclusion in the trial will be clearly delineated if they are present. These include, but are not limited to the following as defined by VARC 2: Frailty, Hostile chest, porcelain aorta, IMA or other critical conduit crossing the midline or adherent to the posterior table of sternum, severe right ventricular (RV) dysfunction. The surgeons' consultation notes shall specify the medical or anatomic factors leading to that conclusion. At least one of the cardiac surgeon assessors must have interviewed and examined the patient.	☐	☐	
5. The study patient provides informed consent and agrees to comply with all required post-procedure follow-up visits, including annual visits up to 5 years	☐	☐	
Exclusion Criteria (From IRB-approved protocol)			
1. Heart Team assessment of operability (the heart team considers the patient to be a good surgical candidate)	☐	☐	
2. Evidence of an acute myocardial infarction ≤ 1 month (30 days) before the intended treatment [defined as: Q wave MI, or non-Q wave MI with total CK elevation of CK-MB ≥ twice normal in the presence of MB elevation and/or troponin level elevation (WHO definition)]	☐	☐	
3. Untreated, severe, left sided valvular heart disease including mitral regurgitation or stenosis, and aortic regurgitation or stenosis	☐	☐	

4. Mean pulmonary artery pressures ≥40mmHG and PVR >4 woods units as assessed by right heart catheterization	☐	☐	
5. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure. Examples of permanent implant would include any new heart valve. Implantation of a permanent pacemaker is excluded.	☐	☐	
6. Patients with planned concomitant surgical or transcatheter ablation for Atrial Fibrillation	☐	☐	
7. Leukopenia (WBC < 3000 cell/mL), acute anemia (Hgb < 9 g/dL), Thrombocytopenia (Plt < 50,000 cell/mL)	☐	☐	
8. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of screening evaluation	☐	☐	
9. Need for emergency surgery for any reason	☐	☐	
10. Left ventricular ejection fraction <40%	☐	☐	
11. Echocardiographic evidence of intra-cardiac mass, thrombus or vegetation	☐	☐	
12. Active upper GI bleeding within 3 months (90 days) prior to procedure	☐	☐	
13. A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure	☐	☐	
14. Recent CVA clinically confirmed (by neurologist) or neuroimaging confirmed stroke or transient ischemic attack (TIA) within 6 months (180 days) of the procedure	☐	☐	
15. Estimated life expectancy < 1 year	☐	☐	

16. Expectation that patient will not improve despite treatment of tricuspid regurgitation	☐	☐	
17. Currently participating in another investigational cardiac device study or any other clinical trial, including drugs or biologics. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials	☐	☐	
18. Active bacterial endocarditis within 6 months (180 days) of procedure	☐	☐	
19. Patients with signs or symptoms of SVC syndrome, or hepatic cirrhosis not felt due to passive congestion from TR	☐	☐	
20. Subject unable to personally provide informed consent	☐	☐	
21. FEV1<30% of predicted	☐	☐	
22. MELD score >21	☐	☐	

*****All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, and medical record review.

III. Statement of Eligibility

This subject is ☐ **eligible** / ☐ **ineligible** for participation in the study.

Signature:	Date:
Printed Name:	

APPENDIX E: HIGH RISK DOCUMENTATION

Documentation of High Risk/Inoperability

Subject ID#_____ was evaluated by the heart team on (date) _____ and is unsuitable for surgery due to:

☐Probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement (specifically, the probability of death or serious, irreversible morbidity is $\geqslant$ 50%).

☐The subject was interviewed and examined by the heart failure physician (name) _____, MD on (date): _____

☐The subject was interviewed and examined by the cardiac surgeon (name) _____, MD on (date): _____

☐Other factors, which would elevate the patient's surgical risk which are unique to this patient and not reflected in the risk score calculation include*:

_____
_____
_____
_____
_____
_____
_____

*The cardiac surgeon's consultations note must specify the medical or anatomic factors leading to this conclusion.

_____ _____

Signature of Site Investigator Date