Abbott	Clinical Investigation Plan Cover Page

NCT Number: NCT03227757
TRILUMINATE
Trial to Evaluate Treatment with Abbott Transcatheter Clip Repair System in Patients with Moderate or Greater Tricuspid Regurgitation (TRILUMINATE)
Study Document No: Protocol 16-517
Version 2.0
Date: 01-FEB-2018

Sponsor

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PROTOCOL #16-517

Trial to Evaluate Treatment with Abbott Transcatheter Clip Repair System in Patients with Moderate or Greater Tricuspid Regurgitation (TRILUMINATE)

Protocol Number	#16-517
Version Number	Version 2.0
Date	01 February 2018
[redacted]	[redacted]
Planned Number of Sites and Region(s)	Up to 25 Sites in Europe, Canada and United States of America
[redacted]	[redacted]
Trial Type	A prospective single arm multi-center trial in EU, Canada and US sites
[redacted]	[redacted]
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COMPLIANCE STATEMENT:

This trial will be conducted in accordance with this Protocol/Clinical Investigational Plan, the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812, 21 CFR Part 54, 21 CFR Part 11, 45 CFR Part 46, and OUS ISO14155) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the trial will be approved by the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) of the respective investigational site and by the applicable regulatory authorities.

PROTOCOL SUMMARY

Trial Name and Number	TRILUMINATE Trial Number #16-517
Title	Trial to Evaluate Treatment with Abbott Transcatheter Clip Repair System in Patients with Moderate or Greater Tricuspid Regurgitation (TRILUMINATE)
Objectives	To evaluate performance of the Tricuspid Valve Repair System (TVRS) in patients with symptomatic moderate or greater tricuspid regurgitation who are deemed appropriate for percutaneous transcatheter intervention by the site heart team.
Intended Use	The Tricuspid Valve Repair System (TVRS) is intended for reconstruction of the insufficient tricuspid valve through tissue approximation.
Investigational or Trial Device	Tricuspid Valve Repair System (TVRS)
Targeted number of subjects to receive study device	A minimum of 85 subjects will be enrolled and undergo the TVRS procedure in up to 25 sites [redacted]
Clinical Trial/Investigation Design	Prospective, Single Arm, Multi-Center Trial. Patients will be evaluated at baseline, discharge, 30 days, 6 months, 1 year, 2 years, and 3 years
Primary Effectiveness Endpoint	Echocardiographic Tricuspid Regurgitation (TR) reduction at least 1 grade at 30 days post-procedure, to be tested against a pre-specified performance goal.
Primary Safety Endpoint	A composite of Major Adverse Event (MAE) at 6-months, to be tested against a pre-specified performance goal. Major Adverse Events (MAE) occurring after femoral vein puncture. MAE as listed below will be adjudicated by the Clinical Events Committee: • Cardiovascular Mortality, • Myocardial Infarction (MI), • Stroke, • New onset renal failure, • Endocarditis requiring surgery • Non-elective Cardio-Vascular (CV) surgery for TVRS device-related AE post-index procedure.
Secondary Endpoints	**Acute Secondary Endpoints:** • Acute Procedural Success (APS): Successful implantation of the TVRS Clip with resulting at least 1 grade reduction in TR severity as determined by the

	Echocardiography Core Laboratory (ECL) assessment of a discharge echocardiogram (30-day echocardiogram will be used if discharge echocardiogram is unavailable or uninterpretable). Subjects who die or undergo tricuspid valve surgery before discharge are an APS failure. • Acute Device Success: Successful access, delivery of the Clip and removal of device delivery system. Successful delivery of the Clip is the deployment of the device as planned, with no additional unplanned surgery or re-intervention related to the device or access procedure. • Implant Success Rate: Successful delivery and deployment of the Clip(s) with achievement of leaflet approximation(s) and retrieval of the delivery catheter • Total Procedure Time: defined as the time elapsed from the first of any of the following: intravascular catheter placement or trans-esophageal echocardiogram (TEE), to the removal of the last catheter and TEE • Device Time: defined as the time the Steerable Guide Catheter is placed in the right atrium until the time the TVRS Delivery System is retracted into the Steerable Guide Catheter • Fluoroscopy Duration: defined as the duration of exposure to fluoroscopy during the TVRS procedure • Length of hospital stay for the index TVRS procedure • Location to which subject was discharged (home, home health or another facility) ○ If subject discharged to another facility, length of stay at facility to which subject was discharged **Clinical Composite Endpoints:** • MAE at discharge, 30 days,1 year, 2 years and 3 years **Clinical Component Endpoints:** Clinical Endpoints at 30 days, 6 months, 1 year, 2 years and 3 years: • Components of MAE • All-cause mortality • NYHA Functional Class • Tricuspid valve surgery (including type of surgery) • New use of any cardiac rhythm management devices (Pacemakers, Implantable Cardioverter-Defibrillator (ICD), and Cardiac Resynchronization Therapy (CRT)), including reason for intervention • Additional TVRS intervention and reason for intervention

	Additional Clinical Endpoints: • Major bleeding at 30 days • Pulmonary Thromboembolism at 30 days • New Onset Renal Failure at 30 days and 6 months • New Onset Liver Failure at 30 days and 6 months • New onset atrial fibrillation at 30 days, 6 months and 1 year. • Change in diuretic(s) used at 30 days, 6 months, and 1 year (as compared to baseline) <u>Patient-reported Quality of Life (QoL) and Health Economics and Outcomes Research (HEOR) Endpoints: at Baseline, 30 days, 6 months, 1 year, 2 years and 3 years*:</u> • Distance walked in the 6-Minute Walk Test (6MWT distance or 6MWD) • KCCQ QoL scores • SF-36 QoL scores • Number and duration of re-hospitalizations and reason for re-hospitalization (i.e., heart failure, cardiovascular, non-cardiovascular) *Actual rates/scores and the relative change from baseline to each follow-up time point. <u>Prevalence of Device or Procedure-Related Adverse Events:</u> Device or procedure-related adverse events will be broken down into those that occur within 30 days of the procedure and those that occur after 30 days of the procedure. Examples of procedure or device-related adverse events are: • Myocardial perforation • Damage to tricuspid valve apparatus • Access Site bleeding requiring surgery • Non-vascular bleeding <u>Echocardiographic Endpoints</u> Echocardiographic endpoints will be assessed by the Echocardiography Core Laboratory (ECL) and reported at baseline, discharge, 30 day, 6 months, 1 year, 2 year, and 3 year post-implantation (unless indicated).

	• TR Severity Grade • Effective Regurgitant Orifice Area (EROA) • Regurgitant Volume • Regurgitation Jet Area • Vena Contracta Width • Proximal Isovelocity Surface Area (PISA) Radius • Inferior Caval Vein Diameter • Tricuspid Annular Diameters (Antero-Posterior (A-P) and Septal-Lateral (S-P)) • Tricuspid Annular area • Tricuspid Valve Area • Tenting Area (At baseline only) • Tenting Distance (At baseline only) • Tricuspid Leaflet Tethering Distance (At baseline only) • Right Ventricular End Diastolic Dimension (RVEDD) • Right Ventricular End Systolic Dimension (RVESD) • Right Ventricular Fractional Area Change • Right Ventricular Systolic Pressure (RVSP) • Right Atrial Volume • Tricuspid Annular Plane Systolic Excursion (TAPSE) • Right Ventricular Free Wall Strain • Mean Tricuspid Valve Gradient • Cardiac Output • Forward Stroke Volume (Left Ventricle) • Left Ventricular Ejection Fraction (LVEF) • Single Leaflet Device Attachment • Embolization of the TVRS Clip or TVRS System components • Tricuspid Valve Stenosis
Exploratory Endpoints	<u>Hemodynamics through Right Heart Catheterization:</u> Right heart catheter measurements at: • Immediately before TVRS procedure: Measurements to include: right atrial a-wave/v-wave, right atrial and ventricular pressures, pulmonary resistance, Pulmonary Artery (PA) pressures and cardiac output), • Post-procedure Right Atrial Catheterization, immediately after TVRS procedure (right-atrial a-wave/v-wave, right atrial pressure)
Subject Follow-up	Subjects will have scheduled office visit evaluations at the following time points (Schedule details in **Table 2**):

	• Baseline • Discharge • 30 days • 6 months • 1 year • 2 years • 3 years
Key Inclusion Criteria	**General Inclusion Criteria:** 1. Age ≥18 years and ≤90 years at time of consent and must not be a member of a vulnerable population. 2. Subject or a legally authorized representative (where allowed per local regulations; refer to **Section 5.1.1**) must provide written informed consent prior to any trial related procedure 3. Subject must agree not to participate in any other clinical trial for a period of one year following the index procedure 4. In the judgment of the investigator at the site, subject has been adequately treated per applicable standards (including medical management), including treatment for coronary artery disease, mitral regurgitation and heart failure (e.g., with cardiac resynchronization therapy, revascularization, and/or optimal medical therapy as appropriate; see APPENDIX II: Definitions for definition of optimal therapy) at least 30-days prior to index procedure. The Eligibility Committee must concur that the subject has been adequately treated. 5. New York Heart Association (NYHA) Functional Class II (conditional), III, or ambulatory IV a. Subjects with moderate TR: Only NYHA Class III or IV may be considered for inclusion b. Subjects with severe or greater TR: NYHA II, III, or IV may be considered for inclusion 6. No indication for left-sided or pulmonary valve correction (Left sided heart valve disease or pulmonary stenosis needs to be adequately treated for at least 30-days prior to study enrollment for TR treatment) 7. The Site Heart Team [redacted] concur the benefit-risk analysis supports intervention for tricuspid regurgitation per current guidelines for the management of valvular heart disease (refer to Section 5.1.1) and that the subject is at high risk for tricuspid valve surgery . 8. In the judgment of the TVRS implanting Investigator, femoral vein access is determined to be feasible and can accommodate a 25 Fr catheter.

	Echocardiographic Inclusion Criteria: 9. Moderate or greater (≥2+) Tricuspid Regurgitation determined by the assessment of a qualifying transthoracic echocardiogram (TTE) and transesophageal echocardiogram (TEE) confirmed by the Echocardiography Core Lab (ECL) (refer to **Appendix VIII**). [redacted]. 10. Tricuspid valve anatomy determined to be suitable for implantation (e.g., no severe leaflet defects preventing proper placement of the TVRS, Ebstein Anomaly) determined by the site heart team 11. Tricuspid valve anatomy evaluable by TTE and TEE
Key Exclusion Criteria	**General Exclusion Criteria:** 1. Subject is currently participating in another clinical trial that has not yet completed its primary endpoint. 2. Pregnant or nursing subjects and those who plan pregnancy in the period up to 1 year following index procedure. Female subjects of child-bearing potential must have a negative pregnancy test done within 7 days prior to the index procedure per site standard test. 3. Severe uncontrolled hypertension Systolic Blood Pressure (SBP) ≥ 180 mmHg and/or Diastolic Blood Pressure (DBP) ≥ 110 mm Hg) 4. Systolic Pulmonary Artery Pressure >60mmHg (echo determined) 5. Prior tricuspid valve leaflet surgery or any currently implanted prosthetic tricuspid valve, or any prior transcatheter tricuspid valve procedure. 6. Mitral Regurgitation moderate-severe or greater severity (≥3+) 7. Pacemaker or ICD leads that would prevent appropriate placement of the TVRS Clip 8. Active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic disease (i.e. noncompliant, perforated). 9. MI or known unstable angina within prior 30 days to enrollment 10. Percutaneous coronary intervention within prior 30 days to enrollment 11. Hemodynamic instability defined as systolic pressure < 90 mmHg with or without afterload reduction, cardiogenic

	shock or the need for inotropic support or intra-aortic balloon pump or other hemodynamic support device. 12. Cerebrovascular Accident (CVA) within prior 3 months to enrollment 13. Chronic dialysis 14. Bleeding disorders or hypercoagulable state 15. Active peptic ulcer or active gastrointestinal (GI) bleeding 16. Contraindication, allergy or hypersensitivity to dual antiplatelet and anticoagulant therapy **Note**: Contraindication to either antiplatelet or anticoagulant therapy (individually not both therapies) is not an exclusion criterion. 17. Active infections requiring current antibiotic therapy (if temporary illness, patients may enroll 4 weeks after discontinuation of antibiotics with no active infection). 18. Known allergy or hypersensitivity to device materials 19. In the judgment of the investigator, a condition that could limit a patient's ability or unwillingness to participate in the study, comply with study required testing and/or follow-up visits or that could impact scientific integrity of the study 20. Evidence of intracardiac, inferior vena cava (IVC), or femoral venous mass, thrombus or vegetation. 21. Life expectancy of less than 12 months due to non-cardiac conditions **Echocardiographic Exclusion Criteria:** 22. Tricuspid valve stenosis 23. Left Ventricular Ejection Fraction (LVEF) ≤20% 24. Tricuspid valve leaflet anatomy which may preclude clip implantation, proper clip positioning on the leaflets or sufficient reduction in TR. This may include: a. Evidence of calcification in the grasping area b. Presence of a severe coaptation defect (> 2cm) of the tricuspid leaflets
[redacted]	[redacted]

1.0 INTRODUCTION

1.1 Trial Objective

To evaluate safety and effectiveness of the Tricuspid Valve Repair System (TVRS) in patients with symptomatic moderate or greater tricuspid regurgitation (TR) who are deemed appropriate for percutaneous transcatheter intervention by the site heart team.

1.2 Trial Design

The TRILUMINATE Trial is a prospective, single arm, multi-center study of the TVRS for treating symptomatic moderate or greater TR in patients currently on medical management and who are deemed high risk for tricuspid valve surgery and appropriate for percutaneous transcatheter intervention.

A minimum of 85 subjects will be prospectively enrolled and undergo the TVRS procedure in up to 25 sites in Europe, Canada and the United States:

[redacted]

All subjects will have scheduled office visit evaluations at baseline, discharge, 30 days, 6 months, 1 year, 2 years, and 3 years.

2.0 BACKGROUND INFORMATION

2.1 Background and Rationale

2.1.1 Tricuspid Regurgitation Description and Etiology

Similar to the etiologies of mitral regurgitation, tricuspid regurgitation (TR) results from either degenerative disease of the leaflets (primary or degenerative TR) or from pathologic dilation of the right ventricle (secondary or functional TR). Both result in mal-coaptation of the leaflets, which allows blood flow back into the right atrium during systole. Lead-induced TR (not observed in MR) is caused by either pacemaker or implantable cardioverter-defibrillator (ICD) lead impairment of the tricuspid valve preventing proper coaptation. TR has long been an overlooked condition and not clinically understood. By the time TR manifests in the form of clinical symptoms, the patient is usually much sicker.

Current treatment guidelines for TR indicate medical therapy to address venous congestion (e.g., diuretics) and/or treatment of the underlying disease to reduce TR (e.g., surgery). Percutaneous treatments are currently not commercially available for treatment of TR.

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2.1.4 TVRS Trial Rationale

Tricuspid regurgitation occurs when the tricuspid valve fails to close properly, causing blood to flow backwards into the right atrium. If left untreated, TR can lead to right heart enlargement and right heart failure. In the US alone, there is an estimated 1.6 million patients suffering from TR[17]. Additionally, an estimated 50% of patients with mitral regurgitation have moderate to severe tricuspid regurgitation[18]. TR is currently undertreated by surgery. In the US, surgeons treat only 5,500 patients per year, most of them in conjunction with left heart surgeries. When treating the valves, surgeons choose repair 90% of the time versus replacement (10%)[19].

Per the ESC guidelines for surgical and interventional treatment of tricuspid regurgitation (2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease[20]), surgery is indicated (Class I) in patients with either: 1) severe TR undergoing left-sided valve surgery or, 2) symptomatic with severe isolated primary TR without severe right ventricular (RV) dysfunction. Surgery should be considered (Class IIA) in patients with moderate tricuspid regurgitation undergoing left-sided valve surgery. Similarly, the 2017 AHA/ACC Guidelines (2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease[21]) indicate: 1) surgery for patients with severe TR undergoing left-sided surgery (Class I), or 2) surgery can be beneficial for mild or greater FTR at the time of left-sided surgery with either tricuspid annular dilatation or prior evidence of right HF (Class IIa), or 3) surgery can be beneficial for severe primary TR who are unresponsive to medical therapy (Class IIa). Although surgery is a Class I recommendation for severe TR patients undergoing tricuspid valve (TV) surgery carry a high risk of surgical mortality rate of approximately 8% - 18%[22,23,24] and a higher rate of

[16] Avenatti E, Barker CM, Little SH. Tricuspid regurgitation repair with a MitraClip device: the pivotal role of 3D transoesophageal echocardiography. Eur Heart J Cardiovasc Imaging. 2017 Mar 1;18(3):380.
[17] Stuge O., Liddicoat J., et al. JTCS 2006;132:1258-61
[18] Argarwal et al. Circ Cardiovasc Interv 2009;2:565-573
[19] Rogers JH.Circulation2009:119: 2718-25
[20] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017 Sep 21;38(36):2739-2791.
[21] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017 Jun 20;135(25):e1159-e1195.
[22] Ratnatunga CP, Edwards MB, Dore CJ, Taylor KM. Tricuspid valve replacement: UK Heart Valve Registry mid-term results comparing mechanical and biological prostheses. Ann Thorac Surg. 1998 Dec;66(6):1940-7.
[23] Moraca RJ, Moon MR, Lawton JS, Guthrie TJ, Aubuchon KA, Moazami N, Pasque MK, Damiano RJ Jr. Outcomes of tricuspid valve repair and replacement: a propensity analysis. Ann Thorac Surg. 2009 Jan;87(1):83-8
[24] McCarthy PM, Bhudia SK, Rajeswaran J, Hoercher KJ, Lytle BW, Cosgrove DM, Blackstone EH. Tricuspid valve repair: durability and risk factors for failure. J Thorac Cardiovasc Surg. 2004 Mar;127(3):674-85.

35% for repeat tricuspid valve surgery[25]. Additionally, many patients are refractory to medical therapy and continue with high morbidity and mortality rates associated with TR. There is an unmet need for patients who are refractory to medical therapy whose only current option is surgery which is associated with high risks and may not be appropriate for a subset of these patients. With no other currently available options, TR will persist and gradually increase in severity; thus, having increased morbidity and mortality rates as the condition progresses[26]. A percutaneous approach that is effective and safe is thus an appealing alternative.

Abbott proposes to initiate a clinical trial to evaluate the performance of a modified version of the MitraClip NY system, called the Tricuspid Valve Repair System, for percutaneous treatment of TR.

2.2 Summary of Investigational Device

2.2.1 Name of the Investigational Device

The investigational device to be used in this trial is the Tricuspid Valve Repair System (TVRS).

2.2.2 Intended Indication for Use

The Tricuspid Valve Repair System (TVRS) is intended for reconstruction of the insufficient tricuspid valve through tissue approximation.

2.2.3 Description of the Investigational Device

The TVRS configuration consists of two parts: 1) a Clip Delivery System, which includes an implantable Clip [redacted], a Steerable Sleeve and a Delivery Catheter; and 2) a Steerable Guide Catheter which includes a dilator [redacted]

The Clip Delivery System is used to advance and manipulate the implantable TVRS Clip for proper positioning and placement on the tricuspid valve leaflets. The Clip Delivery System is designed to deploy the implant in a way that requires multiple steps to ensure safe delivery of the device. The Steerable Guide Catheter provides a conduit to access the tricuspid valve and with the addition of Steerable Sleeve to position the Clip relative to the valve. The Delivery Catheter is designed to deliver and deploy the Clip. The Steerable Guide and Clip Delivery System are steered and actuated by the use of control knobs, levers and fasteners [redacted]

The implantable Clip is fabricated with metal alloys and polyester fabric that are commonly used in cardiovascular implants. The Clip can be repeatedly opened, closed and inverted by deliberate manipulations of the Delivery Catheter Handle. The Clip positions are designed to allow the Clip to grasp and approximate the leaflets of the tricuspid valve.

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[25] Bernal JM, Morales D, Revuelta C, Llorca J, Gutiérrez-Morlote J, Revuelta JM. Reoperations after tricuspid valve repair. J Thorac Cardiovasc Surg. 2005 Aug;130(2):498-503.

[26] Bruce CJ, Connolly HM. Right-sided valve disease deserves a little more respect. Circulation. 2009 May 26;119(20):2726-34.

[redacted]

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3.0 CLINICAL TRIAL/INVESTIGATION FLOW AND FOLLOW-UP SCHEDULE

For screening, each subject must undergo clinical assessments and echocardiography; both transesophageal echocardiogram (TEE) and transthoracic echocardiogram (TTE) are acquired. **Figure 2** shows the overall flow of the trial.

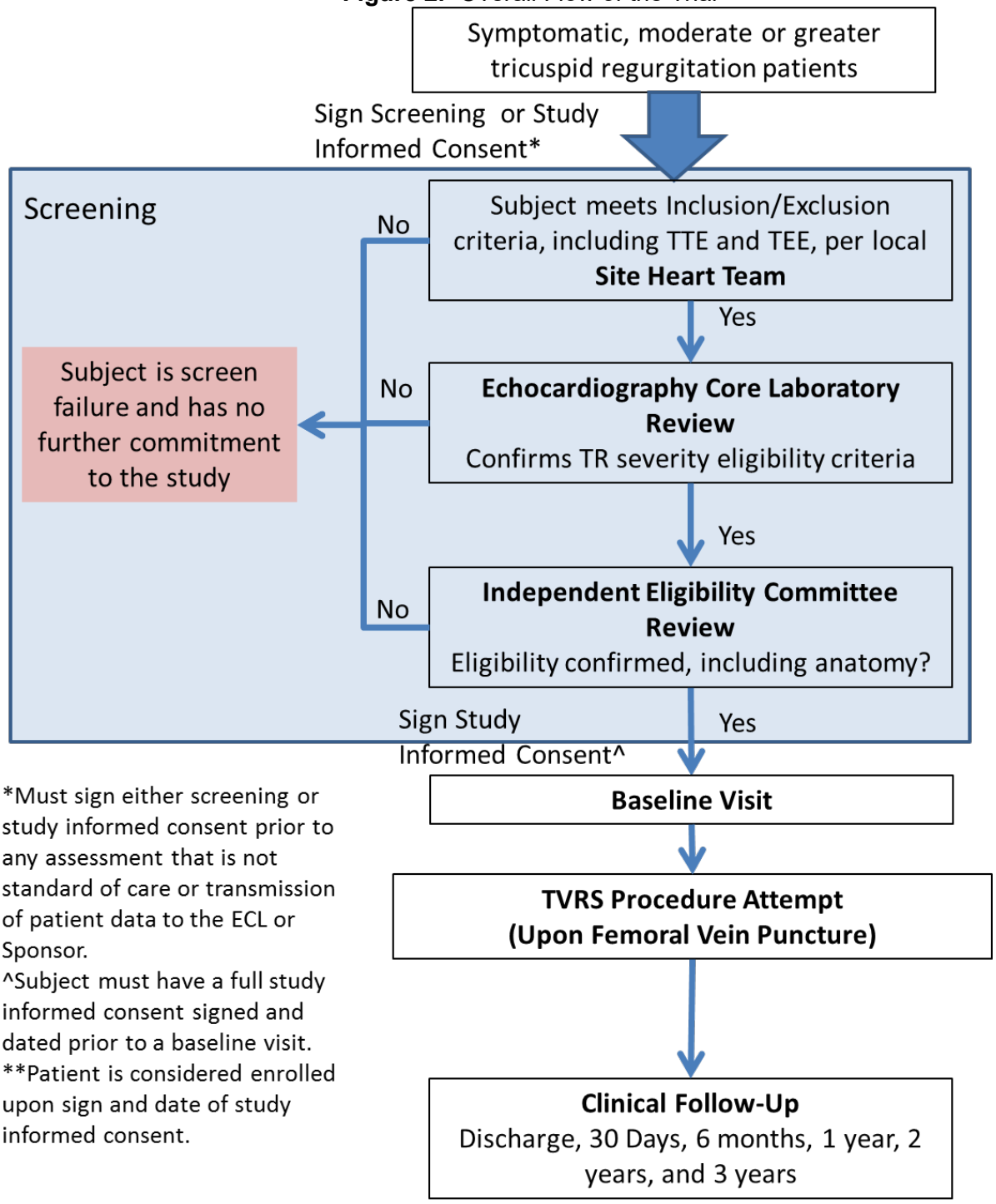
Subjects will be screened for study eligibility by the Investigator as well as the Site Heart Team per the inclusion and exclusion criteria. A cardiac surgeon and an echo specialist will assess subjects for eligibility criteria for surgical appropriateness and echocardiography, respectively.

The TTE and TEE will be submitted to the Echocardiography Core Laboratory (ECL) for assessment of TR severity. Once the subject is deemed by the ECL to meet TR severity and the subject meets all inclusion and none of the exclusion criteria, an Independent Eligibility Committee [redacted] will review pertinent medical history to make the final determination regarding eligibility of prospective subjects, including eligibility of tricuspid valve anatomy (see **APPENDIX IX**). Once the Eligibility Committee confirms that the subject is eligible for the TVRS procedure in the trial, the subject may be scheduled for the TVRS procedure.

[redacted]

Enrolled subjects will undergo clinical evaluations at baseline, discharge, 30 days, 6 months, 1 year, 2 years, and 3 years following the TVRS procedure (see **Table 2** for Clinical Evaluation Schedule).

Figure 2: Overall Flow of the Trial



*Must sign either screening or study informed consent prior to any assessment that is not standard of care or transmission of patient data to the ECL or Sponsor.
^Subject must have a full study informed consent signed and dated prior to a baseline visit.
**Patient is considered enrolled upon sign and date of study informed consent.

3.1 Number of Subjects to be Enrolled

Eligible subjects who have signed and dated study informed consent are considered enrolled in the TVRS TRILUMINATE Trial. [redacted]

A minimum of 85 subjects will be enrolled and undergo the TVRS procedure at up to 25 investigational sites. [redacted]

3.2 Measures Taken to Avoid and Minimize Bias

The following steps will be taken to minimize bias in the conduct of the trial and analyses of clinical data.

3.2.1 Subject Recruitment

Investigational sites will attempt to recruit subjects who meet trial eligibility criteria.

- Candidates will be considered for the trial after they have been informed of trial requirements and have signed and dated the informed consent form. See **Section 5.2** Subject Screening and Informed Consent for additional details on subject screening and informed consent process.
- Transthoracic and transesophageal echocardiographic criteria for trial eligibility will be confirmed by an independent Echocardiography Core Laboratory.
- All baseline tests and assessments must be completed prior to the procedure.
- Subjects will be eligible for the procedure only after the sites' clinical personnel have confirmed and documented that the subject has met all eligibility criteria, the ECL has confirmed the TR severity and tricuspid valve anatomy eligibility criteria, and the Eligibility Committee has confirmed that the subject is on optimal medical therapy, high-risk for tricuspid valve surgery, determine eligibility of tricuspid valve anatomy, and the benefit-risk analysis supports utilization of percutaneous transcatheter intervention.

3.2.2 Site Heart Team

[redacted] The site heart team will assess subject eligibility based on the subject being at high risk for tricuspid valve surgery, the benefit-risk analysis supports intervention for tricuspid regurgitation per current guidelines (see Section 5.1.1) and anatomic suitability for the percutaneous TVRS procedure based on clinical and echocardiographic criteria.

3.2.3 Administration of Assessments

A standardized script will be used when administering the assessments (NYHA Functional Class, 6MWT, and QoL questionnaires). To minimize bias and undue influence, the QoL questionnaires must be completed by the subject or his/her legal representative (where allowed per local regulations). In the latter case, a note to file must be completed to document the inability of subject to complete the questionnaire.

3.2.4 Review of Echocardiographic Images by the Independent Echocardiographic Core Lab

The ECL will confirm subject's screening echocardiography images for TR severity eligibility criteria are met per the 2017 ASE guideline for TR grading[27], and defined in **Appendix VIII**. Subjects failing the criteria will be considered a screen failure and not allowed into the trial. Additionally, the ECL will be responsible for assessing TR severity and echocardiographic analyses at all visits (baseline and follow-ups) and operate according to the ECL Manual of Operations.

[redacted]

[redacted]

3.2.6 Safety and Effectiveness Monitoring

- All adverse events will be reviewed [redacted].
- Adverse events requiring adjudication will be submitted to an independent Clinical Events Committee (CEC; **Section 11.8.3**).
- A Data Safety Monitoring Board (DSMB) will review accumulating safety data as described in **Section 11.8.2**

3.3 Follow-Up Compliance

The Sponsor will work with investigational sites to maintain a high follow-up compliance as follows:

1. Sponsor will emphasize to the site the importance of subject follow-up during site initiation visits and subsequent communications. Site should communicate the importance to each subject.
2. Sites will be informed to promptly reschedule any missed subject visits, and to reinforce the necessity of a follow-up visit.

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[27] Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, Little SH, Shah DJ, Shernan S, Thavendiranathan P, Thomas JD, Weissman NJ. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr. 2017 Apr;30(4):303-371.

3. Site is advised to involve Sponsor when needed. Example: Arrange alternate transportation if a scheduled visit is missed due transportation/travel issues, or due to subject illness
4. Sites should document reasons for any subject withdrawals from the trial, and request agreement for a follow-up call from the investigator at the end of the trial.
5. Sites should monitor follow-up rates closely to promptly identify and address any issues.

Additionally, investigational sites will be educated on the importance of maintaining low rates of withdrawals, and will be expected to make all effort to maintain low withdrawals during trial conduct. Withdrawals from the trial will require discussion between investigator and the Sponsor.

[redacted]

4.0 ENDPOINTS

4.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is echocardiographic TR reduction at least 1 grade at 30 days post-procedure, to be tested against a pre-specified performance goal.

4.2 *Primary Safety Endpoint*

The primary safety endpoint is a composite of Major Adverse Event (MAE) at 6-months to be evaluated against a pre-specified performance goal.

MAE is defined as a composite of:

- Cardiovascular Mortality,
- MI,
- Stroke,
- New onset renal failure,
- Endocarditis requiring surgery, and
- Non-elective CV surgery for TVRS device-related AE post-procedure.

4.3 Secondary Endpoints

4.3.1 Acute Secondary Endpoints

- Acute Procedural Success (APS): Successful implantation of the Clip with resulting at least 1 grade reduction in TR severity as determined by the Echocardiography Core Laboratory (ECL) assessment of a discharge echocardiogram (30-day echocardiogram will be used if discharge echocardiogram is unavailable or uninterpretable). Subjects who die or undergo tricuspid valve surgery before discharge are an APS failure.

- Acute Device Success: Successful access, delivery of the Clip and removal of device delivery system. Successful delivery of the Clip is the deployment of the device as planned, with no additional unplanned surgery or re-intervention related to the device or access procedure.

- Implant Success Rate: Successful delivery and deployment of the Clip(s) with achievement of leaflet approximation(s) and retrieval of the delivery catheter.

- Total Procedure Time: Total Procedure Time is defined as the time elapsed from the first of any of the following: intravascular catheter placement or trans-esophageal echocardiogram (TEE), to the removal of the last catheter and TEE.

- Device Time: Device time is defined as the time the Steerable Guide Catheter is placed in the right atrium until the time the TVRS Delivery System is retracted into the Steerable Guide Catheter.

- Fluoroscopy Duration: Fluoroscopy duration is defined as the duration of exposure to fluoroscopy during the TVRS procedure.

- Length of hospital stay for the index TVRS procedure

- Location to which subject was discharged (home, home health or another facility)
    - If subject discharged to another facility, length of stay at facility to which subject was discharged

4.3.2 Clinical Composite Endpoints

- MAE at discharge, 30 days,1 year, 2 years and 3 years

4.3.3 Clinical Components Endpoints

- Clinical Endpoints will be assessed at 30 days, 6 months, 1 year, 2 years and 3 years:
  - Components of MAE
  - All-cause mortality
  - NYHA Functional Class
  - Tricuspid valve surgery (including type of surgery),
  - New use of any cardiac rhythm management devices (Pacemakers, ICDs, and CRT), including reason for intervention
  - Additional TVRS intervention and reason for intervention

- Additional Clinical Endpoints:
  - Major bleeding at 30 days
  - Pulmonary Thromboembolism at 30 days
  - New Onset Renal Failure at 30 days and 6 months
  - New Onset Liver Failure at 30 days and 6 months
  - New onset atrial fibrillation at 30 days, 6 months and 1 year.
  - Change in diuretic(s) used at 30 days, 6 months, and 1 year (as compared to baseline)

4.3.4 Patient Reported Endpoints

Patient-reported Quality of Life (QoL) and Health Economics and Outcomes Research (HEOR) Endpoints: at baseline, 30 days, 6 months, 1 year, 2 years and 3 years*:

- Distance walked in the 6-Minute Walk Test (6MWT distance or 6MWD)
- KCCQ QoL scores
- SF-36 QoL scores
- Number and duration of re-hospitalizations and reason for re-hospitalization (i.e., heart failure, cardiovascular, non-cardiovascular)

*Actual rates/scores and the relative change from baseline to each follow-up time point.
Note: As applicable to patients in the US trial sites, it is anticipated that the patients enrolled in the TRILUMINATE trial will be U.S. Medicare beneficiaries age 65 and over.

4.3.5 Device or Procedure-Related Adverse Events

Prevalence of Device or Procedure-Related Adverse Events

[redacted] Examples of device-related adverse events are:

- Myocardial perforation
- Damage to tricuspid valve apparatus
- Access Site bleeding requiring surgery
- Non-vascular bleeding

4.3.6 Echocardiographic Endpoints

Echocardiographic endpoints will be assessed by the Echocardiography Core Laboratory (ECL) and reported at baseline, discharge, 30 day, 6 months, 1 year, 2 year, and 3 year post-implantation (unless indicated).

- TR Severity Grade
- Effective Regurgitant Orifice Area (EROA)
- Regurgitant Volume
- Regurgitation Jet Area
- Vena Contracta Width
- PISA Radius
- Inferior Caval Vein Diameter
- Tricuspid Annular Diameters (A-P and S-L)
- Tricuspid Annular area
- Tricuspid Valve Area
- Tenting Area (At baseline only)
- Tenting Distance (At baseline only)
- Tricuspid Leaflet Tethering Distance (At baseline only)
- Right Ventricular End Diastolic Dimension (RVEDD)
- Right Ventricular End Systolic Dimension (RVESD)
- Right Ventricular Fractional Area Change
- Right Ventricular Systolic Pressure (RVSP)
- Right Atrial Volume
- Tricuspid Annular Plane Systolic Excursion (TAPSE)
- Right Ventricular Free Wall Strain
- Mean Tricuspid Valve Gradient
- Cardiac Output
- Forward Stroke Volume (Left Ventricle)
- Left Ventricular Ejection Fraction (LVEF)
- Single Leaflet Device Attachment
- Embolization of the TVRS Clip or TVRS System components
- Tricuspid Valve Stenosis

4.4 Exploratory Endpoints

Right Heart Catheterization: Right heart catheter measurements at:

- Immediately before TVRS procedure: Measurements to include: right atrial a-wave/v-wave, right atrial and ventricular pressures, pulmonary resistance, PA pressures and cardiac output),
- Post-procedure Right Atrial Catheterization, immediately after TVRS procedure (right-atrial a-wave/v-wave, right atrial pressure)

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

The trial will enroll a minimum of 85 subjects who will undergo the TVRS procedure. This trial will enroll male and female subjects from the heart failure population who have at least moderate grade TR, and satisfy the general and echocardiographic inclusion and exclusion criteria. Subjects must sign and date the informed consent prior to conducting any trial-specific procedures not considered standard of care.

Any patient data transmitted from their institution to the ECL or Sponsor must have prior signed and dated informed consent.

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate subject. If some of the clinical and laboratory tests are not included in site standard tests, they must be done, but after signed and dated informed consent is obtained. Subjects must meet ALL of the inclusion criteria to be considered for the clinical evaluation. If ANY of the exclusion criteria are met, the subject is excluded from the clinical evaluation and will not qualify for the TVRS procedure.

5.1.1 General Inclusion Criteria

Subjects must meet all of the following inclusion criteria to participate in the trial:

1. Subject must be ≥18 years and ≤90 years at time of consent and must not be a member of a vulnerable population.
2. Subject or a legally authorized representative* (where allowed per local regulations) must provide written informed consent prior to any trial related procedure.
3. Subject must agree not to participate in any other clinical trial for a period of one year following the index procedure.
4. In the judgment of the investigator at the site, the subject has been adequately treated per applicable standards (including medical management), including for coronary artery disease, mitral regurgitation and heart failure (e.g., with cardiac resynchronization therapy, revascularization, and/or optimal medical therapy as appropriate; see APPENDIX II: Definitions for definition of optimal therapy) at least 30-days prior to index procedure. The Eligibility Committee must concur that the subject has been adequately treated.
5. New York Heart Association (NYHA) Functional Class II (conditional), III, or ambulatory IV
    a. Subjects with moderate TR: Only NYHA Class III or IV may be considered
    b. Subjects with severe or greater TR: NYHA II, III, or IV may be considered for inclusion
6. No indication for left-sided or pulmonary valve correction (Left sided heart valve disease or pulmonary stenosis needs to be adequately treated for at least 30-days prior to study enrollment for TR treatment).
7. The Site Heart Team [redacted] concur benefit-risk analysis supports intervention for tricuspid regurgitation per current guidelines for the management of valvular heart disease[28, 29] and that the subject is at high risk for tricuspid valve surgery.

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* For Switzerland Only: Subject must provide written informed consent prior to any trial related procedure. A legally authorized representative will not be allowed to provide informed consent for a patient.

[28] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Jul 11;70(2):252-289.

[29] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL;

8. In the judgment of the TVRS implanting Investigator, femoral vein access is determined to be feasible and can accommodate a 25 Fr catheter.

5.1.2 Echocardiographic Inclusion Criteria

9. Moderate or greater (≥2+) Tricuspid Regurgitation determined by the assessment of a qualifying transthoracic echocardiogram (TTE) and transesophageal echocardiogram (TEE) confirmed by the Echocardiography Core Lab (ECL) (Refer to **Appendix VIII**). [redacted]
10. Tricuspid valve anatomy determined to be suitable for implantation (e.g., no severe leaflet defects preventing proper placement of the TVRS, Ebstein Anomaly) determined by the site heart team
11. Tricuspid valve anatomy evaluable by TTE and TEE

5.1.3 General Exclusion Criteria

Subjects who meet any of the following exclusion criteria may not participate in the trial:

1. Subject is currently participating in another clinical trial that has not yet completed its primary endpoint.
2. Pregnant or nursing subjects and those who plan pregnancy in the period up to 1 year following index procedure. Female subjects of child-bearing potential must have a negative pregnancy test done within 7 days prior to the index procedure per site standard test.

   Note: Female patients of childbearing potential should be instructed to use safe contraception (e.g., intrauterine devices, hormonal contraceptives: contraceptive pills, implants, transdermal patches hormonal vaginal devices, injections with prolonged release.) It is accepted, in certain cases, to include subjects having a sterilised regular partner or subjects using a double barrier contraceptive method. However, this should be explicitly justified in special circumstances arising from the study design, product characteristics and/or study population.

3. Severe uncontrolled hypertension (SBP ≥ 180 mmHg and/or DBP ≥ 110 mm Hg)
4. Systolic Pulmonary Artery Pressure >60mmHg (echo determined)
5. Prior tricuspid valve leaflet surgery or any currently implanted prosthetic tricuspid valve, or any prior transcatheter tricuspid valve procedure.
6. Mitral Regurgitation moderate-severe or greater severity (≥3+)
7. Pacemaker or ICD leads that would prevent appropriate placement of TVRS Clip
8. Active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic disease (i.e. noncompliant, perforated).
9. MI or known unstable angina within prior 30 days prior to enrollment
10. Percutaneous coronary intervention within prior 30 days prior to enrollment

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ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017 Sep 21;38(36):2739-2791.

11. Hemodynamic instability defined as systolic pressure < 90 mmHg with or without afterload reduction, cardiogenic shock or the need for inotropic support or intra-aortic balloon pump or other hemodynamic support device.
12. Cerebrovascular Accident (CVA) within prior 3 months prior to enrollment
13. Chronic dialysis
14. Bleeding disorders or hypercoagulable state
15. Active peptic ulcer or active gastrointestinal (GI) bleeding
16. Contraindication, allergy or hypersensitivity to dual antiplatelet and anticoagulant therapy.
    Note: Contraindication to either antiplatelet or anticoagulant therapy (individually not both therapies) is not an exclusion criterion.
17. Active infections requiring current antibiotic therapy (if temporary illness, patients may enroll 4 weeks after discontinuation of antibiotics with no active infection).
18. Known allergy or hypersensitivity to device materials
19. In the judgment of the investigator a condition that could limits a patient's ability or unwillingness to participate in the study, comply with study required testing and/or follow-up visits or that could impact scientific integrity of the study.
20. Evidence of intracardiac, inferior vena cava (IVC), or femoral venous mass, thrombus or vegetation.
21. Life expectancy of less than 12 months due to non-cardiac conditions

5.1.4 Echocardiographic Exclusion Criteria:

22. Tricuspid Stenosis
23. Left Ventricular Ejection Fraction (LVEF) ≤20%
24. Tricuspid valve leaflet anatomy which may preclude clip implantation, proper clip positioning on the leaflets or sufficient reduction in TR. This may include:
    a. Evidence of calcification in the grasping area
    b. Presence of a severe coaptation defect (> 2cm) of the tricuspid leaflets

5.2 Subject Screening and Informed Consent

5.2.1 Subject Screening

Subjects admitted for a procedure must be screened for clinical trial eligibility by a member of the clinical trial/investigation team (physician and/or research coordinator) previously trained to the clinical trial Protocol, and if applicable will be entered into a site specific screening log.

Subjects meeting the general inclusion and exclusion criteria will be asked to sign and date an informed consent. These patients will then be entered into the screening log (as applicable, also the reason for screen failure as well as supporting data will be entered into the log).

Screening imaging will be used for the final assessment of subject eligibility. Subjects who do not satisfy echocardiographic inclusion and exclusion criteria (screen failure) will not undergo the TVRS procedure in this clinical trial/investigation. These subjects will be followed for 30 days after consent for adverse events, then withdrawn from the study.

Patient data will be collected following enrollment into the trial.

Screening of a subject for possible inclusion in the trial may commence once a subject has been identified as symptomatic, having moderate or greater grade tricuspid regurgitation. Subject's general medical

eligibility must be assessed by the sites through subject's interview and subject's medical record review prior to the TVRS procedure and within the time windows stipulated (see **Table 2** for more details). Relevant standard of care tests performed prior to obtaining informed consent can be used to determine eligibility if those tests were within the screening time window. Signed and dated informed consent **must** be obtained prior to any test/evaluation that is not standard of care. Additionally, signed and dated informed consent is **required** prior to any transmission of patient data to the ECL or Sponsor.

Site Heart Team will evaluate the following assessments [redacted]:

- Subject meets all general and echocardiographic inclusion criteria
- Subject does not meet any of the general and echocardiographic exclusion criteria
- Subject is evaluated by the Site Heart Team to confirm that they are adequately treated per applicable standards, including treatment for coronary artery disease, right ventricular dysfunction, mitral regurgitation, tricuspid regurgitation, and heart failure. Subjects with current or prior symptoms of heart failure and reduced LVEF should be on stable optimally up-titrated medical therapy recommended according to current guidelines as standard of care for heart failure therapy in the United States and Europe. See '**APPENDIX II: Definitions'** for definition of optimal therapy. Additionally, the Site Heart Team must confirm that the subject is appropriate for percutaneous transcatheter intervention.
- Clinical, physical, and labs exams must be performed:
  - Medical history
  - Weight, temperature, blood pressure and heart rate
  - Modified Rankin Scale assessment
  - Perform a pregnancy test, as appropriate
  - Measure BNP or NT-proBNP level
  - Measure AST or ALT level

[redacted]

- If Site Heart Team deems this subject is at high risk for tricuspid valve surgery and an appropriate candidate for TVRS, their TEE and TTE images will be submitted to the independent ECL.

  [redacted]

  - Site must review the TTE and TEE images and confirm that subject has TR and suitable tricuspid valve anatomic criteria, without intracardiac mass, thrombus or vegetation. Trained Abbott personnel may provide support to sites in reviewing TTE/TEE images.
- After the ECL has confirmed subject eligibility, sites will be notified by the Sponsor to compile and submit the following information for Eligibility Committee review:
  - Obtain and review Subject's medical records and history.
  - Complete a physical exam, including an assessment of subject's cardiac status and vital signs measures (e.g. height, weight, heart rate, blood pressure and temperature)
  - Assess subject's NYHA Functional Class and Modified Rankin Scale
  - Have the subject examined by the investigator to assess optimization level of his/her medications, and appropriateness for TVRS.

- If patient does not meet any of the screening requirements, then the subject is considered a screen failure.

5.2.2 Study Informed Consent

The Investigator or designee, who has been trained on the protocol, will explain the nature and scope of the trial, potential risks and benefits of participation, and answer questions for the subjects. All subjects, or their legally authorized representatives* (where allowed per local regulations), must sign and date the Institutional Review Board (IRB)/Ethics Committee (EC) approved informed consent form prior to any clinical trial/investigation-specific procedures. The ICF must also be signed by the investigator or designate (if allowed per country specific regulations). The completed ICF must be kept in the subject's medical records. The whole consenting process, date, and provisioning of a copy to the subject must be documented in the subject's medical records.

Subjects who belong in the Vulnerable Population (definition in **Appendix II**) will not be allowed into this trial.

For US subjects: In addition, an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA), must be obtained from the subject or their legally authorized representative.

5.2.3 Enrollment of Medicare Beneficiaries (US Cohort only)

Early use of the TVRS system indicates that patients that are candidates for the therapy are an older patient population typically managed under Medicare. Investigator-driven studies showed mean ages of 78 +/- 7 years (N=18, Braun et al)[30] and 76.6 +/- 10 years (N=64, Nickenig et al)[31]. It is expected that enrolled patients in the TRILUMINATE study will be within this age range, with the demographic characteristics and cardiovascular risk factors representative of the Medicare patient population as part of the overall cohort. These criteria are not expected to have a negative effect on the recruitment or retention of underrepresented populations. Section 15 describes how all enrolled subjects, including Medicare beneficiaries, may be affected by the device under investigation.

5.3 Subject Enrollment

Subjects are enrolled in the TRILUMINATE Trial upon signing and dating the informed consent form. [redacted]

* For Switzerland Only: A legally authorized representative will not be allowed to provide informed consent for a patient.

[30] Braun D, Nabauer M, Orban M, Orban M, Gross L, Englmaier A, Rösler D, Mehilli J, Bauer A, Hagl C, Massberg S, Hausleiter J. Transcatheter treatment of severe tricuspid regurgitation using the edge-to-edge repair technique. EuroIntervention. 2017 Feb 3;12(15):e1837-e1844.

[31] Nickenig G, Kowalski M, Hausleiter J, Braun D, Schofer J, Yzeiraj E, Rudolph V, Friedrichs K, Maisano F, Taramasso M, Fam NP, Bianchi G, Bedogni F, Denti P, Alfieri O, Latib A, Colombo A, Hammerstingl C, Schueler R. Transcatheter Treatment of Severe Tricuspid Regurgitation with the Edge-to-Edge: MitraClip Technique. Circulation. 2017 Mar 23.

[redacted]

5.4 Subject Discontinuation

Withdrawal:

Each enrolled subject shall remain in the trial until completion of the required follow-up period; however, a subject's participation in any clinical trial is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Subject withdrawal by physician as clinically-indicated
- Subject lost-to follow-up as described below

The Sponsor must be notified of the reason(s) for subject discontinuation. The site will provide this information to the Sponsor. Investigators must also report this to their respective IRB/EC as defined by their institution's procedure(s).

No additional follow–up will be required or data recorded from subjects once withdrawn from the trial, except for the status (deceased/alive).

However, if a subject withdraws from the study due to problems related to the investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical investigation.

Lost-to-Follow-up:
If the subject misses two consecutive scheduled follow-up time points, and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost to follow-up. Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following, at each contact time point.

For all countries, except Switzerland:

- A minimum of 3 telephone calls over a period of 10 days to contact the subject or his/her relative/caregiver (where allowed per local regulations) should be recorded in the source documentation, including date, time, and name of site personnel trying to make contact.
- If these attempts are unsuccessful, a certified or registered letter with confirmed receipt should be sent to the subject. The registered letter will request the subject to contact the site.
- If the above attempts are unsuccessful, the patient's general practitioner shall be contacted to investigate about the subject's whereabouts and his/her health status (where allowed per local regulations).

For Switzerland Only:

- In the event that the 3 phone calls made over a 10-day period to reach the patient are unsuccessful, the patient's general practitioner shall be contacted regarding the patient's health status at the same time that the registered letter is sent to the subject. This modification

corresponds to the quick measures for capturing the whereabouts and state of health of subjects by the Swiss Competent Authority and permitted by regional regulations.
- In case of a subject not being able to be located, the monitor will verify that adequate measures have been undertaken to contact the subject's treating General Practitioner and exchange data about the whereabouts and health status of the subject.

If a subject misses one or more non-consecutive follow-up contact time points, it will be considered a missed visit. The subject may then return for subsequent visits. If the subject misses two consecutive follow-up time points the subject will be considered lost-to-follow-up.

However, if a subject withdraws from the study due to problems related to the investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical investigation.

[redacted]

[redacted]

5.6 Expected Duration of Each Subject's Participation

Three (3) Years

5.7 Number of Subjects Required to be Included in the Clinical Investigation

At least 85 subjects will be enrolled and undergo the TVRS procedure to obtain 85 analysis subjects (i.e., subjects who will be included in the analysis of endpoints).

[redacted]

[redacted]

5.9 Trial Completion

A Trial Completion eCRF must be completed for each patient when:
- the subject is considered lost to follow-up per the above definition or
- the subject withdraws from the Trial or
- the subject is withdrawn due to screen failure or
- the investigator withdraws the subject from the trial or
- the subject dies or
- the subject completes the Trial (e.g., 3 year follow-up time point has been reached) or
- the sponsor terminates the Trial.

Sponsor must be notified of the reason for subject discontinuation. The site will provide this information on the eCRF. Investigators must also report this to their EC/IRB as defined by their institution's procedure. Subjects will not be replaced.

6.0 TREATMENT AND EVALUATION OF THE TVRS

After patients successfully completed screening, the subsequent visits will be performed in the following order: Baseline, Index Procedure, Discharge, 30 day, 6 months, 1 year, 2 years and 3 years visits. Details are provided below.

6.1 Baseline Clinical Assessments

[redacted] a baseline visit must be completed (may occur on the day of, but prior to the TVRS procedure). Per **Table 2: Clinical Evaluation Schedule,** clinical assessments at baseline include medical history, weight, temperature, heart rate, blood pressure, the Short Form Health Survey (SF-36) Quality of Life (QoL) questionnaire, Kansas City Cardiomyopathy Questionnaire (KCCQ), New York Heart Association (NYHA) Functional Class, Six Minute Walk Test (6MWT) distance, blood test (includes BNP or NT-ProBNP, CK or CK-MB, blood urea nitrogen, serum creatinine, and AST or ALT) and medical history assessments. History of heart failure hospitalizations in the prior 1-year will be collected as part of the medical history at the baseline visit. Concomitant cardiovascular medications, including dosage, will also be collected at this visit.

A 12-lead ECG must be performed within 24 hours prior to the TVRS procedure to rule out an acute myocardial infarction (**Table 2: Clinical Evaluation Schedule**).

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[32] Nishimura, et al. ACC/AHA 2008 Guideline Update on Valvular Heart Disease: Focused Update on Infective Endocarditas: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2008; 118(8):887-894.

[redacted]

6.5 Follow-up for All Subjects

Required clinical follow-up will be performed at the following intervals for all subjects with TVRS procedure attempt, regardless of whether a TVRS Clip was successfully implanted:

- Discharge post-TVRS procedure
- 30 days [redacted] follow-up office visit (this visit must be conducted even if subject is in hospital)
- 6 months [redacted] follow up office visit
- 1 year [redacted] follow up office visit
- 2 years [redacted] follow up office visit
- 3 years [redacted] follow up office visit
- Discontinuation

Follow-up visits will be calculated from the date of the Procedure. Follow-up assessments can be performed at any point in the window, and should be conducted, whenever possible, by the same individual who performed the baseline tests. The subject should be followed at the investigational site where the subject was enrolled, and may be followed at another investigational site only with prior agreement from that site's Investigator and from the Sponsor.

During the physical examination at the 30-day follow-up clinic visit, the implanting or treating investigator shall examine the integrity of the TVRS Clip. At the 30-day, 6-month, 1-year, 2-year and 3-year follow-up visits, all subjects must be examined by the Investigator. Subjects must continue to take baseline medications without change during follow-up, unless clinically (medically) necessary. If there are any cardiovascular medication changes (including dosage changes), these changes should be documented on the electronic case report form. In general, neurohormonal antagonists should not be changed. Subjects implanted with the TVRS Clip must also be evaluated for device integrity. Required tests and procedures outlined below must be completed. Timing of specific tests will follow the Clinical Evaluation Schedule (**Table 2**) outlined above. All visits and tests must be completed even if the subject is in hospital.

- 12-lead ECG
- Blood draw

- Brief physical exam including vital signs (weight, heart rate, blood pressure and temperature)
- Echocardiogram – TTE at all follow-up visits and TEE at 30-day visit only
- Modified Rankin Scale (Assessment of mRS should additionally be done at 90 days after onset of stroke)
- 6-Minute Walk Test (6MWT) (excluding discharge and 30-day follow-up visit) – See **APPENDIX VI** for 6 Minute Walk Test Guidelines
- Concomitant cardiovascular medications assessment
- NYHA Functional Class assessment
- QoL questionnaires to be completed by the subject; Note: To minimize bias and undue influence, the QoL questionnaires will be completed by the subject, unless the subject is unable to complete the questionnaire on their own (a note to file must be completed to document the inability of subject to complete the questionnaire)
- Assess and record adverse events
- Assess and record protocol deviations

All subjects should continue to be monitored and treated per applicable standards of care consistent with the subject's condition. All subjects must be followed by the heart failure specialist investigator at all scheduled follow-up visits. The site Principal Investigator should collaborate with the other site investigators as applicable in determining the treatment strategy for all subjects enrolled at their site. The electronic case report forms will document changes in treatment strategy (i.e. new use of CRT, PCI, tricuspid valve surgery, and/or mitral valve surgery) and who was involved with determining changes in treatment strategy. Subjects implanted with the Clip must be evaluated for device integrity.

[redacted]

6.6 Additional Follow-up Visits

Additional subject visits may occur as clinically warranted. The following information must be collected as applicable:

- Adverse events
- Concomitant Cardiovascular Medications
- Hospitalizations
- Tricuspid valve surgery
- Additional TVRS procedure(s)

6.7 Additional Interventions for TR Reduction

It may be necessary for a subject to undergo additional interventions for TR reduction, such as an additional TVRS procedure or tricuspid valve surgery. [redacted]

Requirements for this visit are as follows:

- 12-lead ECG

[redacted]

- Blood draw (Note: if serum creatinine is elevated by at least 0.5 mg/dl on any visit compared to the prior visit or to baseline, an additional serum creatinine must be obtained between 30 and 45 days later to determine whether the increase is persistent)
- Weight, temperature, blood pressure and heart rate
- Transthoracic Echocardiogram (TTE)
- Concomitant cardiovascular medications assessment
- Assess and record adverse events
- Assess and record protocol deviations

Other scheduled follow-up visits from the date of the initial TVRS procedure must be conducted.

6.8 Heart-Related Office Visits

A Heart-Related Office Visit eCRF should be completed if a subject is seen for a heart related reason at the investigational site or at any other facility. Information pertaining to adverse events, heart failure medication changes or hospitalizations, as appropriate, should also be collected.

If an echocardiographic imaging study is performed at any visit, whether or not it is a study related visit, echocardiography images should be submitted to the ECL in a timely manner.

6.9 Tricuspid/Mitral Valve Surgery

Tricuspid and/or mitral valve surgery should not be performed during the follow-up period, unless deemed necessary by the site investigator(s). Tricuspid and/or mitral valve surgery will be considered a protocol deviation, unless the subject experiences a complication (e.g., endocarditis, clip detachment or leaflet injury) from the TVRS procedure. Subjects who undergo tricuspid and/or mitral valve surgery will continue to be followed per this Clinical Protocol. [redacted]

[redacted]

6.10 Explanted TVRS Clip

The TVRS Clip may be explanted during tricuspid valve surgery or an autopsy. If possible, fluoroscopic images with side views of the device should be obtained prior to explant. Following explant of the TVRS Clip(s) during surgery, the subject will continue to be followed as defined in **Section 6.4: Follow-up for All Subjects**. Explant information will be captured on the tricuspid Valve Surgery Form or Death Form.

7.0 ADVERSE EVENTS

To comply with worldwide standards and guidelines on clinical trial adverse event reporting, Abbott has developed uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

7.1 Definitions

7.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Note 1: This definition includes events related to the investigational medical device.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

7.1.2 Serious Adverse Event

If the AE meets any of the criteria below, it is regarded as a serious adverse event (SAE).

1) Led to a death,
2) Led to a serious deterioration in health that either:
   a) Resulted in a life-threatening illness or injury, or
   b) Resulted in a permanent impairment of a body structure or a body function, or
   c) Required in-patient hospitalization or prolongation of existing hospitalization, or
   d) Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
3) Led to fetal distress, fetal death or a congenital abnormality or birth defect.
4) An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the subject and/or may require intervention to prevent one of the outcomes listed in this definition.

Note 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

Note 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

7.1.3 Device Deficiency/Device Malfunction

Device deficiency (DD) is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended. **Note:** Performance specifications include all claims made in the labeling of the device.

A device malfunction (DM) is the failure of a device to meet its performance specifications or otherwise perform as intended, when used in accordance with the instructions for use or CIP.

7.2 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate eCRF form. Determination should be based on assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility, and patient condition (pre-existing condition).

7.2.1 Unanticipated (Serious Adverse) Device Effect [U(S)ADE]

Unanticipated serious adverse device effect (USADE) refers to 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 subjects.

7.3 Adverse Event/Device Deficiency/Product Experience Reporting

7.3.1 Adverse Event Reporting

All adverse events will be collected on each subject through the 3-year follow-up visit.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be recorded on the AE eCRF page.

Non-cardiac related abnormal laboratory values will not be considered AEs unless:
1) the investigator determined that the value is clinically significant,
2) the abnormal lab value required intervention, or
3) the abnormal lab value required subject termination from the study.

The Investigator will monitor the occurrence of AEs for each subject during the course of the clinical trial/investigation and report as required by this Protocol in **Section 7** per AE and SAE definitions. AEs need to be collected as of the time point of subject enrollment on the appropriate AE eCRF form. Additional information with regards to an adverse event should be updated within the appropriate case report form.

A fax form will be made available to allow the investigator to report SAEs in the event the entry cannot be made in the EDC (SM FORM 589: SAE Notification). This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Study site	Reporting timelines
All Study Sites	SAEs must be reported no later than 3 calendar days from the day the study personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

The date the site staff became aware that the event met the criteria of a serious adverse event must be recorded in the source document.

Serious adverse events that occurred in the user or persons other than the study subject should not be entered in the EDC system however needs to be reported via the SAE Notification Form provided by Sponsor (SM FORM 589: SAE Notification).

The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

7.3.2 Unanticipated Serious Adverse Device Effect Reporting to Sponsor and IRB

Abbott requires the Investigator to report any USADE to the sponsor within 3 calendar days of the investigator's knowledge of the event, unless local requirements are more stringent, and to the IRB/EC per IRB/EC requirements.

7.3.3 Device Deficiency/Device Malfunction Reporting

All device deficiencies/malfunctions should be reported within the EDC System on the appropriate eCRF form. A fax form will be made available to allow the investigator to report device deficiencies/malfunctions in the event that the entry cannot be made in the EDC (SM FORM 589: Device Deficiency (DD) Report Form). This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

In case a device deficiency/malfunction occurred before the patient ID is assigned, the device deficiency should be reported to the Sponsor via Abbott customer service via the fax form FRM2015541-ABT.

The investigator should report all DDs/DMs to the Sponsor as soon as possible but no later than outlined below.

Study sites	Reporting timelines
All Study Sites	DDs/DMs must be reported no later than 3 calendar days from the day the study personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

The device, if not implanted or not remaining in the subject, should be returned to Abbott.

Device deficiencies/malfunctions should be reported to the IRB/EC per the investigative site's local requirements.

7.3.4 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report the SAEs and DDs/PEs to the country regulatory authority, per local requirements. For Germany only: German specific reporting requirements are outlined in the Germany Addendum #1.

Clinical trial SAEs and device deficiencies reportable per MEDDEV 2.7/3 regulations will be submitted to European Competent Authorities by the Abbott Clinical Safety Group or designee. Contact details are provided in Appendix III.

7.4 Safety Monitoring by Data Safety Monitoring Board

The DSMB will serve in an advisory role to Abbott to ensure safety by reviewing cumulative data from the clinical trial at prescribed intervals for the purpose of safeguarding the interests of trial participants.

The DSMB may consider a recommendation for modifications or termination of the trial based on any perceived safety concerns regardless of statistical significance. The recommendations of the DSMB are not binding, and all final decisions related to trial modifications rest with Abbott.

8 ADJUDICATION OF EVENTS

8.1 The Clinical Events Committee (CEC)

The Clinical Events Committee is comprised of qualified physicians who are not investigators in the trial. The CEC will review and adjudicate pre-specified events reported by trial investigators or identified by the Safety & Surveillance personnel/designate for the trial as documented in CEC Manual of Operations (MOPs).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents in order for clinical investigation-related monitoring, audits, IRB/EC review and regulatory inspections to be performed.

Subjects providing informed consent are agreeing to allow Sponsor and/or its designee access and copying rights to pertinent information in their medical records concerning their participation in this clinical investigation. The investigator will obtain, as part of the informed consent, permission for clinical investigation monitors or regulatory authorities to review, in confidence, any records identifying the subjects in this clinical investigation. This information may be shared with regulatory agencies; however, Sponsor undertakes not to otherwise release the subject's personal and private information.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Selection of Clinical Sites and Investigators

Sponsor will select investigators qualified by training and experience, to participate in the investigation of the Clinical Investigation device. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the Principal Investigator or multidisciplinary team at the site.

11.2 Protocol Amendments

Approved Protocol amendments will be provided to the Investigators by the Sponsor prior to implementing the amendment. The Principal Investigator is responsible for notifying the IRB/EC or equivalent committee of the Protocol amendment (administrative changes) or obtaining IRB's/EC's approval of the Protocol amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the Protocol amendment. Other regulatory bodies will be notified of protocol amendments, as required per country regulation.

Acknowledgement/approval by the IRB/EC of the Protocol amendment must be documented in writing prior to implementation of the Protocol amendment. Copies of this documentation must also be provided to the Sponsor.

11.3 Training

11.3.1 Site Training

All Investigators/trial personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator meeting, a site initiation visit or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of Investigators/trial personnel will include, but is not limited to, the Protocol requirements, investigational device usage, echocardiographic imaging, electronic case report form completion and trial personnel responsibilities. All Investigators/trial personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigator/trial personnel must not perform any trial-related activities that are not considered standard of care at the site.

[redacted]

[redacted]

11.3.3 Training of Sponsor's Monitors

Sponsor and/or designated monitors will be trained to the Protocol, case report forms and investigational device usage (as appropriate). Documentation of this training will be according to written procedures.

11.4 Monitoring

Sponsor and/or designee will monitor the study over its duration according to the pre-specified monitoring plan which will include the planned extent of source data verification.

[redacted]

Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

The investigator understands and accepts the obligation to conduct the research study according to the Protocol and applicable regulations, and has signed the Investigator Agreement/Clinical Study Agreement.

The Investigator and his/her staff have sufficient time and facilities to conduct the study and that they have access to an adequate number of appropriate subjects to conduct the study.

Source documentation (including original medical records) must be available to substantiate proper informed consent procedures, adherence to Protocol procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information. The Investigator/site will permit access to such records. A monitoring visit sign-in log will be maintained at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the study monitor with a suitable working environment for review of study-related documents.

11.5 Deviations from Protocol

The Investigator will not deviate from the Protocol for any reason without prior written approval from Sponsor except in cases of medical emergencies, when the deviation is necessary to protect the rights, safety and well-being of the subject or eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing. All deviations must be reported to the Sponsor. In subject-specific deviations from the Protocol, a Protocol deviation case report form will be completed. The occurrence of Protocol deviations will be monitored by the Sponsor for evaluation of investigator compliance to the Protocol and regulatory requirements and dealt with according to written procedures. Investigators will inform their IRB/EC or equivalent committee of all Protocol deviations in accordance with their specific IRB/EC or equivalent committee reporting policies and procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the investigator and/or delegate
- Telephoning the investigator and/or delegate
- Corresponding with the investigator and/or delegate

Repeated non-compliance with the signed agreement, the Protocol or any other conditions of the study may result in further escalation in accordance with the Sponsor's written procedures including securing compliance or, at its sole discretion; Sponsor may terminate the investigator's participation in the study.

[redacted]

11.6 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical investigation records, including source documentation, for inspection and duplication during a Quality Assurance audit. In the event that an investigator is contacted by a Regulatory Agency in relation to this clinical investigation, the Investigator will notify Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide Sponsor with copies of all correspondence that may affect the review of the current clinical investigation (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). Sponsor may provide any needed assistance in responding to regulatory audits.

11.7 Sponsor Support to Clinical Trial/Investigation Site for Regulatory Body Inspection

In the event that an Investigator is contacted by a Regulatory Agency in relation to this clinical investigation, the Investigator will notify the Sponsor immediately and IRB as appropriate. The Investigator and research coordinator must be available to respond to reasonable requests and inspection queries made during the inspection process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current clinical investigation. The Sponsor may provide any needed assistance in responding to regulatory inspections.

11.8 Committees

11.8.1 Study Steering Committee

The Steering Committee is assigned by the Sponsor and comprises the Primary Investigator, as specified on the cover page of this Protocol, the Study Chairman (if applicable) and four/five dedicated members from the investigational sites. The Chairman of the core laboratories and other sponsor's personnel may also participate in the Committee meetings if appropriate. Meeting minutes from this committee will be filed with the sponsor.

The Steering Committee is responsible for overseeing the scientific and operational aspects of the study. This committee will meet regularly to monitor patient enrollment, general data collection and non-compliance with the investigation plan at individual centers, to review and act upon recommendations of the Data and Safety Monitoring Board (DSMB), to review operational issues that may arise and warrant a Protocol amendment or other corrective action and to determine policy regarding any publications arising from data generated from the performance of the study.

11.8.2 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) is an independent multidisciplinary group that is restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. The DSMB is typically composed of at least two physicians with relevant interventional experience (e.g., vascular surgeon, interventional radiologist, interventional cardiologist) and a biostatistician and is responsible for making recommendations regarding endpoint analyses and any potentially significant patient safety-related observations. The composition of the DSMB, frequency of the DSMB sessions and the statistical monitoring guidelines are described in detail in the DSMB charter. DSMB meeting minutes and recommendations are forwarded to Abbott Vascular.

11.8.3 Clinical Events Committee (CEC)

The Clinical Events Committee (CEC) is an independent adjudication body comprised of qualified physicians who are not participants in the trial. The CEC will review and adjudicate events as defined in the CEC charter and according to definitions provided in this Protocol. (See **Section 8.1**).

11.8.4 Eligibility Committee

The Eligibility Committee consisting of a Cardiac Surgeon, an Interventionalist and an Echocardiographer reviews data provided by the investigational site and echo data from the echo core laboratory, and conducts clinical assessment. The Eligibility Committee finally decides whether a patient can be enrolled in the clinical trial or not (**Appendix IX**).

12. DATA HANDLING AND RECORD KEEPING

Data Management will include documentation of the systems and procedures used in data collection for the duration of the trial.

All CRF data collection will be performed through a secure web portal and all authorized personnel with access to the Electronic Data Capture (EDC) system must use an electronic signature access method to enter, review or correct data. Passwords and electronic signatures will be strictly confidential.

All CRF data will be downloaded from the EDC system and reformatted into a data structure acceptable to Abbott Vascular. The data will be subjected to consistency and validation checks within the EDC system and will be subject to supplemental validation following download.

At the conclusion of the trial, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be archived for each investigational site and a backup copy archived with Abbott Vascular.

For the clinical trial/investigation duration, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical trial/investigation progress records, laboratory reports, electronic case report forms, signed ICFs, device accountability records, correspondence with the IRB/EC and clinical trial/investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical trial/investigation.

12.1 Source Documentation

Regulations and GCP require that the Investigator maintain information in the subject's original medical records that corroborates data collected on the case report forms. In order to comply with these regulatory requirements/GCP, the following information should be included in the subject record at a minimum and if applicable to the investigation:

- Medical history/physical condition of the subject before involvement in the trial sufficient to verify Protocol entry criteria
- Dated and signed notes on the day of entry into the trial referencing the Sponsor, Protocol number or name, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- Adverse events reported and their resolution including supporting documents such as discharge summaries, catheterization laboratory reports, ECGs, and lab results including documentation of site awareness of SAEs and of investigator device relationship assessment of SAEs.

- Study required laboratory reports and 12-lead ECGs, reviewed and annotated for clinical significance of out of range results.
- Notes regarding Protocol-required and prescription medications taken during the trial (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the trial
- Any other data required to substantiate data entered into the CRF

12.2 Electronic Case Report Form Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the Protocol and eCRF completion. eCRF data will be collected for all patients that are enrolled into the trial.

12.3 Record Retention

The Sponsor will archive and retain all documents pertaining to the trial as per the applicable regulatory record retention requirements. The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical trial/investigation records.

12.4 Investigational Devices

12.4.1 Investigational Device Accountability

Abbott ships investigational devices only to the site Principal Investigator or his/her designee at each site.

The Investigator will maintain adequate records of the receipt and disposition of the investigational device, including part number and serial number, date used, patient ID number and treating physician. Inventory Accountability Log supplied by the Sponsor will be used. The Inventory Accountability Log must document the disposition of all investigational devices including those that have been returned to Sponsor.

All investigational devices that are associated with a device failure or device deficiency must be returned immediately to the Sponsor.

13. ETHICAL CONSIDERATION

13.1 Institutional Review Board/Medical Ethics Committee Review

Institutional Review Board (IRB)/ Ethics Committee (EC) approval for the Protocol and ICF/other written information provided to the patient will be obtained by the Principal Investigator at each investigational site prior to participation in this clinical trial/investigation. The approval letter must be received prior to the start of this clinical trial/investigation and a copy must be provided to the Sponsor. No changes will be made to the Protocol or ICF or other written information provided to the patient without appropriate approvals, including IRB/EC, the Sponsor, and/or the regulatory agencies.

Until the clinical trial/investigation is completed, the Investigator will advise his/her IRB/EC of the progress of this clinical trial/investigation, per IRB/EC requirements. Written approval must be obtained from the IRB/EC yearly to continue the clinical trial/investigation, or according to each institution's IRB/EC

requirements (US studies only). Further, any amendments to the Protocol as well as associated ICF changes will be submitted to the IRB/EC and written approval obtained prior to implementation, according to each institution's IRB/EC requirements.

No investigative procedures other than those defined in this Protocol will be undertaken on the enrolled subjects without the written agreement of the IRB/EC and the Sponsor.

14. PUBLICATION POLICY

The data and results from the trial are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical trial. The Investigators will not use the Clinical trial/investigation-related data without the written consent of the Sponsor for any other purpose than for Clinical trial/investigation completion or for generation of publication material, as referenced in the Clinical trial/investigation Site Agreement. The publication and/or presentation of results from a single clinical trial/investigation site are not allowed until publication and/or presentation of the multi-center results. The Sponsor acknowledges that the trial's Principal Investigator intends to publish a multi-center publication regarding the clinical trial/investigation results. The Sponsor must receive any proposed publication and/or presentation materials at least 60 days prior to the proposed date of the presentation or the initial submission of the proposed publication in order for the materials to be reviewed by the Sponsor in compliance with the Sponsor's publication policy set forth in the Clinical trial/investigation Site Agreement.

The Sponsor will register the Clinical Investigation on www.clinicaltrials.gov, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. Sponsor shall be responsible for any such registration and results posting as required by ClinicalTrials.gov. Institution and/or Principal Investigator(s) shall not take any action to register the Trial. A full report of the pre-specified outcomes, including any negative outcomes, will be made public through the ClinicalTrials.gov website according to the requirements of Section 801 of the FDA Amendments Act.

15. RISK ANALYSIS

15.1 Anticipated Clinical Benefits

The causes of tricuspid regurgitation (TR) can be classified as degenerative (or primary) when due to abnormal tricuspid valve (TV) pathology, functional (or secondary), or induced by pacemaker or defibrillator leads[1]. Functional tricuspid regurgitation (FTR) is the most common and an increasingly recognized source of morbidity in patients with left-sided valvular heart disease, particularly those with chronic mitral valve regurgitation (MR)[2]. FTR occurs mainly from tricuspid annular dilation and right ventricular enlargement, which can result from heart failure due to myocardial or valvular causes, right ventricular volume and pressure overload, or dilation of cardiac chambers.

Current guidelines indicate medical therapy (i.e. diuretics) to address venous congestion and/or treatment of the underlying disease to reduce TR. Surgical treatment of FTR is recommended at the time of left sided valve repair[3]. FTR may diminish or disappear as right ventricular function improves following treatment for the underlying cause. If Functional tricuspid regurgitation (FTR) is left untreated at the time of surgical mitral valve repair, significant residual FTR can negatively impact perioperative outcomes, functional class, and survival. TR does not reliably resolve after successful mitral valve surgery.

Severe TR is an independent predictor of long-term mortality given that 1-year survival rate in patients with severe TR is 65% compared with 90% of patients without TR[4]. If treated surgically, it is often in late

stage of the disease with poor outcomes. Operative mortality in high risk patients has been reported to be 22%[5].

Tricuspid Valve Repair System (TVRS) would be used to treat symptomatic moderate or severe TR subjects who are not responding to medical therapy. Left untreated these patients will continue to progress with higher morbidity and mortality rates associated with this disease.

[redacted]

- [redacted]

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Risks associated with the TVRS and procedure, together with their likely incidence, is described in the IFU and **Appendix IV**. There may be risks related to the device that are unknown at present. Likewise, the exact frequency of the risk may be unknown.

15.3 Residual Risks Associated with the Investigational Device, as Identified in the Risk Analysis Report

The residual risks to the patient was identified from the literature review or the complaint data review.

15.4 Risks Associated with Participation in Clinical Investigation

The risks related to the procedure have been included in Appendix IV.

15.5 Possible Interactions with Protocol-Required Concomitant Medications

The most prevalent risks associated with the anticoagulant and antiplatelet medications have been included in Appendix IV.

15.6 Steps that will be Taken to Control or Mitigate the Risks

In-depth recommendations, special precautions and instructions regarding patient selection, device handling, device placement and system removal are included in the IFU.

Risks associated with the use of the TVRS during this clinical study are minimized through device design, investigator selection and training, pre-specified patient eligibility requirements, study monitoring to ensure adherence to the protocol and the use of a DSMB.

These risk management aspects are detailed below:

[redacted]

Investigator Selection and Training: It is also stated in the IFU that the devices can only be used by physicians who have received appropriate training on how to use the device. This statement is interpreted to mean that the physician users are expected to be aware of the known and foreseeable safety risks associated with the use of the devices including the surgical and/or non-surgical treatment of these conditions.

- Only physicians who are skilled in the manipulation of catheter based technology in the vasculature and heart, and have a good understanding of the risks associated with these manipulations, will be selected as investigators for this trial. In addition, site investigators will undergo training on the techniques required to optimally place the device on the tricuspid leaflets. The physician users are expected to be aware of the known and foreseeable safety risks associated with the use of the devices including the surgical and/or non-surgical treatment of these conditions.
- Emergency surgical back-up should be available as per the institution's standard procedures. The Sponsor will be available to provide technical support to answer questions regarding the function and operation of the TVRS.
- Each case would be proctored by an Abbott field personnel.
- Pre-specified patient eligibility requirements - as stated in **Section 5** of the protocol.

Ensuring Strict Adherence to the Clinical Protocol

The trial will be carefully monitored by the Sponsor monitor (or designee) to ensure adherence to the Clinical Investigational Plan. Adverse events and device deficiencies will be reported to Abbott /designee and will be monitored internally for safety surveillance purposes. A DSMB will be used for the study. Stopping rules will be discussed with the DSMB and applied for subject safety through enrollment

15.7 Risk to Benefit Rationale

Current treatments for clinically significant TR are generally limited to medical management and/or tricuspid valve repair or replacement. Medical management may reduce symptoms and improve quality of life in some patients, but fails to address the underlying pathophysiology of TR (e.g., malcoaptation of tricuspid valve leaflets). Tricuspid valve replacement (TVR) is associated with high mortality and morbidity. Frequently, TVR is performed in critically ill patients with high frequency of re-intervention. Patients with clinically significant TR who are difficult for tricuspid valve surgery have limited therapeutic

options and present with a high rate of heart failure hospitalizations, poor quality of life, and impaired functional capacity. [redacted]

[redacted]

[redacted]

APPENDIX I: ABBREVIATIONS AND ACRONYMS

6MWT or 6MWD – Six Minute Walk Test (Distance)
AE – Adverse Event
APS – Acute Procedural Success
CRO – Contract Research Organization
CRT or CRT-D – Cardiac Resynchronization Therapy Device
CV - Cardiovascular
CVA – Cerebrovascular Accident
DBP – Diastolic Blood Pressure
DD or DM – Device Deficiency or Device Malfunction
DSMB – Data Safety Monitoring Board
EC – Ethics Committee
ECL – Echocardiographic Core Laboratory
eCRF – Electronic Case Report Form
EFS – Early Feasibility Study
EROA – Effective Regurgitant Orifice Area
ESC – European Society of Cardiology
FDA – Food and Drug Administration
IB – Investigator Brochure
ICD - Implantable cardioverter-defibrillators
ICF – Informed Consent Form
IFU - Instruction for Use
IRB – Institutional Review Board
IVC – Inferior Vena Cava
KCCQ – Kansas City Cardiomyopathy Questionnaire
LVEF – Left Ventricular Ejection Fraction
MAE – Major Adverse Event
MI – Myocardial Infarction
MR – Mitral Regurgitation
NYHA – New York Heart Association
PAP – Pulmonary Artery Pressure
PISA – Proximal Isovelocity Surface Area
QoL – Quality of Life
RA – Right Atrium
RV – Right Ventricle
RVEDD - Right Ventricular End Diastolic Dimension
RVEDV – Right Ventricle End Diastolic Volume
RVEF - Right Ventricular Ejection Fraction
RVESD - Right Ventricular End Systolic Dimension
RVESV - Right Ventricular End Systolic Volume
RVSP - Right Ventricular Systolic Pressure
SBP – Systolic Blood Pressure
SF-36 – Short Form 36
SLDA – Single Leaflet Device Attachment
STS – Society of Thoracic Surgery
TAPSE - Tricuspid Annular Plane Systolic Excursion
TEE – Trans-esophageal Echocardiogram
TR – Tricuspid Regurgitation

TTE – Transthoracic Echocardiogram
TVRS – Tricuspid Valve Repair System
VC – Vena Contracta

APPENDIX II: DEFINITIONS

ANTICIPATED ADVERSE EVENT
Derived from ISO14155, MEDDEV 2.7.3: an effect which by its nature, incidence, severity or outcome has been previously identified as "POTENTIAL COMPLICATIONS AND ADVERSE EVENTS", as documented in the IFU or CIP (**Appendix IV**).

ATRIAL FIBRILLATION (AF)
Per Heart Rhythm Society Guidelines

- **Paroxysmal**: Recurrent (≥ 2) atrial fibrillation episodes that terminate spontaneously within 7 days.
- **Persistent**: Atrial fibrillation that is sustained beyond 7 days, or lasting less than 7 days but necessitating pharmacologic or electrical cardioversion.
- **Longstanding Persistent AF**: Continuous atrial fibrillation of greater than 1 year duration.
- **Permanent**: Atrial fibrillation in which cardioversion has failed or not been attempted.

DEATH (All Cause)
All deaths regardless of cause. Death is further divided into 2 categories

1. CARDIOVASCULAR DEATH (VARC)
Per the Valve Academic Research Consortium (VARC)[5] as any one of the following:

- Any death due to proximate cardiac cause (e.g. MI, cardiac tamponade, worsening heart failure)
- Unwitnessed death and death of unknown cause
- All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
- Death caused by non-coronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease

2. NON-CARDIOVASCULAR DEATH
Any death not covered by the VARC definitions of Cardiovascular Death, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

DEVICE EMBOLIZATION
Detachment of the deployed TVRS Clip from the tricuspid leaflets as assessed by the study site.

Diagnosis and management of any occurrence or suspected occurrence of device embolization will be per the site investigator's best medical judgment. Some recommendations for clinical diagnosis and management of device embolization include but are not necessarily limited to those outlined below:

- **Diagnosis**:
  - Observation of patient's clinical symptoms,
  - Assessment of Clip status via TTE examination of valve, and/or
  - Fluoroscopy and/or x-ray imaging.
- **Management** will depend on the specific patient's clinical situation and will be determined by the site investigator's best medical judgment including assessment of overall risks and benefits of further intervention. Some methods of management to consider are:
  - Continued regular clinical monitoring of the patient and the embolized device;
  - Transcatheter manipulation method(s) to stabilize device position;

- Removal through percutaneous approach and/or
- Removal through surgical approach.

DEVICE THROMBOSIS
Formation of an independently moving thrombus on any part of the TVRS Clip evidenced by echocardiography or fluoroscopy. If the TVRS Clip is explanted or an autopsy is performed, this diagnosis should be confirmed.

ENDOCARDITIS
A diagnosis of endocarditis based on the following Duke criteria, from The ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease, JACC, Vol 32, No.5,November 1, 1998:pg1541, Table 21)

Endocarditis is based on the confirmation of either Pathological Criteria or Clinical Criteria.

Diagnosis for Clinical Criteria of Endocarditis must at least meet 1 of the following combinations:

- 2 major criteria or
- 1 major plus 3 minor criteria or
- 5 minor criteria

Pathological Criteria

Microorganisms: culture or histology in a vegetation, in a vegetation that has embolized, or in an intracardiac abscess, OR

Pathological lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis

OR

Clinical Criteria

Major Criteria

Persistently positive blood cultures:

Typical organisms for endocarditis: *Streptococcus viridans, S bovis*, "HACEK" group, community acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus

Persistent bacteremia:

≥ 2 positive cultures separated by ≥12 hours or ≥ 3 positive cultures ≥ 1 h apart or 70% blood culture samples positive if ≥ 4 are drawn

Evidence of endocardial involvement

Positive echocardiogram
- Oscillating vegetation
- Abscesses
- Valve perforation
- New partial dehiscence of prosthetic valve

New valvular regurgitation

Minor Criteria

Predisposing heart condition:
Mitral Valve Prolapse, bicuspid aortic valve, rheumatic or congenital heart disease, intravenous drug use
Fever
Vascular phenomena:
Major arterial emboli, septic pulmonary emboli, mycotic aneurysm, intracranial hemorrhage, Janeway lesions
Immunologic phenomena
Glomerulonephritis, Osler's nodes, Roth spots, and rheumatoid factor
Positive blood culture: not meeting major criteria
Echocardiogram: positive but not meeting major criteria

ETIOLOGY OF TRICUSPID REGURGITATION
Will be determined as Degenerative, Functional, or Lead-Induced.

- **Degenerative Tricuspid Regurgitation**
  Tricuspid regurgitation primarily due to abnormality of the tricuspid apparatus

- **Functional Tricuspid Regurgitation**
  Global or regional right ventricular wall motion abnormalities causing leaflet restriction or tethering with or without dilatation of the tricuspid annulus, but with no significant abnormalities of the tricuspid leaflets
- **Lead-Induced Tricuspid Regurgitation**
  ICD or pacemaker trans-tricuspid lead directly interfering with leaflet coaptation.

GASTROINTESTINAL COMPLICATIONS
Complications as a result of the TVRS procedure affecting the gastrointestinal tract requiring surgery. May include fecal impaction, bowel obstruction, etc.

HOSPITALIZATION (ALL-CAUSE)
Defined as admission to inpatient unit or ward in the hospital for at least 24 hours, including emergency department stay. Excludes hospitalizations planned for pre-existing conditions, unless there is worsening in the baseline condition.

HEART FAILURE HOSPITALIZATION
Defined as an event that meets the following criteria:

A. Requires hospitalization with treatment in any inpatient unit or ward in the hospital for at least 24 hours, including emergency department stay,

AND

B. Subject has clinical signs and/or symptoms of heart failure, including new or worsening dyspnea, orthopnea, paroxysmal nocturnal dyspnea, increasing fatigue, worsening functional capacity or activity intolerance, or signs and/or symptoms of volume overload,

AND

C. Results in intravenous (e.g, diuretic or vasoactive therapy) or invasive (e.g., ultrafiltration, IABP, mechanical assistance) treatment for heart failure.

For the purpose of this protocol, overnight stays at nursing home facilities, physical rehab or extended care facilities, including hospice, do not meet the protocol definition of hospitalization.

OTHER CARDIOVASCULAR HOSPITALIZATION
Defined as treatment in any inpatient unit or ward in the hospital for at least 24 hours, including emergency department stay for conditions such as coronary artery disease, acute myocardial infarction, hypertension, cardiac arrhythmias, cardiomegaly, pericardial effusion, atherosclerosis and peripheral vascular disease, not related to heart failure as defined.

NON-CARDIOVASCULAR HOSPITALIZATION
Hospitalizations that are not heart failure or other cardiovascular hospitalizations, as defined above, will be categorized as non-cardiovascular hospitalizations.

LIVER FAILURE
New onset liver failure is defined as elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 15 times the ULN.

MAJOR ADVERSE EVENT (MAE)
MAE is a CEC-adjudicated composite of cardiovascular mortality, stroke, myocardial infarction, new onset renal failure, endocarditis requiring surgery, and non-elective cardiovascular surgery for TVRS device related adverse events occurring after the index procedure

MAJOR BLEEDING
Major bleeding is defined as bleeding ≥ Type 3 based on a modified Bleeding Academic Research Consortium (BARC)[33] definition:

- Type 3
  - Type 3a
    - Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)
    - Any transfusion with overt bleeding
  - Type 3b
    - Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)
    - Cardiac tamponade
    - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
    - Bleeding requiring intravenous vasoactive agents
  - Type 3c
    - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
    - Subcategories confirmed by autopsy or imaging or lumbar puncture
    - Intraocular bleed compromising vision
- Type 4: CV Surgery-related bleeding

[33] Mehrana R, Rao SV, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;123:2736-2747.

- Perioperative intracranial bleeding within 48 h
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
- Chest tube output ≥2L within a 24-h period

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

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin)
†Cell saver products are not counted

MAJOR VASCULAR COMPLICATION
Any major complication, relating to, or affecting, the circulatory system as a result of the TVRS procedure, including new onset of any of the following:

- Hematoma at access site >6 cm.;
- Retroperitoneal hematoma;
- Arterio-venous fistula;
- Symptomatic peripheral ischemia/ nerve injury with clinical signs or symptoms lasting >24 hours;
- Vascular surgical repair at catheter access sites;
- Pulmonary embolism;
- Ipsilateral deep vein thrombus; or
- Access site-related infection requiring intravenous antibiotics and/or extended hospitalization.

MODIFIED RANKIN SCALE SCORE DESCRIPTIONS

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

MYOCARDIAL INFARCTION
Myocardial infarction (MI) classification and criteria for diagnosis is defined as follows:

Peri-procedural MI (≤ 72 hours after TVRS procedure)
Mandatory: CK-MB (preferred) ≥10x ULN within 72 hrs. post-TVRS procedure in patient with normal baseline CK-MB

OR

Mandatory: CK-MB ≥5x ULN within 72 hrs. post-TVRS procedure in patient with normal baseline CK-MB *plus* new pathological Q-waves in ≥2 contiguous leads, or new LBBB

Post-surgery
Mandatory: CK-MB ≥10x ULN (preferred) within 24 hrs. of cardiothoracic surgery *plus 1 of the following:*

- New pathological Q-waves in ≥2 contiguous leads or new persistent LBBB on ECG ≥30 min. and ≤72 hrs. post-CABG cardiothoracic surgery, or

- New substantial wall motion abnormalities by imaging except new septal or apical abnormalities.

Spontaneous MI (>72 hours after TVRS procedure)
Any one of the following criteria:

- Detection of rise and/or fall of cardiac biomarkers (CK-MB) with at least one value above the upper limits of normal (ULN), together with evidence of myocardial ischemia with at least one of the following:

    - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]
    - New pathological Q waves in at least two contiguous leads
    - Imaging evidence of 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.

NEW YORK HEART ASSOCIATION CLASSIFICATION (NYHA CLASS)

Class I	Patients with cardiac disease but without resulting limitations of physical activity.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. Patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. Patients are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

NON-ELECTIVE (i.e., URGENT or EMERGENT) CARDIOVASCULAR SURGERY FOR DEVICE RELATED EVENTS
Cardiovascular surgical procedure performed for device related complication requiring surgery within 24 hours of onset of adverse event, including events found during scheduled follow-up. If non-urgent surgery was performed within 24 hours of the onset of the adverse event but was not required within this timeframe, it will not be considered “non-elective”. Examples of Device Related Complications that may

lead to non-elective cardiovascular surgery include, myocardial perforation, Single Leaflet Device Attachment (confirmed by Echo Core Lab), embolization of the TVRS Clip or TVRS System components, iatrogenic atrial septal defect, or the need for tricuspid valve replacement instead of repair due at least in part to the TVRS procedure or the presence of the TVRS Clip.

OPTIMAL MEDICAL THERAPY OR OPTIMAL THERAPY

For Tricuspid Regurgitation: Currently per ESC 2012 guidelines, the only medical therapy described is, "Diuretics reduce congestion. Specific therapy of the underlying disease is warranted." These TR patients typically would have some level of left heart failure by the time TR is detected. Hence, optimal therapy for TR at the present time will follow that defined for patients with left heart failure issues, example mitral regurgitation.

For Mitral Regurgitation: Subjects with current or prior symptoms of heart failure and reduced LVEF should be on stable optimally uptitrated medical therapy recommended according to current guidelines (J Am Coll Cardiol. 2013 Jun 5. doi:pii: S0735-1097(13)02114-1.) as standard of care for heart failure therapy in the United States. This minimally includes an ACE-inhibitor (ACE-I) at stable doses for 30 days prior to subject enrollment in the trial, if tolerated, and a beta blocker (carvedilol, sustained release metoprolol succinate, or bisoprolol) for 90 days prior to subject enrollment in the trial, if tolerated, with a stable up-titrated dose for 30 days prior to subject enrollment in the trial. This also includes an Angiotensin II Receptor Blocker (ARB) at stable doses for 30 days prior to subject enrollment in the trial, if tolerated, when ACE-I is not tolerated. Stable is defined as no more than a 100% increase or a 50% decrease in dose.

If the subject is intolerant to ACE-I, ARB, or beta blockers, documented evidence must be available. In those intolerant to both ACE-I and ARB, combination therapy with hydralazine and oral nitrate should be considered. Therapeutic equivalence for ACE-I substitutions is allowed within the trial enrollment stability timelines. Aldosterone receptor antagonists [or mineralocorticoid receptor antagonists] are recommended in patients with NYHA class II-IV heart failure and who have LVEF of 35% or less, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. If aldosterone inhibitor therapy is to be administered, it must be initiated and optimized at least 30 days prior to trial enrollment. Stability criteria are the same as for other neurohormonal antagonists. Eplerenone requires dosage stability for 30 days prior to subject enrollment in the trial similar to the other agents. Diuretics may be used as necessary to keep the subject euvolemic. All heart failure therapeutics and dosages should be documented in the electronic case report forms.

It is recognized that approximately two-thirds of patients with HF have underlying CAD (ischemic cardiomyopathy). Therefore, it is imperative that appropriate treatment for CAD be used, according to the ACC/AHA Guidelines for Heart Failure. Specific recommendations listed in those guidelines are listed as follows:

- Use of nitrates and beta blockers for the treatment of angina,
- Coronary revascularization according to recommended guidelines in patients who have both HF and angina,
- Patients with coronary artery disease and HF should be treated in accordance with recommended guidelines for chronic stable angina,
- Use of antiplatelet agents for prevention of MI and death in patients with HF who have underlying coronary artery disease

In addition, revascularization (i.e., percutaneous coronary intervention, etc.) should occur prior to subject enrollment in the trial as applicable.

RENAL FAILURE
For this trial, new onset renal failure is defined as new need for dialysis or a creatinine increasing to 3.5 mg/dL or greater
Note: Increase of creatinine less 1.0 mg/dL over baseline is NOT considered renal failure

SINGLE LEAFLET DEVICE ATTACHMENT (SLDA)
Defined as unilateral TVRS detachment from one leaflet as assessed by the study site and confirmed by the ECL. Reasons for TVRS Detachment include leaflet tearing, TVRS unlocking, TVRS fracture or inadequate TVRS placement. Not included are any fractures or other failures of the TVRS that do not result in TVRS detachment from one or both leaflets.

STROKE/CEREBROVASCULAR ACCIDENT and TIA
Cerebrovascular Accident (Stroke) is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Stroke may be classified as ischemic or hemorrhagic with appropriate sub-definitions or as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic.

An entity closely related to ischemic stroke is transient ischemic attack (TIA). TIA is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction. The difference between TIA and ischemic stroke is the presence of infarction. In the absence of affirmative evidence confirming the presence or absence of infarction, a symptom duration of 24 hours will be used to distinguish TIA from ischemic stroke. By definition, TIA does not produce lasting disability.

The assessment of disability resulting from the stroke will be performed by the modified Rankin Scale (mRS). Assessment of the mRS should occur at all scheduled visits through 24 months and at 90 days after stroke onset. This approach will maximize the detection of new strokes, assist in ongoing evaluation of events previously determined to be TIAs, and provide an accepted and reliable indicator of the long-term impact of a given stroke. A disabling stroke is one that results (at 90 days after stroke onset) in an mRS score of 2 or more and in an increase of at least one mRS category from the individual's pre-stroke baseline. A non-disabling stroke is one that results (at 90 days after stroke onset) in an mRS score of less than 2 or that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline.

Although imaging (typically, MRI for acute and chronic ischemia and haemorrhage, and CT for acute and chronic haemorrhage and chronic ischemia) is often used to supplement the clinical diagnosis of stroke, a diagnosis of stroke may be made on clinical grounds alone.

Diagnostic criteria

Acute episode of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one 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 non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist* Confirmation of the diagnosis by at least one 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 central nervous system tissue. Hemorrhagic – An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. Undetermined – An acute episode where there is insufficient information to allow categorization as ischemic or hemorrhagic.
Stroke definitions† Disabling stroke – a mRS score of 2 or more at 90 days and an increase of at least one mRS category from an individual's pre-stroke baseline Non-disabling stroke – a mRS score of less than 2 at 90 days or one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline

*Patients with non-focal 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.

SYMPTOMATIC TRICUSPID REGURGITATION
Symptomatic refers to limitation of physical activity (i.e. NYHA Classification II, III or IV)

TRICUSPID VALVE STENOSIS
Defined as a tricuspid valve orifice of ≤ 1.0 cm^2 and/or mean gradient ≥5 mmHg as measured by the Echocardiography Core Laboratory. Other parameters (PHT ≥ 190 msec or CW TV VTI >60 cm) may also suggest significant tricuspid stenosis.

TRICUSPID REGURGITATION SEVERITY
TR grading will be based on a 5-point scale: mild, moderate, severe, very severe and torrential. Mild, moderate, and severe will be graded based on the 2017 ASE Guidelines (Zoghbi 2017). Massive and torrential have been developed by the Echo Scientific Committee to provide further granularity in the range beyond severe. See **Appendix VIII** for further grading information.

VULNERABLE POPULATION (ISO14155 Definition)
Defined as subject whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples of populations which may contain vulnerable subjects include: Individuals with lack of or loss of autonomy due to

immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects may include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.

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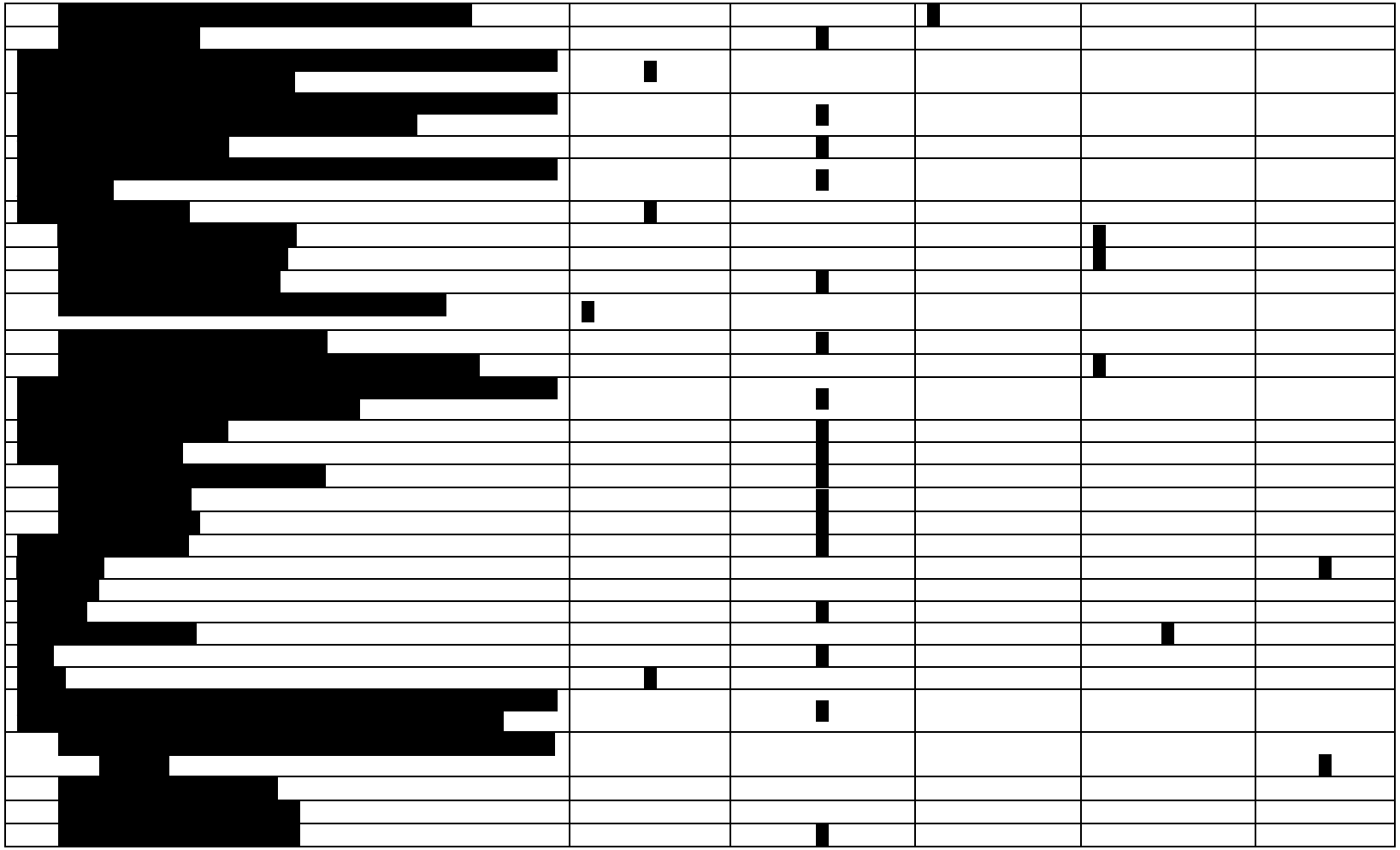

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APPENDIX V: MONITORING EXPOSURE TO IONIZING RADIATION

(1) Implanting Investigator Training

Prior to treating patients with the TVRS Clip, all implanting investigators shall complete the TVRS therapy training curriculum, including training to this section of the study Clinical Investigational Plan.

(2) Pre, Peri and Post-TVRS Procedure

The implanting investigator shall be responsible for patient radiation levels and shall ensure that radiation dose accumulation is continuously monitored during the procedure (NCRP 2010). Documentation of dose levels shall be in accordance with the individual requirements of the respective institution's quality management program. In addition, the following shall apply:

a. Dose Measurements required for TVRS procedure

Where the fluoroscopy system has the functionality for the output of data, the following dose measurements shall be recorded in the subject records and reported in the eCRFs.

- Total fluoro time: to be reported in minutes
- Total number of fluoro frames: to be reported as whole numbers, no associated units
- Air kerma-area product (P_{KA}) (dose area product): to be reported in Gy cm^2
- Air kerma at the reference point ($K_{a,r}$): to be reported in Gy
- Peak skin dose ($D_{skin,\ max}$): to be reported in Gy

Investigational centers that are unable to provide the information due to the limitations oftheir fluoroscopy systems are exempt from the reporting requirements.

b. Substantial Radiation Dose Level (SRDL)

The SRDL is a trigger level to initiate follow-up of a radiation dose that may produce a clinically relevant injury in an average patient. Procedures, such as the MitraClip procedure, that are performed using biplane fluoroscopy systems are a special situation because the dose received from each plane should be considered independently when the fields do not overlap. When they do overlap, the doses are additive and if it is uncertain whether the fields overlap, it should be assumed that they do.

The following are suggested values for first and subsequent notifications and the SRDL based upon a $100cm^2$ field at the subject's skin. The implanting investigator should adjust the notifications and the SRDL proportionally to the actual procedural field size.

When the SRDL has been exceeded, the implanting investigator shall document the dose exceeded and the justification for the radiation dose level used (NCRP 2010).

Suggested values for first and subsequent notifications and the SRDL (NCRP 2010)

Dose Metric	First Notification	Subsequent Notifications (increments)	SRDL
$D_{skin,max}$	2 Gy	0.5 Gy	3 Gy
$K_{a,r}$	3 Gy	1 Gy	5 Gy
P_{KA}	300 Gy cm^2*	100 Gy cm^2*	500 Gy cm^2*
Fluoroscopy time	30 min	15 min	60 min

* Assuming a 100 cm^2 field at the subject's skin. For other field sizes, the P_{KA} values should be adjusted proportionally to the actual procedural field size (*e.g.*, for a field size of 50 cm^2, the SRDL value for P_{KA} would be 250 Gy cm^2).

(1) Acute Evaluation

Subjects 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 and report any observations to the site Principal Investigator or designee During the physical examination at the 30-day follow-up clinic visit, the site Principal Investigator or designee shall examine the integrity of the subject's skin at or near the beam entrance site. If there is evidence of skin injury, the site Principal Investigator or designee shall report it as an adverse event in accordance with the adverse event reporting requirements.

(2) Long-term Evaluation

The site Principal Investigator or designee is responsible for the ongoing collection and monitoring of radiation doses. An examination of the subject's skin at or near the beam entrance site shall be performed by the site Principal Investigator or designee. If skin injury resulting from radiation exposure during the MitraClip procedure is ongoing beyond the 30-day follow-up, the site Principal Investigator or designee should arrange for follow-up care. Observations of skin injury shall be reported as an adverse event in accordance with the adverse event reporting requirements.

APPENDIX VI: 6 MINUTE WALK TEST GUIDELINES – AMERICAN THORACIC SOCIETY

Six minute walk test will be performed as outlined in the published guidelines by the American Thoracic Society.

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories.. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002 Jul 1;166(1):111-7.

American Thoracic Society

ATS Statement: Guidelines for the Six-Minute Walk Test

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED BY THE ATS BOARD OF DIRECTORS MARCH 2002

CONTENTS

PURPOSE AND SCOPE

This statement provides practical guidelines for the 6-minute walk test (6MWT). Specifically, it reviews indications, details factors that influence results, presents a brief step-by-step protocol, outlines safety measures, describes proper patient preparation and procedures, and offers guidelines for clinical interpretation of results. These recommendations are not intended to limit the use of alternative protocols for research studies. We do not discuss the general topic of clinical exercise testing.

As with other American Thoracic Society statements on pulmonary function testing, these guidelines come out of a consensus conference. Drafts were prepared by two members (P.L.E. and R.J.Z.) and were based on a comprehensive Medline literature search from 1970 through 2001, augmented by suggestions from other committee members. Each draft responded to comments from the working committee. The guidelines follow previously published methods as closely as possible and provide a rationale for each specific recommendation. The final recommendations represent a consensus of the committee. The committee recommends that these guidelines be reviewed in five years and in the meantime encourages further research in areas of controversy.

BACKGROUND

There are several modalities available for the objective evaluation of functional exercise capacity. Some provide a very complete assessment of all systems involved in exercise performance (high tech), whereas others provide basic information but are low tech and are simpler to perform. The modality used should be chosen based on the clinical question to be addressed and on available resources. The most popular clinical exercise tests in order of increasing complexity are stair climbing, a 6MWT, a shuttle-walk test, detection of exercise-induced asthma, a cardiac stress test (e.g., Bruce protocol), and a cardiopulmonary exercise test (1, 2). Other professional organizations have published standards for cardiac stress testing (3, 4).

Assessment of functional capacity has traditionally been done by merely asking patients the following: "How many flights of stairs can you climb or how many blocks can you walk?" However, patients vary in their recollection and may report overestimations or underestimations of their true functional capacity. Objective measurements are usually better than self-reports. In the early 1960s, Balke developed a simple test to evaluate the functional capacity by measuring the distance walked during a defined period of time (5). A 12-minute field performance test was then developed to evaluate the level of physical fitness of healthy individuals (6). The walking test was also adapted to assess disability in patients with chronic bronchitis (7). In an attempt to accommodate patients with respiratory disease for whom walking 12 minutes was too exhausting, a 6-minute walk was found to perform as well as the 12-minute walk (8). A recent review of functional walking tests concluded that "the 6MWT is easy to administer, better tolerated, and more reflective of activities of daily living than the other walk tests" (9).

The 6MWT is a practical simple test that requires a 100-ft hallway but no exercise equipment or advanced training for technicians. Walking is an activity performed daily by all but the most severely impaired patients. This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes (the 6MWD). It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. It does not provide specific information on the function of each of the different organs and systems involved in exercise or the mechanism of exercise limitation, as is possible with maximal cardiopulmonary exercise testing. The self-paced 6MWT assesses the submaximal level of functional capacity. Most patients do not achieve maximal exercise capacity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test. However, because most activities of daily living are performed at submaximal levels of exertion, the 6MWD may better reflect the functional exercise level for daily physical activities.

INDICATIONS AND LIMITATIONS

The strongest indication for the 6MWT is for measuring the response to medical interventions in patients with moderate to severe heart or lung disease. The 6MWT has also been used as a one-time measure of functional status of patients, as well as a predictor of morbidity and mortality (*see* Table 1 for a list of these indications). The fact that investigators have used the 6MWT in these settings does not prove that the test is clinically useful (or the best test) for determining functional capacity or changes in functional capacity due to an intervention in patients with these diseases. Further studies are necessary to determine the utility of the 6MWT in various clinical situations.

Am J Respir Crit Care Med Vol 166. pp 111–117, 2002
DOI: 10.1164/rccm.166/1/111
Internet address: www.atsjournals.org

Formal cardiopulmonary exercise testing provides a global assessment of the exercise response, an objective determination of functional capacity and impairment, determination of the appropriate intensity needed to perform prolonged exercise, quantification of factors limiting exercise, and a definition of the underlying pathophysiologic mechanisms such as the contribution of different organ systems involved in exercise. The 6MWT does not determine peak oxygen uptake, diagnose the cause of dyspnea on exertion, or evaluate the causes or mechanisms of exercise limitation (1, 2). The information provided by a 6MWT should be considered complementary to cardiopulmonary exercise testing, not a replacement for it. Despite the difference between these two functional tests, some good correlations between them have been reported. For example, a significant correlation ($r = 0.73$) between 6MWD and peak oxygen uptake has been reported for patients with end-stage lung diseases (36, 37).

In some clinical situations, the 6MWT provides information that may be a better index of the patient's ability to perform daily activities than is peak oxygen uptake; for example, 6MWD correlates better with formal measures of quality of life (38). Changes in 6MWD after therapeutic interventions correlate with subjective improvement in dyspnea (39, 40). The reproducibility of the 6MWD (with a coefficient of variation of approximately 8%) appears to be better than the reproducibility of 1-second forced expiratory volume in patients with chronic obstructive pulmonary disease (COPD) (8, 41–43). Questionnaire indices of functional status have a larger short-term variability (22–33%) than does the 6MWD (37).

The shuttle-walking test is similar to the 6MWT, but it uses an audio signal from a tape cassette to direct the walking pace of the patient back and forth on a 10-m course (44–47). The walking speed is increased every minute, and the test ends when the patient cannot reach the turnaround point within the required time. The exercise performed is similar to a symptom-limited, maximal, incremental treadmill test. An advantage of the shuttle walking test is that it has a better correlation with peak oxygen uptake than the 6MWD. Disadvantages include less validation, less widespread use, and more potential for cardiovascular problems.

CONTRAINDICATIONS

Absolute contraindications for the 6MWT include the following: unstable angina during the previous month and myocardial infarction during the previous month. Relative contraindications include a resting heart rate of more than 120, a systolic blood pressure of more than 180 mm Hg, and a diastolic blood pressure of more than 100 mm Hg.

Patients with any of these findings should be referred to the physician ordering or supervising the test for individual clinical assessment and a decision about the conduct of the test. The results from a resting electrocardiogram done during the previous 6 months should also be reviewed before testing. Stable exertional angina is not an absolute contraindication for a 6MWT, but patients with these symptoms should perform the test after using their antiangina medication, and rescue nitrate medication should be readily available.

Rationale

Patients with the previously mentioned risk factors may be at increased risk for arrhythmias or cardiovascular collapse during testing. However, each patient determines the intensity of their exercise, and the test (without electrocardiogram monitoring) has been performed in thousands of older persons (31, 48–50) and thousands of patients with heart failure or cardiomyopathy (32, 51, 52) without serious adverse events. The contraindications listed previously here were used by study investigators based on their impressions of the general safety of the 6MWT and their desire to be prudent, but it is unknown whether adverse events would occur if such patients performed a 6MWT; they are, therefore, listed as relative contraindications.

TABLE 1. INDICATIONS FOR THE SIX-MINUTE WALK TEST

Pretreatment and posttreatment comparisons
Lung transplantation (9, 10)
Lung resection (11)
Lung volume reduction surgery (12, 13)
Pulmonary rehabilitation (14, 15)
COPD (16–18)
Pulmonary hypertension
Heart failure (19, 20)
Functional status (single measurement)
COPD (21, 22)
Cystic fibrosis (23, 24)
Heart failure (25–27)
Peripheral vascular disease (28, 29)
Fibromyalgia (30)
Older patients (31)
Predictor of morbidity and mortality
Heart failure (32, 33)
COPD (34, 35)
Primary pulmonary hypertension (10, 36)

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

SAFETY ISSUES

1. Testing should be performed in a location where a rapid, appropriate response to an emergency is possible. The appropriate location of a crash cart should be determined by the physician supervising the facility.
2. Supplies that must be available include oxygen, sublingual nitroglycerine, aspirin, and albuterol (metered dose inhaler or nebulizer). A telephone or other means should be in place to enable a call for help.
3. The technician should be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association–approved cardiopulmonary resuscitation course. Advanced cardiac life support certification is desirable. Training, experience, and certification in related health care fields (registered nurse, registered respiratory therapist, certified pulmonary function technician, etc.) are also desirable. A certified individual should be readily available to respond if needed.
4. Physicians are not required to be present during all tests. The physician ordering the test or a supervising laboratory physician may decide whether physician attendance at a specific test is required.
5. If a patient is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed by a physician or a protocol.

Reasons for immediately stopping a 6MWT include the following: (*1*) chest pain, (*2*) intolerable dyspnea, (*3*) leg cramps, (*4*) staggering, (*5*) diaphoresis, and (*6*) pale or ashen appearance.

Technicians must be trained to recognize these problems and the appropriate responses. If a test is stopped for any of these reasons, the patient should sit or lie supine as appropriate depending on the severity or the event and the technician's assessment of the severity of the event and the risk of syncope. The following should be obtained based on the judgment of the technician: blood pressure, pulse rate, oxygen saturation, and a physician evaluation. Oxygen should be administered as appropriate.

TECHNICAL ASPECTS OF THE 6MWT

Location

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. If the weather is comfortable, the test may be performed outdoors. The walking course must be 30 m in length. A 100-ft hallway is, therefore, required. The length of the corridor should be marked every 3 m. The turnaround points should be marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.

Rationale. A shorter corridor requires patients to take more time to reverse directions more often, reducing the 6MWD. Most studies have used a 30-m corridor, but some have used 20- or 50-m corridors (52–55). A recent multicenter study found no significant effect of the length of straight courses ranging from 50 to 164 ft, but patients walked farther on continuous (oval) tracks (mean 92 ft farther) (54).

The use of a treadmill to determine the 6MWD might save space and allow constant monitoring during the exercise, but the use of a treadmill for 6-minute walk testing is not recommended. Patients are unable to pace themselves on a treadmill. In one study of patients with severe lung disease, the mean distance walked on the treadmill during 6 minutes (with the speed adjusted by the patients) was shorter by a mean of 14% when compared with the standard 6MWD using a 100-ft hallway (57). The range of differences was wide, with patients walking between 400–1,300 ft on the treadmill who walked 1,200 ft in the hallway. Treadmill test results, therefore, are not interchangeable with corridor tests.

REQUIRED EQUIPMENT

1. Countdown timer (or stopwatch)
2. Mechanical lap counter
3. Two small cones to mark the turnaround points
4. A chair that can be easily moved along the walking course
5. Worksheets on a clipboard
6. A source of oxygen
7. Sphygmomanometer
8. Telephone
9. Automated electronic defibrillator

PATIENT PREPARATION

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn.
3. Patients should use their usual walking aids during the test (cane, walker, etc.).
4. The patient's usual medical regimen should be continued.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Patients should not have exercised vigorously within 2 hours of beginning the test.

MEASUREMENTS

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.
3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Compete the first portion of the worksheet (*see* the APPENDIX).
4. Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation (SpO_2) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact (56, 57). Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.

   The rationale for measuring oxygen saturation is that although the distance is the primary outcome measure, improvement during serial evaluations may be manifest either by an increased distance or by reduced symptoms with the same distance walked (39). The SpO_2 should not be used for constant monitoring during the exercise. The technician must not walk with the patient to observe the SpO_2. If worn during the walk, the pulse oximeter must be lightweight (less than 2 pounds), battery powered, and held in place (perhaps by a "fanny pack") so that the patient does not have to hold or stabilize it and so that stride is not affected. Many pulse oximeters have considerable motion artifact that prevents accurate readings during the walk. (57)
5. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale (*see* Table 2 for the Borg scale and instructions [58]).
6. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.
7. Instruct the patient as follows:

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

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

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

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

   Start now, or whenever you are ready."

TABLE 2. THE BORG SCALE

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

This Borg scale should be printed on heavy paper (11 inches high and perhaps laminated) in 20-point type size. At the beginning of the 6-minute exercise, show the scale to the patient and ask the patient this: "Please grade your level of shortness of breath using this scale." Then ask this: "Please grade your level of fatigue using this scale."

At the end of the exercise, remind the patient of the breathing number that they chose before the exercise and ask the patient to grade their breathing level again. Then ask the patient to grade their level of fatigue, after reminding them of their grade before the exercise.

8. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
9. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

    After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."

    When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."

    When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."

    When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."

    When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."

    Do not use other words of encouragement (or body language to speed up).

    If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

    When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

    When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.
10. Post-test: Record the postwalk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"
11. If using a pulse oximeter, measure SpO_2 and pulse rate from the oximeter and then remove the sensor.
12. Record the number of laps from the counter (or tick marks on the worksheet).
13. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
14. Congratulate the patient on good effort and offer a drink of water.

QUALITY ASSURANCE

Sources of Variability

There are many sources of 6MWD variability (*see* Table 3). The sources of variability caused by the test procedure itself should be controlled as much as possible. This is done by following the standards found in this document and by using a quality-assurance program.

Practice Tests

A practice test is not needed in most clinical settings but should be considered. If a practice test is done, wait for at least 1 hour before the second test and report the highest 6MWD as the patient's 6MWD baseline.

Rationale. The 6MWD is only slightly higher for a second 6MWT performed a day later. The mean reported increase ranges from 0 to 17% (23, 27, 40, 41, 54, 59). A multicenter study of 470 highly motivated patients with severe COPD performed two 6MWTs 1 day apart, and on average, the 6MWD was only 66 ft (5.8%) higher on the second day (54).

Performance (without an intervention) usually reaches a plateau after two tests done within a week (8, 60). The training effect may be due to improved coordination, finding optimal stride length, and overcoming anxiety. The possibility of a practice or training effect from tests repeated after more than a month has not been studied or reported; however, it is likely that the effect of training wears off (does not persist) after a few weeks.

Technician Training and Experience

Technicians who perform 6MWTs should be trained using the standard protocol and then supervised for several tests before performing them alone. They should also have completed cardiopulmonary resuscitation training.

Rationale. One multicenter study of older people found that after correction for many other factors, two of the technicians had mean 6MWDs that were approximately 7% lower than the other two sites (31).

Encouragement

Only the standardized phrases for encouragement (as specified previously here) must be used during the test.

Rationale. Encouragement significantly increases the distance walked (42). Reproducibility for tests with and without encouragement is similar. Some studies have used encouragement every 30 seconds, every minute, or every 2 minutes. We have chosen every minute and standard phrases. Some studies (53) have instructed patients to walk as fast as possible. Although larger mean 6MWDs may be obtained thereby, we recommend that such phrases not be used, as they emphasize initial speed at the expense of earlier fatigue and possible excessive cardiac stress in some patients with heart disease.

TABLE 3. 6MWD SOURCES OF VARIABILITY

Factors reducing the 6MWD
Shorter height
Older age
Higher body weight
Female sex
Impaired cognition
A shorter corridor (more turns)
Pulmonary disease (COPD, asthma, cystic fibrosis, interstitial lung disease)
Cardiovascular disease (angina, MI, CHF, stroke, TIA, PVD, AAI)
Musculoskeletal disorders (arthritis, ankle, knee, or hip injuries, muscle wasting, etc.)
Factors increasing the 6MWD
Taller height (longer legs)
Male sex
High motivation
A patient who has previously performed the test
Medication for a disabling disease taken just before the test
Oxygen supplementation in patients with exercise-induced hypoxemia

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; 6MWD = 6-minute walking distance.

Supplemental Oxygen

If oxygen supplementation is needed during the walks and serial tests are planned (after an intervention other than oxygen therapy), then during all walks by that patient oxygen should be delivered in the same way with the same flow. If the flow must be increased during subsequent visits due to worsening gas exchange, this should be noted on the worksheet and considered during interpretation of the change noted in 6MWD. The type of oxygen delivery device should also be noted on the report: for instance, the patient carried liquid oxygen or pushed or pulled an oxygen tank, the delivery was pulsed or continuous, or a technician walked behind the patient with the oxygen source (not recommended). Measurements of pulse and SpO_2 should be made after waiting at least 10 minutes after any change in oxygen delivery.

Rationale. For patients with COPD or interstitial lung disease, oxygen supplementation increases the 6MWD (17, 59, 61, 63). Carrying a portable gas container (but not using it for supplemental oxygen) reduced the mean 6MWD by 14% in one study of patients with severe respiratory disability, but using the container to deliver supplemental oxygen during the exercise increased the mean 6MWD by 20–35% (59).

Medications

The type of medication, dose, and number of hours taken before the test should be noted.

Rationale. Significant improvement in the distance walked, or the dyspnea scale, after administration of bronchodilators has been demonstrated in patients with COPD (62, 63), as well as cardiovascular medications in patients with heart failure (19).

INTERPRETATION

Most 6MWTs will be done before and after intervention, and the primary question to be answered after both tests have been completed is whether the patient has experienced a clinically significant improvement. With a good quality-assurance program, with patients tested by the same technician, and after one or two practice tests, short-term reproducibility of the 6MWD is excellent (37). It is not known whether it is best for clinical purposes to express change in 6MWD as (*1*) an absolute value, (*2*) a percentage change, or (*3*) a change in the percentage of predicted value. Until further research is available, we recommend that change in 6MWD be expressed as an absolute value (e.g., the patient walked 50 m farther).

A statistically significant mean increase in 6MWD in a group of study participants is often much less than a clinically significant increase in an individual patient. In one study of 112 patients (half of them women) with stable, severe COPD, the smallest difference in 6MWD that was associated with a noticeable clinical difference in the patients' perception of exercise performance was a mean of 54 m (95% confidence interval, 37–71 m) (64). This study suggests that for individual patients with COPD, an improvement of more than 70 m in the 6MWD after an intervention is necessary to be 95% confident that the improvement was significant. In an observational study of 45 older patients with heart failure, the smallest difference in 6MWD that was associated with a noticeable difference in their global rating of worsening was a mean of 43 m (20). The 6MWD was more responsive to deterioration than to improvement in heart failure symptoms.

Reported Mean Changes in 6MWD After Interventions

Supplemental oxygen (4 L/min) during exercise in patients with COPD or interstitial lung disease increased mean 6MWD by approximately 95 m (36%) in one study (59). Patients taking an inhaled corticosteroid experienced a mean 33 m (8%) increase in 6MWD in an international COPD study (16). Patients with COPD in a study of the effects of exercise and diaphragmatic strength training experienced a mean increase in 6MWD of 50 m (20%) (65). Lung volume reduction surgery in patients with very severe COPD has been reported to increase 6MWD by a mean of 55 m (20%) (13).

Cardiac rehabilitation in patients referred with various heart diseases increased 6MWD by a mean of 170 m (15%) in a recent study (66). In 25 older patients with heart failure, an angiotensin-converting enzyme inhibitor medication (50 mg captopril per day) improved 6MWD a mean of 64 m (39%) compared with a mean increase of only 8% in those receiving a placebo (19).

Interpreting Single Measurements of Functional Status

Optimal reference equations from healthy population-based samples using standardized 6MWT methods are not yet available. In one study, the median 6MWD was approximately 580 m for 117 healthy men and 500 m for 173 healthy women (50). A mean 6MWD of 630 m was reported by another study of 51 healthy older adults (55). Differences in the population sampled, type and frequency of encouragement, corridor length, and number of practice tests may account for reported differences in mean 6MWD in healthy persons. Age, height, weight, and sex independently affect the 6MWD in healthy adults; therefore, these factors should be taken into consideration when interpreting the results of single measurements made to determine functional status. We encourage investigators to publish reference equations for healthy persons using the previously mentioned standardized procedures.

A low 6MWD is nonspecific and nondiagnostic. When the 6MWD is reduced, a thorough search for the cause of the impairment is warranted. The following tests may then be helpful: pulmonary function, cardiac function, ankle–arm index, muscle strength, nutritional status, orthopedic function, and cognitive function.

Conclusions

The 6MWT is a useful measure of functional capacity targeted at people with at least moderately severe impairment. The test has been widely used for preoperative and postoperative evaluation and for measuring the response to therapeutic interventions for pulmonary and cardiac disease. These guidelines provide a standardized approach to performing the 6MWT. The committee hopes that these guidelines will encourage further research into the 6MWT and allow direct comparisons among different studies.

This statement was developed by the ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories.

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APPENDIX

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

Lap counter: _

Patient name: _____ Patient ID# _____

Walk # _____ Tech ID: _____ Date: _____

Gender: M F Age: ____ Race: ____ Height: ___ft ____in, ____ meters

Weight: _____ lbs, _____kg Blood pressure: _____ / _____

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

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

	Baseline	End of Test
Time	___:___	___:___
Heart Rate	_____	_____
Dyspnea	____	____ (Borg scale)
Fatigue	____	____ (Borg scale)
SpO_2	____ %	____%

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

Other symptoms at end of exercise: angina dizziness hip, leg, or calf pain

Number of laps: ____ (×60 meters) + final partial lap: _____ meters =

Total distance walked in 6 minutes: _____ meters

Predicted distance: _____ meters Percent predicted: _____%

Tech comments:

Interpretation (including comparison with a preintervention 6MWD):

APPENDIX VII: MONITORING PLAN

A copy of the Monitoring Plan can be obtained upon request from the Clinical Project Manager for the study (see Appendix III for contact information).

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