Clinical **TRI**al to Eva**LU**ate Cardiovascular Outco**M**es **IN** P**A**tients Treated with the **T**ricuspid Valv**E** Repair System Pivotal (TRILUMINATE Pivotal)
Protocol #: ABT-CIP-10249

Sponsor: Abbott

Version F

June 30th, 2022

Version	[redacted]
Date	[redacted]
Study Co-Primary Investigators	[redacted]
Steering Committee	[redacted]
Planned Number of Subjects, Sites and Regions	[redacted]
Clinical Investigation Type	[redacted]

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Clinical Investigation Monitor	Abbott (Sponsor)
Electronic Data Capture Software	[redacted]
Echocardiography Core Laboratory	
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NATIONAL COORDINATING CLINICAL INVESTIGATOR / STUDY PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

[Coordinating Clinical Investigator / Study Principal Investigator]

Printed name:
Signature:
Date:

Printed name:
Signature:
Date:

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

Site Principal Investigator

Printed name:
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Date:

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COMPLIANCE STATEMENT:

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812 and OUS ISO14155:2020) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical investigation will be approved by the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) of the respective investigational site and by the applicable regulatory authorities (e.g., FDA, PMDA, MHRA, etc.).

Protocol Summary

Trial Name and Number	Clinical **TRI**al to Eva**LU**ate Cardiovascular Outco**M**es **IN** P**A**tients Treated with the **T**ricuspid Valv**E** Repair System Pivotal (TRILUMINATE Pivotal) CIP No. ABT-CIP-10249
Device Under Investigation	TriClip™
Objective	The objective of this trial is to evaluate the safety and effectiveness of the TriClip™ device in improving clinical outcomes in symptomatic patients with severe tricuspid regurgitation (TR) who have been determined by the site's local heart team to be at intermediate or greater estimated risk for mortality or morbidity with tricuspid valve surgery.
Design	TRILUMINATE Pivotal is a prospective, multicenter, randomized, controlled, clinical trial of the TriClip™ device in symptomatic subjects with severe TR. Selected subjects will have to be determined by the site's local heart team to be at intermediate or greater estimated risk for mortality or morbidity with tricuspid valve surgery. The trial will randomize approximately 450 eligible subjects at up to 80 sites, in a 1:1 ratio to receive either: • The TriClip™ Device (Device) Group: Subjects will undergo TriClip™ implantation and will continue to be managed on medical therapy, per physician discretion, or • Medical Therapy (Control) Group: Subjects will continue to be managed on medical therapy, per physician discretion. The primary endpoint will be assessed when the first 350 randomized subjects complete 12-month follow-up, with additional powered secondary endpoints evaluated when all randomized subjects complete 24-month follow-up. Up to 3 roll-in subjects per implanter will be permitted at sites without prior experience of TriClip™ device for treatment of the tricuspid valve. Subjects in the Control group will be allowed to cross-over to the Device group after the 12-month follow-up is complete. An adaptive design with sample size re-estimation will be incorporated.

	In addition, up to 200 subjects will be enrolled into a concurrent Single-arm cohort. This cohort will comprise subjects with tricuspid valve anatomies, where: • The likelihood of achieving TR reduction to moderate or less is low, and • The likelihood of achieving TR reduction of at least 1 grade (as assessed using a 5-grade scale) is high Determination of enrollment into the Single-arm cohort will be made by an independent eligibility committee. An imaging sub-study (comprised of Cardiac magnetic resonance imaging, computed tomography and/or real-time echo) of approximately 100 subjects will be conducted to evaluate quantitative parameters associated with TR reduction.
Key Inclusion Criteria	• In the judgment of the sites local heart team, subject has been adequately treated per applicable standards (including medical management) and stable for at least 30 days. The patient must be optimally treated, and confirmed with the EC: • Medical therapy for TR • Medical and/or device therapy, for mitral regurgitation, atrial fibrillation, coronary artery disease and heart failure • Subject is symptomatic with Severe TR despite being optimally treated, as described above.TR severity is determined by the assessment of a qualifying transthoracic echocardiogram (TTE) confirmed by the Echocardiography Core Lab (ECL). The ECL will also request a transesophageal echocardiogram (TEE) to confirm TR etiology. Note: If any cardiac procedure(s) occur after eligibility was determined and prior to TriClip™ procedure, TR severity 30-day after the cardiac procedure(s) will be reassessed • The cardiac surgeon of the site local heart team (consisting of one interventionalist, one cardiac surgeon, one heart failure specialist and one echocardiologist) concur that the patient is at intermediate or greater estimated risk for mortality or morbidity with tricuspid valve surgery. • New York Heart Association (NYHA) Functional Class II, III or ambulatory IV
Key Exclusion Criteria	• Systolic pulmonary artery pressure (sPAP) > 70 mmHg or fixed pre-capillary pulmonary hypertension as assessed by right heart catheterization (RHC) • Severe uncontrolled hypertension Systolic Blood Pressure (SBP) ≥ 180 mmHg and/or Diastolic Blood Pressure (DBP) ≥ 110 mm Hg)

	• Any prior tricuspid valve procedure that would interfere with placement of the TriClip™ device
	• Indication for left-sided (e.g. severe mitral regurgitation) or pulmonary valve correction in the prior 60 days
	• Pacemaker or ICD leads that would prevent appropriate placement of the TriClip™
	• Tricuspid valve stenosis
	• Left Ventricular Ejection Fraction (LVEF) ≤20%
	• Tricuspid valve leaflet anatomy which may preclude clip implantation, proper clip positioning on the leaflets or sufficient reduction in TR. This may include:
	  • Evidence of calcification in the grasping area
	  • Presence of a severe coaptation defect (> 2cm) of the tricuspid leaflets
	  • Severe leaflet defect(s) preventing proper device placement
	  • Ebstein Anomaly
	• Tricuspid valve anatomy not evaluable by TTE and TEE

Primary Endpoints	**Randomized cohort** The primary endpoint is a hierarchical composite of all-cause mortality or tricuspid valve surgery, heart failure hospitalizations, and quality of life improvement assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 12 months. The endpoint will be compared between the Device group and the Control group and evaluated in a hierarchical fashion as follows: • Time to all-cause death or tricuspid valve surgery • Number of Heart Failure (HF) Hospitalizations • Improvement of ≥15 points in KCCQ from baseline **Single-arm Cohort** The primary endpoint is survival at 12 months with a quality of life improvement (using KCCQ) of at least 10 points compared to baseline.
Secondary Endpoints	**Randomized Cohort** The following secondary endpoints will be assessed at the same time of the primary endpoints for labeling claims: • TR Reduction to moderate or less at 30-day post procedure. The endpoint will be assessed as the proportion of subjects who have moderate or less TR at 30 days. • Freedom from major adverse events (MAE) at 30 days after procedure attempt (femoral vein puncture). Components of MAE consist of the following: ○ Cardiovascular Mortality,

	○ New Onset Renal Failure, ○ Endocarditis Requiring Surgery, and ○ Non-Elective Cardiovascular Surgery for TriClip™ device-related AE post-index procedure. • Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) at 12 months • Change in Six Minute Walk Test (6MWT) at 12 months In addition, the following secondary endpoints will be assessed after all randomized subjects complete 24 months follow-up: • Recurrent HF hospitalizations at 24 months • Freedom from all-cause mortality, tricuspid valve surgery, and tricuspid valve intervention at 24 months **Single-arm Cohort** • TR Reduction by at least one grade at 30-day post procedure as compared to baseline. • Freedom from major adverse events (MAE) occurring after procedure attempt (femoral vein puncture) at 30 days. Components of MAE consist of the following: ○ Cardiovascular Mortality, ○ New Onset Renal Failure, ○ Endocarditis Requiring Surgery, and ○ Non-Elective Cardiovascular Surgery for TriClip™ device-related AE post-index procedure. • Change in 6MWT at 12 months, as compared to baseline • Recurrent HF hospitalizations at 12 months compared to the 12 months prior to enrollment • Freedom from all-cause mortality and tricuspid valve surgery at 12 months
Descriptive Endpoints	The following descriptive endpoints will be assessed and reported: • Technical Success • Device Success • Procedural Success • Incidence of peripheral edema requiring hospitalization at 12 months, and annually through 24, 36, 48, and 60 months • Incidence of ascites at 12 months, and annually through 24, 36, 48, and 60 months

	• Incidence of IV diuretic administration (including outpatient clinics) at 12 months, and annually through 24, 36, 48, and 60 months
	• Change in KCCQ score from baseline through 30 days, 6 months, 12 months, and annually through 24, 36, 48, and 60 months
	• SF-36 QoL scores at baseline, 30 days, 12 months and 24 months (and change from baseline to follow-up)
	• Change in NYHA Functional Class (III/IV to I/II) from baseline through 30 days, 6 months, 12 months, and annually through 24, 36, 48, and 60 months
	• Change in 6MWT from baseline through 30 days, 6 months, 12 months, and annually through 24, 36, 48, and 60 months
	• Change in BNP/NT-proBNP from baseline through 30 days, 6 months, 12 months, and annually through 24, 36, 48, and 60 months
	• Change in gamma-GGT from baseline through 30 days, 6 months, 12 months, and annually through 24, 36, 48, and 60 months
	• Change in patient weight from baseline through 30 days, 6 months,12 months, and annually through 24, 36, 48, and 60 months
	• Change in kidney function (assessed using eGFR) from baseline through 30 days, 6 months, 12 months, and annually through 24, 36, 48, and 60 months
	• Change in liver function (assessed using the MELD score) from baseline through 30 days, 6 months, 12 months, and annually through 24, 36, 48, and 60 months
	• Change in right ventricular volumes assessed from baseline through 30 days, 6 months, 12 months post procedure, and annually through 24, 36, 48, and 60 months
	• Echocardiographic endpoints assessed from baseline through 30 days, 6 months, 12 months, and annually through 24, 36, 48, and 60 months as follows:
	  • TR severity grade
	  • Tricuspid valve annulus diameter
	  • Effective Regurgitant Orifice Area (EROA)
	  • Regurgitant Volume
	  • Vena Contracta (VC) Width
	  • Right Ventricular End Diastolic Dimension (RVEDD)
	  • Right Ventricular Fractional Area Change
	  • Left Ventricular End Diastolic Volume (LVEDV)
	  • Left Ventricular End Systolic Volume (LVESV)
	  • Tricuspid Annular Plane Systolic Excursion (TAPSE)

	• Cardiac Output • Forward Stroke Volume (Left Ventricle) • Inferior Vena Cava Dimension • Same endpoints as assessed with echocardiography to be obtained from MRI/CT in the subset of patients participating in the imaging sub-study at baseline, 30 days and 12 months
Sample Size / Targeted Number of Subjects to Receive Study Device	Approximately 450 subjects will be randomized in a 1:1 ratio at up to 80 sites, out of which approximately 225 are expected to receive the TriClip™ device. Up to 200 additional subjects will be enrolled into a concurrent Single-arm cohort, all of whom will receive the TriClip™ device. Up to 3 roll-in subjects per implanter may be enrolled at sites with operators who do not have prior or recent experience using the TriClip™ device.
Subject Follow-up	Upon randomization, subjects will be scheduled for a "Treatment" visit. At the "Treatment" visit, Device group subjects will undergo the TriClip™ procedure and Control group subjects will be seen by a Heart Failure specialist for a physical exam, including vital signs, cardiac health status and evaluation of heart failure medications. The Treatment visit must be completed within 14 days of randomization. Subjects will have required follow-up evaluations at these time points post- "Treatment" visit: Discharge (not applicable to control subjects), 30 days, 6 months, 12 months, 18 months and annually thereafter through 5 years.

1 INTRODUCTION

There is growing evidence that untreated, severe, tricuspid regurgitation (TR) is an independent predictor of mortality. Current standard of care for the treatment of TR is medical therapy. Patients who are severely symptomatic have the option to undergo tricuspid valve surgery, which is associated with a high rate of morbidity and mortality (1) (2). Transcatheter repair of the tricuspid valve has gained considerable interest recently due to the minimally invasive nature of the procedures. The TriClip™ device is a less invasive percutaneous device designed to mimic surgical repair techniques by approximating the leaflets of the tricuspid valve. It is based on the same concept as the MitraClip® system, a percutaneous edge-to-edge repair technique for the treatment of mitral regurgitation, which received CE Mark in 2008, and FDA approval in 2013. The safety and efficacy of the MitraClip® has been well documented in over 1000 scientific publications. More than 80,000 patients have been treated with the MitraClip® system since CE Mark and FDA approval. The TriClip™ operates in a similar fashion to the MitraClip® system, with a modified delivery system to facilitate access and treatment of the tricuspid valve.

The primary objective of this trial is to demonstrate the safety and effectiveness of the TriClip™ device in improving clinical outcomes in symptomatic patients with severe TR, who are at intermediate or greater estimated risk for mortality or morbidity with tricuspid valve surgery. This randomized controlled trial will compare the device under investigation (TriClip™ device) to Control (Medical Therapy).

This clinical trial will be conducted in accordance with this Clinical Investigational Plan (CIP). All investigators involved in the conduct of the clinical investigation will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

2 BACKGROUND AND RATIONALE

2.1 Background

2.1.1 Tricuspid Regurgitation Description and Etiology

TR, or tricuspid valve insufficiency, is a failure of the tricuspid valve to close completely during systole resulting in leakage or “regurgitation” of blood from the right ventricle (RV) to the right atrium with each contraction of the RV. Symptoms associated with TR, include ascites, peripheral edema, hepatomegaly, decreased appetite, jugular vein enlargement and/or abdominal fullness (1). Additionally, TR severity is associated with decreased survival regardless of LVEF or pulmonary artery pressure (2).

Normal tricuspid valve closure is facilitated by the presence of anterior, posterior and septal leaflets at the interface of the right atrium and right ventricle. The 3 leaflets arise from the tricuspid annulus and are tethered to the RV via chordae tendinae and papillary muscles. Valve function is dependent on the proper form and function of all components of the valve complex.

Similar to the etiologies of mitral regurgitation, TR results from either degenerative disease of the leaflets (known as primary or degenerative TR) or from pathologic annular dilation which may be in conjunction with RV dilation (known as secondary or functional TR). Both result in mal-coaptation of the leaflets, which allows blood to flow backwards into the atrium. The

presence of either a pacemaker or an implantable cardioverter-defibrillator (ICD) lead that prevents proper coaptation of the leaflets can result in what is known as lead-induced TR (3). Persistent TR results in a volume-overloaded RV, which eventually leads to right heart failure.

Functional TR due to RV enlargement is the most common etiology (4). It is often associated with pulmonary hypertension (primary or secondary), RV dysfunction and/or atrial fibrillation. Of the three leaflets, the anterior leaflet is the one that is most affected by annular dilation. The septal leaflet is attached to the septum whose dilation is minimal, and dilation of the posterior leaflet is limited by the adjacent diaphragm. As the tricuspid annulus dilates, the anterior and posterior leaflets are pulled apart from the septal leaflet (**Figure 1**) creating gaps resulting in regurgitant jets from the right ventricle.

Figure 1: Tricuspid valve annular dilation

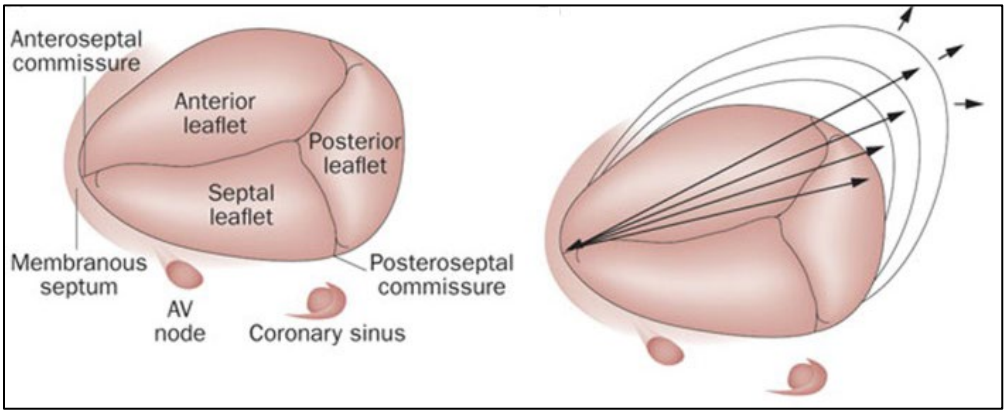


Image modified from Tornos et. al (7)

It was initially thought that treatment of mitral regurgitation (usually concomitant to TR), would also result in a reduction of TR (5). This perception has resulted in the tricuspid valve receiving little or no attention by the clinical community, thus being referred to as the “forgotten valve”. However, more recent analyses have shown that despite correction of left-sided valve disease, TR continues to worsen in some patients (6). Symptoms of TR are not evident until the regurgitation is significant. By the time of detection, patients are generally sicker with multiple co-morbidities putting them at high risk for cardiovascular surgery. Outcomes in patients with severe TR are significantly worse than those without TR, as demonstrated by multiple studies (2; 7; 8; 9).

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) (10; 1). Outcomes with isolated tricuspid valve surgery are suboptimal and have an associated 8% in-hospital mortality which increases to 37% for patients who undergo repeat surgery (11). Similarly, Bernal et al., reported high in-hospital mortality (35%) for a similar population of patients undergoing reoperation (12). Consequently, isolated tricuspid valve surgeries are rarely performed. Although recent studies have indicated that outcomes with tricuspid valve surgery have improved, current recommendations for isolated tricuspid valve surgery are limited to a Class II indication (1).

Tricuspid valve surgery is a Class I indication for severe TR patients at the time of left-sided valve surgery, per ACC/AHA valvular guidelines (10). Although 2017 ACC/AHA indication for TR intervention has not changed significantly (10), the 2017 ESC/EACTS guidelines for surgery encourages earlier surgical intervention (13). Surgical treatment for moderate or less TR continues to be a Class II indication. Therefore, the tricuspid valve is often untreated during the time of left-sided valve surgery, especially in patients with moderate or less TR severity. Left untreated, TR severity is known to continue to progress in approximately 30% of these patients; thus, increasing the patient's potential for morbidity/mortality risk with repeat operation to address the tricuspid valve (14).

2.1.2 MitraClip® Experience in Treatment of Mitral Regurgitation

Extensive clinical evidence has shown the safety and efficacy of the MitraClip® System in various worldwide trials involving over 4,000 patients to date. This collective data supports clinical safety of this device, effectiveness in mitral regurgitation (MR) reduction and improvements in echocardiographic measures of left ventricular (LV) function, and obvious improvement in patient Quality of Life (QoL). The MitraClip® received CE Mark in 2008 and FDA Approval in 2013 for percutaneous treatment of MR. The success of MitraClip® has driven physician interest in using a similar approach for reducing TR.

The first human procedure using the predicate MitraClip® System was performed on June 27, 2003 in Caracas, Venezuela. Only one procedure was performed in Venezuela.

Since then, in the United States, the MitraClip® System has been studied under an Investigational Device Exemption (IDE G030064). The initial IDE consisted of three cohorts: EVEREST I (feasibility study), EVEREST II (safety and effectiveness study) and REALISM (continued access study). More recently a new IDE was initialed, (IDE G120024) to confirm safety and performance of the MitraClip® System in patients with functional mitral regurgitation.

EVEREST II was a prospective, multi-center, randomized controlled trial where patients with moderate-to-severe (3+) or severe (4+) MR were randomized in a 2:1 ratio between the Device group (MitraClip® device) and the Control group (mitral valve surgery). The trial enrolled 279 patients, 184 in the Device group and 95 in the Control group and were followed for 5 years. At 5 years, the rate of the composite endpoint of freedom from death, surgery, or 3+ or 4+ MR in the as-treated population was 44.2% versus 64.3% in the percutaneous repair and surgical groups, respectively ($p = 0.01$). The difference was driven by increased rates of 3+ to 4+ MR (12.3% vs. 1.8%; $p = 0.02$) and surgery (27.9% vs. 8.9%; $p = 0.003$) with percutaneous repair. After percutaneous repair, 78% of surgeries occurred within the first 6 months. Beyond 6 months, rates of surgery and moderate-to-severe MR were comparable between groups. Five-year mortality rates were 20.8% and 26.8% ($p = 0.4$) for percutaneous repair and surgery, respectively. In multivariable analysis, treatment strategy was not associated with survival.

The most recent study, COAPT, began enrollment on December 27, 2012 and completed on June 23, 2017, with a total of 614 patients at 78 centers in the United States and Canada. COAPT is a prospective, multicenter, randomized, parallel-controlled trial to evaluate the preliminary safety and effectiveness of the percutaneous MitraClip® System in patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy. The

primary safety end point was freedom from device-related complications at 12 months; the rate for this end point was compared with a prespecified objective performance goal of 88.0%.

Of the 614 patients who were enrolled in the trial, 302 were assigned to the device group and 312 to the control group. The annualized rate of all hospitalizations for heart failure within 24 months was 35.8% per patient-year in the device group as compared with 67.9% per patient-year in the control group (P<0.001). The rate of freedom from device-related complications at 12 months was 96.6% (P <0.001 for comparison with the performance goal). Death from any cause within 24 months occurred in 29.1% of the patients in the device group as compared with 46.1% in the control group (P<0.001).

Overall, the MitraClip® clinical trials have shown consistently excellent safety and efficacy profile. Reduction of MR severity has shown improvements in symptoms, improved QoL measurements, and functional improvements in patients who had significant MR.

2.1.3 MitraClip® Experience in Tricuspid Regurgitation

As of February 2019, there have been at least 20 published manuscripts representing approximately 200 patients who have been treated with the MitraClip® device on the tricuspid valve as off-label/Compassionate Use. In general, selected patients are described to have significant tricuspid regurgitation with symptomatic heart failure (NYHA III or IV). Patients had at least 1 co-morbidity reported and were deemed to be high risk for surgical intervention by the site heart team.

The reports indicate that most patients received at least 1 MitraClip® device resulting in reduction in TR of at least 1 grade in > 90% of the cases. Some reports have also indicated that reduction in echocardiographic measurements of vena contracta area and width, EROA, annular diameter, and TR volume were achieved. Low rates of adverse events and no device-related complications were reported. Observations from key publications where cohorts of consecutively treated patients have been studied are briefly described below:

- Nickenig et al. has reported on the largest cohort to date which included data from 64 patients treated with the MitraClip® at 10 centers (15). All patients had symptomatic moderate to massive TR, were on optimal medical treatment, and were considered unsuitable for surgery. The MitraClip® device was used either for isolated tricuspid valve regurgitation (n=42) or for concomitant mitral and tricuspid valve (n=22) regurgitation. At baseline, 93% of patients were in NYHA III/IV, 82% had LVEF <50%, and 95% experienced dyspnea. Ninety-seven percent (97%) of the patients had 1 or more clip deployed at the tricuspid valve. Post-procedure, 91% of the patients had at least 1 grade reduction in TR. No intraprocedural death, cardiac tamponade, emergency surgery, stroke, myocardial infarction or major vascular complications were reported. There were 3 (5%) in-hospital deaths.
- Orban et al. presented data with minimum 6 months follow-up on patients (n=50) who had the tricuspid valve treated using the MitraClip® (16). Of the 50 patients treated, 36 received the device for concomitant mitral and tricuspid valve treatment (N=36), while 14 patients received the device for isolated TR treatment. A clip was successfully deployed in 94% of the cases. Post procedure, a majority (90%) of patients showed at least a 1 grade reduction in TR severity and 79% had 1 class improvement in NYHA at 6-month follow-up. Six-month clinical results demonstrated a 44% increase in 6MWT distance

and a trend of an average 6-point improvement in MLHFQ (Minnesota Living with Heart Failure Questionnaire). Eight (n=8) patients died, 14 patients had HF hospitalization, 2 patients underwent tricuspid valve surgery, and 2 patients underwent a second tricuspid valve MitraClip® procedure.

- Besler et al. presented data on 117 patients, the largest cohort to date, with a median follow-up of 184 days (17). Of the 117 patients treated, 74 received the device for concomitant mitral and tricuspid valve treatment, while 43 patients received the device for isolated TR treatment. Procedural success (TR reduction ≥1) was achieved in 81% of patients. Of the patients reports, 24 died and 21 were readmitted for heart failure. Procedural success independently predicted the time free of death and admission for heart failure irrespective of concomitant mitral regurgitation.
- Braun et al. recently reported 1 year follow-up, the longest to date, on patients (n=24) who had the tricuspid valve treated with the MitraClip® (18). During one-year follow-up nine patients died (37.5%) with causes of death including end-stage heart failure in four patients, sepsis in two patients, STEMI in one patient and unknown causes in two patients. The rate of patients with TR ≤2 improved from 4% (1/24) at baseline to 87% of the surviving patients (13/15) at one-year follow-up (p<0.001). Two patients underwent a second edge-to-edge procedure due to recurrent severe TR. The percentage of patients in NYHA ≤II improved from 0% (0/24) at baseline to 67% of the surviving patients (10/15) at one-year follow-up (p<0.001).

Overall, the data show either a reduction in TR severity or other echocardiographic parameter(s) (i.e. vena contracta width, vena contracta area, etc.), along with an improvement in clinical symptoms, and/or improvement in quality of life measurements. No concerns associated with device safety have yet been reported.

2.1.4 TriClip™ Experience

The TRILUMINATE trial, initiated to obtain CE mark approval, is a prospective, single-arm, multi-center study of the Abbott transcatheter TriClip™ using a clip-based edge-to-edge repair technique. The objective of the trial is to evaluate the safety and effectiveness of the TriClip™ in patients with symptomatic moderate or greater TR who are deemed appropriate for percutaneous transcatheter intervention by the site heart team.

In general, patients who were NYHA class II or greater, with no left-sided heart disease, and who were treated per applicable standards (including medical management) were included in the study. Patients were excluded from the study if they had systolic pulmonary artery pressure >60mmHg, a prior tricuspid valve procedure, or either pacemaker or ICD leads which would inhibit proper TriClip™ placement. First a cardiac surgeon at the site assessed surgical risk status. Then the ECL graded the severity of TR. Finally, patients were presented to an Independent Eligibility Committee (EC) that included a cardiac surgeon, an interventionalist, and an echocardiographer who reviewed pertinent medical history to make the final determination regarding eligibility of prospective subjects, including eligibility of tricuspid valve anatomy. Once the EC confirmed that the subject was eligible for the TriClip™ procedure, the subject was scheduled for the TriClip™ procedure.

As of the data cut-off date (November 29, 2018), at which time the first 85 subjects treated with the TriClip™ reached their 30 day follow-up, 14 subjects had been treated in the US and 73

subjects had been treated outside of US (total 87 subjects) in the TRILUMINATE trial (CE mark trial). Out of the 87 subjects, 85 had completed their 30-day follow-up. Mean age of the study population was 77.8 ± 7.9 years, and a majority of the subjects were female (65.9%). All subjects had moderate or greater TR, with the majority (94.0%) having severe TR. A majority of the subjects had significant comorbidities including atrial fibrillation (91.8%), hypertension (85.9%), and renal disease (45.9%) being the most common. All subjects were symptomatic with NYHA ≥II, with a majority (74.7%) of the subjects being in NYHA III/IV. Subjects had diminished quality of life and functional capacity with a mean KCCQ score of 52.19 ± 21.85 points and a mean 6-minute walk test (6MWT) distance of 277.47 ± 137.20 m.

An average of 2.2 ± 0.8 clips were implanted per procedure with at least 1 clip implanted in all subjects. Implant success and acute device success rates were each 100%, and the acute procedural success rate was 91.6%. Of the 185 clips implanted in 85 subjects, 77.3% were in the anterior-septal leaflet position, 20.0% in the septal-posterior position and 2.7% in the anterior-posterior position. Mean total procedure, device, and fluoroscopy durations were 152.7 ± 57.8 min, 75.2 ± 43.1 min and 23.3 ± 17.8 min respectively.

Primary effectiveness endpoint of TR reduction of least 1 grade at 30-days was successfully met. At 30 days, 86.6% of subjects had their TR reduced by at least 1 grade, with a one-sided 97.5% lower confidence limit of 77.3%, which was significantly greater than the pre-specified performance goal of 35% ($p < 0.0001$). At 30 days, a significantly greater proportion (79.8%) of subjects showed improvement in NYHA functional class and were categorized as NYHA class I or II compared to 25.3% of subjects at baseline. Subjects experienced a significant improvement in their quality of life assessed using the Kansas City Cardiomyopathy Questionnaire, with scores improving from 52.19 ± 21.85 at baseline to 67.24 ± 22.24 at 30 days, a mean improvement of 14.20 ± 16.74 points. Similarly, subjects improved their 6MWT distance from 277.47 ± 137.20 at baseline to 304.46 ± 109.74 at 30 days, a mean improvement of 47.5 ± 69.7m.

The primary safety endpoint of MAE rate at 6 months was met successfully. Through 6 months follow-up, the MAE rate estimated by the Kaplan-Meier method was 6%, less than the pre-specified performance goal of 39% ($p<0.0001$). Three (3) subjects experienced cardiovascular mortality, 1 subject experienced myocardial infarction, and 1 subject experienced new onset renal failure. No subjects experienced stroke or non-elective cardiovascular surgery for TriClip™ device related adverse events occurring after the index procedure. The data demonstrates that the TriClip™ can be used to repair the tricuspid valve and reduce TR with excellent procedural success and associated clinical outcomes. Subjects experienced a significant improvement in quality of life and functional capacity at 30 days post procedure. No safety concerns were identified, with only 5 subjects experiencing a major adverse event through 6-month follow-up.

2.2 Rationale for Conducting this Clinical Investigation

Optimal medical therapy for the treatment of TR has not been well defined. Medical treatment primarily revolves around the use of diuretics; however, a proportion of patients continue to progress and suffer from the symptoms of TR. Current treatment options for TR are surgical repair or replacement. Typically, these procedures are done in conjunction with left-sided cardiac surgical procedures (e.g. Aortic Valve and/or Mitral Valve). Isolated tricuspid valve surgery is typically not offered to patients, particularly those with prior cardiac surgeries

performed. Consequently, there are a large group of patients with TR, who are left with no options besides medical therapy, and hence the disease state in these patients will continue to progress with the natural morbidity and mortality course associated with the disease. The TriClip™ procedure provides a new, less-invasive avenue for the treatment of TR, with the expectation that treatment of TR will have a beneficial impact on the clinical sequelae that is associated with worsening TR.

Clinical experience with the use of the MitraClip® for treatment of TR, combined with early clinical experience associated with the use of the TriClip™ in the TRILUMINATE trial, indicate that percutaneous edge-to-edge repair is safe and reduces TR and heart failure symptoms. The rationale for conducting this clinical investigation is to generate scientific evidence to demonstrate the safety and clinical benefit of the device in TR patients.

This clinical investigation proposes to build on the current experience and attempts to fill an important clinical evidence gap for patients who continue to suffer from symptomatic TR despite medical therapy.

3 CLINICAL INVESTIGATION OVERVIEW

3.1 Clinical Investigation Objective

The objective of this trial is to evaluate the safety and effectiveness of the TriClip™ device in improving clinical outcomes in symptomatic patients with severe TR who have been determined by the site's local heart team (consisting of one interventionalist, one cardiac surgeon, one heart failure specialist and one echocardiologist) to be at intermediate or greater estimated risk for mortality or morbidity with tricuspid valve surgery.

3.2 Device To Be Used in the Clinical Investigation

3.2.1 Name of the Device Under Investigation

The device under investigation to be used in this trial is the TriClip™. Further information can be found in the Instructions for Use (IFU) for the respective region.

Device Name	Model/Type	Serial/Lot Controlled	Manufacturer	Region/Country	Investigational or Market Released
TriClip Steerable Guide Cath CLIN	TSGC0203	Serialized	Abbott	USA/Canada	Investigational
TriClip Steerable Guide Cath	TSGC0202	Serialized	Abbott	European Union (EU)	Market Released
TriClip NT Clip Delivery Sys CLIN	TCDS0203-NT	Serialized	Abbott	USA/Canada	Investigational
TriClip NT Delivery Sys	TCDS0202-NT	Serialized	Abbott	EU	Market Released

TriClip XT Clip Delivery Sys CLIN	TCDS0203-XT	Serialized	Abbott	USA/Canada	Investigational
TriClip XT Delivery Sys	TCDS0202-XT	Serialized	Abbott	EU	Market Released

The newest generation TriClip™ device (TriClip™ G4) will also be included in the trial. Further information regarding the TriClip™ G4 device can be found in the Instructions for Use (IFU) for the respective region (see below). Sites in the EU may use the TriClip™ G4 device only after it is CE marked and commercially available for participating study sites (using the commercial product).

Device Name	Model/Type	Serial/Lot Controlled	Manufacturer	Region/Country	Investigational or Market Released
TriClip Steerable Guide Cath CLIN	TSGC0203	Serialized	Abbott	USA/Canada	Investigational
TriClip Steerable Guide Cath CE	TSGC0202	Serialized	Abbott	European Union (EU)	Market Released
TriClip G4 NT Clip Delivery Sys CLIN	TCDS0303-NT	Serialized	Abbott	USA/Canada	Investigational
TriClip G4 NT Delivery Sys CE	TCDS0302-NT	Serialized	Abbott	EU	Market Released
TriClip G4 XT Clip Delivery Sys CLIN	TCDS0303-XT	Serialized	Abbott	USA/Canada	Investigational
TriClip G4 XT Delivery Sys CE	TCDS0302-XT	Serialized	Abbott	EU	Market Released
TriClip G4 NTW Clip Delivery Sys CLIN	TCDS0303-NTW	Serialized	Abbott	USA/Canada	Investigational
TriClip G4 NTW Delivery Sys CE	TCDS0302-NTW	Serialized	Abbott	EU	Market Released
TriClip G4 XTW Clip Delivery Sys CLIN	TCDS0303-XTW	Serialized	Abbott	USA/Canada	Investigational

TriClip G4 XTW Delivery Sys CE	TCDS0302-XTW	Serialized	Abbott	EU	Market Released

3.2.2 Intended Indication for Use

The TriClip™ is intended for the treatment of patients with symptomatic, severe tricuspid valve regurgitation, whose symptoms and TR severity persist despite being treated optimally with medical therapy. Where applicable, refer to the approved IFU in the respective region/country for the intended use of the TriClip™ device.

3.2.3 Description of the Device Under Investigation (TriClip)

Detailed information of the device can be found in the IFU. Briefly, the TriClip™ configuration consists of two parts: 1) a Clip Delivery System, which includes an implantable Clip (TriClip™ device), a Steerable Sleeve and a Delivery Catheter; and 2) a Steerable Guide Catheter which includes a dilator (**Figure 2**).

The Clip Delivery System is used to advance and manipulate the implantable TriClip™ 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 (**Figure 2**).

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. The Clip is available in two sizes with differing grasping widths: the NT (17mm) and XT (22mm).

In addition, the TriClip™ G4 system gives users the option to perform simultaneous and/or independent gripper actuation through the manipulation of new Delivery Handle controls (i.e. Controlled Gripper Actuation feature) and two redesigned Gripper lines. The TriClip™ G4 Implant is available in 4 sizes including 2 additional Implant sizes: NTW and XTW, which have Implant Arms that are approximately 50% wider than the NT and XT Implant sizes (**Figure 3**).

Figure 2: TriClip™ Configuration

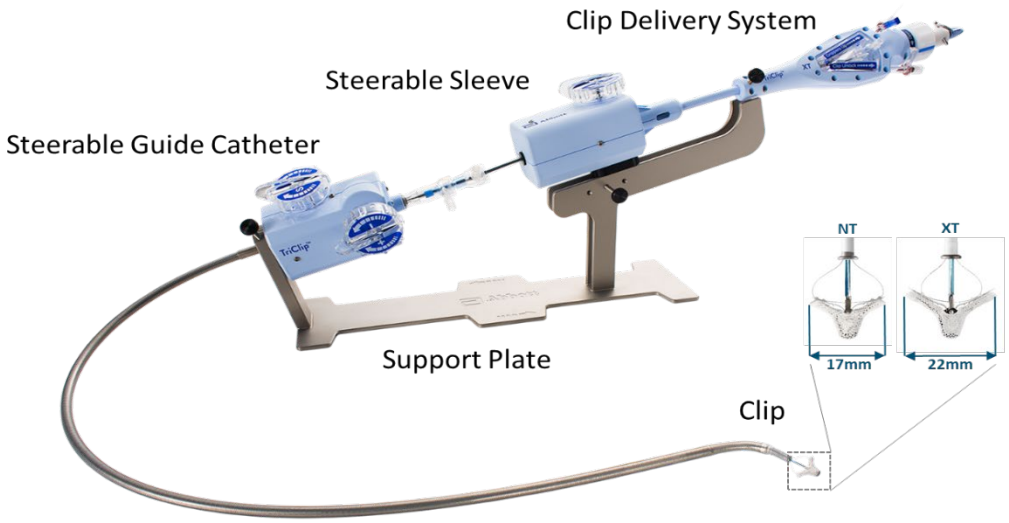
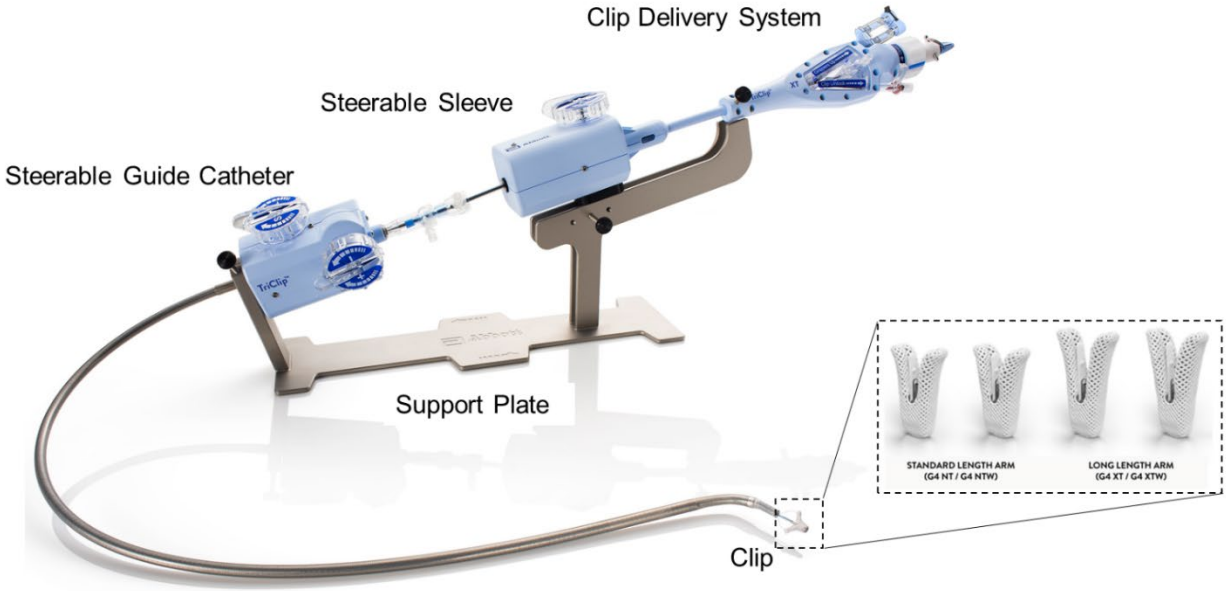


Figure 3: TriClip™ G4 Configuration



3.2.4 Summary of Preclinical Studies

Two non-GLP studies were performed with the MitraClip® NT device to evaluate injury and healing in the healthy, porcine tricuspid valve and surrounding structures.

An acute study was conducted to assess the ability to coapt two tricuspid leaflets and evaluate injury and trauma to the tricuspid valve and surrounding structures post deployment. One MitraClip® was implanted in one animal, successfully coapting two tricuspid leaflets. Upon gross examination of the tricuspid valve and surrounding tissues, significant injury was not observed.

A four week chronic study was conducted to assess the healing profile in the porcine tricuspid valve and evaluate the long term hemodynamic response after implantation with the MitraClip® device in one animal. The animal was implanted with two MitraClip® devices in the tricuspid valve and survived to the four week time point without any adverse events. Prior to termination, right sided hemodynamics were assessed and it was determined that there were no relevant hemodynamic changes. Gross pathology and histological evaluation of the implanted tricuspid valve showed that both clips were appropriately encapsulated in fibrous tissue. Tissue bridging between the coapted leaflets was also observed grossly and histologically. Overall, healing was appropriate for the four week time point and was similar to the healing observed at four weeks in the chronic GLP porcine mitral valve safety study.

A chronic GLP safety study was performed with a 30 day and 90 day follow-up endpoint. Twelve animals (n=6 at 30 days; n=6 at 90 days) were assessed for 3 endpoints: 1) overall health, 2) device deployment and hemodynamics, and 3) tissue response to the clip. There were no clinically relevant changes in the clinical pathology and no clinically relevant gross or histological changes in non-cardiac organs, myocardium, or tricuspid valve attributed to the test device at either time point. There was near complete tissue encapsulation of the clip at 30 days and complete encapsulation and endothelialization at 90 days. There was no evidence of clip embolization or thrombosis and the inflammatory response was determined to be appropriate. The pre-determined safety endpoints of the acceptance criteria were met for all 12 animals including no observed adverse clinically relevant gross or histological changes in the myocardium or tricuspid valves attributed to the test article.

3.2.5 Device Handling

The Sponsor requires clinical sites to store all investigational products according to the labeling and Instructions for Use in a secure area to prevent unauthorized access or use.

4 CLINICAL INVESTIGATION DESIGN

TRILUMINATE Pivotal trial is a prospective, multicenter, randomized, controlled, clinical trial of the TriClip™ device in symptomatic subjects with severe TR, who have been determined by the site's local heart team to be at intermediate or greater estimated risk for mortality or morbidity with tricuspid valve surgery.

The trial consists of two cohorts: a Randomized cohort and a Single-arm Cohort. Determination as to whether a patient is placed in the randomized arm or Single-arm will be made by the independent eligibility committee. Patients will be placed in the Single-arm cohort if they meet the following criteria:

- The likelihood of achieving TR reduction of at least 1 grade (as assessed using a 5-grade scale, See **Appendix XII**) is high, and
- The likelihood of achieving TR reduction to moderate or less (≤ 2) is low

All other patients will be randomized.

After the patient has been determined to meet all general inclusion/exclusion criteria, and prior to randomization, the patient's echocardiographic and key clinical data will be submitted for review to confirm eligibility. First, the site will be required to submit echocardiograms to the echocardiography core laboratory (ECL) for confirmation of TR severity. Initial assessment of clippability will be performed based on consultation between the site heart team, the ECL and Abbott proctors. Finally, an independent eligibility committee (EC) will assess each potential subject and confirm that the potential subject has been optimally treated with medical therapy (drug and device), ensure the tricuspid valve is amenable to the TriClip™ device and confirm overall eligibility. See **Figure** for study flow chart. Subsequently, the EC will determine whether the patient will be considered for the Randomized or Single-arm of the trial.

Potential subjects who have concurrent severe mitral regurgitation will not be immediately eligible for the trial. These subjects must be treated for the MR first and re-assessed at a later stage for inclusion into the trial.

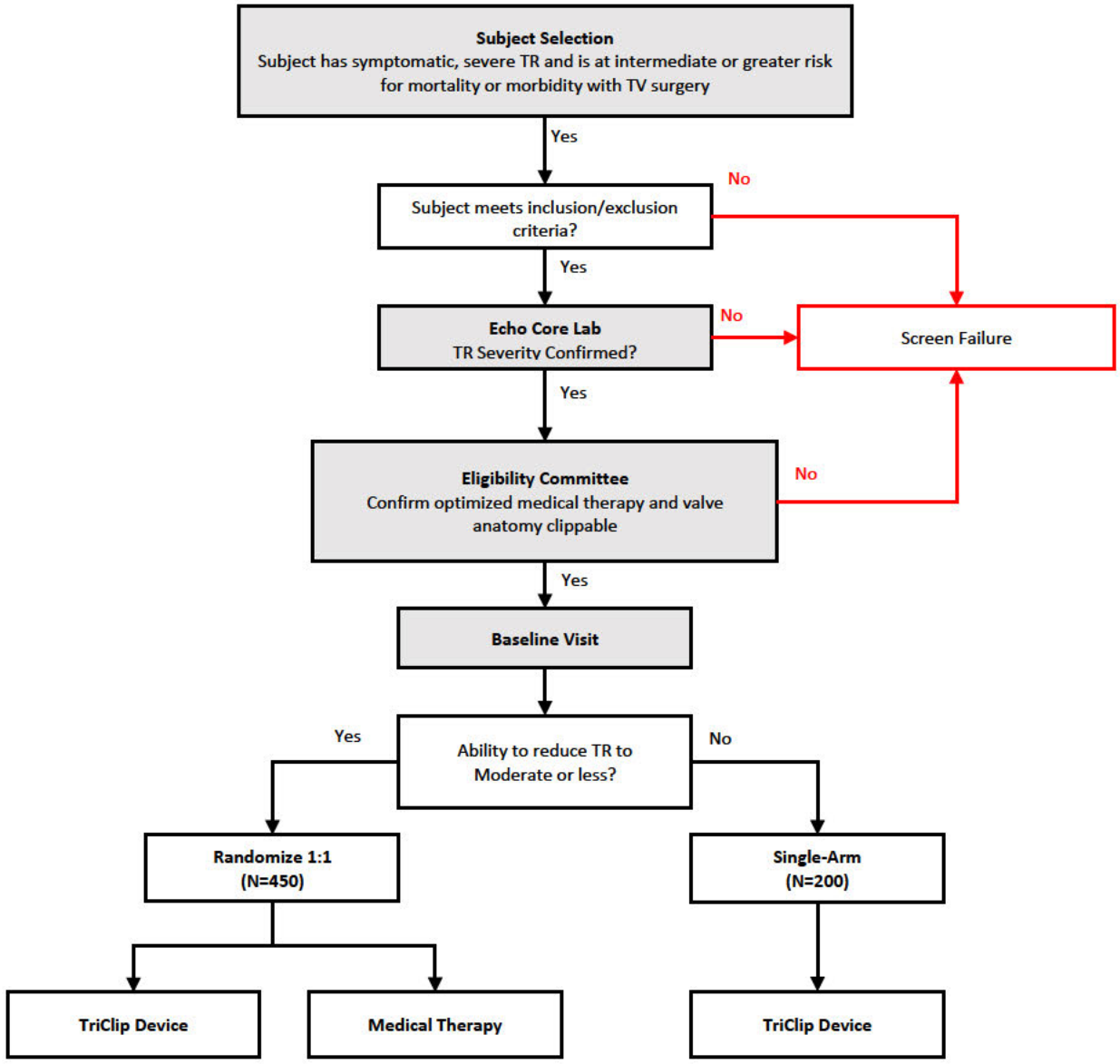
Randomization will occur in approximately 450 eligible subjects in a 1:1 ratio to receive either the TriClip™ device or medical therapy (control group), at up to 80 sites as follows:

- **TriClip™ Device (Device) Group:** Eligible subjects will undergo the TriClip™ procedure and will continue to be managed on medical therapy, per physician discretion.
- **Medical Therapy (Control) Group:** Eligible subjects will not undergo the TriClip™ procedure but will continue to be managed on medical therapy, per physician discretion.

The Single-arm cohort will enroll up to 200 eligible subjects and all subjects will receive the TriClip™ device.

Additionally, up to 3 roll-in subjects will be permitted per implanter without prior experience of transcatheter treatment of the tricuspid valve. The trial will be conducted in US, Canada and Europe, with a minimum of 50% of the subjects in each cohort enrolled in the US.

Figure 4: Study Flow Chart



Prior to randomization, subjects will first undergo baseline assessment. After the baseline assessment, the subject will undergo randomization to receive either the TriClip™ or continue on Medical Therapy. If randomized to receive the TriClip™ device, the subject will undergo the TriClip™ implantation procedure within 14 days of randomization during the Treatment visit. Post-procedure follow-up (discharge, 30-day, 6-month, 1-year, 18-month 2-year, 3-year, 4-year, and 5-year) will capture clinical, echocardiographic, and safety data. Subjects who are randomized to the Medical Therapy (Control) Group will follow the same visit schedule except for discharge. For the Control Group "Treatment" visit, subjects will be seen by the HF specialist, and will undergo a physical exam, including vital signs, cardiac health status and evaluation of heart failure medications. Medications in both groups are to be continued, unless change is deemed necessary per physician discretion. Assessments, such as KCCQ, 6MWT,

SF-36 and NYHA during the follow-up visits (30-day visit and afterwards) will be performed by blinded study personnel.

The primary and secondary endpoints (See Section 5) will be evaluated when the first 350 subjects have completed their 12-month visit. Additional secondary endpoints will be evaluated in the Randomized cohort when the 450 patients complete their 24-month follow-up. An independent Clinical Events Committee (CEC) will adjudicate events including cause of death, HF hospitalization and components of major adverse events. The independent ECL will assess echocardiographic endpoints.

The Sponsor has designed this clinical investigation to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risk Analysis section of this clinical investigation plan for details.

4.1 Clinical Investigation Procedures and Follow-up Schedule

Each subject will be followed until their 5-year visit. Clinical Investigation visits will occur at Baseline (after confirmation of eligibility), Treatment visit, Discharge (not applicable to control subjects), 30-days, 6 months, 12 months, 18 months, and annually through 60 months (5 years).

4.2 Measures Taken to Avoid and Minimize Bias

Due to the nature of the treatment in the two randomized groups, the subject, some site personnel and some Sponsor personnel will be aware of treatment assignment. The following steps will be taken to minimize bias in the conduct of the trial and analyses of clinical data.

4.2.1 Subject Recruitment and Randomization

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

- Candidates will be considered for the trial after they have been informed of trial requirements and have signed the informed consent form. See Section 6.2 Subject Screening and Informed Consent for additional details on subject screening and informed consent process.
- Transthoracic echocardiographic criteria for trial eligibility will be confirmed by an independent ECL
- All baseline tests and assessments must be completed prior to randomization
- Subjects will be randomized 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 eligibility criterion, the EC has confirmed that the subject is on optimal therapy, the tricuspid valve is clippable and have assigned the subject to the appropriate treatment arm. Subjects assigned to the Single-arm will not be randomized.
- Randomization will be stratified by site and performed using permuted blocks (random block sizes), and block sizes will not be disclosed to the sites.
- A centralized randomization service will be used.

4.2.2 Maintaining Similar Levels of Follow-up

To maintain similar levels of contact between the investigational site and subjects, all subjects will have a "Treatment" visit. During the "Treatment" visit for the Control group, subjects will be

seen by a HF specialist, and will undergo a physical exam, including vital signs, cardiac health status and evaluation of heart failure medications. Subjects in the Device group will undergo the TriClip™ procedure during the "Treatment" visit.

4.2.3 Administration of Assessments

Site personnel assessing NYHA Functional Class, administering the 6MWT and QoL questionnaires during the follow up visits (30-day visit and afterwards) will be blinded to the subject's treatment assignment and will not be involved in day-to-day activities of the TRILUMINATE Pivotal trial. Additionally, personnel performing these assessments will not have access to the electronic case report forms (eCRFs). A standardized script will be used when administering the assessments and the subject will be reminded to not reveal their treatment history to the administrator. 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 (in such cases, a note to file must be completed to document the inability of subject to complete the questionnaire).

4.2.4 Eligibility Committee (EC)

An independent EC will comprise, at a minimum, representatives from the following specialties: heart failure specialist, interventional cardiologist and echocardiologist. The EC will determine if the subject is being managed according to optimized medical therapy, evaluate the clippability of the tricuspid valve and determine whether the subject will be enrolled in the Randomized or Single-arm cohort. Review will be performed via teleconference with presentation (i.e. Webex) or other formats on a regular basis (i.e. weekly) between the EC, ECL representative, and a study site(s) representative(s) of the proposed subject(s). The composition, guiding policies, and operating procedures governing the EC are described separately in the charter.

4.2.5 Review of Echocardiography Images

TR severity and other echocardiographic measurements will be assessed by an independent ECL at screening, baseline and follow-up. Prior to enrollment, the ECL will confirm subject's screening echocardiography images for TR severity per the guideline for TR grading (defined in **Appendix XII)**. Finally, the ECL will be responsible for assessing TR severity and echocardiographic analyses at all visits (baseline and follow-ups).

4.2.6 Safety and Effectiveness Monitoring

- All adverse events will be reviewed by Abbott Clinical Safety team.
- Adverse events requiring adjudication will be submitted to an independent CEC. See section 11.7.4.
- A Data Monitoring Committee (DMC) will review accumulating safety and effectiveness data as described in Section 11.7.3.

4.2.7 Follow-Up Compliance

The Sponsor will work with investigational sites to maintain high follow-up compliance. The following are strategies for increasing compliance:

- During the site initiation visit, the Sponsor will emphasize to the site the importance of subject follow-up, and that the site should communicate this importance to each subject.

- Sites should promptly reschedule any missed subject visits, and to reinforce the necessity of a follow-up visit to subjects.
- If a scheduled visit is missed due to subject illness, transportation issues, or travel, the site should:
    - Reinforce the necessity of follow-up visits;
    - Identify alternate transportation sources, and involve the Sponsor if necessary.
- Sites will be instructed to ask subjects who withdraw during the trial to provide the reason for withdrawal and ask them if the investigator may contact them to check their vital status at the end of the trial follow-up.
- Follow-up rates will be monitored closely so follow-up problems may be identified and addressed as soon as possible.
- For subjects lost-to-follow-up, sites may be requested to examine the Social Security Death Index to determine subject status (only the status will be sent to Sponsor, not any subject identifying information).

In addition to aforementioned steps, investigational sites will be educated on the importance of maintaining low rates of withdrawals in both Device and Control groups, and will be expected to make all efforts to maintain low withdrawals during trial conduct. If necessary, an independent service (e.g. Hawthorne Effect) may be utilized to provide in-home visits to aid in follow-up compliance. Withdrawals from the trial may need discussion between investigator and the Sponsor.

4.3 Continued Access Study Procedures and Follow-up Schedule

Following the completion of enrollment in both the randomized and single-arm cohorts of the TRILUMINATE Pivotal trial, subjects from eligible sites will be enrolled into a continued access study. Details of the continued access study procedures and follow-up schedule are included in Appendix XVI.

4.4 Suspension or Early Termination of the Clinical Investigation

No formal statistical rule for early termination of the clinical investigation for insufficient effectiveness of the device under investigation is defined.

The Sponsor reserves the right to discontinue the clinical investigation at any stage or reduce the follow-up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

- Unanticipated adverse device effect (e.g., UADE) occurs and it presents an unreasonable risk to the participating subjects
- Any oversight committee (e.g., Steering Committee, Data Monitoring Committee) makes a recommendation to stop or terminate the clinical investigation (such as higher frequency of anticipated adverse device effects)
- Further product development is cancelled

Should the clinical investigation be discontinued by the Sponsor, subjects will be followed per routine hospital practice with device-related AEs reported to the Sponsor as per vigilance/commercial reporting requirements.

Should early termination occur, the investigator shall return all clinical investigation materials (including devices) to the Sponsor, and provide a written statement as to why the premature termination has taken place to the IRB/EC (if applicable). All applicable clinical investigation documents shall be subject to the same retention policy as detailed in Section 12.5 of the CIP. A Principal Investigator, IRB/EC or regulatory authority may suspend or prematurely terminate participation in a clinical investigation at the investigational sites for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If the Sponsor suspends or prematurely terminates the clinical investigation at an individual site in the interest of safety, the Sponsor will inform all other Principal Investigators.

If suspension or premature termination occurs, the Sponsor will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following the subjects enrolled in the clinical investigation, and the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her site, if appropriate. Additionally, an effort will be made to hasten the release of results if the study is terminated early.

5 ENDPOINTS

5.1 Randomized Cohort

5.1.1 Primary Endpoint

The primary endpoint is a hierarchical composite of all-cause mortality or tricuspid valve surgery, heart failure hospitalizations, and quality of life improvement assessed using the KCCQ at 12 months. The endpoint will be evaluated in a hierarchical order as follows:

- Time to all-cause death or tricuspid valve surgery
- Number of Heart Failure (HF) Hospitalizations
- An Improvement of ≥15 points in KCCQ from baseline

HF Hospitalization includes any of the following:

1) Hospitalization (≥ 24 hours) with the primary reason for admission as acute decompensated HF and administration of intravenous or mechanical heart failure therapies, especially IV administration of diuretic therapy.

2) An unscheduled or unplanned admission to the emergency department, hospital outpatient observation unit, or hospital inpatient unit, and IV administration of diuretic therapy. Overnight stays for IV administration of diuretic therapy at nursing home facilities, physical rehab or extended care facilities, including hospice, will be included in the definition of hospitalization if related to heart failure.

3) Subject arrives in emergency department with clinical presentation meeting the criteria of HF, but dies in the emergency department before hospital admission.

Elective heart failure “tune-ups” that occur following the TriClip™ procedure and prolong hospitalization will not count as a heart failure hospitalization.

Based on the current experience, it is expected that the Device group may experience a mortality benefit, improved freedom from heart failure symptoms, as well as a quality of life improvement when their TR is treated.

The primary endpoint will be evaluated once 350 subjects have completed 12-month follow-up. An adaptive design with sample size re-estimation will be performed prior to assessment of the primary endpoint. If the sample size needs to be increased to maintain adequate study power, then the primary endpoint will be evaluated once the 12-month follow-up is completed with the larger sample size.

The primary endpoint must be met for the study to be successful.

5.1.2 Powered Secondary Endpoints

The following secondary endpoints will be assessed at the same time of the primary endpoint for labeling claims:

- TR Reduction to moderate or less at 30-day post procedure. The endpoint will be assessed as the proportion of subjects who have moderate or less TR at 30 days.
- Freedom from major adverse events (MAE) occurring after procedure attempt (femoral vein puncture) at 30 days. Components of MAE consist of the following:
    - Cardiovascular Mortality,
    - New Onset Renal Failure,
    - Endocarditis Requiring Surgery, and
    - Non-Elective Cardiovascular Surgery for TriClip™ device-related AE post-index procedure.
- Change in KCCQ at 12 months
- Change in 6MWT at 12 months

The following secondary endpoints will be assessed after all randomized subjects complete 24-month follow-up for additional labeling claims:

- Recurrent HF hospitalizations at 24 months
- Freedom from all-cause mortality, tricuspid valve surgery, and tricuspid valve intervention at 24 months

5.1.3 Descriptive Endpoints

The following descriptive endpoints will be assessed and reported:

- Technical Success at exit from procedure room: Alive with successful access, delivery and retrieval of the device delivery system, and deployment and correct positioning of a Clip, and no need for additional unplanned or emergency surgery or re-intervention related to the device or access procedure
- Device Success at 30-day post-procedure: Alive with original intended Clip(s) in place, and no additional surgical or interventional procedures related to access or device since completion of the original procedure, and intended performance of the Clip(s) (i.e. ≥1 grade improvement in TR severity, no embolization, single leaflet device attachment, absence of para-device complications)
- Procedural Success at 30-day post-procedure: Device success, and no device or procedure related SAE
- Incidence of peripheral edema requiring hospitalization at 12 months, and annually through 24, 36, 48, and 60 months

- Incidence of ascites at 12 months, and annually through 24, 36, 48, and 60 months
- Incidence of IV diuretic administration (including outpatient clinics) at 12 months, and annually through 24, 36, 48, and 60 months
- Change in KCCQ score from baseline through 30 days, 6 months, 12 months and annually through 24, 36, 48, and 60 months
- SF-36 QoL scores at baseline, 30 days, 12 months and 24 months (and change from baseline to follow-up)
- Change in NYHA Functional Class (III/IV to I/II) from baseline through 30 days, 6 months, 12 months and annually through 24, 36, 48, and 60 months
- Change in 6MWT from baseline through 30 days, 6 months, 12 months and annually through 24, 36, 48, and 60 months
- Change in BNP/NT-proBNP from baseline through 30 days, 6 months, 12 months, and annually through 24, 36, 48, and 60 months
- Change in gamma-GGT from baseline through 30 days, 6 months, 12 months, and annually through 24, 36, 48, and 60 months
- Change in patient weight from baseline through 30 days, 6 months, 12 months and annually through 24, 36, 48, and 60 months
- Change in kidney function (assessed using eGFR) from baseline through 30 days, 6 months, 12 months and annually through 24, 36, 48, and 60 months
- Change in liver function (assessed using the MELD score) from baseline through 30 days, 6 months, 12 months and annually through 24, 36, 48, and 60 months
- Echocardiographic endpoints assessed from baseline through 30 days, 6 months, 12 months and annually through 24, 36, 48, and 60 months post procedure, as follows:
    - TR severity grade
    - Tricuspid valve annulus diameter
    - Effective Regurgitant Orifice Area (EROA)
    - Regurgitant Volume
    - Vena Contracta Width
    - Right Ventricular End Diastolic Dimension (RVEDD)
    - Right Ventricular Fractional Area Change
    - Left Ventricular End Diastolic Volume (LVEDV)
    - Left Ventricular End Systolic Volume (LVESV)
    - Tricuspid Annular Plane Systolic Excursion (TAPSE)
    - Cardiac Output
    - Forward Stroke Volume (Left Ventricle)
    - Inferior Vena Cava Dimension

5.2 Single-arm Cohort

5.2.1 Primary Endpoint

The primary endpoint of the Single-arm cohort is survival at 12 months with quality of life improvement (assessed using KCCQ) of at least 10 points compared to baseline. In this cohort of sick patients in which it is believed TR cannot be reduced to moderate or less, it is expected that there will still be significant improvement in quality of life at 12 months post treatment.

A group sequential design with one interim analysis will be performed. The primary endpoint will be evaluated once the first 100 subjects have completed 12-month follow-up. If the primary endpoint is successfully met at the interim analysis, the Single-arm cohort endpoints will be summarized descriptively for all additional subjects enrolled after the first 100. If unsuccessfully met, the primary endpoint will be re-analyzed when all enrolled subjects in the Single-arm cohort have completed 12 months follow-up.

5.2.2 Secondary Endpoints

The following secondary endpoints will be assessed at the same time of the primary endpoint:

- TR Reduction by at least one grade at 30-day post procedure as compared to baseline.
- Freedom from MAE occurring after procedure attempt (femoral vein puncture) at 30 days. Components of MAE consist of the following:
    - Cardiovascular Mortality,
    - New Onset Renal Failure,
    - Endocarditis Requiring Surgery, and
    - Non-Elective Cardiovascular Surgery for TriClip™ device-related AE post-index procedure.
- Change in 6MWT at 12 months, as compared to baseline
- Recurrent HF hospitalizations at 12 months compared to the rate of heart failure hospitalizations in the prior 12 months
- Freedom from all-cause mortality and tricuspid valve surgery at 12 months

5.2.3 Descriptive Endpoints

The following descriptive endpoints will be assessed and reported for all subjects enrolled into the Single-arm cohort:

- Technical Success at exit from procedure room: Alive with successful access, delivery and retrieval of the device delivery system, and deployment and correct positioning of a Clip, and no need for additional unplanned or emergency surgery or re-intervention related to the device or access procedure
- Device Success at 30-day post-procedure: Alive with original intended Clip(s) in place, and no additional surgical or interventional procedures related to access or device since completion of the original procedure, and intended performance of the Clip(s) (i.e. ≥1 grade improvement in TR severity, no embolization, single leaflet device attachment, absence of para-device complications)
- Procedural Success at 30-day post-procedure: Device success, and no device or procedure related SAE
- Incidence of peripheral edema requiring hospitalization at 12 months, and annually through 24, 36, 48, and 60 months
- Incidence of ascites at 12 months, and annually through 24, 36, 48, and 60 months
- Incidence of IV diuretic administration (including outpatient clinics) at 12 months, and annually through 24, 36, 48, and 60 months
- Change in KCCQ score from baseline through 30 days, 6 months, 12 months and annually through 24, 36, 48, and 60 months

- SF-36 QoL scores at baseline, 30 days, 12 months and 24 months (and change from baseline to follow-up)
- Change in NYHA Functional Class (III/IV to I/II) from baseline through 30 days, 6 months, 12 months and annually through 24, 36, 48, and 60 months
- Change in 6MWT from baseline through 30 days, 6 months, 12 months and annually through 24, 36, 48, and 60 months
- Change in BNP/NT-proBNP from baseline through 30 days, 6 months, 12 months, and annually through 24, 36, 48, and 60 months
- Change in gamma-GGT from baseline through 30 days, 6 months, 12 months, and annually through 24, 36, 48, and 60 months
- Change in patient weight from baseline through 30 days, 6 months, 12 months and annually through 24, 36, 48, and 60 months
- Change in kidney function (assessed using eGFR) from baseline through 30 days, 6 months, 12 months and 24, 36, 48, and 60 months
- Change in liver function (assessed using the MELD score) from baseline through 30 days, 6 months, 12 months and annually through 24, 36, 48, and 60 months
- Echocardiographic endpoints assessed from baseline through 30 days, 6 months, 12 months and annually through 24, 36, 48, and 60 months post procedure, as follows:
    - TR severity grade
    - Tricuspid valve annulus diameter
    - Effective Regurgitant Orifice Area (EROA)
    - Regurgitant Volume
    - Vena Contracta Width
    - Right Ventricular End Diastolic Dimension (RVEDD)
    - Right Ventricular Fractional Area Change
    - Left Ventricular End Diastolic Volume (LVEDV)
    - Left Ventricular End Systolic Volume (LVESV)
    - Tricuspid Annular Plane Systolic Excursion (TAPSE)
    - Cardiac Output
    - Forward Stroke Volume (Left Ventricle)
    - Inferior Vena Cava Dimension

5.3 Imaging Sub-Study Endpoints

A sub-study will be included to assess various measurements of TR severity and the effect of changes in TR on clinical endpoints. Cardiac magnetic resonance imaging (MRI) and/or cardiac-gated computed tomography (CT) will be used as a basis for comparison to echocardiographic measurements. MRI and CT will be assessed at both baseline and 30 days, and CT will be assessed at 12 months on a total of at least 50 and up to 100 subjects at up to 15 qualified sites. Sites will be qualified based on their ability to perform the required MRI and CT acquisitions. Quantitative assessments of TR as well as right ventricular function will be compared between MRI, CT and TTE at baseline and at follow-up. TEE may be evaluated when available.

Abbott will qualify relevant sites for MRI and CT acquisition through an experienced core laboratory. Any enrolled subject is eligible for participation in the sub-study provided they agree

to undergo cardiac MRI/CT at the pre-specified time points described above. Each MRI/CT acquisition must be performed within 72 hours of the TTE acquisition at the specified time points. A separate cardiac MRI/CT acquisition protocol will be developed and provided to the participating sites in order to ensure uniform acquisition.

5.4 Health Economic Data

During the course of the trial, Abbott (or third-party designee) will collect health economic data. This includes gathering information regarding hospitalizations (index or otherwise). The data required may include billing information for items such as hospital care, physician services, laboratory tests and diagnostic procedures. The Institution shall submit health economic data using eCRFs for the TriClip™ procedure and subsequent hospitalization events during the study follow-up period.

6 SUBJECT SELECTION AND WITHDRAWAL

6.1 Subject Population

This clinical investigation will enroll male and female subjects selected from the specified clinical investigation population. Subjects must provide written informed consent prior to conducting any investigation-specific procedures not considered standard of care.

This investigation is designed to treat patients who present with symptomatic severe TR despite being optimized on medical therapy. Additionally, the site heart team would have determined that the patient is at intermediate or greater estimated risk for mortality or morbidity with tricuspid valve surgery. The eligibility criteria for the trial are described below.

6.2 Subject Screening and Informed Consent

6.2.1 Subject Screening

Potential patients presenting at the clinical sites will be fully informed about the clinical investigation, following the established Informed Consent process. Once Informed Consent is obtained, the clinical investigation-specific screening procedures may begin.

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

Patients meeting general inclusion criteria and no exclusion criteria will be asked to sign an Informed Consent form if they wish to participate in the clinical investigation.

Screening of a subject for possible inclusion in the trial may commence once a subject has been identified as being symptomatic with severe TR despite optimal medical therapy. Subject's general medical eligibility must be assessed by the site through subject interviews and medical record review prior to the TriClip™ procedure and within the time windows stipulated (see **Table 1** 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.

Screening assessments within 90 days prior to Eligibility Committee Review:

- Transthoracic and transesophageal echocardiographic (TTE and TEE) images to be obtained and submitted to the ECL. Site must review the TEE images and confirm that subject has TR and suitable tricuspid valve anatomy, without intracardiac mass, thrombus or vegetation. Abbott personnel may provide support to sites in reviewing TEE images. See Appendix X and XI for echo protocol.
    - If the TEE is not standard of care at the site, the subject must provide informed consent prior to the echocardiographic study.
- Medical history must be obtained, including review of subject's medical records.
- Physical exam including vital signs (weight, heart rate and blood pressure)
- Blood test performed.
- Right heart catheterization to assess and rule out pulmonary hypertension as the cause of TR.
- Subject is examined by the site investigator experienced in treating heart failure, to assess the subject for appropriateness and optimization of medical and device therapy.
- Subject is evaluated by the site local heart team to confirm that they are adequately treated per applicable standards, including for coronary artery disease, left ventricular dysfunction, mitral regurgitation, TR and heart failure. Subjects with current or prior symptoms of heart failure and reduced LVEF must be on stable GDMT recommended according to current guidelines as standard of care for heart failure therapy in the United States. See '**APPENDIX II: Definitions'** for definition of optimal therapy.
- NYHA Functional Class assessment.
- A 12-lead ECG must be performed.
- Subject's pertinent medical information will be assessed by the EC. After the ECL has confirmed subject eligibility, sites will be notified by Sponsor to compile and submit information to assess clippability to the EC.

The following screening information must be captured on the appropriate electronic Case Report Forms (eCRFs):

- Inclusion and Exclusion criteria
- Demographics (e.g., age at time of consent, gender, race/ethnicity)
- Informed Consent date

In case the subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject is considered a screening failure. The Principal Investigator or the delegated clinical investigation personnel will record the screening failure in the hospital records and on a screening log as required.

6.2.2 Informed Consent

The Investigator or his/her authorized designee (if applicable) will conduct the Informed Consent process, as required by applicable regulations and the center's IRB/EC. This process will include a verbal discussion with the subject on all aspects of the clinical investigation that are

relevant to the subject's decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. Subjects must be informed about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect subject's legal rights. Financial incentives will not be given to the subject. Subjects may be compensated for time and travel directly related to the participation in the clinical investigation. The subject shall be provided with the Informed Consent form written in a language that is understandable to the subject and has been approved by the center's IRB/EC. The subject shall have adequate time to review, ask questions and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the subject understands the information provided. If the subject agrees to participate, the Informed Consent form must be signed and dated by the subject and thereafter by the person obtaining the consent prior to any clinical investigation-specific procedures. The signed original will be filed in the subject's hospital or research charts, and a copy will be provided to the subject.

Failure to obtain informed consent from a subject prior to clinical investigation enrollment should be reported to Sponsor within 5 working days and to the reviewing center's IRB/EC according to the IRB's/ EC's reporting requirements.

If, during the clinical investigation, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee (if applicable) will provide this information to the subject. If relevant, the subject will be asked to confirm their continuing informed consent in writing.

6.2.2.1 Special Circumstances for Informed Consent

Incapacitated individuals, defined as persons who are mentally ill, mentally handicapped, or individuals without legal authority, are excluded from the study population.

Sites may enroll individuals unable to read or write in this clinical investigation.

Sites will obtain informed consent through a supervised oral process. An independent witness will be present throughout the Informed Consent process. A member of the site's clinical investigation team previously trained to the CIP will read the written Informed Consent form and any other information aloud and explain to the prospective subject or his/her legally acceptable representative and will sign and personally date the Informed Consent form. The witness will also sign and personally date the Informed Consent form attesting that the information was accurately explained, and that informed consent was freely given. In addition, no incentives or financial inducements will be provided to these patients or their legally authorized representatives for their participation in the clinical investigation.

Individuals under the age of 18 or age of legal consent are excluded from the study population.

Pregnant or breastfeeding women are excluded from the study population.

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.

6.3 Eligibility Criteria

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate patient. If some of the clinical and laboratory tests are not included in site standard tests, they must be done but after written informed consent is obtained.

6.3.1 Inclusion Criteria

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

1. In the judgment of the site local heart team, subject has been adequately treated per applicable standards (including medical management) and stable for at least 30 days as follows:
    - Optimized medical therapy for treatment of TR (e.g. diuretics)
    - Medical and/or device therapy, for mitral regurgitation, atrial fibrillation, coronary artery disease and heart failure

    The EC will confirm that the subject has been adequately treated medically.
2. Subject is symptomatic with Severe TR despite being optimally treated as described in (1). TR severity is determined by the assessment of a qualifying TTE and confirmed by the ECL. The ECL will also request a TEE to confirm TR etiology. Note: If any cardiac procedure(s) occur after eligibility was determined, TR severity will need to be re-assessed 30 days after the cardiac procedure(s).
3. The cardiac surgeon of the site local heart team concur that the patient is at intermediate or greater estimated risk for mortality or morbidity with tricuspid valve surgery.
4. New York Heart Association (NYHA) Functional Class II, III or ambulatory class IV
5. In the judgment of the TriClip™ implanting Investigator, femoral vein access is determined to be feasible and can accommodate a 25 Fr catheter.
6. Age ≥18 years at time of consent.
7. Subject must provide written informed consent prior to any trial related procedure.

6.3.2 Exclusion Criteria

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

1. Systolic pulmonary artery pressure (sPAP) > 70 mmHg or fixed pre-capillary pulmonary hypertension as assessed by right heart catheterization (RHC).
2. Severe uncontrolled hypertension Systolic Blood Pressure (SBP) ≥ 180 mmHg and/or Diastolic Blood Pressure (DBP) ≥ 110 mm Hg)
3. Any prior tricuspid valve procedure that would interfere with placement of the TriClip™ device
4. Indication for left-sided (e.g. severe aortic stenosis, severe mitral regurgitation) or pulmonary valve correction prior 60 days. Note: Patients with concomitant Mitral and tricuspid valve disease will have the option of getting their MR treated, and wait 60 days prior to being reassessed for the trial.

5. Pacemaker or ICD leads that would prevent appropriate placement of the TriClip™ Clip.
6. Tricuspid valve stenosis - Defined as a tricuspid valve orifice of ≤ 1.0 cm^2 and/or mean gradient ≥5 mmHg as measured by the ECL
7. Left Ventricular Ejection Fraction (LVEF) ≤20%
8. 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.
    c. Severe leaflet defect(s) preventing proper device placement
    d. Ebstein Anomaly - Identified by having a normal annulus position while the valve leaflets are attached to the walls and septum of the right ventricle.
9. Tricuspid valve anatomy not evaluable by TTE and TEE
10. Active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic disease (i.e. noncompliant, perforated).
11. MI or known unstable angina within prior 30 days
12. Percutaneous coronary intervention within prior 30 days
13. 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.
14. Cerebrovascular Accident (CVA) within prior 90 days
15. Chronic dialysis
16. Bleeding disorders or hypercoagulable state
17. Active peptic ulcer or active gastrointestinal (GI) bleeding
18. 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.
19. Ongoing infection requiring current antibiotic therapy (if temporary illness, patients may enroll 30 days after discontinuation of antibiotics with no active infection).
20. Known allergy or hypersensitivity to device materials
21. Evidence of intracardiac, inferior vena cava (IVC), or femoral venous mass, thrombus or vegetation.
22. Life expectancy of less than 12 months
23. Subject is currently participating in another clinical trial that has not yet completed its primary endpoint.
24. Subject is currently participating in another clinical investigation for valvular heart disease(s).
25. Pregnant or nursing subjects and those who plan pregnancy during the clinical investigation follow-up period. Female subjects of child-bearing potential are required to have a negative pregnancy test done within 7 days of the baseline visit per site standard test. 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 sterilized regular partner or subjects using a double barrier contraceptive method.
26. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.

6.4 Subject Enrollment

A patient is considered enrolled in the clinical investigation from the moment the patient provides written informed consent and has been confirmed to meet all inclusion criteria and none of the exclusion criteria. .

Subjects will be assigned a subject ID upon informed consent and entry into the database. Such subjects are registered in the trial.

6.4.1 Enrollment of Medicare Beneficiaries

This clinical trial will enroll appropriate Medicare beneficiaries that qualify based on the inclusion and exclusion criteria set forth in the trial. This IDE clinical trial adheres to all standards of Medicare coverage requirements set forth by the IDE and clinical trial coverage policies of the Center for Medicare and Medicaid Services (CMS). Section 16, Risks Analysis section, describes how all enrolled subjects, including Medicare beneficiaries, may be affected by the device under investigation.

Subjects enrolled in the clinical investigation are expected to be consistent with the Medicare population based on age range, demographic characteristics and cardiovascular risk factors representative of the Medicare patient population, so as such, the clinical investigation results are expected to be generalizable to the Medicare population.

6.4.2 Historically Under-Represented Demographic Subgroups

The Sponsor intends to implement FDA's guidance on sex-specific data in medical device clinical investigations to ensure adequate representation of women and other traditionally under-represented demographic subgroups in this clinical investigation. To date, experience with transcatheter technologies for the tricuspid valve have shown the treatment population to be a majority female. As noted in the guidance, some barriers to participation of women and ethnic minorities in clinical investigations have traditionally been:

- Lack of understanding about main obstacles to participation of such subgroups in clinical research
- Inclusion/exclusion criteria potentially not needed to define the clinical investigation population may unintentionally exclude specific subgroups
- Under diagnosis of disease etiologies and pathophysiology leading to under referral of demographic subgroups
- Avoidance of specific subgroups by investigators and Sponsors due to the perception that it takes more time and resources to recruit them
- Fear of fetal consequences (for female participants)
- Family responsibilities limiting women's ability to commit time for follow-up requirements

The Sponsor will take the following steps to ensure adequate representation of women and racial or ethnic minorities in this clinical investigation:

- The Sponsor will provide training to investigational site personnel to ensure adequate representation of these demographic subgroups

- The Sponsor will regularly review enrollment data to investigate whether there is underrepresentation of these demographic subgroups
- The Sponsor will regularly review withdrawal rates for under-represented subgroups and compare these rates with that in the overall clinical investigation population
- As appropriate and necessary, the Sponsor will retrain sites on the importance of recruiting and retaining subjects in the clinical investigation
- The Sponsor will approach sites without bias or consideration for specific demographic subgroups
- The Sponsor will have informed consent materials in alternative languages and will work with sites and IRBs/ECs on recruitment materials

6.5 Subject Withdrawal

Each enrolled subject shall remain in the clinical investigation until completion of the required follow-up period; however, a subject's participation in any clinical investigation 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 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 clinical investigation, except for the status (deceased/alive).

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

In case of subject withdrawal, the site should make attempts to schedule the subject for a final clinical investigation visit. At this final follow-up visit, the subject will undergo the following assessments:

- 12-lead ECG
- Blood draw (Same as required for follow-up visits)
- Physical exam including vital signs (weight, heart rate and blood pressure)
- Echocardiogram – TTE
- Modified Rankin Scale (Assessment of mRS should be done only after onset of stroke; not required after 12 months)
- 6-Minute Walk Test (6MWT) – See **APPENDIX XIII** for 6 Minute Walk Test Guidelines
- Concomitant cardiovascular medications assessment
- NYHA Functional Class assessment
- KCCQ QoL questionnaire to be completed by the subject – must be administered by "blinded" study personnel. 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

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:

- A minimum of three 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 initials of site personnel trying to make contact.
- If these attempts are unsuccessful, a letter (certified if applicable) 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).

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 time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

Note: Telephone contact with General Practitioner, non-clinical investigation cardiologist or relative without the presence of the subject or indirect documentation obtained via discharge letters will not be considered as subject contact.

6.6 Total Expected Duration of the Clinical Investigation

The clinical investigation duration is expected to be approximately 11 years, including 6 years for enrollment and 5 years of follow-up.

6.7 Expected Duration of Each Subject's Participation

Each subject will be expected to participate for a duration of five years from Treatment visit.

6.8 Number of Subjects

Approximately 450 subjects will be enrolled in the clinical investigation and randomized 1:1 to either the Device Group or to the Control Group. Enrollment into the Randomized cohort will continue until (1) the sample size re-estimation results are received and (2) enrollment meets the re-estimated sample size. The Single-arm cohort will enroll up to 200 eligible subjects, with enrollment continuing until the Randomized cohort has completed enrollment. Up to 3 roll-in subjects will be permitted per implanter without prior experience with the TriClip™ device.

No site may enroll more than 25% of the total subjects.

6.9 Estimated Time Needed to Select Required Number of Subjects

[redacted]

7 TREATMENT AND EVALUATION OF ENDPOINTS

7.1 Eligibility Committee Review

The EC must confirm the following and determine in which cohort the patient will be placed:

- Tricuspid valve leaflet anatomy is amenable to TriClip™ implantation
- Subject is on optimal medical therapy for both drug and device regimen for any cardiac conditions, per applicable standards.
    - Optimized medical therapy for treatment of TR (e.g. diuretics)
    - Medical and/or device therapy, for mitral regurgitation, atrial fibrillation, coronary artery disease and heart failure

Confirmation of the above eligibility review will be documented.

7.2 Roll-in Subjects

The decision to identify a subject as a roll-in will depend on the level of experience of the Implanter with the device. Roll-in subjects will be designated by the Sponsor as such prior to treatment and will not undergo randomization. An implanter may perform **up to** 3 roll-in procedures prior to beginning the randomization phase of the trial based on the following criteria:

- Implanters that do not have prior experience with the TriClip™ device OR that have not performed a TriClip™ procedure in the prior 12 months may perform up to 3 roll-in procedures upon approval from the Sponsor

The site must receive authorization from the Sponsor to enroll each roll-in case.

7.3 Baseline

7.3.1 Baseline Clinical Assessments

Baseline visit must be performed within 14-days after eligibility has been confirmed by the EC.

Baseline assessments may occur on the day of treatment but prior to randomization (for randomized subjects):

- Baseline TTE imaging must be obtained. If screening TTE imaging was performed within 14 days, then screening images may be used as baseline.
- A physical exam including an assessment of subject's cardiac status and vital signs measures must be completed.
- Blood tests performed.
- Concomitant cardiovascular medications must be documented.
- A 12-lead ECG must be performed.

- Site must reassess subject eligibility and reconfirm that the subject meets eligibility criteria. If there has been significant change in subject's overall condition (i.e. due to recent MI, stroke, etc.), it may be necessary to update assessments completed during the screening process, such as TTE, etc.
- If site is participating in the imaging sub-study, subject must undergo an MRI and CT.
- A standardized script will be used when administering the following assessments:
    - KCCQ and SF-36 QoL questionnaires must 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 (in such cases a note to file must be completed to document the inability of subject to complete the questionnaire).
    - The 6-Minute Walk Test (6MWT) must be administered according to the ATS Statement: Guidelines for the Six-Minute Walk Test, Official Statement of the American Thoracic Society, approved March 2002 (See APPENDIX XIII: 6 Minute Walk Test Guidelines).
    - An assessment of NYHA Functional Class must be completed.

7.4 Randomization

Randomization shall occur within 14-days after eligibility has been confirmed by the EC. Randomization may occur on the day of treatment, but only after baseline assessments have been completed.

For a subject in the randomized arm, the subject will be randomized in a 1:1 ratio between the Device Group or the Control Group according to a computer-generated randomization scheme accessed via the electronic data capture (EDC) system used for data submission.

Subjects will either be assigned the Device Group or the Control Group. Subjects who are randomized to the Device Group must be scheduled for the index procedure within 14 days.

7.5 Blinding

See **Section 4.2.3** for blinding regarding administration of assessments.

7.6 Index Procedure (Roll-In, Device Group and Single-arm Cohort)

The index procedure must be performed within 0 to 14 days after randomization (baseline visit for Single- cohort and Roll-in cohort). If complications arise during the procedure, it may be necessary to convert to an open surgical procedure. 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 TriClip™ System. Refer to the IFU for specific instruction on the use TriClip™ device, including handling requirements, preparation for use and precautions.

7.6.1 Subject Preparation

Subjects will be prepared for the procedure as per the institution's standard practice for a percutaneous procedure and TEE.

Note: Prior to performing the procedure, all Investigators must also undergo documented training by the Sponsor on the TriClip™ System and the CIP. In addition, all Investigators must read and understand the IFU that accompanies the Device.

Femoral vein catheterization will be completed in accordance with the IFU.

7.6.2 Pre-Procedure

7.6.2.1 Pre-Procedure Anticoagulation/Antiplatelet Therapy

Perform pre-procedure anticoagulation/antiplatelet therapy according to institution standard of care for transcatheter cardiac procedures. Otherwise, perform anticoagulation/antiplatelet therapy according to the recommended therapy in this section.

Discontinue the use of warfarin for at least three (3) days prior to the scheduled TriClip™ procedure and it is suggested that the international normalized ratio (INR) is ≤1.7 prior to the TriClip™ procedure. Similarly, discontinue dabigatran or factor Xa inhibitors medications for a sufficient duration to ensure restoration of normal coagulation, or per institution standard of care. Subjects may be treated with heparin during this period at the treating physician's discretion. If heparin is used, it should be discontinued ≥8 hours prior to the TriClip™ procedure for subcutaneous low molecular weight heparin (LMWH) and ≥4 hours prior to the TriClip™ procedure for intravenous unfractionated heparin (UFH).

7.6.2.2 Clopidogrel

A loading dose of clopidogrel (≥300 mg) is recommended within 24 hours prior to the procedure (6-24 hours prior if possible) or immediately following the procedure.

Note: A loading dose of clopidogrel may be considered even if the patient is taking clopidogrel on a daily basis either at home or in the hospital, as long as no other clopidogrel loading dose has been given within 24 hours. However, clopidogrel use is optional and its use is left to the discretion of the investigator.

Aspirin may also be used at operator discretion. If aspirin is to be used, a loading dose of 325 mg acetylsalicylic acid (ASA) may be administered either pre- or immediately post- TriClip™ procedure.

7.6.2.3 Antibiotic Therapy

It is recommended to administer a single dose of intravenous broad spectrum antibiotics approximately one hour prior to initiation of the procedure. The type, dosage and timing of antibiotic is at the Investigator's discretion or institution's standard of care.

7.6.2.4 Pre-procedure TEE Imaging

Prior to the TriClip™ procedure, Device group and roll-in subjects must be assessed to ensure there is no significant change in subject's overall condition (e.g., stroke, MI, active infection, endocarditis, hemodynamic instability, etc. post-randomization) that would preclude treatment. If the subject has experienced any significant change that would preclude treatment, the subject must be treated and rescheduled for the TriClip™ procedure as soon as possible. Subjects are required to complete an additional transesophageal **(TEE) echocardiogram study within 3 days prior to the procedure** to rule out the presence of intracardiac mass, thrombus or vegetation. This echocardiogram may be performed immediately preceding initiation of the

TriClip™ procedure. **This echocardiogram will not be submitted to the ECL.** If an intracardiac mass, thrombus or vegetation or other change in echocardiographic eligibility is identified in the TEE performed immediately preceding the procedure, the procedure should be postponed until the change can be carefully evaluated by site and sponsor. If a thrombus is identified, the subject should be pharmacologically treated to resolve the thrombus and, if successful, the subject should be reassessed as soon as possible to undergo the TriClip™ procedure. Such subjects will be considered enrolled even if they do not undergo the TriClip™ procedure.

7.6.2.5 Pre-procedure ECG and Physical Exam

A 12-lead ECG and physical exam must be performed within 24 hours prior to the procedure.

7.6.2.6 Activated Clotting Time

Prior to the TriClip™ procedure, baseline activated clotting time (ACT) will be determined following femoral vein puncture for the TriClip™ procedure. ACT and heparin administration (or alternative anticoagulation therapy, e.g., bivalirudin) should be recorded.

7.6.2.7 Procedural Anticoagulation Therapy

Following femoral vein puncture, administer intravenous heparin (or alternative anticoagulation therapy, e.g., bivalirudin) in accordance with standard hospital practice. Maintain an ACT (activated clotting time) of > 250 seconds throughout the procedure. Low molecular weight heparin and fondaparinux may not be used for procedural anticoagulation.

7.6.3 TriClip™ Device Placement Procedure

Please refer to IFU including storage and handling requirements, preparation for use, pre-use checks of safety and performance, and precautions to be taken after use. All Investigators must read and understand the IFU that accompanies the Device.

Femoral vein catheterization will be completed in accordance with the IFU.

The Steerable Guide Catheter (Guide) is inserted into the femoral vein. Fluoroscopic and echocardiographic (2D and/or 3D-TEE) guidance will be used during the procedure to visualize the device, vasculature and cardiac/valve anatomy. See **Appendix XIV: Monitoring Exposure to Ionizing Radiation** for requirements for training and data gathering on ionizing radiation required per this protocol. For subjects with renal dysfunction, intravenous contrast should not be used during the procedure unless absolutely necessary.

The Guide is positioned in the Inferior Vena Cava/Right Atrium (IVC/RA) and the TriClip™ Delivery System is inserted into the Guide and properly positioned over the tricuspid valve. The TriClip™ Delivery Catheter is advanced until the TriClip™ emerges from the tip of the Guide into the right atrium. Manipulations of the catheter tip (via the control knobs on the handles) will continue in the right atrium until the Clip is properly oriented perpendicular to the line of coaptation of the tricuspid valve leaflets. The Clip is opened and advanced across the tricuspid valve into the ventricle then pulled back to grasp the leaflets. 2- and/or 3-dimensional echocardiography and color flow Doppler are used to evaluate leaflet insertion, Clip position and TR severity. If the Clip is not positioned properly or TR has not been adequately reduced, additional grasping may be attempted and the Clip may be inverted and retracted into the right atrium as required for additional grasping attempts. When placement is successful, the Clip is

closed and deployed from the Delivery Catheter. The catheters are then removed from the subject.

If placement of one Clip does not result in reduction in TR to a level deemed acceptable by the operator, then additional Clip(s) may be placed to further reduce TR. The Investigator should determine if there is adequate tricuspid valve orifice area to accommodate the additional Clip(s) without creating tricuspid stenosis. A maximum of four (4) Clips will be allowed to be implanted in subjects enrolled in this trial. However, a fifth Clip may be used in the special circumstance if a previous Clip has detached from one leaflet or to stabilize excessive mobility of a previous Clip.

Procedural echocardiograms (TTE and TEE) may be collected immediately post-procedure by the site. Procedural echocardiographic images do not need to be submitted to the ECL.

7.6.4 Post-Implant

Post-implant imaging will be used to confirm any occurrence(s) of worsening of TR severity, tricuspid valve and leaflet condition, and any evidence of device embolization, Single Leaflet Device Attachment (SLDA), bleeding, perforation, etc. Treatments for these will be per physicians' discretion. Final TTE and TEE echocardiograms may be acquired and saved by the site.

Immediately following the TriClip™ procedure, heparin (or alternative anticoagulation therapy, e.g., bivalirudin) should be discontinued and the ACT should be monitored in accordance with hospital protocols. Vascular sheaths should be removed according to usual hospital practice.

Post- TriClip™ procedure anticoagulation is recommended per the Investigator's discretion or as described in Section 7.7.3.

7.7 Post-procedure (Roll-in, Device Group and Single-arm Cohort; In-hospital)

Subjects will receive standard post-cardiac catheterization procedure care as judged appropriate by the Investigator. Subjects should be advised to limit strenuous physical activity for the first month following the TriClip™ procedure or longer, as deemed appropriate by the Investigator.

The medication recommendations below are reflective of the device arm only. For the Control group, subjects should be optimized on medical management prior to enrollment. Frequent changes to medications in the control group should be avoided and only performed if clinically indicated.

7.8 Discharge (Roll-in, Device Group and Single-arm Cohort)

Prior to discharge (Discharge occurs when subject leaves the implanting hospital), the following required tests and procedures should be completed (> 16 hours post TriClip™ procedure and no later than day of discharge) as outlined below, and the information should be captured on the appropriate eCRFs:

- 12-lead ECG
- Blood draw
- Concomitant cardiovascular medication logs

- Physical exam including vital signs (weight, heart rate and blood pressure)
- Echocardiogram (TTE)
- Adverse events
- Protocol deviations
- Device deficiency
- NYHA Functional Class assessment

Each subject implanted with a Clip(s) must be provided the Implant Identification Card, included in each TriClip™ System package. The subject must be instructed to keep this Implant Identification Card on their person at all times. The serial number of all implanted TriClip™ (s) must be recorded on the Implant Identification Card.

7.8.1 Post-Procedure Medications

7.8.1.1 Antibiotic Therapy

Administer additional intravenous doses of antibiotics at approximately 6 and 12 hours (or per institutional guidelines) after the completion of the procedure.

The Investigator should instruct all subjects who receive the TriClip™ device of the need for endocarditis prophylaxis, as recommended in the ACC/AHA 2008 Guideline Update on Valvular Heart Disease: Focused Update on Infective Endocarditis. Subjects should be instructed to notify the Investigator or the subject's primary care physician in the event that a procedure recommended by this Guideline is planned, so that prophylactic antibiotics can be prescribed. A prescription for endocarditis prophylaxis may be provided to the subject at discharge.

7.8.1.2 Antiplatelet/Anticoagulation Therapy

Following placement of the TriClip™ device, anticoagulation therapy is prescribed. If a loading dose of clopidogrel was not given prior to the TriClip™ procedure, it may be administered after the procedure at investigator discretion. Post- TriClip™ procedure anticoagulation is as follows:

1. Reinitiate warfarin, dabigatran or factor Xa inhibitor (if discontinued for the TriClip™ procedure) at pre-procedure levels or as appropriate. If chronic oral anticoagulation is used, aspirin and clopidogrel use are not recommended, but are allowed if otherwise indicated for other conditions.

2. If chronic oral anticoagulation is not used, it is strongly recommended that either daily clopidogrel (75 mg) and/or aspirin (≥75 mg) is administered for 6 months or longer. If aspirin is to be used, a loading dose of 325 mg acetylsalicylic acid (ASA) may be administered either pre- or immediately post- TriClip™ procedure followed by ≥75 mg per day for 6 months or longer at the Investigator's discretion.

7.8.1.3 Management of Hypertension

Subjects should have their blood pressure checked prior to discharge. Subjects should be prescribed medication as necessary following current standard of care to maintain normotensive blood pressure.

7.8.1.4 Cardiovascular Medications

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, and the reason for change must be documented on the electronic case report form.

7.9 "Treatment" Visit (Control Group)

The "Treatment" visit in the Control group must occur between 0 and 14 days after randomization. At the "Treatment" visit, Control group subjects will be seen by the HF specialist investigator, and will undergo a physical exam, including vital signs, cardiac health status and evaluation of heart failure medications.

7.10 Follow-up Assessments

7.10.1 Follow-up CIP Medications

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, and the reason for change must be documented on the electronic case report form.

Subjects should have their blood pressure checked. Subjects should be prescribed medication as necessary following current standard of care to maintain normotensive blood pressure.

7.10.2 Follow-up for All Subjects

Required clinical follow-up will be performed at the following intervals (based on treatment visit) for all subjects with TriClip™ procedure attempt, regardless of whether a TriClip™ was successfully implanted:

- Discharge post-TriClip™ procedure
- 30 days (-3/+14 days) follow-up visit (this visit must be conducted even if subject is in hospital)
- 6 months (180 days ± 28 days) follow up visit
- 1 year (365 days ± 28 days) follow up visit
- 18 months (545 days ± 28 days) follow up visit
- 2 years (730 days ± 28 days) follow up visit
- 3 years (1095 days ± 28 days) follow up visit
- 4 years (1460 days ± 28 days) follow up visit
- 5 years (1825 days ± 28 days) follow up visit

Follow-up visits will be calculated from the date of the Index Procedure (for subjects receiving the device) and the Treatment visit for subjects in the Control group. 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.

At the 30-day follow-up visit, the echocardiographer shall examine the integrity of the TriClip™. 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

TriClip™ 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 1**) outlined below. These clinical assessments are standard assessments for most cardiac/structural heart interventional procedures and therefore should be administered per standard of care at each Institution. All visits and tests must be completed even if the subject is in hospital. Refer to the Schedule of Events table section 7.15 for timing of below listed tests.

- 12-lead ECG
- Blood draw
- Physical exam including vital signs (weight, heart rate and blood pressure)
- Echocardiogram – TTE at all follow-up visits
- Modified Rankin Scale (Required at visits occurring after onset of stroke)
- 6-Minute Walk Test (6MWT)– See **APPENDIX XIII** for 6 Minute Walk Test Guidelines
- Concomitant cardiovascular medications assessment
- NYHA Functional Class assessment
- KCCQ QoL and SF-36 questionnaires to be completed by the subject – must be administered by "blinded" study personnel. 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. 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.

7.11 TriClip™ Intervention in Control Group Subjects or Additional TriClip™ Intervention in Roll-in, Device Group or Single-arm Cohort Subjects

Control group subjects will not be allowed to undergo the TriClip™ procedure until after completion of the 12-month visit. TriClip™ intervention in the Control group prior to the 12-month visit will be considered a major protocol deviation. Prior to TriClip™ procedure attempt in, a Control group subject upon completion of 12-month visit, the subject must be rescreened and evaluated by the ECL and EC to assess eligibility. A 30-Day Post-TriClip™ Follow-up visit must be completed 30 days (-3/+14 days) after the TriClip™ procedure. This visit should still be completed even if the subject is in hospital. The same assessments shall be performed as done for the 30-day follow-up. Following the 30-day post procedure visit the patient will continue with their predetermined visit schedule.

It may be necessary for a roll-in, Device group, single-arm, or cross-over subject to undergo additional TriClip™ procedures. A TTE must be performed within 90 days prior to a TriClip™ procedure in either group. A 30-day Post- TriClip™ Follow-up visit must be completed 30 days (-3/+14 days) after the additional TriClip™ procedure. This visit should still be completed even if

the subject is in hospital. The same assessments shall be performed as done for the 30-day follow-up. If this visit window overlaps with another study follow-up visit window, only one study visit is needed to satisfy these requirements.

7.12 Tricuspid Valve Surgery

For inclusion into this trial, all subjects prior to enrollment are expected to be at intermediate or greater risk for mortality or morbidity post tricuspid valve surgery. If a subject's condition worsens considerably due to TR (regardless of study arm or group assignment), then the subject can undergo tricuspid valve surgery provided that both the heart failure specialist and the surgeon deem that tricuspid valve surgery is required. The sponsor will be notified of this occurrence. A TTE must be performed within 90 days prior to tricuspid valve surgery and provided to the ECL for assessment.

A 30-Day Post-Tricuspid Valve Surgery Follow-up visit must be completed 30 days (-3/+14 days) after the tricuspid valve surgery. This visit should still be completed even if the subject is in hospital. If this visit window overlaps with another study follow-up visit window, only one study visit is needed to satisfy these requirements. Subjects will continue to be followed per this Clinical Investigational Plan.

7.12.1 30-Day Post-Tricuspid Valve Surgery Follow-up

Requirements for the 30-day Post-Tricuspid Valve Surgery Follow-up visit are described below.

- 12-lead ECG
- Blood draw
- Physical exam including vital signs (weight, heart rate and blood pressure)
- Echocardiogram (TTE)
- Modified Rankin Scale (Assessment of mRS should be performed only after onset of stroke, if stroke occurred)
- Concomitant cardiovascular medications assessment
- NYHA Functional Class assessment
- Assess and record adverse events
- Assess and record protocol deviations

7.13 Explanted TriClip™ Device

The TriClip™ device 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 TriClip™ device(s) during surgery, the subject will continue follow-up schedule based on index procedure date. Explant information will be captured on the Tricuspid Valve Surgery Form or Death Form.

7.14 Patient Reported Outcome (PRO) Measures

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item self-administered questionnaire/PRO developed to independently measure the patient's perception of their health

status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life (QOL) within a 2-week recall period.

The SF-36 is a 36 item scale constructed to survey health status and quality of life. The form asks participants to reply to questions according to how they have felt in the previous week. The SF-36 can be summarized into two summary scores representing physical and mental components of health and can also be used to derive health related quality of life index values.

A blinded coordinator or designee will administer KCCQ and SF-36 questionnaires during the follow up visits (30-day visit and afterwards). KCCQ and SF-36 questionnaires must be completed by the subject. It is important the subject understands the meaning of all words and instructions in the questionnaires. The subject should be instructed to ask any questions about the questionnaires if further explanation is needed. Once the questionnaires are completed, the Coordinator or designee will review for completeness to verify that all questions have been answered according to the directions provided.

To minimize bias and undue influence, the KCCQ and SF-36 questionnaires will be completed by the subject, unless the subject is unable to complete the questionnaires on their own (in such cases a note to file must be completed to document the inability of subject to complete the questionnaire).

7.15 Schedule of Events

Table 1: Clinical Evaluation Schedule

CIP Activity	Screening	Baseline	Procedure	Discharge (>16hr post-procedure)	30 days (-3/+14 days)	6 Month (±28 days)	12, 18 months, 2-5 years (±28 days)
Informed Consent Process	X						
Demographics	X						
Physical Examination & Vital Signs	X	X	X[b]	X	X	X	X
Local Heart Team Evaluation	X						
Cardiovascular History	X						
Medical History	X						
Cardiovascular Medications	X	X	X	X	X	X	X
Echocardiogram	X (TTE and TEE)	X (TTE only)[a]	X (TEE only)	X (TTE Only)	X (TTE only)	X (TTE Only)	X[e] (TTE only)
RHC	X						
CT[c]		X[c]			X[c]		X[c] (1 year only)
MRI		X[c]			X[c]		
CBC with differentials and platelet count	X	X[a]		X	X	X	X
Gamma-GGT[d], BNP or NT-proBNP, CK or CK-MB, BUN, serum creatinine, AST, ALT, INR (while on anticoagulation), Bilirubin, Serum Sodium	X	X[a]		X	X	X	X
KCCQ		X			X[g]	X[g]	X[e, g]
SF-36		X			X[g]		X (1 and 2 year only)[g]
6-Minute Walk		X				X[g]	X[e, g]
NYHA FC	X	X		X	X[g]	X[g]	X[g]
12-lead ECG	X	X	X[b]	X	X	X	X
Modified Rankin Scale[f]				X	X	X	X
Hospitalizations	X (prior 12 months)	X	X	X	X	X	X
Adverse Events/Deviation		X	X	X	X	X	X
Device Deficiency			X	X	X	X	X
Withdrawal		X	X	X	X	X	X

[a] If performed within 14 days of assessment for screening, then screening can be used for baseline.
[b] Must be performed within 24 hours prior to procedure (Device, Single-arm and Roll-in Group).

[c] Only required for subjects in the imaging sub study.
[d] Only required for sites with capability.
[e] Not required at 18 months.
[f] Only required at visit after onset of stroke, if stroke occurred.
[g] These assessments during these visits should be completed by blinded personnel

8 ADVERSE EVENTS

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

8.1 Definition

8.1.1 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 medical device under investigation.

As part of ISO 14155 Section 3.2, the Adverse Event definition has the following notes:

Note 1: This definition includes events related to the medical device under investigation or the comparator.

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 medical devices under investigation.

8.1.2 Serious Adverse Event

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

a) Led to a death,
b) Led to a serious deterioration in health of the subject, that either resulted in:
    1. a life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function, or
    3. in-patient hospitalization or prolongation of existing hospitalization, or
    4. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function or
    5. chronic disease
c) fetal distress, fetal death or a congenital abnormality or birth defect.

Note: A planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be an SAE.

8.2 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device under investigation caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate CRF form. Determination should be based on

assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility, and patient condition (pre-existing condition).

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

U(S)ADE 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.

8.2.2 Device Deficiency/Device Malfunction

Device deficiency is defined as an inadequacy in the identity, quality, durability, reliability, usability, safety of performance of an investigational device including malfunction, use errors, or inadequacy in the information supplied by the manufacturer including labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended.

Note 1: The definition includes device deficiencies related to investigational medical device or the comparator.

Note 2: Cyber-security incidents related to the investigational product, shall be reported as device deficiencies

A device malfunction is the failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP, or IB.

8.3 Adverse Event and Device Deficiency/Device Malfunction Reporting

8.3.1 Adverse Event Reporting

Safety surveillance and reporting starts as soon as the patient is enrolled in the clinical investigation. Safety surveillance and reporting will continue until the last follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical investigation, or the subject withdraws from the clinical investigation. All adverse event data, including deaths and device deficiency data, will be collected throughout the time period defined above and will be reported to the Sponsor on an eCRF within an Electronic Data Capture (EDC) database. Additional information, with regard to an adverse event, should be updated on the appropriate eCRF within the EDC.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

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.

An offline form will be made available to allow the investigator to report SAEs in the event the entry cannot be made in the EDC. This does not replace the EDC reporting system. All information must still be entered into the EDC system as soon as feasible.

SAE Reporting

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

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

Sites must record the date the site staff became aware that the event met the criteria of an SAE in the source document. The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

8.3.2 Unanticipated Serious Adverse Device Effect Reporting to Sponsor and IRB

The Sponsor 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.

8.3.3 Device Deficiency/Malfunction Reporting

Sites should report all device deficiencies/malfunctions should be reported on the appropriate eCRF form.

The investigator must report all device deficiencies/malfunctions to the Sponsor as soon as possible but no later than outlined below.

Clinical Sites	Reporting timelines
All Sites	Sites must report device deficiencies/malfunctions to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

Sites must report device deficiencies/malfunctions to the IRB/EC per the investigative site's local requirements.

Sites should return the device, if not implanted or not remaining in the subject, to the Sponsor. Device deficiencies/malfunctions should be reported to the IRB/EC per the investigative site's local requirements.

An offline 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 system. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

8.3.4 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report SAEs and reportable device deficiencies/malfunctions to the country regulatory authority, per local requirements.

9 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical investigation. Additional details on statistical analyses, including justification of clinical investigation design, impact of COVID-19 on the primary endpoint analysis, poolability analyses, subgroup analyses and analysis of descriptive endpoints, are provided in a separate Statistical Analysis Plan (SAP).

9.1 Analysis Populations

9.1.1 Randomized Cohort

The Intention-to-Treat, As-Treated, Per-Protocol and Attempted Procedure populations are defined below. For all the analysis, the duration of follow-up will be calculated from the date of the Treatment visit.

Intent-to-Treat (ITT) Population

[redacted]

As-Treated (AT) Population

[redacted]

Per-Protocol Population

[redacted]

Attempted Procedure (AP) Population

[redacted]

9.1.2 Single-arm Cohort

The analysis for the Single-arm cohort will include all subjects that receive treatment with the TriClip™ device.

Attempted Procedure (AP) Population

[redacted]

9.2 Statistical Analyses

9.2.1 Randomized Cohort

9.2.1.1 Randomized Cohort – Primary Endpoint

The primary endpoint of the Randomized cohort is a composite of all-cause mortality or tricuspid valve surgery, heart failure hospitalizations, and quality of life improvement assessed using the KCCQ at 12 months. The endpoint will be compared between the Device group and Control group in a hierarchical order as follows:

- Time to all-cause death or Tricuspid Valve surgery
- Number of Heart Failure (HF) Hospitalizations
- Improvement of ≥15 points in KCCQ from baseline

The null and alternative hypotheses are stated as:

H_0: None of the components are different between the Device and Control group

H_1: At least one components are different between the Device and Control group

The primary endpoint will be analyzed using the Finkelstein-Schoenfeld method and the null

[redacted]

.

9.2.1.2 Randomized Cohort – Secondary Endpoints

[redacted]

9.2.1.2.1 TR Reduction to Moderate or Less at 30-Days Post Procedure

Subjects in the randomized Device group are expected to experience greater reduction in TR severity than subjects in the Control group. The null and alternative hypotheses are stated as:

[redacted]

9.2.1.2.2 Freedom from Major Adverse Events (MAE) at 30-Day Post Procedure

A composite of cardiovascular mortality, new onset renal failure, endocarditis requiring surgery, and non-elective cardiovascular surgery for TriClip™ device-related adverse event post-index procedure will be used as a secondary measure of safety. The analysis of this secondary endpoint is a one-group test against an objective performance goal for the proportion of subjects in the Attempted Procedure population with the composite of this secondary endpoint of MAE at 30-day post procedure.

[redacted]

9.2.1.2.3 Change in Quality of Life (Kansas City Cardiomyopathy Questionnaire, KCCQ) at 12 Months over Baseline

Improvement in quality of life as measured by the KCCQ test at 12 months from baseline will be a secondary effectiveness endpoint in the comparison of the Device group to the Control group.

[redacted]

[redacted]

[redacted]

9.2.1.2.4 Change in 6MWT at 12 Months over Baseline

Improvement in the 6MWT at 12 months from baseline is an important secondary effectiveness endpoint in the comparison of the Device group to the Control group.
The null and alternative hypotheses are stated as:
H_0: $\mu_{D,\,\Delta 6\mathrm{MWD}} - \mu_{C,\,\Delta 6\mathrm{MWD}} = 0$

[redacted]

[redacted]

[redacted]

9.2.1.2.5 Recurrent HF Hospitalizations at 24 Months

Treatment with the TriClip™ device is expected to reduce the risk of recurrent HF hospitalizations. The null and alternative hypotheses are stated as:

[redacted]

[redacted]

[redacted]

The endpoint will be assessed when all subjects complete 24 months of follow-up. All available follow-up through 24 months at the time of data cut-off will be included in the analysis. Subjects who do not experience any HF hospitalizations will be censored on their data cut-off date.

[redacted]

9.2.1.2.6 Freedom from All-Cause Mortality, Tricuspid Valve Surgery, and Tricuspid Valve Intervention at 24 Months

The difference in risk of all-cause mortality, Tricuspid Valve surgery, or Tricuspid Valve intervention at 24 months between the Device and Control groups is a secondary measure of safety. The null and alternative hypothesis are stated as:

[redacted]

9.2.2 Single-arm Cohort

9.2.2.1 Single-arm Cohort – Primary Endpoint

The primary endpoint of the Single-arm cohort is survival at 12 months with a quality of life improvement (assessed using KCCQ overall score) of at least 10 points at 12 months compared to baseline. This endpoint will be assessed as a proportion of subjects meeting the definition of the endpoint.

[redacted]

[redacted]

9.2.2.2 Single-arm Cohort – Secondary Endpoint

9.2.2.2.1 TR Reduction by at least 1 Grade at 30-Day Post Procedure

The TR reduction by at least 1 grade at 30-day post procedure is the secondary measure of effectiveness for TriClip™ in the Single-arm cohort. The analysis of this secondary endpoint is a one-group test against an objective performance goal of 50%.

[redacted]

9.2.2.2.2 Freedom from Major Adverse Events (MAE) at 30-Day Post Procedure

The freedom from MAE occurring after procedure attempt (femoral vein puncture) at 30 days is the secondary measure of safety for TriClip™ in the Single-arm Cohort. The analysis of this secondary endpoint is a one-group test against an objective performance goal of 80%.

[redacted]

9.2.2.2.3 Change in 6MWT at 12 Months over Baseline

Improvement in the 6MWT distance at 12 months from baseline is an important secondary effectiveness endpoint.

[redacted]

9.2.2.2.4 Recurrent HF Hospitalizations at 12 Months

[redacted]

9.2.2.2.5 Freedom from All-Cause Mortality and Tricuspid Valve Surgery at 12 Months

[redacted]

[redacted]

9.3 Sample Size Calculation and Assumptions

9.3.1 Randomized Arm Cohort

9.3.1.1 Primary Endpoints

Detailed simulations were conducted to determine the sample size required to adequately power the study. The following assumptions were made to evaluate the power to demonstrate the superiority of the Device group to the control group:

- [redacted]

9.3.1.2 Secondary Endpoints

[redacted]

9.3.2 Single-arm Cohort

9.3.2.1 Primary Endpoint

The power calculation for the proportion of subjects with at least a 10 point improvement in KCCQ overall summary score at 12 months compared to baseline is based on the following assumptions:

- [redacted]

[redacted]

9.3.2.2 Secondary Endpoints

[redacted]

9.4 Timing of Analysis

[redacted]

[redacted]

9.5 Subgroup Analysis

Subgroup analysis are provided for the primary endpoint of the Randomized cohort and the Single-arm Cohort. Subgroups for analysis include but are not limited to:

- Sex (Male vs. Female)
- Baseline TR Grading (Grade 3 vs. > Grade 3)
- Baseline NYHA Functional Class (I/II vs. III/IV)
- Baseline Etiology of TR (Primary TR vs. Secondary TR)

[redacted]

9.6 Multiplicity

[redacted]

9.7 Procedures for Accounting for Missing Data

[redacted]

9.8 Sample Size Re-estimation

[redacted]

9.9 Statistical Criteria for Termination

There are no statistical criteria for termination of this clinical investigation.

9.10 Success Criteria

The primary endpoint for the Randomized cohort must be met for the trial to be considered successful.

9.11 Deviations from Statistical Plan

[redacted]

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents for the purpose of performing clinical investigation-related monitoring, audits, IRB/EC review and regulatory inspections.

Subjects providing informed consent are agreeing to allow clinical investigation monitors or regulatory authorities, including foreign countries, 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

The Sponsor will select investigators qualified by training and experience to participate in the clinical investigation. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the clinical investigation.

11.2 Site Principal Investigator Responsibilities

The role of the Site Principal Investigator is to implement, oversee the management of the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation. The principal investigator shall support monitoring and reporting to IRB/EC and local competent authorities as necessary, throughout the conduct of the clinical investigation.

The principal investigator is responsible for ensuring adequate training and qualification of the investigation site team and for maintaining oversight of their activities. The principal investigator may delegate tasks to members of the investigation site team but retains responsibility for the clinical investigation. This also applies when activities are outsourced to an external organization by the principal investigator in which case he/she shall exercise oversight to ensure the integrity of all tasks performed and any data generated by this external organization.

11.3 Clinical Investigation Finances and Agreements

Abbott will finance the clinical investigation and will compensate investigational sites for participation in the clinical investigation per the conditions of agreement between Abbott and the investigational site.

11.4 CIP Amendments

The Sponsor will provide approved CIP amendments to the prior to implementing the amendment. The Principal Investigator is responsible for notifying the IRB/EC or equivalent committee of the CIP amendment (administrative changes) or obtaining IRB's/EC's approval of the CIP amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the CIP amendment.

Sites must document in writing acknowledgement/approval of the CIP amendment by the IRB/EC prior to implementation of the CIP amendment. Sites must also provide copies of this documentation to the Sponsor.

11.5 Training

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

11.6 Monitoring

Sponsor and/or designee will monitor the clinical investigation over its duration according to the CIP-specific monitoring plan which will include the planned extent of source data verification.

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

- The Principal investigator understands and accepts the obligation to conduct the clinical investigation according to the CIP and applicable regulations, and has signed the Investigator Agreement [for US clinical investigations] or the Clinical Trial Agreement [for OUS clinical investigations].
- The Investigator and his/her staff should have sufficient time and facilities to conduct the clinical investigation and should have access to an adequate number of appropriate subjects to conduct the clinical investigation.
- Source documentation (including original medical records) must be available to substantiate proper informed consent procedures, adherence to CIP 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 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 monitor

with a suitable working environment for review of clinical investigation-related documents.

11.7 Deviations from CIP

The Investigator should not deviate from the CIP for any reason 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.

No waivers for CIP deviations will be granted by the Sponsor. All deviations must be reported to the Sponsor using the Deviation CRF. The occurrence of CIP deviations will be monitored by the Sponsor for evaluation of investigator compliance to the CIP and regulatory requirements and dealt with according to written procedures. Investigators will inform their IRB/EC or equivalent committee of all CIP 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 CIP or any other conditions of the clinical investigation 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 clinical investigation.

11.8 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical investigation records, including source documentation, for inspection 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.

11.9 Committees

11.9.1 Steering Committee

The Steering Committee is responsible for overseeing the scientific and operational aspects of the clinical investigation. This committee will meet regularly to monitor subject enrollment, general data collection and non-compliance with the CIP at individual centers, to review and act upon recommendations of the Data Monitoring Committee (DMC), to review operational issues

that may arise and warrant a CIP amendment or other corrective action and to determine policy regarding any publications arising from data generated from the performance of the clinical investigation.

11.9.2 Publications Committee

A Publication Committee shall be established to oversee clinical investigations publications, including publication planning and authorship determinations. Publication Committee membership may include members of the Steering Committee, Principal Investigators, a representative of the Sponsor and a statistician. The Publication Committee will determine policy and strategies regarding individual presentations and/or publications arising from clinical investigation generated data. The committee will also review all external requests for accessing clinical investigation-related data and strategies aligning with the Sponsor's presentation and publication team expectations. The committee will also follow the Sponsor's applicable policies and Standard Operating Procedures.

11.9.3 Data Monitoring Committee (DMC)

The DMC is an independent multidisciplinary group restricted to individuals free of significant conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. The DMC will be composed of at least two physicians with experience relevant to the clinical investigation and a biostatistician.

The DMC will serve in an advisory role to the Sponsor by reviewing cumulative data from the clinical investigation at prescribed intervals for the purpose of safeguarding the interests of enrolled subjects and those patients yet to be enrolled, as well as the continuing validity and scientific merit of the clinical investigation. The committee composition, frequency of meetings, and the data monitoring report guidelines are described in the DMC Charter.

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

11.9.4 Clinical Events Committee (CEC)

The CEC is an independent adjudication body comprised of qualified physicians who are not participants in the clinical investigation. The CEC will review and adjudicate prespecified events reported by investigators or identified by Safety personnel for the clinical investigation as defined in the CEC charter and according to definitions provided in this CIP.

11.9.5 Eligibility Committee

The EC consisting of a Heart Failure Specialist, Implanters (Interventional Cardiologist and Cardiac Surgeon) and an Echocardiologist reviews data provided by the investigational site and echo data from the echo core laboratory, and conducts clinical assessment. The EC finally decides whether a patient can be enrolled in the clinical trial or not, and whether they will be in the Randomized or Single-arm.

11.9.6 Imaging Committee

The Imaging Committee will consist of imaging experts in the field of Echocardiography and Radiology. Members will meet as required and provide input on determining imaging criteria as well as provide oversite on the imaging sub-study.

12 DATA HANDLING AND RECORD KEEPING

Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation. CRF data collection will be performed through a secure web portal and only authorized personnel will access the EDC system using a unique username and password to enter, review or correct data. Passwords and electronic signatures will be strictly confidential. The data will be subjected to consistency and validation checks within the EDC system and supplemental review by the Sponsor.

At the conclusion of the clinical investigation, 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 provided to the investigational sites, if requested.

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

12.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

The Sponsor implements technical and physical access controls to ensure that Personal Information is accessible only to and processed only on a ‘need to know’ basis, including periodic review of access rights, and revocation of access when an individual’s employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the investigational sites to transfer into Sponsor’s data management systems only pseudonymous Personal Information (key-coded) necessary to conduct the Clinical Investigation, such as the patient’s medical condition, treatment, dates of treatment, etc. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. Confidentiality of Personal Information will be observed by all parties involved at all times throughout the clinical investigation. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data.

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including

any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Clinical Investigation data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

12.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, and issuing and resolving data discrepancies. If appropriate, the DMP may be updated throughout the duration of the clinical investigation. All revisions will be tracked and document controlled.

12.3 Source Documentation

Regulations and GCP require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. 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 clinical investigation:

- Medical history/physical condition of the subject before involvement in the clinical investigation sufficient to verify CIP entry criteria
- Dated and signed notes on the day of entry into the clinical investigation referencing the Sponsor, CIP number, 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 assessment of device relationship for SAEs.
- CIP-required laboratory reports and 12-lead ECGs, reviewed and annotated for clinical significance of out of range results (if applicable).

Note: With electronic medical records some clinical sites may be able to annotate that the labs or ECG have been reviewed in the system. For those sites that do not have such capability, the labs or ECG may be able to be printed or signed.

- Notes regarding CIP-required and prescription medications taken during the clinical investigation (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the clinical investigation
- Any other data required to substantiate data entered into the CRF

12.4 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 CIP and CRF completion. The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

Data on CRFs will be collected for all subjects who sign an informed consent form, including subjects who may not meet all inclusion/exclusion criteria during screening, prior to randomization.

Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by the Sponsor. An electronic audit trail will be used to track any subsequent changes of the entered data.

12.5 Record Retention

The Sponsor and Investigator/Site will archive and retain all documents pertaining to the clinical investigation 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 investigation records.

12.6 Investigational Devices Accountability (Applicable for US and Canada Only)

The Sponsor ships investigational products only to the Principal Investigator (the responsible leader of the investigational site) or his/her legal designee of each site, after sites receive documentation of site activation and shipping authorization is complete.

The Investigator or an authorized designee must maintain adequate records of the receipt and disposition of each investigational device, including part number, batch number, and serial number (if applicable), date used, subject identification, and treating physician.

Storage locations for the devices at investigational sites must be locked with access restricted only to investigators and authorized personnel.

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 and Approval

Institutional Review Board (IRB)/Ethics Committee approval for the CIP, ICF and other written information provided to the patient will be obtained by the Principal Investigator at each investigational site prior to consenting and enrolling patients in this clinical investigation. The approval letter must be received prior to the start of this clinical investigation and a copy must be provided to the Sponsor.

Any amendments to the CIP as well as associated ICF changes will be submitted to the IRB/ Ethics Committee and written approval obtained prior to implementation, according to each institution’s IRB/Ethics Committee requirements.

No changes will be made to the CIP or ICF or other written information provided to the patient without appropriate approvals, including IRB/Ethics Committee, the Sponsor, and the regulatory agencies (if applicable).

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

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

14 CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will be concluded when:

- All sites are closed AND
- The final report has been provided to investigators or the Sponsor has provided formal documentation of clinical investigation closure.

The sponsor will submit the clinical investigation report within one year of the end of the investigation.

15 PUBLICATION POLICY

The data and results from the clinical investigation 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 investigation. The Investigators will not use this clinical investigation-related data without the written consent of the Sponsor for any purpose other than for clinical investigation completion or for generation of publication materials, as referenced in the Clinical Trial Agreement. Single-center results are not allowed to be published or presented before the multi-center results. Any proposals for publications or presentations by the investigators must be reviewed and approved by the Sponsor in a timely manner to enable Sponsor review in compliance with the Sponsor's publication policy set forth in the Clinical Trial Agreement.

Upon receiving IDE approval from the FDA, the Sponsor will be responsible for registering this clinical investigation on www.clinicaltrials.gov or any other clinical trials, 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 the ClinicalTrials.gov website. Institution and/or Principal Investigator(s) shall not take any action to register the clinical investigation. A full report of the pre-specified outcomes, regardless of the results, will be made public through the ClinicalTrials.gov website no later than 12 months after clinical investigation completion, as required by section 801 of the FDA Amendments Act. If this clinical investigation is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through the ClinicalTrials.gov website.

16 RISK ANALYSIS

16.1 Anticipated Clinical Benefits

There are no guaranteed clinical benefits associated with participation in this clinical investigation. It is expected that patients participating in this trial will experience the same

benefit that were observed from an ongoing trial with the TriClip™ device. These benefits include, but may not be limited to, the following:

- Reduction in heart failure hospitalization rate
- Improved symptomatic status and quality of life
- A potential for reduced mortality

16.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

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

16.3 Residual Risks Associated with the Device Under Investigation, as Identified in the Risk Analysis Report

Risk analysis for the TriClip™ device has been performed in accordance with the Risk Analysis Plan. The risk analysis utilizes Failure Mode Effect Analysis (FMEA) tool to systematically identify potential hazards associated with the process, design, components and use of the devices. Based upon the preclinical, clinical and bench-testing data, all risks have been identified and determined to be within acceptable levels. The benefit of treating patients with TriClip™ device outweigh the potential risks.

16.4 Risks Associated with Participation in this Clinical Investigation

Protocol required assessments are summarized in Section 7.15, Table 1, Clinical Visits and Schedule of Assessments. Most of these clinical assessments are standard for most cardiac/structural heart interventional procedures and are administered per the standard of care at each institution, and do not constitute an additional risk for the clinical investigation participants.

Study specific assessments that may not be considered standard of care include protocol required transesophageal echocardiography (TEE) assessments performed at screening, baseline and during protocol defined follow up visits. TEE is a commonly used safe technique in cardiac interventions that requires conscious sedation or general anesthesia, depending on hospital standard practice. In the exceptional occasion if complications arise during the TEE procedure, it may be necessary to convert to an open surgical procedure. Emergency surgical back-up should be available as per the institution's standard procedures.

16.5 Possible Interactions with Protocol-Required Concomitant Medications (if applicable)

All medications at baseline and post -procedure (Section 7.8.1) are administered per the current guidelines and are standard of care. Although are no protocol -required medications being used as part of this study, post-procedure antiplatelet/anticoagulation therapy and prophylactic antibiotics for endocarditis as per the standard care (refer to section 7.8.1) are highly recommended. The risks associated with these medications are described in the drug summary of product characteristics.

16.6 Steps Taken to Control or Mitigate Risks

In-depth recommendations, special precautions and instructions regarding patient selection, device handling, device placement and system removal are included in the IFU. 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. Each site/investigator will have access to the IFU.

All investigators involved in the conduct of the clinical investigation will be qualified by education, training, or experience to perform their tasks and this will be documented appropriately. Patients enrolled in the trial will be selected based on the eligibility criteria defined in section 6.3.

Risks associated with the use of the TriClip™ device are minimized through device design. The Delivery System is comprised of the Steerable Sleeve, Delivery Catheter and Implant. The Delivery Catheter is designed to deliver and deploy the Implant. Acceptable performance of the TriClip™ device was confirmed in bench studies.

16.7 Risk to Benefit Rationale

TR results from failure of the tricuspid valve to close completely during systole. The symptoms of TR are not evident until the condition has significantly worsened. Medical therapy for TR is directed towards reducing symptoms by decreasing the fluid overload. Many patients are refractory to medical therapy and continue to suffer. Tricuspid valve surgery is only recommended as a Class I recommendation when the patient is undergoing left sided heart surgery. Isolated tricuspid valve surgery carries a high mortality rate.

The TriClip™ device was studied in TRILUMINATE trial (CE Mark trial) which has demonstrated clinically meaningful reduction in tricuspid valve regurgitation, functional status and quality of life at 30 days post procedure. The study has demonstrated good safety profile with no acute mortality, no major cardiac AEs, low re-intervention for TR and low procedural AEs such as endocarditis and pericardial effusion. Treatment with TriClip™ Device offers a percutaneous, minimally invasive, safe option to reduce TR with short recovery time, amelioration of symptoms and improvement in cardiac function and quality of life in patients with severe TR.

Based on the clinical experience, and bench data, the benefit of TR reduction and improvement of TR symptoms with TriClip™ device outweighs any potential risk associated with this procedure.

17 APPENDIX I: ABBREVIATIONS AND ACRONYMS

6MWT– Six Minute Walk Test

AE – Adverse Event

APS – Acute Procedural Success

CRO – Contract Research Organization

CRF – Case Report Form

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

DMC – Data Monitoring Committee

EC – Eligibility Committee

ECL – Echocardiographic Core Laboratory

eCRF – Electronic Case Report Form

EDC – Electronic Data Capture

EFS – Early Feasibility Study

EROA – Effective Regurgitant Orifice Area

ESC – European Society of Cardiology

FDA – Food and Drug Administration

HF – Heart Failure

IB – Investigator Brochure

ICD - Implantable cardioverter-defibrillator

ICF – Informed Consent Form

IFU - Instructions for Use

IRB – Institutional Review Board

IVC – Inferior Vena Cava

KCCQ – Kansas City Cardiomyopathy Questionnaire

LVEDV – Left Ventricle End Diastolic Volume

LVESV – Left Ventricle End Systolic Volume

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

RVEF - Right Ventricular Ejection Fraction

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

VC – Vena Contracta

18 APPENIX 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 in the IFU or CIP (**Appendix V**).

ASCITES

The accumulation of fluid in the peritoneal cavity, causing abdominal swelling.

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.

BNP/NT-proBNP

B-type natriuretic peptide (BNP) is a hormone produced by your heart. N-terminal (NT)-pro hormone BNP (NT-proBNP) is a non-active prohormone that is released from the same molecule that produces BNP. Both BNP and NT-proBNP are released in response to changes in pressure inside the heart. These changes can be related to heart failure and other cardiac problems. Levels goes up when heart failure develops or gets worse, and levels goes down when heart failure is stable. In most cases, BNP and NT-proBNP levels **are higher in patients with heart failure than people who have normal heart function.**

CARDIOGENIC SHOCK

Sustained SBP ≤90 mmHg for >30 min or the need for intervention (vasopressors/inotropes etc.) to maintain SBP >90 mm Hg

DEATH (All Cause)

All deaths regardless of cause. Death is further divided into 2 categories

1. CARDIOVASCULAR DEATH (VARC-2)

   Per the Valve Academic Research Consortium (VARC-2) 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
- All valve-related deaths including structural or non-structural valve
- dysfunction or other valve-related adverse events

2. NON-CARDIOVASCULAR DEATH

   Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)

DEVICE EMBOLIZATION

Detachment of the deployed TriClip™ 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 TriClip™ evidenced by echocardiography or fluoroscopy. If the TriClip™ is explanted or an autopsy is performed, this diagnosis should be confirmed.

ENDOCARDITIS

A diagnosis of endocarditis based on the following modified Duke criteria, from Infective Endocarditis (IE) in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. Circulation. 2015 Oct 13;132(15):1435-86.

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

Definite IE
Pathological criteria
Microorganisms demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis
Clinical criteria
2 Major criteria, 1 major criterion and 3 minor criteria, or 5 minor criteria
Possible IE
1 Major criterion and 1 minor criterion, or 3 minor criteria
Rejected
Firm alternative diagnosis explaining evidence of IE; or resolution of IE syndrome with antibiotic therapy for ≤4 d; or no pathological evidence of IE at surgery or autopsy with antibiotic therapy for ≤4 d; or does not meet criteria for possible IE as above
Clinical Criteria Major Criteria Blood culture positive for IE Typical microorganisms consistent with IE from 2 separate blood cultures: Viridans streptococci, Streptococcus bovis, HACEK group, Staphylococcus aureus; or community-acquired enterococci in the absence of a primary focus, or microorganisms consistent with IE from persistently positive blood cultures defined as follows: at least 2 positive cultures of blood samples drawn >12 h apart or all 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 h apart) Single positive blood culture for Coxiella burnetii or anti–phase 1 IgG antibody titer ≥1:800 Evidence of endocardial involvement

Echocardiogram positive for IE (TEE recommended for patients with prosthetic valves, rated at least possible IE by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients) defined as follows: oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; abscess; or new partial dehiscence of prosthetic valve or new valvular regurgitation (worsening or changing or pre-existing murmur not sufficient)

Minor Criteria

Predisposition, predisposing heart condition, or IDU

Fever, temperature >38°C

Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions

Immunological phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor

Microbiological evidence: positive blood culture but does not meet a major criterion as noted above (excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serological evidence of active infection with organism consistent with IE

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.

GAMMA-GT/GAMMA-GLUTAMYL TRANSFERASE (GGT)

GGT is an enzyme that is found in many organs throughout the body, with the highest concentrations found in the liver. GGT is elevated in the blood in most diseases that cause damage to the liver.

GASTROINTESTINAL COMPLICATIONS

Complications as a result of the TriClip™ 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 (HF) HOSPITALIZATION

Defined as an event that meets the following criteria:

1) Hospitalization (≥ 24 hours) with the primary reason for admission as acute decompensated HF and administration of intravenous or mechanical heart failure therapies, especially IV administration of diuretic therapy

2) An unscheduled or unplanned admission to the emergency department, hospital outpatient observation unit, or hospital inpatient unit, and IV administration of diuretic therapy.

3) Subject arrives in emergency department with clinical presentation meeting the criteria of heart failure, but dies in the emergency department before hospital admission.

Overnight stays at nursing home facilities, physical rehab or extended care facilities, including hospice, will be included in the definition of hospitalization if related to a heart failure event. Elective heart failure “tune-ups” that occur following the TriClip™ procedure and prolong the Index hospitalization will not count as a heart failure 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 composite of cardiovascular mortality, new onset renal failure, endocarditis requiring surgery, and non-elective cardiovascular surgery for TriClip™ 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)[1] 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

[1] 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.

- 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
  - 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 TriClip™ 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.

MELD SCORE

The Model for End-Stage Liver Disease, or MELD, is a scoring system for assessing the severity of chronic liver disease. The following parameters are used to determine MELD score: Creatinine level, Bilirubin level, INR (international normalized ratio), and serum sodium level. The score is calculated as follows:

Candidates who are at least 12 years old receive an initial MELD(i) score equal to:

0.957 x Loge(creatinine mg/dL) + 0. 378 x Loge(bilirubin mg/dL) + 1.120 x Loge (INR) + 0.643
Laboratory values less than 1.0 will be set to 1.0 when calculating a candidate's MELD score.

The following candidates will receive a creatinine value of 4.0 mg/dL:

- Candidates with a creatinine value greater than 4.0 mg/dL
- Candidates who received two or more dialysis treatments within the prior 7 days
- Candidates who received 24 hours of continuous veno-venous hemodialysis (CVVHD) within the prior 7 days

The maximum MELD score is 40. The MELD score derived from this calculation will be rounded to the tenth decimal place and then multiplied by 10.

For candidates with an initial MELD score greater than 11, the MELD score is then re-calculated as follows: MELD = $MELD_{(i)}$ + 1.32*(137-Na) – [0.033*$MELD_{(i)}$*(137-Na)] Sodium values less than 125 mmol/L will be set to 125, and values greater than 137 mmol/L will be set to 137.

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 TriClip™ procedure)

Mandatory: CK-MB (preferred) ≥10x ULN within 72 hrs. post- TriClip™ procedure in patient with normal baseline CK-MB

OR

Mandatory: CK-MB ≥5x ULN within 72 hrs. post- TriClip™ 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 TriClip™ 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 TriClip™ or TriClip™ System components, iatrogenic atrial septal defect, or the need for tricuspid valve replacement instead of repair due at least in part to the TriClip™ procedure or the presence of the TriClip™.

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." Subjects should be on stable dose of diuretics for 30 days before the screening assessments (such as TTE/TEE). Stable dose is defined as no more than a 100% increase or a 50% decrease in dose.

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.

PERIPHERAL EDEMA

Accumulation of fluid causing swelling in tissues perfused by the peripheral vascular system, usually in the lower limbs

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 TriClip™ detachment from one leaflet as assessed by the study site and confirmed by the ECL. Reasons for TriClip™ Detachment include leaflet tearing, TriClip™ unlocking, TriClip™ fracture or inadequate TriClip™ placement. Not included are any fractures or other failures of the TriClip™ that do not result in TriClip™ 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 is only required at scheduled visits through 24 months after onset of stroke, if stroke occurred. 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 (1), moderate (2), severe (3, 4, 5). Mild, moderate, and severe will be graded based on the 2017 ASE Guidelines (Zoghbi 2017). Further stratification of severe into 3, 4 and 5 have been developed by the Echo Scientific Committee to provide further granularity in the range beyond severe. See Appendix XII for further grading information.

19 APPENDIX III: SITE CONTACT INFORMATION

Contact information for each participating clinical site is available under separate cover by contacting the Sponsor at:

20 APPENDIX IV: REFERENCES

1. *American College ofCardiology/American Heart Association Task Force on Practice Guidelines. 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 F.* **Nishimura, RA, et al.** 22, Jun 10, 2014, J Am Coll Cardiol, Vol. 63, pp. e57-e185.

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8. *Impact of tricuspid regurgitation on survival in patients with chronic heart failure: unexpected findings of a long-term observational study.* **Neuhold S, Huelsmann M, Pernicka E, Graf A, Bonderman D, Adlbrecht C, Binder T, Maurer G, Pacher R, Mascherbauer J.** 11, Mar 2013, Eur Heart J., Vol. 34, pp. 844-852.

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10. *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.* **Nishimura, RA, et al.** 2, Jul 11, 2017, J Am Coll Cardiol. , Vol. 70, pp. 252-289.

11. *Tricuspid valve repair: durability and risk factors for failure.* **McCarthy, PM, et al.** 3, Mar 2004, Thorac Cardiovasc Surg., Vol. 127, pp. 674-685.

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14. *Predictors of secondary tricuspid regurgitation after left-sided valve replacement. .* **Wang G, Sun Z, Xia J, Deng Y, Chen J, Su G, Ke Y.** 9, 2008, Surg Today., Vol. 38, pp. 778-783.

15. *Transcatheter treatment of severe tricuspid regurgitation using the MitraClip system. Presentation at TCT 2016 Conference.* **Jorg Hausleiter, et al.** s.l. : TCT, October 31, 2016.

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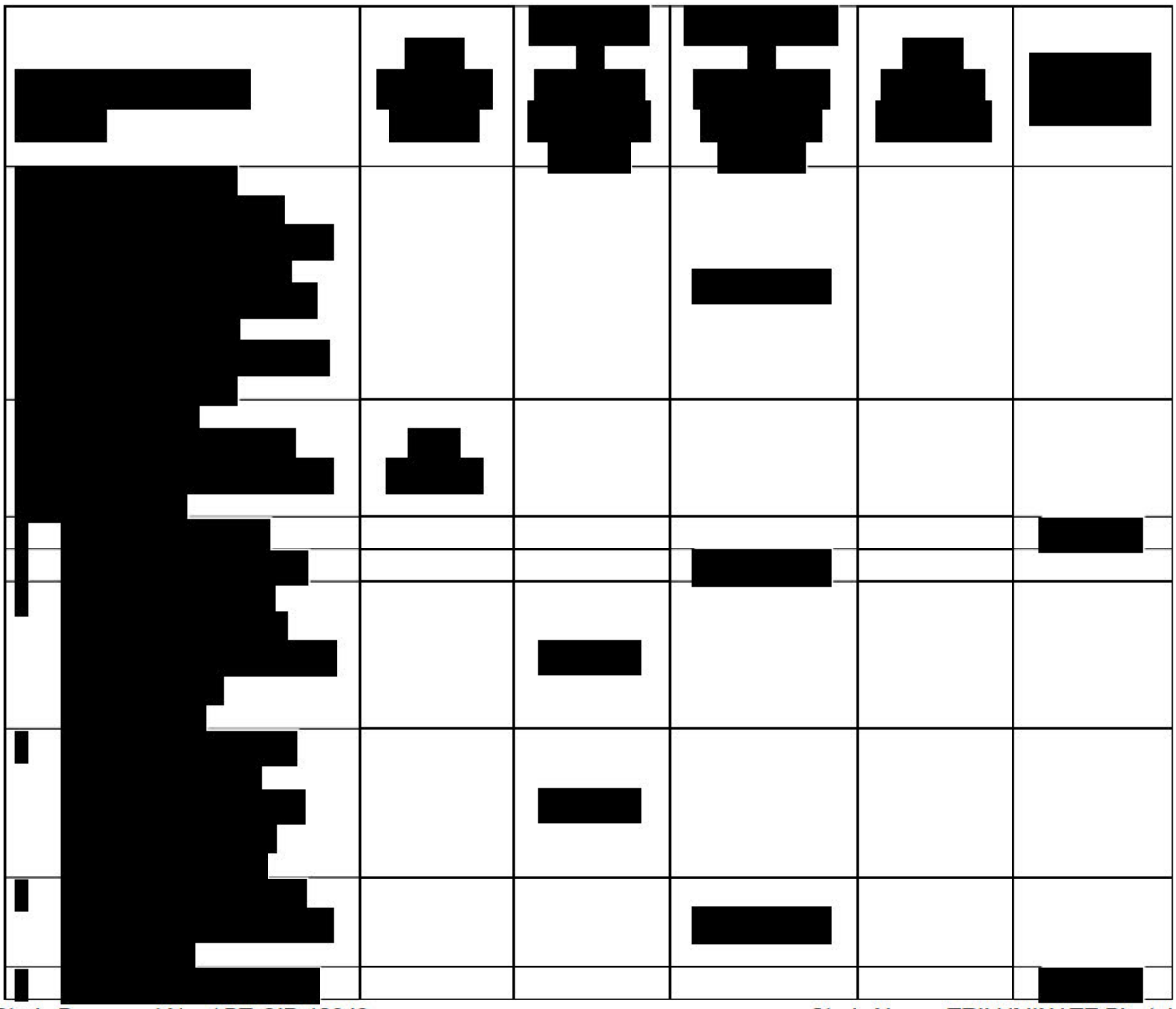
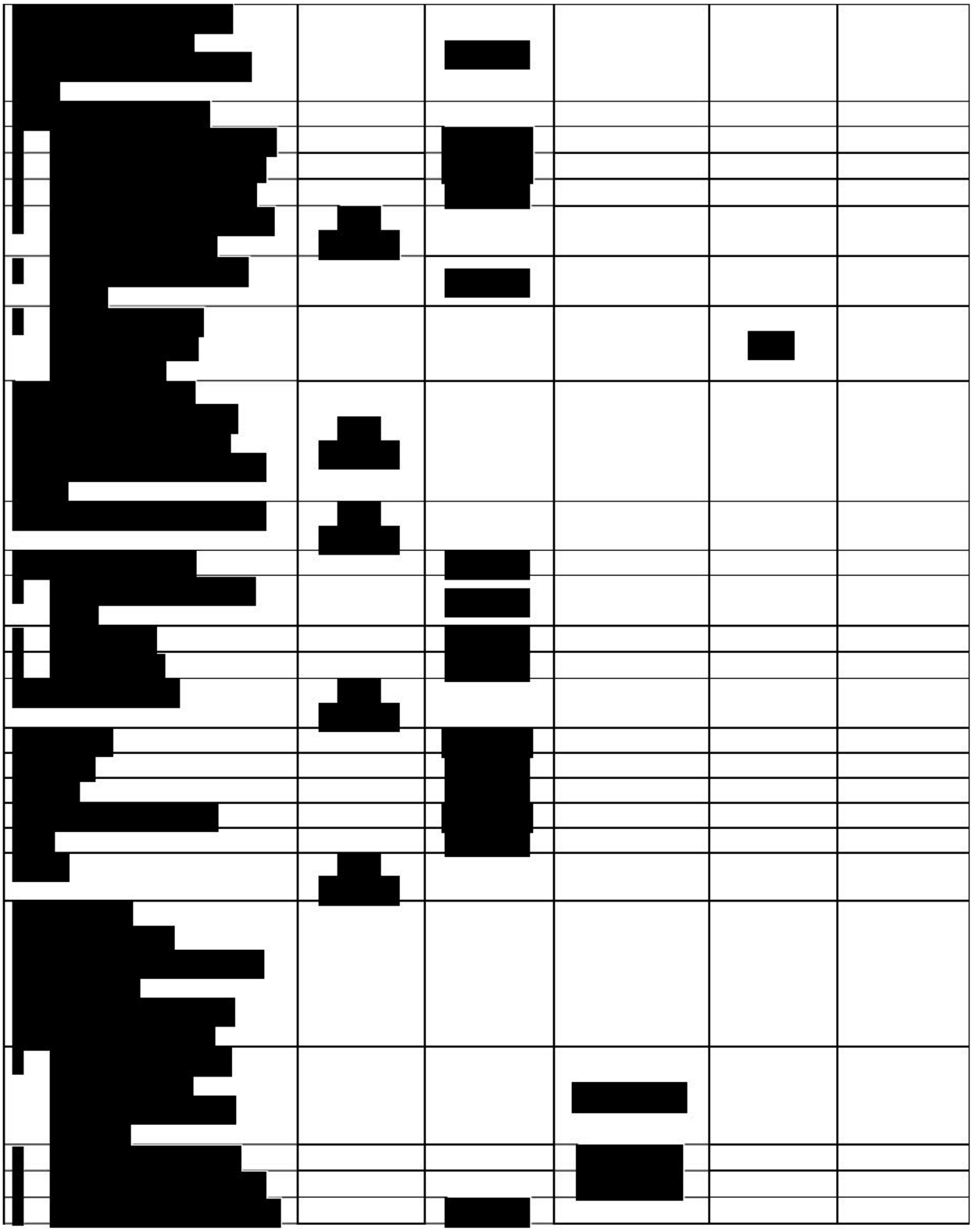
21 APPENDIX V: RATES OF FORSEEABLE ADVERSE EVENTS

[redacted]





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2. Zhu TY, Min XP, Zhang HB, Meng X. Preoperative risk factors for residual tricuspid regurgitation after isolated left-sided valve surgery, Cardiology 2014; 129(4): 242–249
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22 APPENDIX VI: LABELS

[redacted]

23 APPENDIX VII: CASE REPORT FORMS

[redacted]

24 APPENDIX VIII: INFORMED CONSENT FORM

[redacted]

25 APPENDIX IX: MONITORING PLAN

[redacted]

26 APPENDIX X: Transthoracic Echo (TTE) Protocol

[redacted]

[redacted]

27 APPENDIX XI: Transesophageal Echo (TEE) Protocol

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[redacted]

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28 APPENDIX XII: ECHOCARDIOGRAPHY TR GRADING

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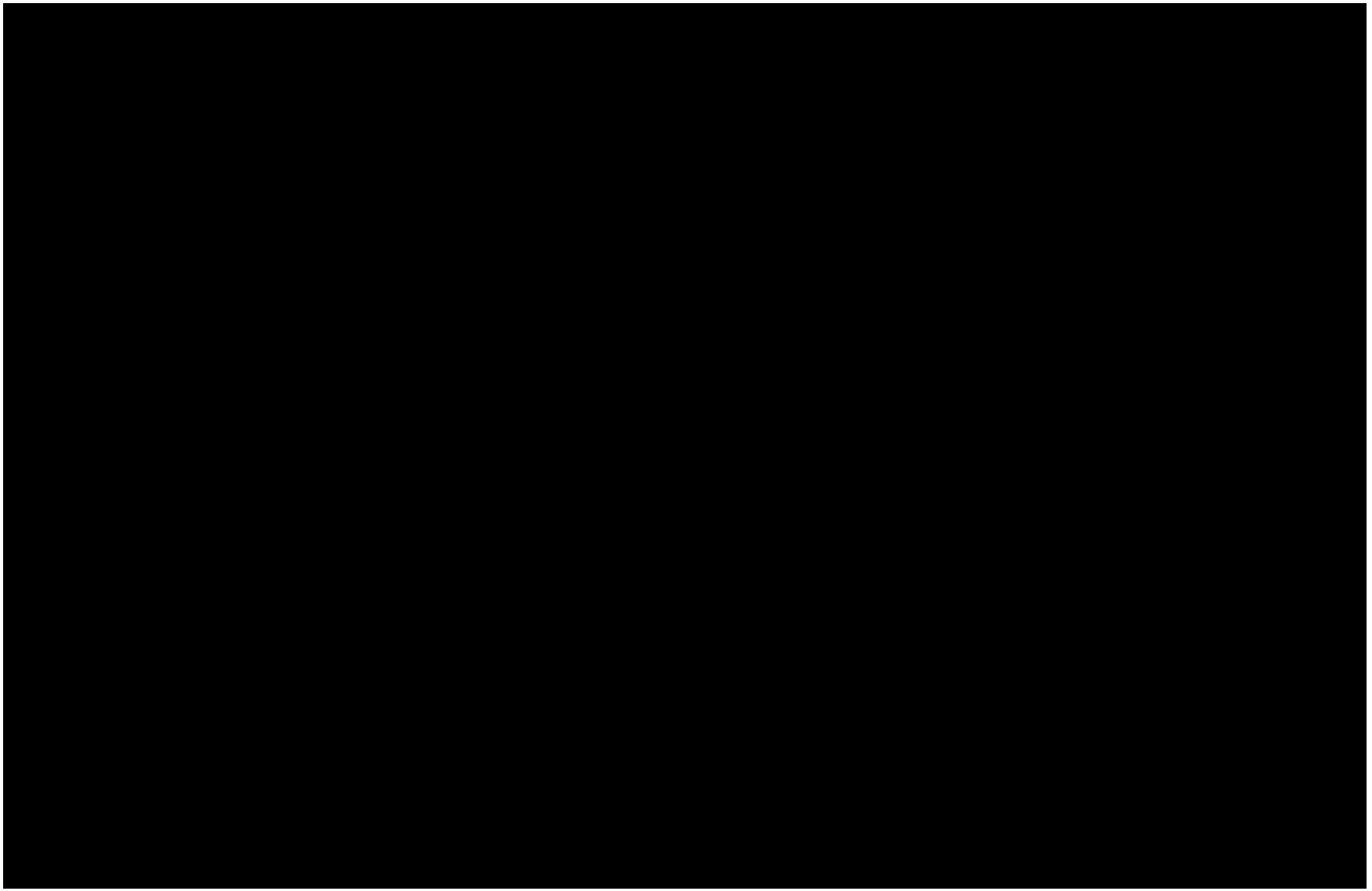

29 APPENDIX XIII: SIX MINUTE WALK TEST GUIDELINES – AMERICAN THORACIC SOCIETY

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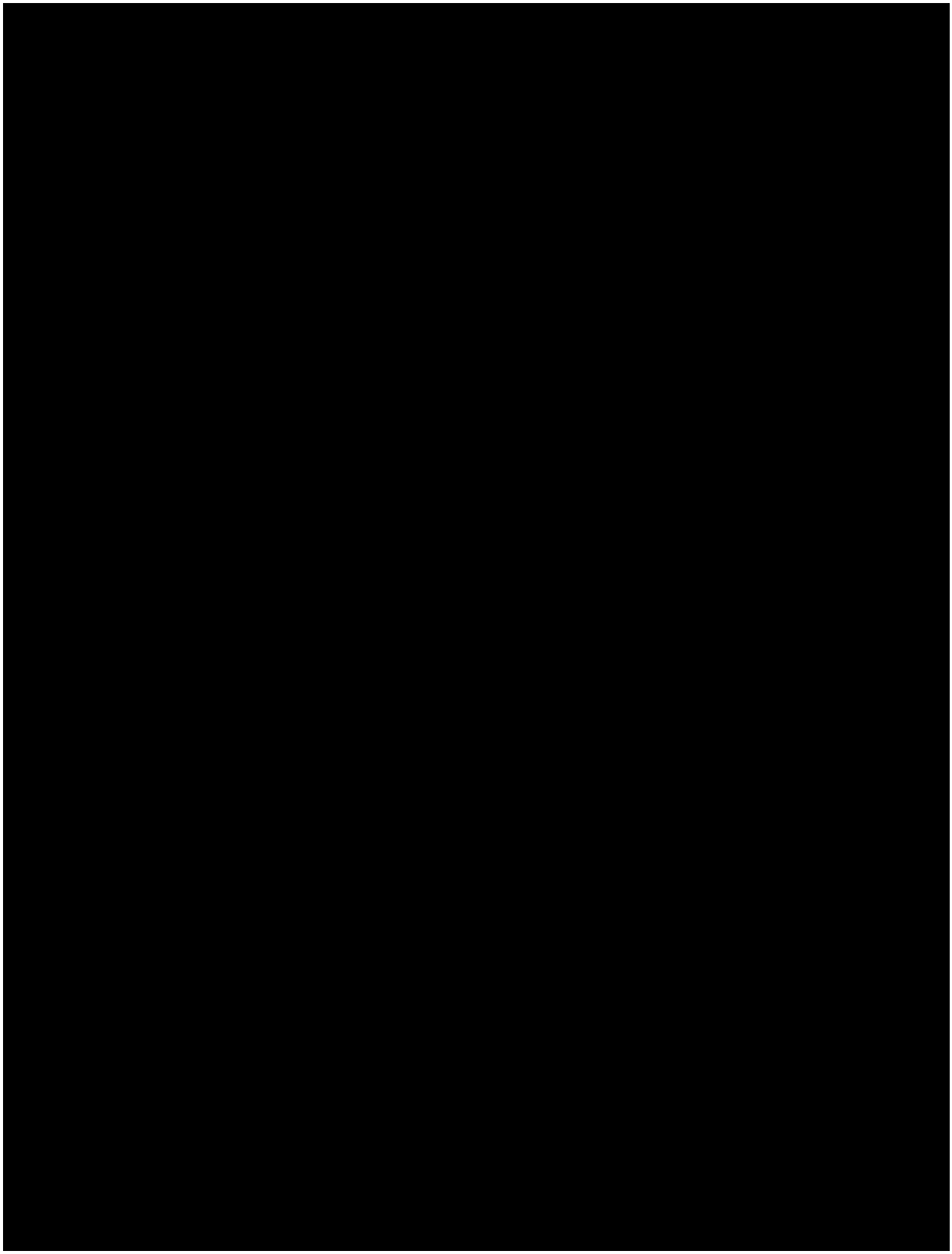

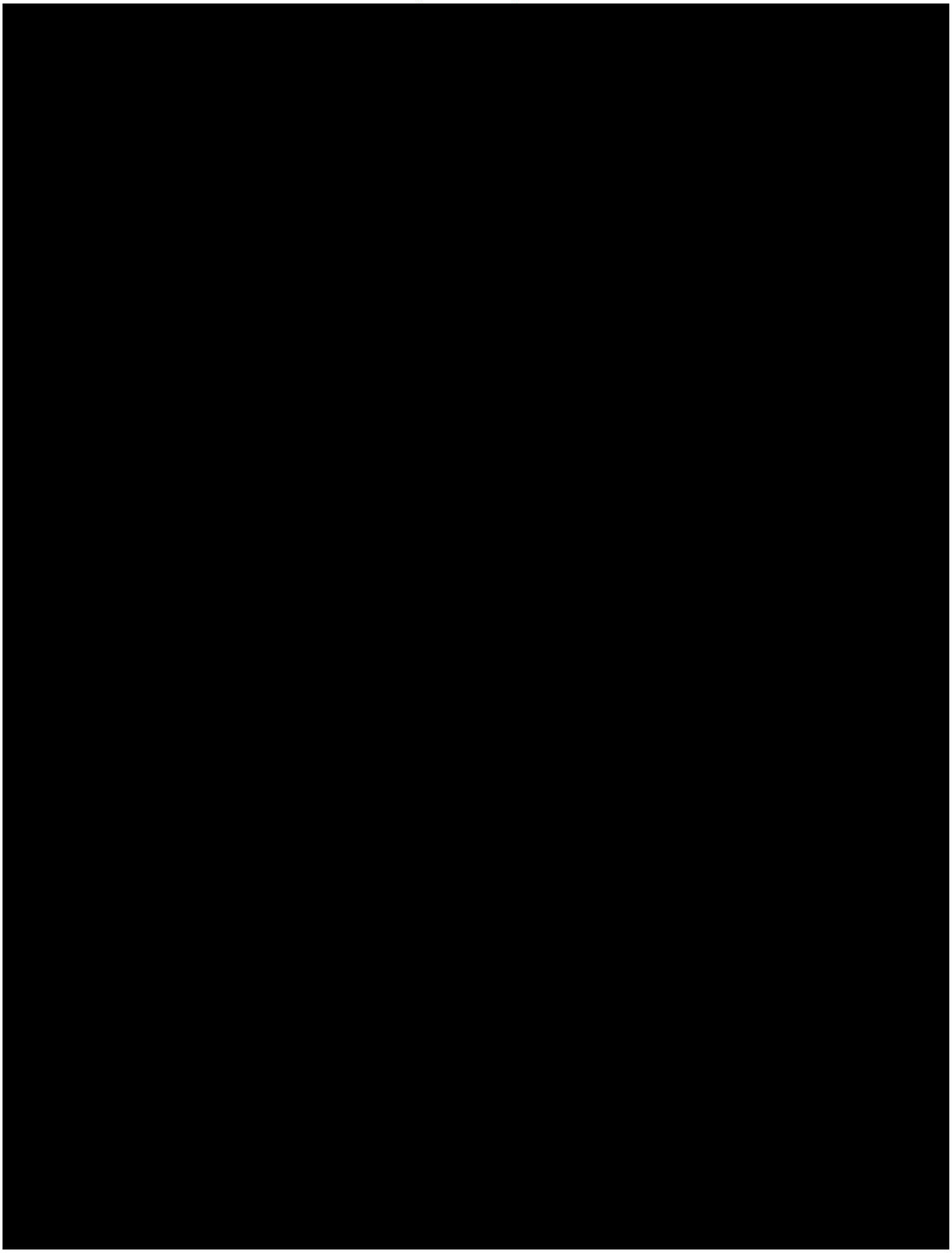

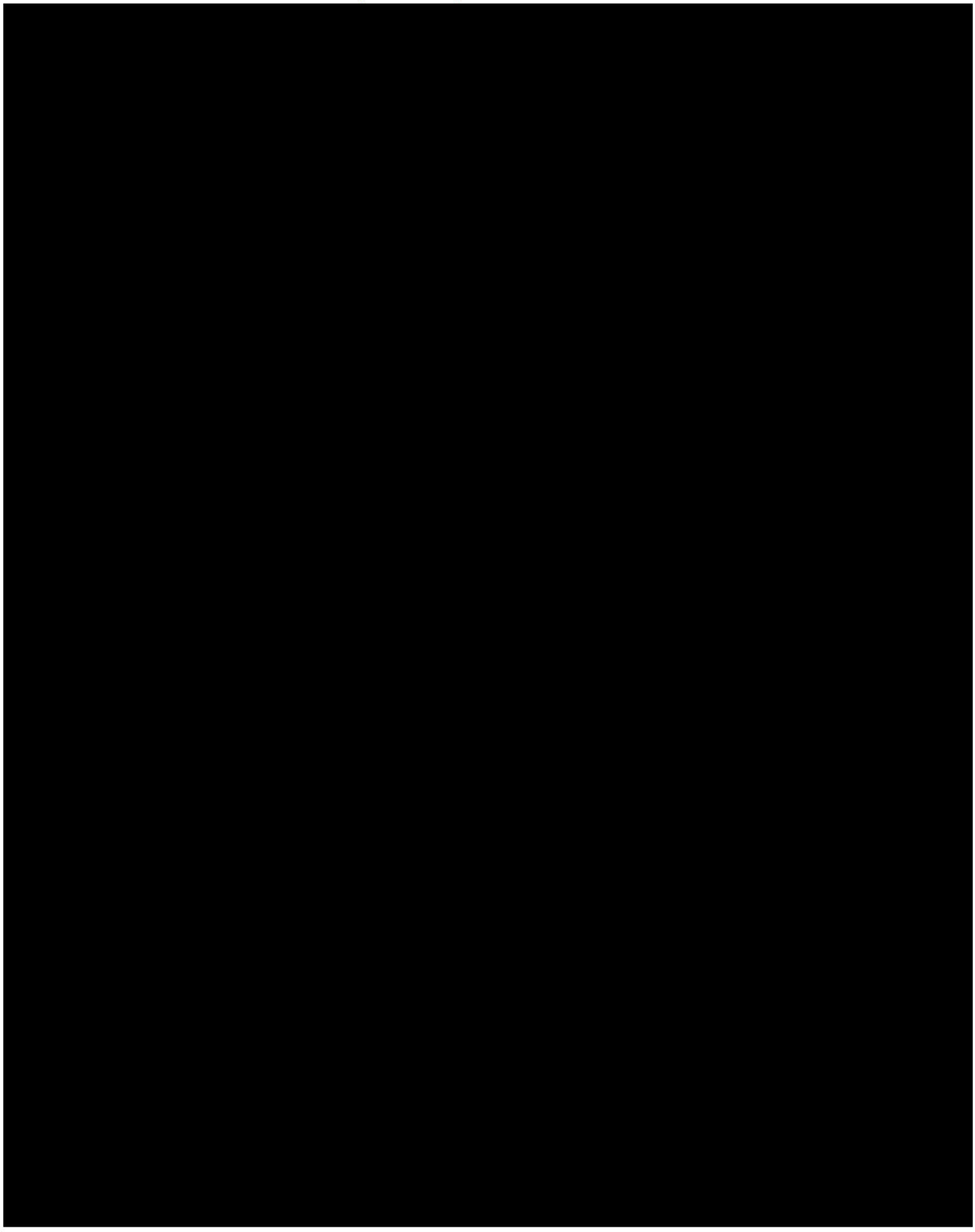

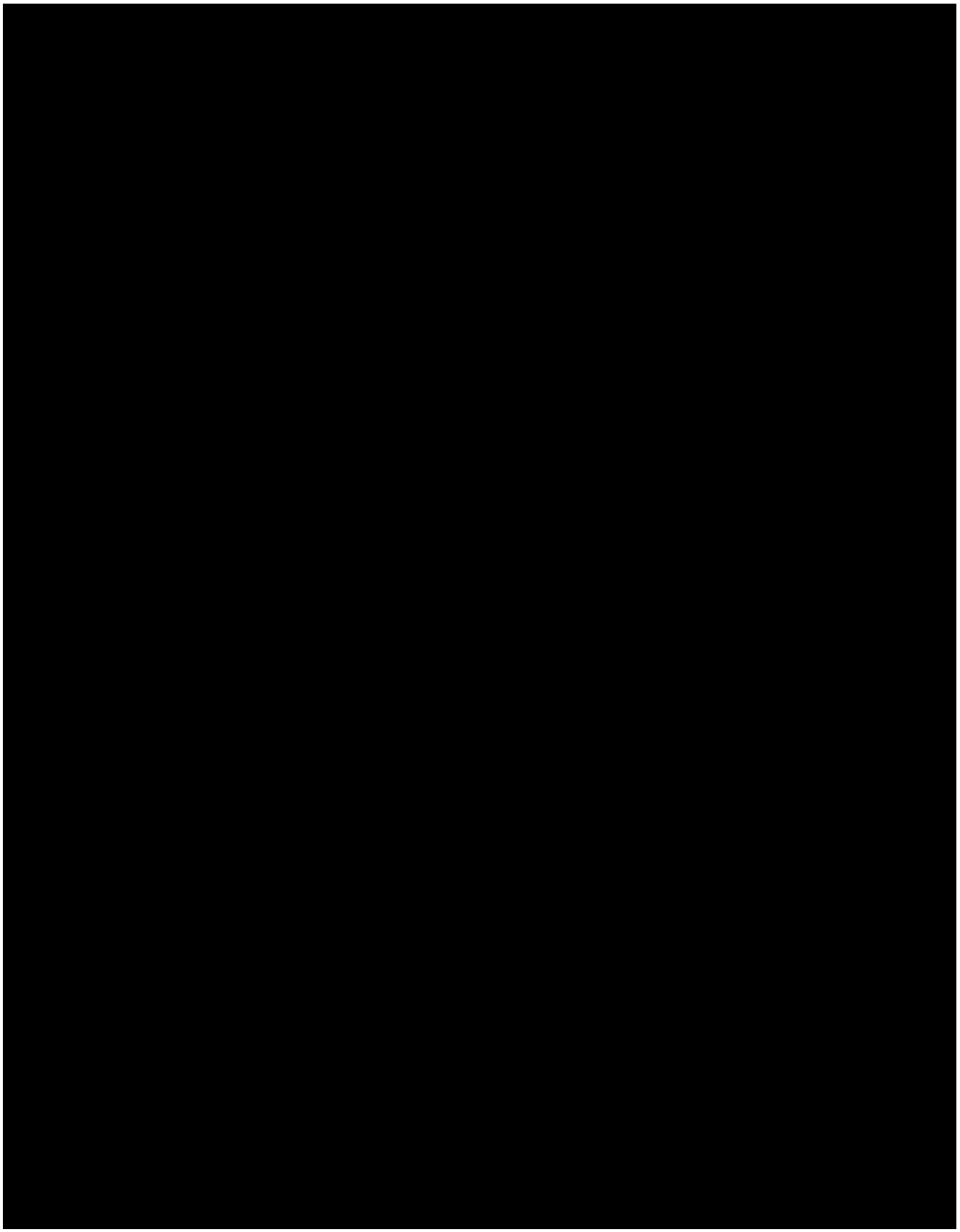

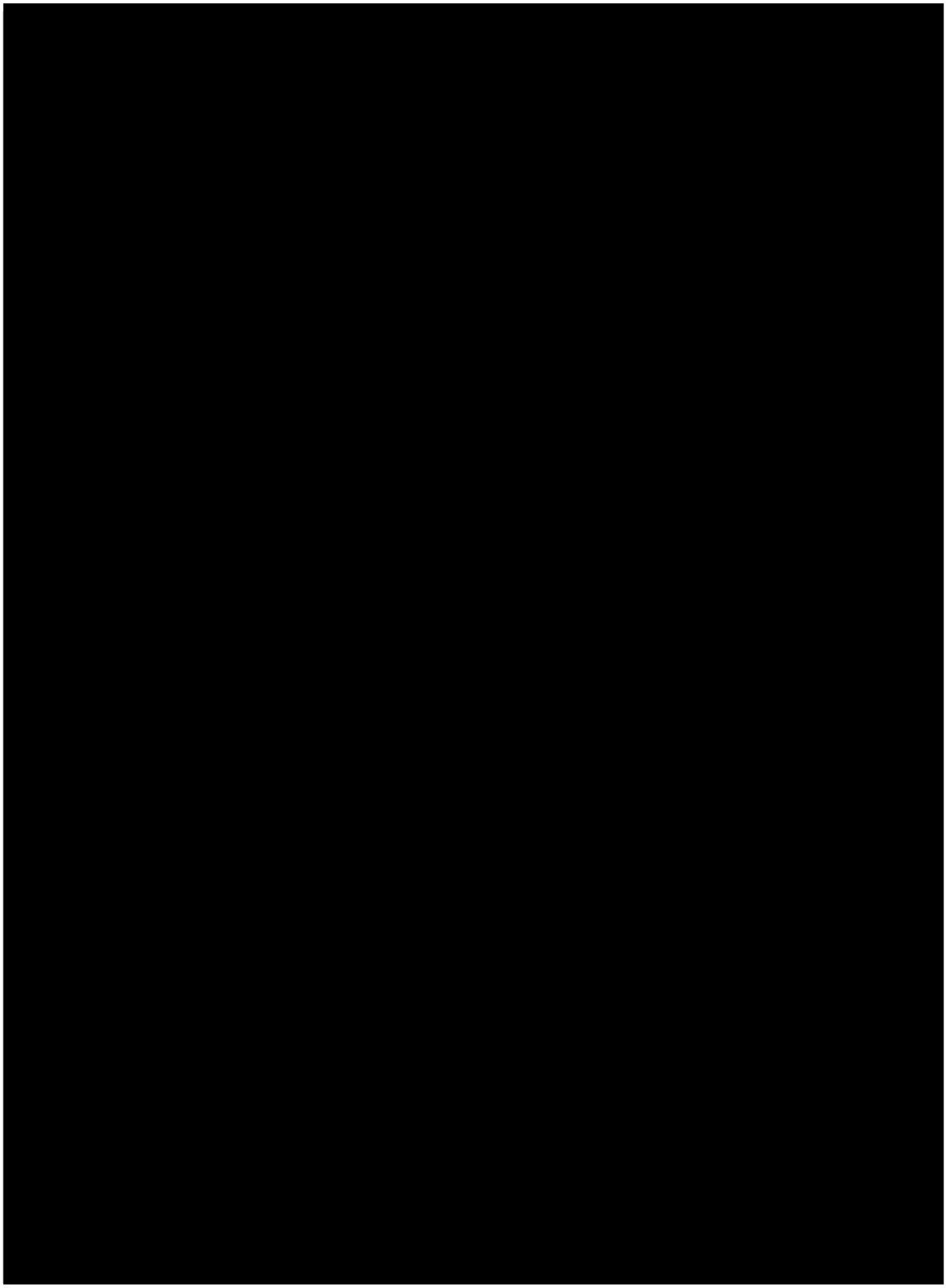

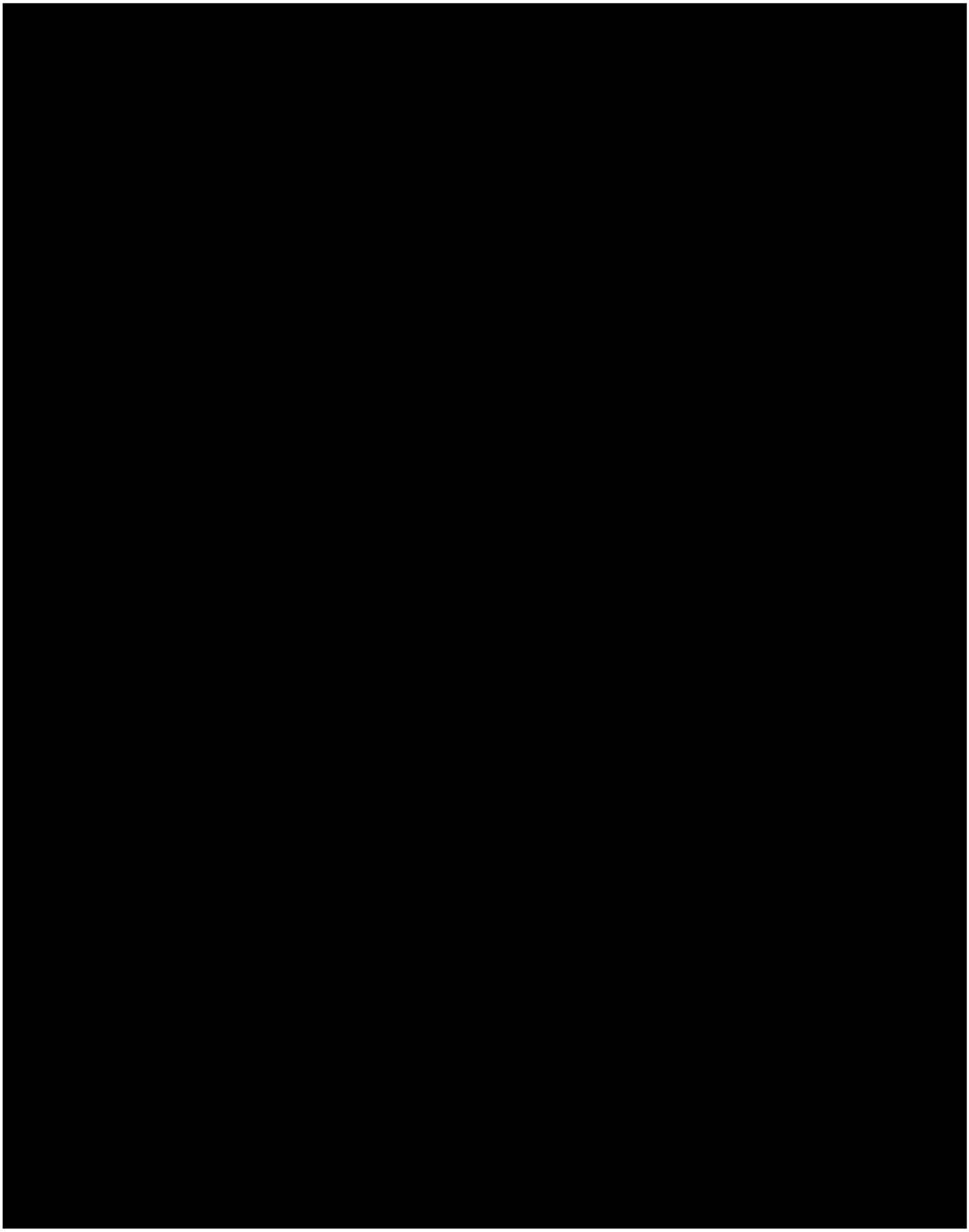

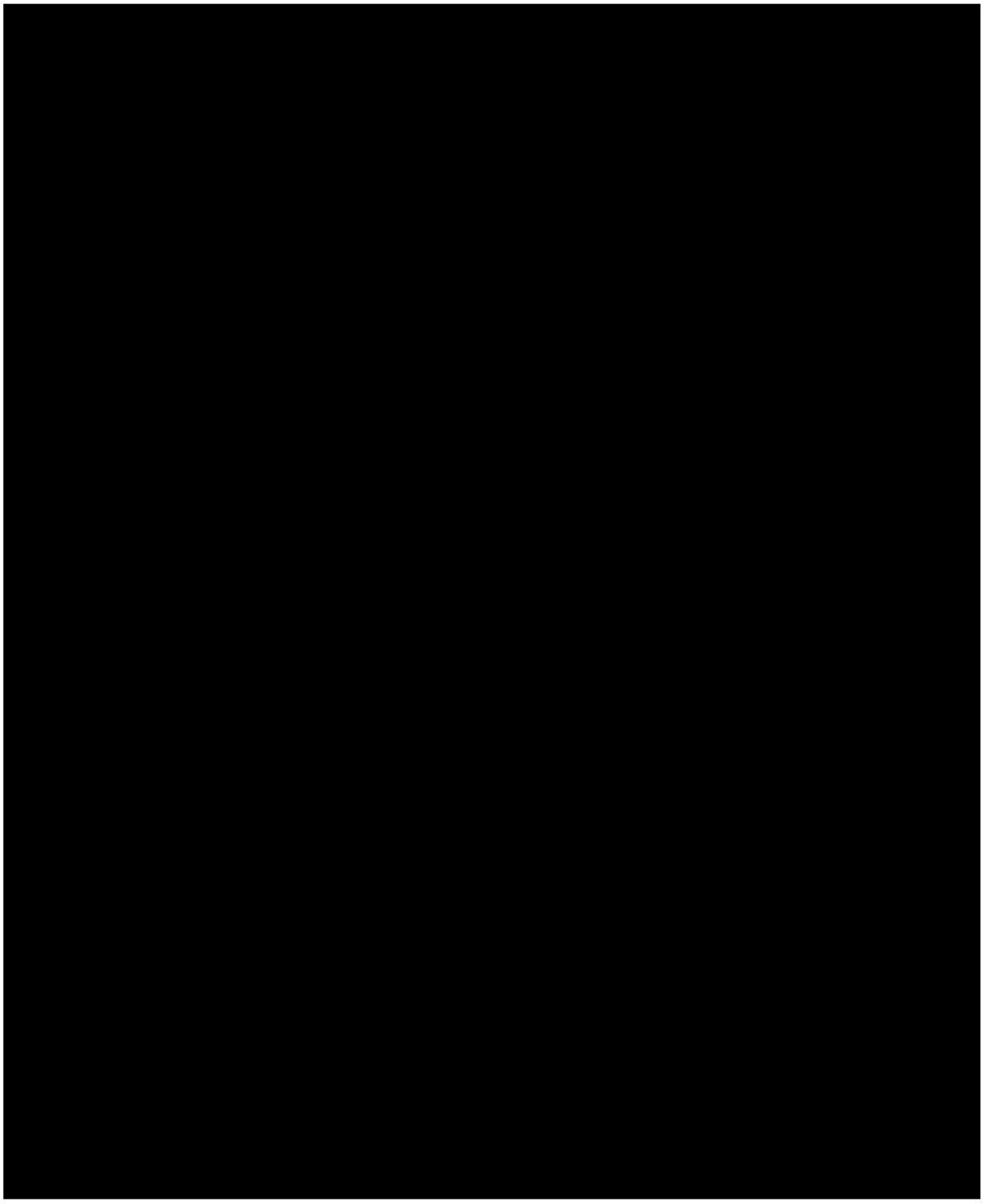

30 APPENDIX XIV: Monitoring Exposure to Ionizing Radiation

(1) Implanting Investigator Training

[redacted]

[redacted]

(1) Acute Evaluation

[redacted]

31 APPENDIX XV: Exceptions from ISO 14155 compliance

Minimal exceptions to ISO 14155:2020 compliance are expected, though these exceptions do not affect the safety and protection of the clinical investigation subjects and do not compromise data quality and security.

- This clinical investigation provides market approved devices in the EU, which will be used within their intended purpose, thus clinical investigation labelling will not be applied, a separate investigator Brochure will not be created, and clinical device accountability will not be set up.

- The study will not be submitted for review to the Competent Authority, only standard vigilance reporting will be observed. Local and/or regional requirements might be still applicable and will be tracked in a study specific Safety Plan.
- Financial disclosures will not be collected from the Investigators.
- separate study risk assessment will not be applied, the applicable risks are described and communicated in the current Clinical Investigational Plan and IFUs for the medical devices under investigation

32 APPENDIX XVI: CONTINUED ACCESS STUDY

[redacted]

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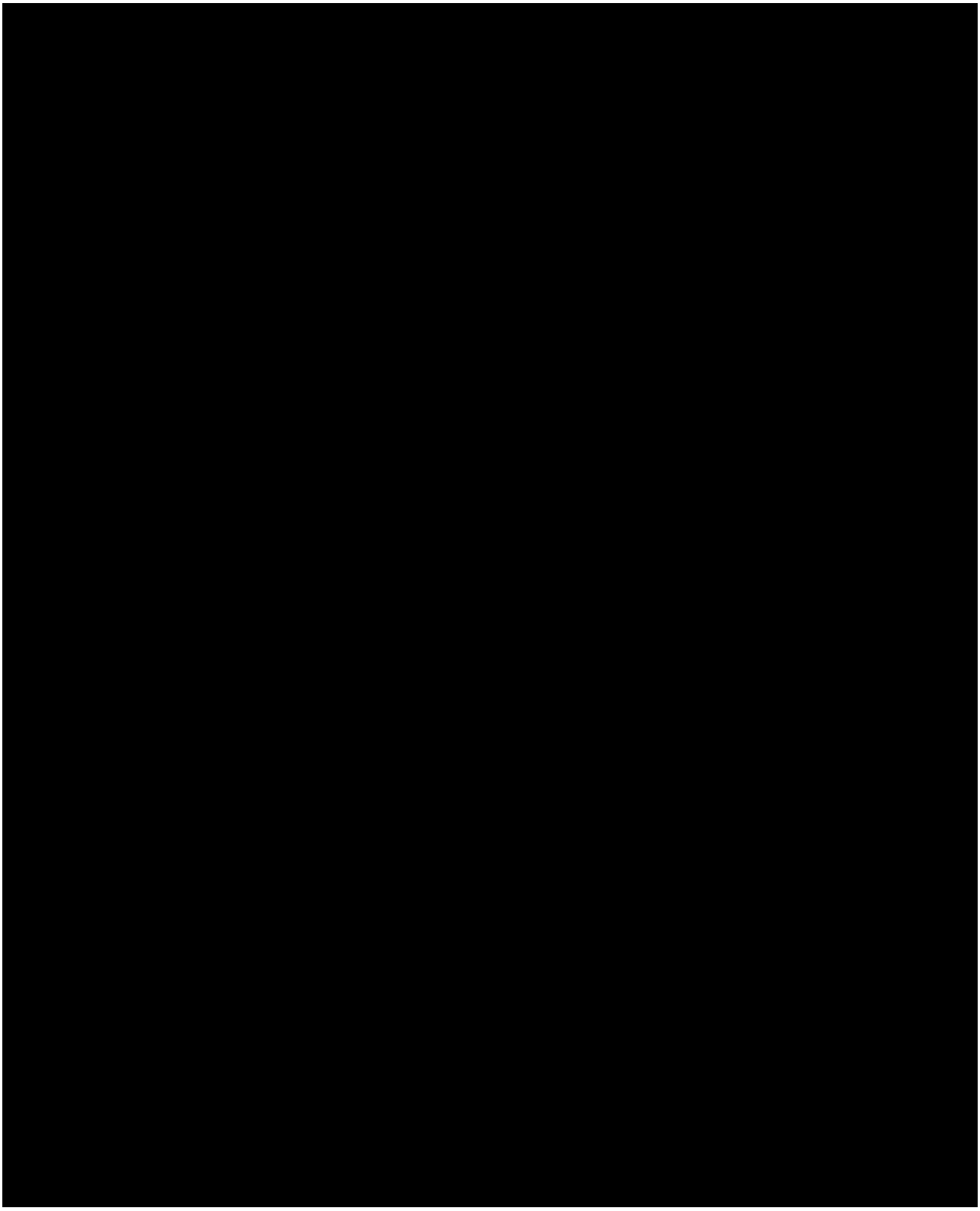
32.6 Schedule of Events



[a] If performed within 14 days of assessment for screening, then screening can be used for baseline.

[redacted]

33 APPENDIX XVII: REVISION HISTORY

Version	Date	Details	Rationale
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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