



BATwire

Implant Kit Study

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CLINICAL INVESTIGATIONAL PLAN



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REVISION HISTORY		
Revision	Date	Description
A v1.0	08/28/2020	Initial release
B v1.0	07/10/2020	<i>Clinical Investigation Plan</i> revised to add a vascular surgeon as a possible trained physician that may perform the BATwire implant procedure
C v1.0	08/18/2021	<i>Clinical Investigation Plan</i> revised to add NT proBNP to screening/baseline values and continued to meet indication after completing screening/baseline. Allow 45 days to complete screening/baseline testing. Clarified ultrasound requirements and added optional x-ray of Barostim system to verify lead electrode placement. Allow for retesting/rescreening of subjects. Clarified that two BATwire implant attempts are permitted. In response to FDA design consideration, updated the number of enrollments to 300 to account for screen failures and the increased number of implanted subjects to be up to 100 in case of imbalances in baseline characteristic between BATwire and BeAT-HF.
D 1.0	03/24/2022	<i>Clinical Investigation Plan</i> revised to: • Increase total enrollment from 300 to 400 as total number implanted may go up to 100 and to adjust for current screen fail rate of 75% • Increase total number of sites from 25 to 35 as total number implanted may go up to 100 • Clarified the use of the carotid duplex ultrasound (CDU) and the Computerized Tomography Angiography (CTA). • Post implant / pre-discharge surgical evaluation defined and required to be done by a study physician according to the Pre-Discharge Worksheet • Clarified that vascular, cardiac thoracic or other surgeon may implant the Barostim device using the current open procedure. • Clarified that vascular or other surgeon credentialed at the study site to perform carotid artery repairs must be present during all implants in case of complications. • Updated statistical section to align with current SAP design consideration revisions. • Updated to include the new model 2104 IPG number, Model 9020 Programmer System and MRI Conditional Use IFU.
E 1.0	11/17/2022	<i>Clinical Investigation Plan</i> revised to: • Revise ENT surgeon to ENT clinician • Remove exclusion of BeAT-HF trial subjects being enrolled • Defined Interventional Cardiologist

ABBREVIATIONS AND ACRONYMS

Abbreviation	Full Text
ACC	American College of Cardiology
ACE-I	Angiotensin Converting Enzyme Inhibitors
AHA	American Heart Association
Ang II	Angiotensin II
ARB	Angiotensin Receptor Blockers
BAT	Baroreflex Activation Therapy
BeAT-HF	CVRx's Barostim System- <u>B</u> aroreflex <u>A</u> ctivation <u>T</u> herapy for <u>H</u> eart <u>F</u> ailure
BRS	Baroreflex Sensitivity
CABG	Coronary Artery Bypass Graft
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CDU	Carotid Duplex Ultrasound
COPD	Chronic Obstructive Pulmonary Disease
CRT	Cardiac Resynchronization Therapy
CSL	Carotid Sinus Lead
CSNS	Carotid Sinus Nerve Stimulation
CTA	Computerized Tomography Angiography
DIG	Digitalis Investigation Group Trial
DMC	Data Monitoring Committee
eGFR	Estimated Glomerular Filtration Rate
ePRO	Electronic Patient Reported Outcomes
ENT	Ear Nose Throat
ESC	European Society of Cardiology
FDA	Food & Drug Administration
GDMT	Guideline-directed Medical Therapy
HF	Heart Failure
HOPE4HF	CVRx's <u>H</u> ealth <u>O</u> utcomes <u>P</u> rospective <u>E</u> valuation for <u>H</u> eart <u>F</u> ailure with EF $\geq$ 40% Trial
HR	Heart Rate
HW	Hall Walk
IAC	Intersocietal Accreditation Commission
ID	Identification
IFU	Instructions for Use
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
LV	Left Ventricular
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
MANCE	Major Adverse Neurological and Cardiovascular Events
MLWHF	Minnesota Living with Heart Failure

Abbreviation	Full Text
MM	Medical Management
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
OR	Operating Room
PTCA	Percutaneous Transluminal Coronary Angioplasty
QoL	Quality of Life
RAAS	Renin-angiotensin-aldosterone system
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SNP	Sodium Nitroprusside
TIA	Transient Ischemic Attack
UADE	Unanticipated Adverse Device Effect

1. BACKGROUND

Heart failure (HF) is a major public health burden that is currently estimated to affect greater than 6.2 million patients in the United States.¹ In the United States alone, each year, more than 600,000 new cases of HF are diagnosed, and over one million hospitalizations occur due to this disease.² Annual cost to the U.S. healthcare system has been estimated at \$38 billion.²

New York Heart Association (NYHA) functional class III HF is associated with poor life expectancy, as the annual mortality rate is approximately 15 to 20% with five-year mortality approaching 50% despite standard-of-care therapy.^{3, 4} Death in these patients is an ever-present threat as they may experience acute decompensated HF or sudden cardiac death at any time.

Despite currently available drug and device therapies, 25% to 35% of patients with HF and a reduced left ventricular ejection fraction (LVEF) remain categorized in NYHA Class III.³ While these patients are not considered sick enough for advanced invasive HF therapies, such as a left ventricular (LV) assist device or cardiac transplantation, they exhibit moderate-to-severe HF symptoms, poor quality of life (QoL), and substantial limitation in exercise capacity. They are also at substantial risk for HF morbidity (e.g., HF hospitalization) and mortality, thereby incurring significant healthcare costs.⁴ Thus, there is a need for new therapies that can improve clinical status and outcomes in these patients. Symptoms and clinical outcomes of HF, irrespective of ejection fraction, include neurohormonal activation involving the sympathetic and renin-angiotensin-aldosterone (RAAS) systems, deranged sympathovagal balance associated with loss of parasympathetic tone and reduced heart rate variability, increased LV filling pressure, fluid retention, and exercise intolerance (Table 1). Therapies such as diuretics, β -blockers, angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), aldosterone blockers (spironolactone, eplerenone), hydralazine, nitrates and cardiac resynchronization therapy (CRT) have formed the cornerstone of HF therapy. Even though these therapies have proven beneficial in improving outcomes over the last several decades, five-year mortality rates and long-term prognosis remain unacceptably high. Recent clinical trials using novel therapies such as positive inotropes, synthetic natriuretic peptides, vasopressin antagonists, and cytokine modulators have yielded disappointing results.

One potential underlying cause of failed therapies is iatrogenic exacerbation of sympathetic activation. A provocative study of hypertensive patients⁵ demonstrated that a combination of diuretic and ARB therapy, despite normalizing systolic and diastolic blood pressures, persistently increased sympathetic activity as assessed by muscle sympathetic nerve activity. These effects have also been observed with acute infusion of dobutamine which resulted in improved cardiac output and relief of pulmonary congestion, but persistently elevated muscle sympathetic nerve activity.

HF prevalence has increased as the population has aged.⁶ Aging itself is known to increase sympathetic activity, reduce parasympathetic control of heart rate, and reduce baroreflex

sensitivity (BRS). Thus, patients may be naturally predisposed to be refractory to therapies that induce sympathetic activation. This notion is supported by a finding that depressed BRS is an independent predictor of outcome in systolic HF patients and is independent of the presence of a β -blocker.⁷ Such autonomic dysfunction has been demonstrated in essential and resistant hypertension patients and in patients with previous myocardial infarct, the most common causes of HF. In contrast to sympathomimetic drugs, a subanalysis of the DIG trial showed that low-dose digitalis improved rates of HF hospitalization and mortality in all HF.⁸ The putative benefits of digitalis, and its persistent use for centuries for the treatment of HF may be explained by studies that have demonstrated a connection between digitalis and increased traffic in the carotid sinus nerve and related afferents, apparently by increasing sensitivity of arterial and cardiopulmonary baroreceptors, the key modulators of autonomic tone and associated peripheral vascular effects including arterial and venous dilation. Thus, therapies which reduce sympathetic activity, such as those that modulate the baroreflex with concomitant vascular effects (Baroreflex Activation Therapy or BAT™), hold promise for the treatment of HF.^{9, 10}

Table 1: Common Physiologic Observations and Mechanisms by which Baroreflex Activation Therapy (BAT) may Confer Benefit

Physiologic Observation in HF	Mechanisms by which BAT has its effect
Reduced Cardiac Output	Arterial vasodilation, reduced central arterial stiffness
Cardiac Arrhythmias and Poor Heart Rate Control	Restored sympatho-vagal balance, arrhythmia suppression, left atrial remodeling
Elevated Sympathetic Nervous and Renin-Angiotensin-Aldosterone Systems	Inhibition of renin secretion, renal artery vasodilation, ↓renal artery stiffness, ↓plasma norepinephrine
Venous Congestion and Increased LV Filling Pressure	Reduced venous neural tone leading to increased venous capacitance; reduced proximal tubule Na and H ₂ O reabsorption, suppressed non-osmotic release of vasopressin
Myocardial Ischemia	Coronary artery vasodilation, LVH regression, ↓HR and myocardial energy demand
Exercise Intolerance	↓muscle sympathetic nerve activity, ↓arterial stiffness, improved peripheral blood flow
Pulmonary Hypertension	Decreased pulmonary vascular resistance and pulmonary artery stiffness
Obstructive Sleep Apnea	Reduced sympathetic tone, decreased carotid body sensitivity to hypoxia, reduced tension of upper airway smooth muscle

1.1. Historical Carotid Sinus Nerve Stimulation

In the mid-1960s, a controlled clinical trial was initiated by Eugene Braunwald and colleagues at the National Institute of Health to assess the effects of carotid sinus nerve stimulation (CSNS) in patients suffering from intractable myocardial ischemia and angina who were refractory to nitrate therapy and on maximum tolerated doses of β -blockers. Activation of the stimulator resulted in immediate cessation of pain and increased duration of exercise tolerance. Nine of eleven patients resumed normal daily activities and discontinued use of nitrates.^{11, 12} During the course of development of a Phase III trial, CABG surgery became widely available and thereby obviating the need for CSNS device therapy (E. Braunwald, personal communication).

Importantly, these studies have demonstrated that while CSNS therapy reduces sympathetic nervous system activity it does not eliminate the sympathetic nervous system response to periods of increased demand. Wallin demonstrated in microneurography studies that muscle sympathetic nerve activity could be recruited during CSNS therapy. Peters et al. in the 1980's demonstrated successful chronic hemodynamic responses to CSNS therapy over a period of six to ten years and showed that the response to CSNS was maintained during daily living conditions and exercise. Specifically, subjects' blood pressure and heart rate could be elevated during episodes of increased demand, such as exercise, compared to their resting values, with the additional benefit of increasing functional capacity. Thus, CSNS was able to modulate blood pressure of patients at rest and during exercise but did not negatively impact the body's ability to recruit sympathetic activity during periods of increased physiologic demand.^{13, 14}

1.2. Barostim Therapy

Building upon the early experience with CSNS therapy, an implantable medical device has been developed to electrically elicit the baroreflex through stimulation of carotid baroreceptors. The CVRx Barostim System, which provides Barostim therapy, resembles a pacemaker system, consisting of a pulse generator implanted in the pectoral region of the chest and a carotid sinus lead which is connected to the pulse generator via flexible wires and to the carotid sinus by an electrode with an insulative backer.

BAT is a neuromodulation therapy that activates the baroreceptors and triggers the body's main cardiovascular reflex, thereby addressing the underlying causes of the progression of HF. By activating the baroreceptors in the wall of the carotid artery, BAT is able to stimulate the afferent and efferent pathways of the autonomic nervous system. The brain responds to BAT by modulating efferent pathways, which relaxes the blood vessels, slows the heart rate and reduces fluid in the body via improved kidney function.

BAT also works to reduce the load on the heart by decreasing arterial resistance, thereby improving the heart's ability to pump blood to the tissues. The increase in parasympathetic tone and decrease in sympathetic drive results in the restoration of autonomic balance, which can improve cardiac structure and function. The effects are dose-dependent and can be titrated to meet the needs of each patient through interactive device programming.

1.3. BAT Randomized Control Clinical Trials

Pre-clinical and small human studies were completed to demonstrate the mechanism of action of BAT.^{15, 16, 17, 18, 19} The success of these studies provided the evidence needed to complete larger randomized studies. Two randomized control clinical trials evaluated the effectiveness and safety of Barostim NEO. The Phase II HOPE4HF and Phase III BeAT-HF clinical trials are described below.

1.3.1. Phase II HOPE4HF Trial

The Phase II HOPE4HF Trial evaluated the safety of Barostim NEO and its effectiveness in improving symptoms in patients suffering from chronic HF. The trial included 146 patients randomized to two groups: 74 patients received Barostim therapy (BAT group) and guideline-directed medical therapy (GDMT) and were compared to 70 patients maintained on GDMT (Control group). Patients with NYHA functional class III HF and ejection fractions <35% on chronic stable GDMT were enrolled in the study.

The event-free rate of all system- and procedure-related major adverse neurological and cardiovascular events (MANCE) was 97.2% (lower 95% confidence bound 91.4%). The efficacy and hospitalization results are shown in Table 2.²⁰ The positive study results were used to obtain CE Marking approval.

Table 2: HOPE4HF Outcomes at Six Months in All Subjects

	BAT (n=74)	Control (n=70)	Difference
Measure	Mean±SE	Mean±SE	Mean±SE
Six-minute hall walk (meters)	59.6 [§] ± 14.1	1.5 ± 13.2	58.1 [†] ± 19.8
MLWHF Quality of life (points)	-17.4 [§] ± 2.8	2.1 ± 3.1	-19.5 [†] ± 4.2
New York Heart Class (% improved)	55% [§]	24% [§]	31% [‡]
LVEF (%)	2.4 [§] ± 1.1	-0.1 ± 1.3	2.5 ± 1.7
NT-proBNP (pg/mL)*	-69 (-504, 198)	129.5 (-67, 619)	-341.5 [‡] ± 189.8
# HF Hospitalizations	-0.49 [†] ± 0.2	-0.05 ± 0.2	-0.44 [†] ± 0.3 52% RR**
# of HF Hospital Days	-6.28 [†] ± 2.7	0.08 ± 1.7	-6.36 [†] ± 3.3 82% RR**

* Non-parametric analyses † p≤0.01; ‡ p≤0.05 §Within group p≤0.05

**RR=relative risk reduction adjusted for 12 months before enrollment HF hospitalizations based on the negative binomial model.

An important pre-defined subgroup analysis was performed on subjects who did not have a CRT device at baseline. Over two-thirds (68%) of the global randomized subjects did not have a CRT device at baseline. As shown in Table 3, compared to the Control group, the BAT group experienced clinically relevant and statistically significant improvements in the six-minute hall walk, MLWHF QoL, NYHA class, LVEF, and NT-proBNP.²¹ In addition, there is evidence that the number of days spent in a hospital for HF six months after commencing therapy compared to six months pre-therapy, was lower in the BAT group versus the Control group.

Table 3: HOPE4HF Outcomes at Six Months in Subjects with No CRT at Baseline

	BAT (n=47)	Control (n=48)	Difference
Measure	Mean±SE	Mean±SE	Mean±SE
Six-minute hall walk (meters)	85.5 [§] ± 20.5	3.6 ± 16.3	81.9 [†] ± 26.8
MLWHF QoL (points)	-21.6 [§] ± 3.6	3.5 ± 3.7	-25.1 [†] ± 5.2
NYHA class (% improved)	48% [§]	27%	21%
LVEF (%)	4.3 [§] ± 1.2	-0.1 ± 1.7	4.4 [†] ± 2.0
NT-proBNP (pg/mL)*	-97 (-504, 93)	116 (-74, 700)	318 [†] ± 274
HF Hosp Days 6M Pre/Post Randomization	-8.89 [§] ± 4.0	0.18 ± 2.2	-9.07 ± 4.7

* Non-parametric analyses

† p≤0.01; ‡ p≤0.05

§ Within group p≤0.05

In summary, the cohort of subjects in the BAT group who did not have CRT at baseline showed consistent improvement across efficacy endpoints. This is particularly evident when compared to the Control group, who demonstrated no improvement and even evidence of deterioration.

1.3.2. Phase III BeAT-HF Clinical Trial

The purpose of the Barostim NEO - Baroreflex Activation Therapy for Heart Failure (BeAT-HF) Trial is to develop valid scientific evidence for the safety and effectiveness of BAT with the Barostim NEO System in subjects with HF, defined as NYHA functional Class III or II (recent history of Class III) and LVEF ≤ 35% despite being treated with the appropriate HF guideline directed therapy, excluding subjects eligible for or actively receiving CRT. BeAT-HF is a prospective trial that enrolled subjects in the United States and the United Kingdom. Eligible subjects were randomized in a 1:1 ratio to receive BAT with an implanted Barostim NEO System in addition to guideline-directed medical therapy (GDMT) (BAT group) or to receive GDMT alone (Control group). The trial has two phases, the initial symptomatic endpoint phase and the long-term morbidity and mortality phase. The symptomatic phase endpoints included the

percent of subjects free of MANCE-related adverse events and baseline to six months change in 6MHW, MLWHF, QOL and NT-proBNP.

At an early, pre-planned interim analysis during the symptomatic phase, a large, important and clinically relevant population was identified. This population is characterized by having a core lab baseline NT-proBNP < 1600 pg/ml, and was subsequently confirmed with a prospective augmented dataset from an independent cohort. In summary, a total of 264 subjects were randomized that met this definition: 130 to BAT group and 134 to Control group. A total of 245 patients completed six months of follow-up.

The pre-market phase established safety with a MANCE-free rate of 97%, which exceeded the performance criteria of 85% with p-value < 0.001. Subjects treated with BAT, compared to the Control group had a significant 60-meter increase in 6MHW distance (p<0.001); 14-point improvement in MLWHF QOL score (p<0.001); and 25% reduction in NT-proBNP (p=0.004) after six months of treatment.²² In addition, the percent of subjects who improved at least one NYHA functional class was significantly higher in the device arm (65%) compared to the control arm (31%) with p<0.001. Results are shown in Table 4 below. These results confirmed that the Barostim NEO device can be used safely while producing positive symptomatic improvements, and that these improvements are validated by the objective evidence from the NT-proBNP improvement.

Table 4: BeAT-HF 6MHW, QOL, NYHA and NT-proBNP at Six Months in Subjects with NT-proBNP<1600

	BAT (n=120)	CONTROL (n=125)	Difference*	
Measure	Mean±SE (or %)	Mean±SE (or %)	Mean (95% CI)	p-value
Six-minute hall walk (meters)	48.6 ± 66.3	-7.9 ± 88.4	60.1 (40.3,79.9)	<0.001
MLWHF Quality of life (points)	-20.7 ± 25.4	-6.2 ± 20.1	-14.1 (-19.2, -8.9)	<0.001
NT-proBNP (% changed)**	-21.1% ± 0.4	3.3% ± 0.3	-24.6% (-37.6, -8.7%)	0.004
NYHA Class (% improved)	65%	31.2%	33.8%	<0.001
*For continuous endpoints, the difference is evaluated based on an ANCOVA model adjusting for the baseline value. **Results modeled parametrically on the log10 scale. Results are converted to percent change from baseline using $[10^{**(\log_{10}(a) - \log_{10}(b))} - 1] = (a - b)/b$. Standard deviation is on log10 scale.				

These positive BeAT-HF findings resulted in FDA PMA P180050 approval on August 16, 2019 with the following indication for use: “The Barostim NEO™ System is indicated for the improvement of symptoms of heart failure—quality of life, six-minute hall walk and functional status—for patients who remain symptomatic despite treatment with guideline-directed medical therapy, are NYHA Class III or Class II (who had a recent history of Class III), have a left ventricular ejection fraction $\leq 35\%$, a NT-proBNP < 1600 pg/ml and excluding patients indicated for Cardiac Resynchronization Therapy (CRT) according to AHA/ACC/ESC guidelines.”^{22, 23, 24}

The following link provides full access to the FDA approval documents:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P180050>

The trial continues with the post-market phase of collecting long-term morbidity and mortality data.

1.4. Conclusions

Results from the HOPE4HF and BeAT-HF randomized control clinical trials are consistent with results from basic science studies, suggesting that the mechanisms of action observed in animal models are relevant to clinical pathophysiology as well.

Both randomized trials demonstrated that the Barostim NEO System is safe and significantly improves functional status, exercise capacity and quality of life. These results are supported by the objective evidence of improvement in NT-proBNP. HOPE4HF also suggested that BAT may significantly reduce the rate of hospitalizations and mean number of days hospitalized for HF.

2. PURPOSE

The purpose of this clinical investigation is to develop valid scientific evidence for the safety and effectiveness of the Barostim System delivered by the BATwire Implant Kit (BATwire Kit) in subjects with heart failure. Subjects may be enrolled if they meet the FDA approved PMA indication for use for the Barostim NEO or Barostim NEO2 device: Subjects who remain symptomatic despite treatment with guideline-directed medical therapy, are NYHA Class III or Class II (who had a recent history of Class III), have a left ventricular ejection fraction $\leq 35\%$, a NT-proBNP < 1600 pg/ml and excludes patients indicated for Cardiac Resynchronization Therapy (CRT) according to AHA/ACC/ESC guidelines.^{22, 23, 24}

3. PROTOCOL

3.1. Study Summary

The BATwire Implant Kit Study is a prospective study of up to 400 subjects enrolled at up to 35 U.S. sites. Up to 100 subjects will be implanted with the Barostim System using the BATwire Kit after all screening is complete and all enrollment criteria are met. The study will evaluate the implant experience, safety and effectiveness of the BATwire kit. This is a single arm study comparing observed results to historical results using a non-inferior statistical methodology. A single center will not be permitted to implant more than 20% of the total number of implanted subjects.

Up to 30 subjects will be implanted during the initial safety evaluations. During these evaluations, implants will continue uninterrupted unless recommended otherwise by the DMC or FDA. Implanting will resume beyond the safety evaluations once the FDA approves expansion to implant additional subjects.

A subject may be enrolled in the study if they meet the indication for use (<https://cvrx.com/heart-failure-trial-results/>) and has provided written consent. Subjects will be implanted when they have met all enrollment criteria and after all Screening/Baseline measurements have been obtained. The device will be activated prior to being discharged. Follow-up visits will occur at 0.5, 1, 2, 3, 6- and 12-months post implant. Once the 12 month visit has been completed, the subject is withdrawn from the study and followed in a commercial setting. Figure 1 provides a schematic of the study design and Table 5 outlines the procedures to be conducted at each visit.

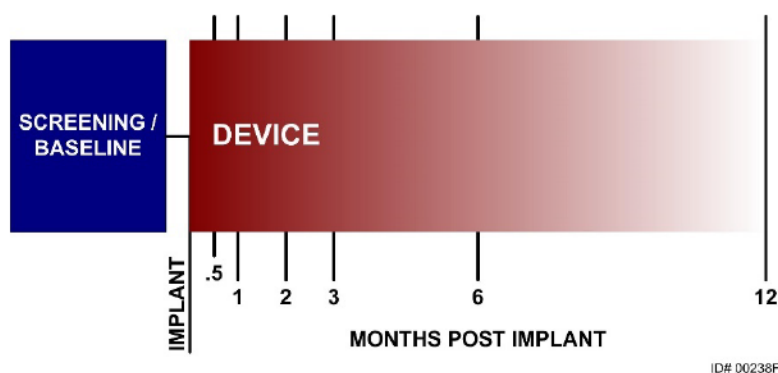


Figure 1: Study Schematic

Safety evaluations will be performed and submitted to the Data Monitoring Committee (DMC) and the FDA as described in Section 3.5.1.

The total study duration is anticipated to be approximately 2.5 years; however, the duration of an individual subject enrollment will depend on when he or she entered the study.

Table 5: Time and Events Schedule

Procedure			Months Since Implant					
	Screening / Baseline	Implant / Activation	0.5	1	2	3	6	12*
Subject Informed Consent	X							
Assess Enrollment Criteria	X							
Demographics/Medical History	X							
Physical Assessment	X	X	X	X	X	X	X	X
Subject Medications	X	X	X	X	X	X	X	X
Serum Biomarkers	X [†]							
Carotid Duplex Ultrasound (CDU) &/or Computed Tomography Angiography (CTA)	X [†]	X ^{††}				X [§]	X [§]	X
Echocardiogram	X [†]						X	X
Ultrasound		X						
Fluoroscopy		O				O	O	
X-ray of Barostim System		O				O	O	
Pre-Discharge Evaluation		X						
Evaluation by ENT Clinician	X [†]	X ^{††}		X		X ^{**}	X ^{**}	X ^{**}
Six-Minute Hall Walk	X [†]						X	
MLWHF Questionnaire	X [†]						X	
NYHA Functional Class	X [†]						X	
Implantable / Wearable Device Information***	X						X	X
Adverse Events	X	X	X	X	X	X	X	X
Device Programming Evaluation		X	X	X	X	X	X	O

X=Required; O=Optional

[†]Within 45 days of implant (60 days if a proctor is required)

^{††}If required post implant / pre-discharge (see Section 3.4.18)

[§]CTA must be done if required (see Section 3.4.10)

*The 12-month CTA will determine if follow-up continues past 12-months (see Section 3.4.33).

**If required (see Section 3.4.17)

***For subjects with an implantable or wearable device

3.2. Eligibility Criteria

Prior to enrollment (i.e. prior to signing an informed consent), in the investigator's opinion, the subject meets the FDA Indication for Use per the System Reference Guide, 900120-001 (https://www.cvr.com/wp-content/uploads/2020/07/900120-001A_BAROSTIM-NEO_Heart-Failure_Reference-Guide_US-Commercial.pdf).

3.2.1. Inclusion Criteria

To be eligible for this study, in addition to meeting the FDA Indication for Use, subjects must meet all of the following inclusion criteria:

1. Age at least 21 years and no more than 80 years at the time of enrollment.
2. Appropriate candidate for the surgery as determined by an evaluation from the implanting physician using a carotid duplex ultrasound (CDU) and/or a computed tomography angiography (CTA) (per Section 3.4.10) and a review of medical history (including existence of infections that may increase implant risk). Evaluation must confirm the following within 45 days of the Barostim implant (60 days allowed if a proctor is required):
 - Appropriate medical condition and medical history for implantation of the Barostim System AND
 - Anatomy that enables this implant procedure, with no vascular structures or orientations or neck anomalies that would be obstructive to the implantation path AND
 - The artery planned for the Barostim implant must have:
 - A carotid bifurcation below the level of the mandible AND
 - No ulcerative carotid arterial plaques AND
 - No carotid atherosclerosis producing a 30% or greater stenosis in linear diameter in the internal carotid AND
 - No carotid atherosclerosis producing a 30% or greater stenosis in linear diameter in the distal common carotid AND
 - Have had no prior surgery, radiation, or endovascular stent placement in the carotid artery or the carotid sinus region AND
 - Able to discontinue the use of antiplatelet drugs (e.g., aspirin) in advance of the procedure, if required.
3. Six-minute hall walk (6MHW) ≥ 150 m AND ≤ 400 m within 45 days prior to implant (60 days allowed if a proctor is required).
4. Serum estimated glomerular filtration rate (eGFR) ≥ 25 mL/min/1.73 m² using the CKD-EPI method within 45 days prior to the Barostim implant (60 days allowed if a proctor is required).
5. Body mass index ≤ 40 kg/m² within 45 days prior to the Barostim implant (60 days allowed if a proctor is required).
6. If female and of childbearing potential, must use a medically accepted method of birth control (e.g., barrier method with spermicide, oral contraceptive, or abstinence) and agree to continue use of this method for the duration of the study. Women of childbearing potential must have a negative pregnancy test within 14 days prior to the Barostim implant.

7. Subjects implanted with a cardiac rhythm management device that does not utilize an intracardiac lead, or implanted with a neurostimulation device, must be approved by the CVRx Clinical department.
8. At the end of screening and baseline, the subject still meets the Barostim Indication for Use.
9. Signed a CVRx-approved informed consent form for participation in this study.

3.2.2. Exclusion Criteria

If any of the following criteria are met, subjects are not eligible for this study:

1. Received cardiac resynchronization therapy (CRT) within six months of enrollment or is actively receiving CRT.
2. Any of the following contraindications:
 - Baroreflex failure or autonomic neuropathy
 - Uncontrolled, symptomatic cardiac bradyarrhythmias
 - Known allergy to silicone or titanium
3. Unstable ventricular arrhythmias.
4. Presence of baseline cranial nerve dysfunction at risk from cervical interventions on the carotid bifurcation determined by the Ear, Nose and Throat (ENT) examination.
5. Subjects with any surgery that has occurred, or is planned to occur, within 45 days of the Barostim implant.
6. Recent history (within 6 months of implant) of significant and uncontrolled bleeding.
7. Known and untreated hypercoagulability state.
8. An inappropriate study candidate as evidenced by:
 - Solid organ or hematologic transplant, or currently being evaluated for an organ transplant.
 - Has received or is receiving LVAD therapy or chronic dialysis.
 - Current or planned treatment with intravenous positive inotrope therapy.
 - Primary pulmonary hypertension.
 - Severe COPD or severe restrictive lung disease (e.g., requires chronic oral steroid use or home oxygen use).
 - Heart failure secondary to a reversible cause, such as cardiac structural valvular disease, acute myocarditis and pericardial constriction.
 - Clinically significant cardiac structural valvular disease.

- Unable or unwilling to fulfill the protocol medication compliance and follow-up requirements, for reasons including but not limited to an unresolved history of alcohol or substance abuse or psychiatric disorder.
 - Active malignancy.
 - Any other serious medical condition that may adversely affect the safety of the participant or validity of the study, in the opinion of the investigator.
 - Life expectancy less than one year.
9. Any of the following within 3 months prior to the Barostim implant.
- Myocardial infarction
 - Unstable angina
 - Percutaneous coronary intervention (e.g., CABG or PTCA)
 - Cerebral vascular accident or transient ischemic attack
 - Sudden cardiac death
 - Surgical cardiac intervention (e.g., cardiac ablation, valve replacement)
10. Enrolled and active in another (e.g., device, pharmaceutical, or biological) clinical study unless approved by the CVRx Clinical department.

3.3. Visit Windows

The following are allowable date ranges for each study visit.

Time Point	Date Ranges
Screening / Baseline	Date of visit(s)
Implant / Activation (0)	Within 120 days from Date of Informed Consent
0.5 Month	14 days post implant $\pm$ 7 days
1 Month	30 days post implant $\pm$ 7 days
2 Months	60 days post implant $\pm$ 15 days
3 Months	90 days post implant $\pm$ 15 days
6 Months	180 days post implant $\pm$ 30 days
12 Months	365 days post implant $\pm$ 30 days

3.4. Procedures

3.4.1. Equipment, Instrumentation and Support

Commercially available products:

1. Carotid Sinus Lead (CSL)
2. Implantable Pulse Generator (IPG)
3. Programmer System

CVRx will provide the following:

1. BATwire Implant Kit (preloaded with CSL)
2. BATwire Implant Kit Instruction for Use
3. Barostim Instructions for Use
4. All required forms and agreements
5. Shipping materials to return devices and study data
6. Protocol, implantation and device operation training
7. Field support for implants and follow-ups as available
8. Template for subject identification cards

The Participating Institution will provide:

1. Expertise in the care and management of subjects with heart failure
2. Equipment and expertise for Barostim CSL and IPG implantation, which includes equipment and facilities capable of immediate airway control by anesthesia and open surgery by a surgeon.
3. IAC vascular testing accreditation or equivalent with carotid duplex ultrasound imaging apparatus and expertise in assessing carotid sinus patency and anatomy.
4. Equipment and expertise in using CTAs and portable ultrasound to assess carotid sinus patency and anatomy.
5. Optional: Equipment and expertise to perform fluoroscopy and X-ray.
6. Capabilities and facilities to collect all required data.

3.4.2. Investigator Certification

CVRx certifies that all investigators participating in this study will fully execute the CVRx Investigator Agreement for the BATwire Study and that the BATwire Kit will not be provided to any investigator prior to the receipt of the signed agreement and the appropriate implanting team has been established, including

the implanting physician and vascular or other surgeon credentialed to perform carotid artery repairs.

3.4.3. Training

The implanting physician will be a trained electrophysiologist, vascular surgeon, cardiac thoracic surgeon, other Barostim implanting surgeon, or interventional cardiologist (defined as a physician trained on minimally invasive procedures that includes imaging and other diagnostic techniques in the coronary and carotid arteries) with expertise in ultrasound guided procedures. A vascular or other surgeon credentialed to perform carotid artery repairs is required to be present to assist if complications arise, and an anesthesiologist will be necessary to deliver proper anesthesia and airway management. The implanting physician, surgeon and anesthesiologist must be trained on the implant procedure, anesthesia, and Barostim System operation in order to implant the system via the ultrasound guided implant technique.

Specifically, the implanting physicians will be required to participate in at least one cadaveric implant to be trained for proficiency in:

- Using standard ultrasound to identify the carotid sinus and surrounding structure.
- Delivering and placing guidewire with ultrasound guidance
- Using the BATwire Implant Kit to map and place electrode at appropriate location

In addition, a CVRx-certified proctor must be present for at least the first two implants of the Barostim System using the BATwire kit.

3.4.4. Device Accountability / Handling and Storage

This study will utilize CVRx commercially available Implantable Pulse Generators (IPG). The Carotid Sinus Leads (CSL) will be the same as the commercially available lead but will be included in the BATwire Implant Kit. The BATwire Implant Kit will be labeled as Investigational and will require special handling and storage controls. The BATwire Implant Kit will be recorded by model number on a Device Accountability Log along with the serial number of the Carotid Sinus Lead included in the Implant Kit. In addition, the date received, date used (or attempted), subject ID, date returned to CVRx, date destroyed, and any comments will be recorded in the Device Accountability Log.

Upon conclusion of the study all unused BATwire study materials will be returned to CVRx.

3.4.5. Subject Enrollment Procedure

Subjects may be enrolled once, in the investigator opinion, the subjects meets the FDA Indication for Use. Subjects are considered enrolled in this study when they have signed the approved informed consent form.

If the inclusion and exclusion criteria that are evaluated during screening are not met, the subject should be excluded from the study and not implanted, **even if they have signed an informed consent form**. The investigator will inform the subject and the reasons for ineligibility will be captured within the database. All screen failures must be terminated from the study.

3.4.6. Informed Consent

3.4.6.1. Obtaining Informed Consent

Prior to enrolling in the study, the subject will review informed consent materials with the Principal Investigator or appointed designee. Both the subject and Principal Investigator, or appointed designee, will sign and date the approved study-specific Informed Consent Form. In order to obtain informed consent, each subject must be informed about the investigation, and must sign and date an agreement acknowledging that participation is voluntary. Documentation is required within the subject's medical record and should include enrollment date in the study.

3.4.6.2. Requirements for Informed Consent

CVRx will provide the recommended subject Informed Consent Form template. This informed consent document complies with applicable regulatory guidelines (21CFR Part 50 and the Declaration of Helsinki). The IRB for the study site may alter or amend the text as appropriate, **but the IRB and CVRx must approve the final text of the informed consent before subject enrollment can begin.**

After the information contained in the study-specific informed consent document has been reviewed with each subject, the subject and the investigator (or assigned person giving the consent) must sign and date the Informed Consent Form. A signed informed consent indicates the subject's willingness to participate in the clinical investigation prior to the subject's participation in the study.

The investigator will indicate that the informed consent has been obtained in the appropriate section of the database.

3.4.7. Screening / Baseline

During Screening / Baseline, the following procedures will be completed to properly assess the enrollment criteria:

1. Subject demographics and medical history
2. Physical assessment
3. Subject medications
4. Serum biomarkers performed at local laboratory within 45* days of implant
5. Carotid Duplex Ultrasound (CDU) and/or Computed Tomography Angiography (CTA) within 45* days of implant
6. Echocardiogram within 45* days of implant
7. Evaluation by an ENT clinician within 45* days of implant
8. Six-minute hall walk within 45* days of implant
9. MLWHF Questionnaire within 45* days of implant
10. NYHA Functional Class within 45* days of implant
11. Implantable / Wearable Device Information
12. Adverse events

*60 days is allowed if a proctor is required

3.4.8. Subject Demographics, Medical History, and Physical Assessment

At Screening / Baseline, demographic information will be collected, and the investigator will review and document the subject's general medical history and cardiovascular history. A physical assessment will be performed at Screening / Baseline and at each scheduled follow up visit, and will include, height (at screening), weight, blood pressure, heart rate and other measures (e.g. current or previous exposure to respiratory diseases like influenza and COVID-19). The physical exam should verify that the body mass index meets Eligibility Inclusion Criteria 5 in Section 3.2.1 above met.

3.4.9. Subject Medications

Information regarding prescribed heart failure medications will be collected at each scheduled visit. Subjects will be required to be on optimal, stable, guideline-directed medical therapy (GDMT) for the treatment of heart-failure. The GDMT should follow the AHA/ACC guidelines.²⁵ Subjects should remain on their prescribed medication and same dosing schedule for the duration of the study, unless investigators determine medically necessary changes are needed. This

includes anti-thrombotic and anticoagulant medication (refer to Section 3.4.26.2 for instructions regarding anti-thrombotic and anticoagulant medication before and during the Barostim implant). The reason for any medication change will be documented.

3.4.10. Carotid Duplex Ultrasound (CDU) / Computed Tomography Angiography (CTA)

Screening / Baseline

A carotid duplex ultrasound (CDU) evaluation may be used at Screening / Baseline to determine if the artery planned for the Barostim implant exceeds the maximum level of stenosis and/or meets the Eligibility Inclusion Criteria 2 in Section 3.2.1 above. A CDU assessment must be performed at a local laboratory/clinic. Requirements for the local lab are in Section 3.4.1, “The Participating Institution will provide” sub-section, item #3.

A computed tomography angiography (CTA) evaluation may be used at Screening / Baseline to determine if the artery planned for the Barostim implant meets the Eligibility Inclusion Criteria 2 in Section 3.2.1 above. A CTA must be performed if the CDU was not done in a certified vascular laboratory, there is >0% stenosis in the artery planned for the Barostim implant, or if the CDU cannot determine that all the Eligibility Inclusion Criteria 2 in Section 3.2.1 above are met.

Post Implant / Pre-discharge

Post implant / pre-discharge, based on the study physician’s opinion, if there is evidence of a clinically significant neck hematoma, carotid bruit, cervical thrill, other vascular injuries or abnormalities, or post-operative bleeding, then a CTA must be performed prior to discharge.

Three and Six Month Follow-up

A CDU will be repeated at three and six months, unless the CDU is suboptimal, of non-diagnostic quality, or cannot be done in a certified vascular laboratory, then a CTA must be done.

Twelve Month Follow-up

A CTA will be used at twelve months to determine if a subject’s follow-up continues past 12-months (see Section 3.4.33).

Every effort should be made to have the same person perform the CDU or CTA for a given subject throughout the course of the study.

A copy of all images (e.g., DICOM) from the CDU / CTA must be sent to CVRx.

3.4.11. Echocardiogram

Echocardiogram measurements will be obtained at Screening / Baseline and during follow-up at the 6- and 12-month visits. The echocardiogram is performed at the site, there is no core laboratory. The echocardiogram must include at least the biplane and apical 4-chamber images.

A copy of all images from the echocardiography must be sent to CVRx.

3.4.12. Serum Biomarkers

Serum biomarkers will be taken at Screening / Baseline to assess heart failure status (NT-proBNP), chronic kidney disease status (eGFR), and a pregnancy test (if required) to ensure the eligibility of each subject (Eligibility Inclusion Criteria 4 & 6 in Section 3.2.1 above).

3.4.13. Ultrasound

Ultrasound is used during the implant procedure to enable non-invasive visualization of the lead and electrode while it is being delivered and deployed. If image capture is available on the ultrasound machine, then images should be taken to document delivery and deployment of the lead.

A copy of all images from the ultrasound must be sent to CVRx.

3.4.14. Fluoroscopy

Fluoroscopy is optional during the implant procedure to verify lead electrode placement. Fluoroscopy enables non-invasive visualization of the lead and electrode while it is being delivered and deployed. Images may then be taken to document electrode placement relative to flow within the artery as well as location relative to other anatomical landmarks. Additional optional follow-up fluoroscopy images at 3- and 6-months can then be taken to assess electrode movement relative to images taken at implant.

A copy of all images from the fluoroscopy must be sent to CVRx.

3.4.15. X-ray of the Barostim System

X-ray is optional during the implant procedure or pre-discharge to verify lead electrode placement. X-ray enables non-invasive visualization of the lead and electrode. Images may be taken to document electrode placement location

relative to other anatomical landmarks. Additional optional follow-up X-ray images at 3- and 6-months can then be taken to assess electrode movement relative to images taken at implant.

A copy of all X-ray images must be sent to CVRx.

3.4.16. Conventional Angiography

Conventional angiography (or CTA as defined in 3.4.10 above) must be performed post implant / pre-discharge, based on the study physician's opinion, if there is evidence of a clinically significant neck hematoma, carotid bruit, cervical thrill, other vascular injuries or abnormalities, or post-operative bleeding.

3.4.17. Evaluation by Ear Nose Throat (ENT) Clinician

The ENT clinician must be trained on the implant procedure and is required to be a sub-investigator in the study. The ENT clinician will evaluate if the subject is excluded due to Eligibility Exclusion Criteria 4 in Section 3.2.2 above. They will also document signs or symptoms of injury or stimulus of regional nerves. Such signs and symptoms might include facial palsy/paralysis, altered speech, altered sense of taste, respiratory constriction, stertorous breathing, excessive salivation, vomiting and/or regurgitation not associated with a gastro-intestinal disorder, altered sensory and motor function of tongue, altered sensory function of pharynx and oropharynx, or altered sensation in external auditory canal. The evaluation may include a laryngoscopy.

All subjects will have an evaluation by an ENT clinician at Screening / Baseline to check for any previously existing neurological deficit. The evaluation may use either an indirect laryngoscopy (using a mirror through the mouth) or a direct laryngoscopy with a scope.

The subjects may require an evaluation by an ENT clinician post implant if injuries are present as defined in Section 3.4.18 below.

The subject will also have an evaluation by the ENT clinician at 1-month post implant to evaluate for potential nerve or other ENT injuries. The evaluation includes a complete evaluation of cranial nerve dysfunction, including all cranial nerves at risk from cervical interventions on the carotid bifurcation, such as cranial nerves V, VII, IX, X, XI, and XII. The exam may include a laryngoscope and direct visualization of the vocal cords. The must be done with the Barostim therapy turned OFF (e.g., therapy programmed OFF or inhibited using a magnet).

If the 1-month ENT evaluation shows evidence of potential nerve damage, then quarterly ENT evaluations up to 12 months are required until resolved or it is determined to be permanent at 12 months. These exams may include a

laryngoscope. For injuries present at the 1-month visit that are related to cranial nerves IX and X, quarterly ENT evaluations are mandatory.

Every effort should be made to have the same ENT clinician perform the evaluation for a given subject throughout the course of the study.

3.4.18. Pre-Discharge Evaluation Post Implant

A study clinician, including implanters, vascular surgeons (or other surgeons credentialed to perform carotid artery repairs), ENT clinician or other investigators, will conduct a pre-discharge evaluation to assess the vascular, speech, swallowing and cranial nerves as described below. The evaluation must be done with the Barostim therapy turned OFF (e.g., therapy programmed OFF or inhibited using a magnet). The examination must be documented and include all evaluations as required on the Pre-Discharge Worksheet (750734-001).

Vascular assessment

Evaluate for the presence of a clinically significant neck hematoma, carotid bruit, cervical thrill, other vascular injuries or abnormalities, or post-operative bleeding. Based on the study physician's opinion, if there is evidence of any of these abnormalities or injuries from the implant procedure, then a CTA or conventional angiography must be performed prior to discharge. A vascular surgeon consult is recommended.

Specifically, the following will be evaluated:

- Does the subject have any vascular injury described above due to the implant procedure?
- Does the subject have any evidence of post-operative bleeding?
- Does the subject have any evidence of a clinically significant post-operative hematoma?

Speech assessment

Evaluate for difficulty speaking in a normal voice, a change in voice, difficulty with phonation or other speech issues related to the implant procedure. If any significant speech abnormalities from the implant procedure are present, a full evaluation by an ENT clinician that includes a laryngoscope is required pre-discharge or within 2 working days of discharge.

Specifically, the following will be evaluated:

- Ask the subject to assess their voice quality on a scale of 1-5, with 5 being their pre-implant voice. Did the subject assess their voice quality as a 2 or below?

- Ask the subject to say “ah” for at least 5 seconds (or equal to the phonation time prior to surgery). Is subject unable to maintain 5 seconds, or equal to pre-implant phonation, whichever is less?
- Ask the subject to say the first six months of the year with clarity (or with equal clarity from pre-implant). Is the subject unable to clearly speak these months?

Swallowing assessment

Subject must be observed swallowing before resumption of oral intake is allowed. Prior to discharge, the subjects must swallow liquids and solids without choking or aspiration. If subject is unable to swallow liquids or solids without choking or aspiration, a formal swallowing study (such as a test using barium) is required.

Specifically, the following will be evaluated:

Begin with #1 and only move to the next step if the subject passes the current step. To move to the next step, the subject must complete the current step without choking. The subject must also be able to say “ah” clearly after each swallow tested.

1. Dry swallow of saliva
2. Swallow 1 cracker (at least 1/2 teaspoon volume)
3. Swallow 1/2 teaspoon water
4. Swallow 1/2 ounce of water
5. Swallow a normal volume of liquids and solids (based on the subject’s regular diet)

Was the subject unable to complete steps 1-5 above without choking or aspiration?

Cranial nerve assessment

Evaluate for any dysfunction of the nerves listed below. If any significant cranial nerve dysfunction or abnormalities from the implant procedure are present, a full evaluation by an ENT clinician that includes a laryngoscope is required pre-discharge. The subject should not be discharged until the evaluation by the ENT clinician can be completed.

Specifically, the following will be evaluated:

Cranial Nerve V (Trigeminal Nerve)

1. Ask subject to open mouth. Any deviation to the left or right that was not present pre-implant?

2. Ask subject to move jaw side to side. Does subject have difficulty moving jaw to either side that was not present pre-implant?
3. Ask subject to clench their teeth. Does the subject feel any weakness on either side that was not present pre-implant?

Marginal mandibular branch of cranial nerve VII (Facial Nerve)

1. Ask the subject to sit and look straight ahead. Is there any eye droop, tremors, tics, lip corner droop, drooling, asymmetry, or expressionless face that was not present pre-implant?
2. Ask the subject to show their teeth while frowning. Are there deviations to one side that was not present pre-implant?

Cranial nerve IX (Glossopharyngeal Nerve) and Cranial nerve X (Vagus Nerve)

1. Ask subject to say “ah”. Did the soft palate fail to elevate or was there a deviation of the uvula to the right or left that was not present pre-implant?
2. Ask the subject to say “ahhhh” as long possible. Did the subject have any abnormal voicing, hoarseness, weakness or coughing that was not present pre-implant?

Cranial nerve XI (Accessory Nerve)

1. Ask the subject to maintain a turned head position against your hand while you try to push the head back to the midline. Did the subject have any weakness that was not present pre-implant?
2. Ask the subject to push their head forward against your hand while you push the head backwards. Was the subject unable to push their head backwards that was not present pre-implant?
3. Ask the subject to shrug their shoulders. Was the subject unable to do so in a symmetric manner that was not present pre-implant?

Cranial nerve XII (Hypoglossal Nerve)

1. Ask the subject to stick out their tongue. Was the subject unable to protrude their tongue past their lips, or was there any deviation that was not present pre-implant?
2. Ask the subject to move their tongue from side to side. Was there any inability to move to the left or right that was not present pre-implant?
3. Ask the subject to push their tongue against a tongue depressor. Was there any weakness that was not present pre-implant?

3.4.19. Six-Minute Hall Walk (6MHW)

A 6MHW will be performed at Screening / Baseline and at the 6 month visit. The Screening / Baseline 6MHW must meet Eligibility Inclusion Criteria 3 in Section 3.2.1 above. Subjects who do not complete the walk at Screening / Baseline are excluded. It is very important that each subject attempts to complete each 6MHW assessment. The reasons for inability to do the walk, or for stopping the walk early, will be collected.

Instructions for performing the 6MHW are provided in Appendix 1 Six-Minute Hall Walk. These instructions include the definition of a complete hall walk, and a clear and well defined script that provides site personnel with exact verbiage to use with the subjects during the test. The length of the corridor should be marked every 3 meters to provide an easy way to accurately measure the distance walked.

3.4.20. Minnesota Living With Heart Failure Quality of Life Questionnaire

The Minnesota Living with Heart Failure quality of life (MLWHF) questionnaire will be administered at Screening / Baseline and at the 6 month visit.

It is recommended that it is provided to the subject at the beginning of the visit prior to any subject interaction, in an effort to minimize the potential influence of healthcare providers. The questionnaire is to be completed during the visit and should not be sent home with the subject. Subjects should answer the questions without being influenced by others such as their spouse or family members.

The investigator or research coordinator will provide instructions on how to complete the questionnaire to the subject. If possible, the same clinician should instruct the subject throughout the course of the study. If the subject has questions regarding the questionnaire, the clinician should only discuss the mechanics of filling out the forms and not discuss questions. If it is not possible for the subject to self-administer the questionnaire, the investigator or designee may choose to read the materials to the subject and record their responses.

Instructions for performing the MLWHF questionnaire are provided in Appendix 2 Minnesota Living with Heart Failure Quality of Life Questionnaire.

3.4.21. New York Heart Functional Class Assessment

The NYHA class will be administered at Screening / Baseline and at the 6 month visit. The NYHA Class assessment at Screening / Baseline determines eligibility in addition to establishing a baseline value. The NYHA Class assessment will be completed by the PI or as delegated by the PI to a person qualified to perform the assessment. Every effort should be made to have the same person perform the assessment for a given subject throughout the course of the study.

3.4.22. Re-testing During Screening/Baseline

Each test or procedure required as part of the screening/baseline visit should only be done once. Requests for repeat testing during screening/baseline must receive prior approval from the CVRx Clinical department.

3.4.23. Implantable / Wearable Device Information

Information from an implantable or wearable device (e.g., CRM arrhythmia device, implanted pressure monitors, etc.) is collected from subjects that have an existing implanted/wearable device at Screening / Baseline, and at the 6-month and 12-month visit. Every attempt should be made to capture complete and accurate activity over the prior 6 months.

3.4.24. Adverse Event

At all visits, all new adverse events that occurred since the last visit should be reported (see Section 3.5). Any ongoing adverse event should be updated and evaluated to see if they have been resolved. If a hemispheric neurological event is confirmed (e.g., TIA, stroke, amaurosis fugax) and is related to the procedure or device, then brain imaging with computerized tomography angiography (CTA) that includes both the extra-cranial and intracranial arteries, along with a neurologic consultation should be performed.

3.4.25. Re-screening Subjects

Re-screening of subjects who previous failed the eligibility criteria may be permitted with CVRx Clinical department approval. If the CDU/CTA is within six months of implant, it does not need to be redone.

3.4.26. System Implantation Procedure Testing and Data

Once the subject has completed all Screening / Baseline measurements and has been determined to meet all eligibility criteria, the subject may be implanted. If a subject is undergoing a therapy utilizing a device with an electrical sensing channel, contact CVRx prior to the implant procedure.

If an implant is attempted using the BATwire Implant Kit, but is aborted for any reason, then the subject may have a re-attempt at the BATwire implant approach within 30 days of initial BATwire attempt. The decision for a re-attempt will be based on implanter's medical opinion and CVRx Clinical Department approval. If after the first or second BATwire attempt, it is determined that the BATwire approach is not possible, then at the discretion of the implanting physician the

subject may be immediately, or at any point in the future, be implanted using the commercially approved approach.

If the screening and baseline measurements are not within the window to implant as described in the time and events table due to the second implant attempt, these will not be considered deviations from the protocol, as the subject had the initial attempt within protocol defined window.

If the subject is not implanted with the device using the BATwire implant Kit, the subject will be followed for 30 days post attempted implant to assess any adverse events. Once the 30-day period is complete, the subject is withdrawn from the study.

3.4.26.1. System Implantation

All implanting physicians must be appropriately trained and proctored on system implantation, mapping and recommended anesthetic regimen in order to implant the Barostim System. The procedures for implanting physician training are described in Section 3.4.3.

The procedure will be performed unilaterally. It is recommended that the implanting physician place the carotid sinus lead on the right side; however, the lead may be placed on the left side if factors such as subject anatomy indicate that the left side would be preferable.

In some instances, an acute response may not be observed during the procedure. In these situations, the lead should be placed based on the best-mapped anatomical location. Often, this results in a sufficient chronic response.

Subjects must remain hospitalized for at least one overnight stay post-surgery to evaluate for complications.

In a continuous effort to reduce potential risks associated with the implantation of the Barostim System, the following restrictions are mandated:

- All subjects will have an endotracheal intubation during implant.
- Only a trained and proctored implanting physician may perform any part of the surgical procedure.
- A vascular or other surgeon credentialed at the study site to perform carotid artery repairs must be present during all implants in case of complications.
- If the subject has a prior cardiac rhythm management device implanted, testing should be completed during the procedure to

confirm that the Barostim System does not interfere with the therapy being delivered by the cardiac rhythm management device.

- Subjects on anticoagulation therapy should be managed according to the ACC/AHA/ESC Guidelines for the Management of Atrial Fibrillation.^{26, 27}
- The site should follow their standard discharge procedures, including evaluation of the subject for evidence of periprocedural strokes, bleeding and potential injury from the implant. In addition, a qualified study physician must perform and document a detailed exam to rule out any study related injuries as per Section 3.4.18. Evidence of a cranial nerve injury requires a formal consult by the ENT clinician that includes a laryngoscopy. Evidence of difficulty swallowing solids or liquids after the procedure requires a formal swallowing study (such as a test using barium) to rule out aspiration. Evidence of a clinically significant hematoma formation after the procedure requires a CT angiogram to rule out a vascular injury.

3.4.26.2. Anesthetic and Medication Management

The Goals of Anesthetic Management for the implant procedure are:

- Preservation of the carotid artery (sinus) baroreceptor sensitivity via the usage of anesthetic agents that minimally inhibit the baroreceptor reflex during electrode placement and testing.
- Avoidance of the administration of volatile anesthetics and minimization of the usage of intra-operative medications that may interfere with the baroreflex or cause hemodynamic instability until baroreceptor mapping and electrode placement are completed.
- Allowance of the prompt emergence of subjects in the operative theater at the conclusion of the surgical procedure.

It is generally recommended that subjects continue their preoperative therapy with beta-blockers and aspirin to minimize the potential risks of peri-operative stroke, or myocardial infarction. Subjects should be able to discontinue the use of antiplatelet drugs (e.g., aspirin) in advance of the procedure (see Section 3.2.1, Eligibility Inclusion Criteria 2).

Other medications that reduce blood pressure are to be withheld during the preoperative period. If the investigator determines that withholding these medications may compromise subject safety, intravenous nitroglycerin or nitroprusside may be administered to reduce pressure to levels no lower than those observed prior to medication withdrawal.

Physician judgement supersedes the following, but these are considerations for anticoagulation and antiplatelet therapy management and the Barostim implant:

- To reduce the risk of bleeding or hematoma at the surgical site, Warfarin (such as Coumadin) should be discontinued 5 days prior to implant.
- Dabigatran (such as Pradaxa) should be discontinued 4 days prior to surgery.
- Apixaban (such as Eliquis) and Rivaroxaban (such as Xarelto) should be stopped 48 hours prior to the implant procedure.
- In subjects with high thrombotic risk the implanting physician will determine if the subject will need bridging of the anticoagulation therapy with low molecular weight heparin (LMWH, such as Lovenox or Arixtra).
- If the subject is on dual antiplatelet therapy, consider discontinuing Clopidogrel (such as Plavix) 7 to 10 days prior to the implant procedure.
- Prioritize anticoagulation therapy risk-of-stroke over hematoma.

The management of anti-thrombotic and anti-coagulant medications done through the appropriate laboratory evaluations, as determined by the site, may include, but is not limited to, prothrombin time (PT), activated partial prothrombin time (aPTT), international normalized ratio (INR) or other coagulation factor assays.

3.4.27. System Replacement

The Implantable Pulse Generator (IPG) may need to be replaced during the study due to battery depletion. IPG replacements due to normal battery depletion will not be reported as adverse events. The battery lifetime of the IPG is dependent on a combination of device therapy settings and the lead impedance value as specified in the Barostim System Instructions for Use. The replacement procedure may be performed under local anesthesia.

3.4.28. Device Programming

The device programming evaluation may include a series of tests to evaluate the subject's response to various parameter settings. These tests evaluate the hemodynamic response to changes in pulse amplitude, pulse width, and pulse frequency. Refer to the System Reference Guide for specific ranges or limitations regarding programmed settings.

To ensure that the programmed settings are being evaluated relative to the subject's healing and post-surgical recovery, a device programming evaluation will be required as detailed in Table 5. A programming evaluation may or may not result in changes to the programmed settings.

If any changes are made to the programmed settings, the physician or delegated clinician should assess symptoms at rest and walking to ensure that in the physician's or delegated clinician's opinion the subject is not experiencing any adverse reactions to the device programming. If the subject is experiencing any adverse reactions, the device programming must be adjusted to alleviate any adverse reactions.

Programming decisions will primarily be evaluated through blood pressure and heart rate.

Measurements may be influenced by the surrounding environment and subject emotional status. As such, efforts should be made to provide an environment that is as quiet and stress free as practical. The number of representatives from the clinical site and sponsor should be limited to as few as possible when performing these assessments. However, at least one person at each programming session should be a clinician (physician, nurse, nurse practitioner or physician's assistant).

It is recommended that the subject demonstrate the following hemodynamic values using cuff measurements to begin making any programming changes:

- Subject is asymptomatic at rest
- Heart rate > 55 beats per minute
- Systolic blood pressure > 100 mmHg
- Diastolic blood pressure > 60 mmHg

For subject safety during the reprogramming procedure, assess symptoms and use cuff measurements to assess the hemodynamic values listed below. It is recommended that testing be stopped and return to the previous programmed settings or lower settings as necessary, at any time if:

- Subject is symptomatic at rest
- Heart rate < 50 beats per minute
- Systolic blood pressure < 90 mmHg
- Diastolic blood pressure < 50 mmHg
- Problematic tissue stimulation is noted

As the device programming adjustments are being conducted, non-invasive arterial blood pressure waveforms (optional), blood pressure, heart rate, and any observations (sensations, disturbances, etc.) may be obtained and recorded at each setting that is tested.

Transient bradycardia and/or hypotension is anticipated when making programming adjustments and should only be considered an adverse event if an intervention (beyond reprogramming) is required, or the event is associated with

an additional untoward effect. Likewise, transient electrical stimulation of non-vascular tissues is not considered an adverse event. Those events not considered to be adverse events should be noted on the case report forms.

The results of all programming evaluations will be reviewed with the clinician to determine final programming settings. Final programmed parameters will be selected that provide an acceptable hemodynamic response without posing a safety concern for the subject and without causing subject symptoms. After a subject has been programmed to receive therapy, reprogramming to lower therapeutic settings (including OFF) should be performed with care.

The subject will be discharged from the hospital with the device turned ON. CVRx strongly suggests subjects remain at the hospital for at least 2 hours post-programming for observation prior to being discharged. The clinician should also assess symptoms to ensure that in the physician's opinion the subject is not experiencing any adverse reactions to the device programming. If the subject is experiencing any adverse reactions, the device programming should be adjusted to alleviate any adverse reactions.

CVRx personnel will assist clinicians with programming of the device. CVRx personnel may have extensive interaction with subjects; however, this involvement must occur in strict compliance with the following guidelines:

- A designated and authorized clinician must be present for and approve all device programming. If the Investigator does not designate a clinician for device programming evaluations, the investigator will default as the clinician for device programming evaluations for the study.
- All routine (i.e., non-emergent) device programming must occur at the research site under the direction and supervision of the investigator or other designated and authorized clinician.
- It is permissible for the clinician to step out of the room while the device is programmed but the clinician should remain in the immediate vicinity.
- Except in an emergency situation, it is not permissible for device re-programming to occur at any off-site location (such as another clinician's office near the subject's home).

3.4.29. Subject Follow-Up

The total study duration is anticipated to be approximately 5 years; however, the duration of an individual subject enrollment will depend on when he or she entered the study.

Study visits will occur at 0.5, 1, 2, 3, 6 and 12 months post implant. When the 12-month visit is complete, the subject may transition to commercial care as described in Section 3.4.33.

3.4.30. Electronic Patient Reported Outcomes (ePRO)

Throughout the study, subjects may receive emails with a link from the database requesting them to complete surveys on their current health. The contact information will only be visible to the site. Questions may include: listing any recent hospitalizations or emergency room visits, any changes to medications, any recent illnesses, or current health status. The completed questionnaire will be visible to both the sponsor and site.

3.4.31. Discontinuation of Therapy

Circumstances may arise during the study requiring temporary or permanent discontinuation of therapy for a subject. This may include a serious adverse event, a concurrent illness or other medical condition where continued therapy would not be in the best interest of the subject, or subject's wish.

If the discontinuation is temporary, the reason for the discontinuation should be clearly noted in the subject's medical records.

3.4.32. Termination of Therapy

In general, careful consideration should be given to whether the device is turned off immediately or if therapy is gradually reduced over a period of time. It is important that each subject be adequately monitored during this transition period. If explantation of the device is required, it is recommended to wait at least 30 days following termination of therapy prior to explanting the device to allow for an assessment of subject's status. The investigator should discuss the options for either leaving the IPG in place or for explanting the IPG including the potential risks of each. It is recommended that the Carotid Sinus Lead should not be explanted, and the lead should be left implanted with the lead capped.

If the IPG is removed, the subject should be followed for at least 30 days post-explant for any possible adverse events. If the subject has any ongoing serious adverse events at this time, they should continue to be followed until resolution of these events or the subject's condition is stable. The final status of the IPG should be documented in the subject's medical records as well as in the study database. A study termination form should be completed.

3.4.33. Final Study Visit at 12 Months

At the 12-month visit, if the subject has any ongoing serious system-related adverse events they should continue to be followed for 30 days from the 12-month visit. After 30 days they should be withdrawn from the study and followed using standard medical care. Follow-up will continue beyond the 12-month visit if new

stenosis >40% is observed on the 12-month CTA until it is determined that the lesions progress, regress or stabilize. This follow-up may continue up to 60 months.

If the subject decides not to continue to receive therapy, please refer to Section 3.4.32, *Termination of Therapy*.

A study termination form should be completed indicating the “subject completed study per protocol” and the date of the final study visit.

3.4.34. Withdrawal of a Subject

A subject may be withdrawn from the study at any time by the investigator for a variety of reasons including, but not limited to, the subject not following study-related directions, or a serious reaction develops. A subject may also choose to voluntarily withdraw consent for the study or from receiving further study treatment at any time. Once a subject withdraws from the study they will be permanently excluded from participation and will not be allowed reenter the study.

The investigator should discuss the decision with the subject and clearly document the reason, date of discussion and who participated in the discussion along with the items discussed in the subject’s medical record.

If an implant is attempted using the BATwire Implant Kit, but is aborted for any reason, then the subject will be followed for 30 days post attempted implant to assess any adverse events. Once the 30-day period is complete, the subject is withdrawn from the study. At the discretion of the implanting physician, the subject may immediately, or at any point in the future, be implanted using a commercially approved approach.

3.5. Safety Evaluation

3.5.1. Safety Reporting

Safety evaluations will be submitted to the Data Monitoring Committee (DMC) and the FDA after the 5th, 10th, 20th and 30th subject implanted is followed for 30 days. The safety evaluations will include all relevant safety data available up to the 12-month follow-up visit, including CDU / CTA assessments. During these evaluations, implants will continue uninterrupted unless recommended otherwise by the DMC or FDA.

3.5.2. Adverse Event Definition

An adverse event is defined as any undesirable clinical occurrence that affects the health or safety of the subject. An underlying disease or symptoms associated with the underlying disease that were present at the time of enrollment is not reportable. However, any increase in the severity of the underlying disease or symptoms above the levels existing at enrollment is to be reported as an adverse event. If an adverse event leads to multiple outcomes that sequentially worsen, the worst adverse event is reported. For example, a hematoma leading to infection would be reported as an infection.

3.5.3. Adverse Event Reporting

Once a subject is enrolled, all adverse events must be reported until the subject is withdrawn, or the study is completed.

3.5.4. Adverse Event Relatedness

Investigators will be asked to assess the potential relationship of the adverse event to the Barostim System and/or to the implant. The following definitions will be used:

System-Related

- Related:** An adverse event that results from the presence or performance of the device or any other component of the system.
- Unknown:** An adverse event that cannot be determined to have a causal relationship with the device or any other component of the system.
- Not Related:** An adverse event that has been determined to not have a causal relationship with the device or any other component of the system.

Procedure-Related

- Related:** An adverse event that occurs due to the system implantation procedure. Events must start within 30 days of initial implant or device changeout.
- Unknown:** An adverse event that cannot be determined to have a causal relationship with the implantation procedure.
- Not Related:** An adverse event that has been determined to not have a causal relationship with the implantation procedure.

Some events may be classified as both system- and procedure-related, such as: arterial thrombosis, infection including explant, device migration, and hypotension.

3.5.5. Serious Adverse Event

A Serious Adverse Event is defined as an adverse event that led to death, or led to serious deterioration in the 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 or prolonged 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.

Clarification on SAEs:

- The term "life-threatening" in the definition above refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Permanent is defined as 12 months from implant
- Impairment must impact daily events and lifestyle for at least 3 months
- Prolonged hospitalization must include either an Intensive Care Unit stay or >48 hours prolonged stay
- Planned hospitalization for a pre-existing condition or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.
- An in-patient or prolonged hospitalization that did not require medical intervention is not considered a serious adverse event.

Note: All Serious Adverse Events (SAEs) must be reported to CVRx within 10 working days after the site first learns of the event.

3.5.6. Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect means "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, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

If an adverse event is determined to meet the definition of a UADE, CVRx will immediately conduct an evaluation. If a UADE that represents an unreasonable risk for subject health, or a product performance failure becomes apparent, immediate action will be taken and the appropriate authorities will be notified. The investigator will be notified of the results of this evaluation. All UADE must be reported to CVRx within 10 working days after the site first learns of the event, and must be reported to all investigators, FDA and IRBs.

3.5.7. Adverse Event Closure

For the purposes of this study, stabilization of the condition will constitute closure of the adverse event. For example, if a subject experiences a stroke resulting in paralysis, the event will be considered closed (by either “not resolved, no follow-up deemed necessary” or “resolved with residual effects”) when the subject’s condition is stable. The event will not be considered “ongoing” due to the paralysis.

3.5.8. Unavoidable Events

Events that are unavoidable and expected to occur with any surgical procedure of this type shall not be reported as adverse events. These include:

- Anesthesia related nausea/vomiting within 24 hours
- Intubation related transient throat irritation, voice change, or swallowing discomfort
- Low-grade fever within 48 hours
- Incisional pain within 72 hours
- Mild to moderate bruising/ecchymosis of surgical sites within 72 hours
- Sleep problems within 72 hours
- Back pain related to lying on table within 72 hours
- Mild swelling and/or drainage from incision within 48 hours
- Numbness at or adjacent to incisions that occur immediately post-procedure
- Pain/irritation/minor bleeding during removal of sutures
- Urinary retention immediately post-procedure with removal of the Foley catheter
- Possible constipation and/or dehydration that may occur within 72 hours post procedure

3.6. Endpoints

3.6.1. Primary Safety Endpoint: Freedom from Serious Adverse Events (SAEs) related to the implantation of the lead using the BATwire Implant Kit through 30 days post-implant

To demonstrate the safety of implanting the Barostim lead using the BATwire Implant Kit using all serious adverse events that are related to the BATwire lead implantation that occur between implant, or attempted implant, and 30 days post implant.

Hypothesis:

$$H_0: p_p \leq p_s - \delta$$

$$H_a: p_p > p_s - \delta$$

where p_p is the event free rate in subjects where the planned implant procedure uses the BATwire Implant Kit to place the lead and p_s is the event free rate in the BeAT-HF treatment arm subjects in the intended use population where the implant procedure used a surgical placement of the lead. A non-inferiority margin (δ) of 10% is specified to ensure that the event free rate is sufficiently comparable between an ultrasound guided and surgically placed lead and that only clinically acceptable outcomes lead to a conclusion of non-inferiority.

Primary safety endpoint events are adjudicated by the Adverse Event Committee (AEC) as described in the AEC charter.

Safety follow-up begins at the time of actual or attempted device implant. All subjects implanted using the BATwire Implant Kit or attempted to be implanted using the BATwire Implant Kit are included in this endpoint.

Analysis and Sample Size:**Analysis:**

- Farrington-Manning non-inferiority hypothesis test
- Non-inferiority margin = 10%
- Alpha = 0.05

Sample Size:

- Power > 80%
- Event-free rate = 96%
- Sample size = 62 subjects with an implant attempted

Summary:

If the one-sided p-value is less than 0.05, the null hypothesis will be rejected. This rejection criteria is equivalent to the lower bound of a one-sided 95% Farrington-Manning confidence interval for the difference in proportions being greater than -10%.

3.6.2. Primary Effectiveness Endpoint: Physical Function as Measured by 6 Month Change in Six-Minute Hall Walk

To demonstrate that treatment with the Barostim System implanted using the BATwire Implant Kit results in an improvement in 6MHW at 6 months that is

non-inferior to the improvement when implanting a Barostim System using a surgically implanted lead.

Hypothesis:

$$H_0: \mu_p \leq \mu_s - \delta$$

$$H_a: \mu_p > \mu_s - \delta$$

where μ_p is the mean improvement in 6MHW from baseline to 6 months in subjects where the implant procedure used the BATwire Implant Kit to place the lead and μ_s is the mean improvement in the BeAT-HF treatment arm subjects in the intended use population where the implant procedure was surgical placement of the lead. A non-inferiority margin (δ) of 30 meters is specified to ensure that the change in 6MHW is sufficiently comparable between an ultrasound guided and surgically placed lead and only clinically meaningful improvements in 6MHW distance lead to a conclusion of non-inferiority.

Analysis and Sample Size:**Analysis:**

- ANCOVA linear regression model
- Non-inferior margin = 30 meters
- Alpha = 0.025 (one-sided)

Sample Size:

- Power = 80%
- Standard deviation = 67 m
- Sample size = 60 subjects implanted

Summary:

The null hypothesis will be rejected if the lower bound of the two-sided 95% confidence interval for the difference between groups in mean change in 6MHW distance is greater than $-\delta$.

3.6.3. Ancillary Objectives

The following objectives will be evaluated for exploratory and supportive purposes. No formal hypotheses are provided.

3.6.3.1. Ancillary Objective 1: 6- and 12-Month Change in Echocardiogram Parameters

To describe the change at 6 and 12 months in various echocardiogram parameters.

This objective includes an evaluation of left ventricular ejection fraction. Across several historical cardiac resynchronization studies that included NYHA III subjects, the average difference between CRT and no CRT in LVEF improvement was approximately 2.6%.^{28, 29, 30, 31} The CRT average improvement was approximately 4.3%. The objective would be to demonstrate that the LVEF improvement with Barostim therapy implanted using the BATwire Implant Kit is consistent with the benefit observed in CRT.

3.6.3.2. Ancillary Objective 2: Describe Morbidity and Mortality Outcomes

To describe the following morbidity and mortality outcomes and combination of outcomes using rates and days alive and free of morbidity:

- Hospitalization for worsening heart failure, LVAD, heart transplant, angina
- All-cause, cardiovascular and heart failure mortality
- Hospitalizations, occurrence and treatments for arrhythmias, such as atrial fibrillation, atrial flutter, ventricular fibrillation, ventricular tachycardia

3.6.3.3. Ancillary Objective 3: Implantation Technique

To describe the outcomes of delivery and fixation of the lead via the BATwire Implant Kit. These will include: Guidewire delivery and placement under ultrasound guidance, dilation of tissue via the BATwire Delivery Tool, mapping of electrode position, lead electrode placement verification, intraoperative therapy response, and lead impedance.

3.6.3.4. Ancillary Objective 4: 6-Month Change in Minnesota Living with Heart Failure Quality of Life Questionnaire

To describe the mean change in points in the MLWHF questionnaire.

3.6.3.5. Ancillary Objective 5: 6-Month Change in NYHA Class

To describe the percent of subjects who improve in NYHA Class.

3.6.3.6. Ancillary Objective 6: Serious Adverse Events related to the Procedure Between Implant and 30 Days Post-implant

The incidence of procedure related serious adverse events occurring between implant and 30 days post-implant will be analyzed descriptively with frequency counts and percentages. All implanted and attempted to be implanted subjects are included in this endpoint.

3.6.3.7. Ancillary Objective 7: Serious Adverse Events related to the Procedure or Barostim System Between Implant and 6 Months Post-implant

The incidence of system or procedure related serious adverse events occurring between implant and 6 months post-implant will be analyzed descriptively with frequency counts and percentages. All implanted and attempted to be implanted subjects are included in this endpoint.

3.6.4. Testing for Superiority

In the event that non-inferiority is demonstrated for both primary endpoints, the endpoints will subsequently be tested for superiority. To account for multiplicity, a hierarchical testing procedure will be used with superiority testing for the primary effectiveness endpoint being conducted first. If superiority is demonstrated for the primary effectiveness endpoint, superiority testing will be performed for the primary safety endpoint.

3.7. Study Sample Size

Due to attrition, the study-wide sample size is driven by the primary effectiveness endpoint, which requires 71 subjects implanted in order to have 60 subjects implanted with valid six-minute hall walks at baseline and six months. Assuming 15% attrition for a valid six-minute hall walk, and the potential for a loss of statistical power due to an imbalance of baseline characteristics, up to 100 subjects will be implanted. Up to 400 subjects may need to be enrolled, assuming up to a 75% screen fail rate.

When approximately 57 subjects are implanted, which is 80% of the minimum sample size of 71, a sample size evaluation will occur. Adjustments in the number needed to implant will range from the minimum of 71 subjects up to a maximum of 100 subjects, and is determined by the observed differences, if any, in baseline characteristics between the BATwire and BeAT-HF subjects. The baseline characteristics to be evaluated are listed in the Statistical Analysis Plan and include:

- Age
- Gender
- Race
- Heart rate
- Systolic and diastolic blood pressure
- 6-minute hall walk distance
- History of coronary artery disease (CAD)
- Left ventricular ejection fraction (LVEF)
- History of myocardial infarction (MI)

- History of CABG
- History of PCI
- History of atrial fibrillation
- History of CKD

The Statistical Analysis Plan contains complete details on the endpoints, analyses, and sample size assumptions.

4. RISK ANALYSIS

4.1. Benefits

All subjects implanted in the study will receive nominal compensation for their time as well as reimbursement for their travel expenses. They will also receive medical care from physicians who are experts in the treatment of heart failure. They will be seen at frequent visits throughout the first 6 months and will continue to receive ongoing care throughout the duration of the study. The BATwire approach may simplify the CSL implant technique and is expected to improve infection control mitigations.

4.2. Risks and Minimization of Risks

It is anticipated that subjects implanted with a device will be exposed to operative and post-operative risks similar to related surgical procedures involving the neck and/or a pacemaker implant. These risks and potential risks of chronic device based baroreflex activation may include, but are not limited to:

- Stroke – a neurological deficit lasting more than 24 hours or less than 24 hours with a brain imaging study showing infarction
- Transient ischemic attack (TIA) – a neurological deficit lasting less than 24 hours without evidence of permanent cerebral infarction
- Systemic embolization – downstream obstruction of a blood vessel by migration of loosened intravascular plaque or clot
- Surgical, intubation or anesthetic complications
- Infection – the need for antibiotics or possible removal of the system
- Wound Complication – including hematoma (i.e., bruising and/or swelling)
- Blood vessels damage – including carotid artery rupture or hemorrhage (sudden and significant blood loss at a site of blood vessel rupture that may require urgent repair during the initial implant, reoperation or transfusion and hematoma compressing the airway)
- Pain – an unpleasant sensory experience
- Nerve Damage/Stimulation – including injury to or stimulation of Cranial, Marginal Mandibular, Glossopharyngeal, Recurrent Laryngeal, Vagus and

Hypoglossal Nerves (difficulty swallowing, numbness in head and neck, facial palsy/paralysis, altered speech, altered sense of taste, respiratory constriction, stertorous breathing, excessive salivation, dry cough, vomiting and/or regurgitation, altered sensory and motor function of tongue, altered sensory function of pharynx and oropharynx, altered sensation in external auditory canal), stimulation of extravascular tissue [muscle twitching (fasciculation), pain, tingling, oral sensations]

- Hypotension – a decrease in systolic and diastolic blood pressure below normal levels that may result in dizziness, fainting, and/or falls
- Hypoperfusion
- Cardiac arrhythmias
- Hypertensive crisis – uncontrolled rise in blood pressure
- Respiratory – including low oxygen saturation, respiratory distress, shortness of breath, airway compromise or nerve damage/stimulation during the procedure
- Tissue erosion/IPG migration – movement of device resulting in need for reoperation
- Injury to baroreceptors – an injury that results in baroreflex failure
- Fibrosis – replacement of normal tissue by the ingrowth of fibroblasts and the deposition of connective tissue
- Allergic Reaction
- General injury to user or patient – may be due to surgical procedure, device use, or interaction with other devices
- Need for reoperation – operation to explant/replace IPG or CSL(s) due to tissue damage, infection, and/or device failure
- Secondary operative procedure – An increase in the complexity and risk of secondary operative procedures of the neck due to scar tissue and the presence of prosthetic material implanted for this device.
- Unretrieved device/lead fragments
- Radiation risks due to CTA and or fluoroscopy – skin reddening, skin tissue injury and a small increased in cancer risk
- Exacerbation of heart failure
- Death

These risks can be minimized through use of strict aseptic technique, compliance with the study protocol and technical implant procedures, adherence to the guidelines for selection of subjects, close monitoring of the subject's physiologic status during the implant and follow-up procedures, and by promptly supplying CVRx with all pertinent information required by this protocol.

4.3. Data Monitoring Committee (DMC)

A Data Monitoring Committee (DMC) will provide independent oversight of the study. As part of this oversight, the DMC will ensure protocol adherence and subject safety.

The DMC will consist of experts from relevant clinical disciplines and will be independent in that they are not involved in the conduct of the study except through their role on the DMC and have no financial or other important connections to the CVRx or CVRx affiliates. CVRx will compensate members at reasonable and customary rates for all expenses associated with their DMC involvement.

4.4. Adverse Events Committee (AEC)

An Adverse Events Committee (AEC) will review and adjudicate adverse events per the AEC Charter. The definitions in the AEC charter will supersede any definitions in this protocol. An initial classification of the adverse event shall be obtained from data provided by the site on the Adverse Event Form. The AEC may reclassify an adverse event reported by the site.

The number and specialty of the members of the AEC are defined in the AEC Charter.

4.5. Clinical Event Committee (CEC)

A Clinical Events Committee (CEC) may adjudicate events such as hospitalizations and deaths. The primary role of the CEC is to adjudicate hospitalizations and deaths.

The number and specialty of the members of the CEC are defined in the CEC Charter.

5. DESCRIPTION OF DEVICE

5.1. Description of Barostim System

A complete description of the commercially available Barostim System is provided in the Barostim System Instructions for Use (IFUs), 900133-001 to -005. CVRx has recently added the Model 2104 Implantable Pulse Generator (IPG) and Model 9020 Programmer System to the commercially available devices for the Barostim System. Once the Model 2104 IPG (NEO2) and the Model 9020 Programmer are introduced into the BATwire Study, they may be labeled either as commercial or investigational since these devices are identical.

Note: In addition, the Barostim System has now been commercially approved for Magnetic Resonance Imaging (MRI) conditional use for added subject safety with specific instructions provided in MRI IFU 900133-004.

The BATwire™ Implant Kit is described in the BATwire Implant Kit Instruction for Use, 900126-001.

The Barostim™ System includes the following components:

- Barostim NEO™ Implantable Pulse Generator, Model 2102
- Barostim NEO2™ Implantable Pulse Generator, Model 2104
- BATwire Implant Kit, Model 1100 (see Section 5.2)
 - Includes Barostim Carotid Sinus Lead Models 1036 or 1037; and implant adapter
- CVRx Programmer System Model 9010 or 9020

The components of the Barostim System are shown in Figure 2.

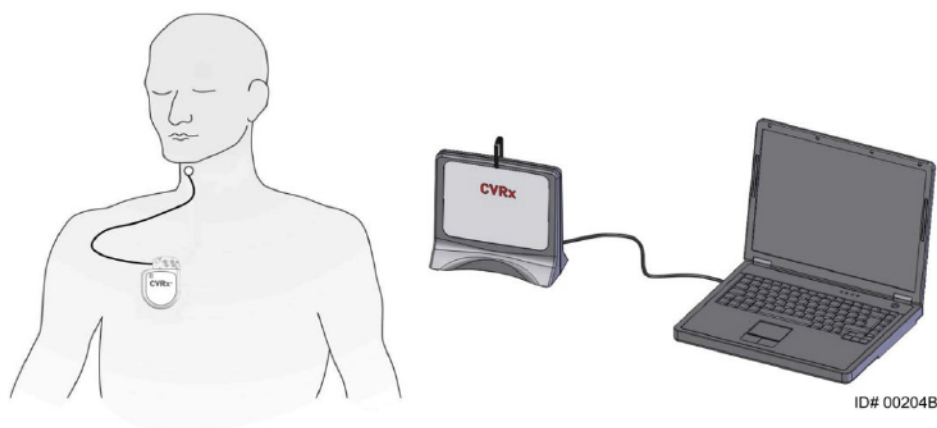


Figure 2: Barostim System

The Barostim NEO and Barostim NEO2 Implantable Pulse Generators (IPGs) are in a hermetic enclosure that contains the battery and circuitry. It provides control of, and delivers, the activation energy through the Barostim Carotid Sinus Lead (CSL) to the baroreceptors.

The CVRx Programmer System (Model 9010 or 9020) gives the physician an interface to the Barostim System IPGs allowing the physician to non-invasively control the method in which the Barostim NEO IPG delivers the activation energy.

5.2. Description of BATwire Implant Kit

The BATwire Implant Kit, Model 1100, tool set consists of two custom guidewires, a guidewire advancement tool, and a CSL delivery tool which delivers the Barostim CSL (see Figure 3 below).

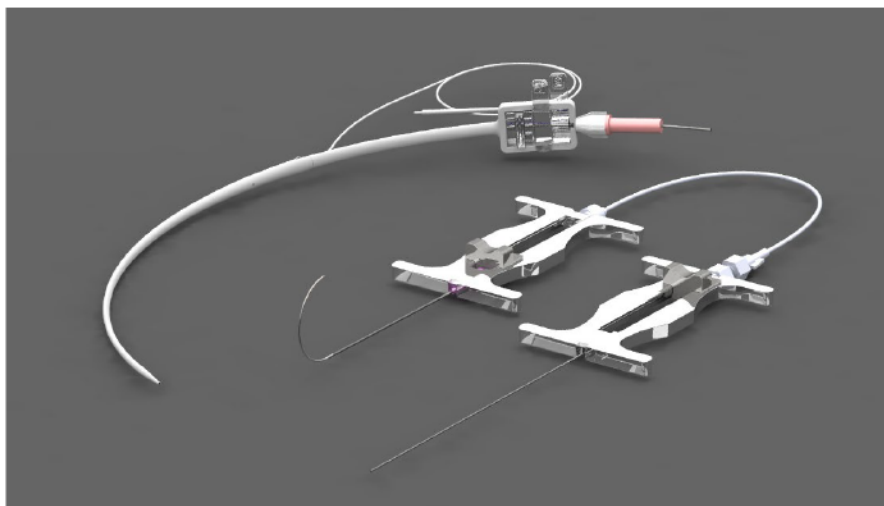


Figure 3: BATwire Implant Kit

5.2.1. Guidewire

The guidewire consists of medical grade nitinol which can be loaded into the guidewire delivery tool. A standard introducer needle is used to access and direct the guidewire through the skin and onto the surface of the carotid sinus at the carotid bifurcation. The nitinol guidewire is shape-set such that it moves towards the skin and away from the carotid bifurcation as it is advanced from the needle. The guidewire is provided in two sizes to allow for anatomic variation in patient population. These are distinguished by the different radius of curvature at the needle portion of the guidewire (0.5" or 0.75" radius). These are sized to address skin to carotid surface distance variation within a subject.

5.2.2. Guidewire Advancement Tool

The guidewire advancer tool is used to orient and advance the guidewire through the introducer needle. This tool ensures that the guidewire advances perpendicular to the carotid sinus and travels up through the skin.

5.2.3. CSL Delivery Tool

A custom CSL delivery tool slides over the nitinol guidewire, dilates the space around the guidewire, and carries the Barostim CSL along the guidewire path to the targeted implant location. The Barostim electrode is exposed on the posterior side of the delivery tool which allows mapping along the carotid sinus. Once the optimal location is identified, the delivery tool separates and deploys the Barostim CSL. Prior to separation of the delivery tool, the entire system can be removed.

6. MONITORING PROCEDURES

Each clinical site will be monitored to ensure that the study is conducted in full compliance with the study protocol, and in accordance with the FDA Guideline for the Monitoring of Clinical Investigations, Good Clinical Practices, and CVRx policy and procedures, and the CVRx Monitoring Plan.

Professionals qualified through training, education and experience will conduct the monitoring of the study. Contact CVRx for additional information on the person responsible for monitoring at the following address:

Clinical Research Department
CVRx, Inc.
9201 West Broadway Avenue North, Suite 650
Minneapolis, MN 55445

7. LABELING

The instructions for use (IFU) pertaining to this protocol are provided in the Barostim System IFUs, 900133-001 to -005, and the BATwire Model 1100 Instruction for Use, 900126-001. The product labels have been provided to FDA in the IDE application and are available upon request.

8. CONSENT MATERIALS

A copy of the informed consent form will be provided to subjects to obtain informed consent.

9. IRB INFORMATION

All investigational sites will be required to have IRB approval and investigator agreements approved before they will be allowed to enroll subjects into this study.

10. OTHER INSTITUTIONS

CVRx will only conduct the investigation at institutions that meet the requirements noted in Section 9 above.

11. RECORDS AND REPORTS

11.1. Investigational Records

The investigator is responsible for the preparation (review and signature) and retention of the records cited below. Records are subject to inspection and must be retained for a period of at least two (2) years (or according to local regulatory requirements) after the investigation is terminated or the date that the records are no longer required for purposes of supporting publications.

- All correspondence which pertains to the investigation
- Subjects' case history records, including: signed subject informed consent form; *all* relevant observations; observations of adverse device events; medical history; CSL application data (i.e., completed CVRx Case Report Forms); documentation of the dates and reasons for any deviation from the protocol
- Copies of Case Report forms and Clinical data
- Signed Investigator Agreement and recent curriculum vitae, both of which also must be submitted to CVRx
- IRB Approval and discourse documentation. A copy of the IRB Approval must be submitted to CVRx.
- In addition to sending to CVRx, a copy of all study images (e.g., CDU / CTA, echocardiogram and fluoroscopy (if applicable)) must be maintained in the subject's record.

11.2. Investigator Reports

Table 6: Investigator Reports

Report	Submit To	Description
Unanticipated Adverse Device Effects (UADE)	IRB (as applicable) & CVRx	UADEs must be reported to CVRx within 10 working days after the site first learns of the event.
Serious Adverse Events (SAE)	CVRx	SAEs must be reported to CVRx within 10 working days after the site first learns of the event.
Withdrawal of IRB Approval	CVRx	Notification within five working days
Progress Report	CVRx, IRB	Periodic report detailing the progress of the study, occurring at least annually.
Deviations from Investigational Plan	IRB & CVRx	Report of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Notification within five working days.

11.3. CVRx Records

CVRx will maintain the following records:

- All significant correspondence which pertains to the investigation
- Signed investigator agreements and curriculum vitae
- System/procedure related Adverse Device Events and complaints
- All case report forms, including samples of subject informed consents, submitted by the investigator; investigational plan and report of prior investigations
- Hospital staff training and study visit reports
- CVRx will own and store the clinical data generated under this protocol.

- CVRx will own and store a copy of the images provided by the sites (e.g., CDU / CTA, echocardiogram and fluoroscopy)

11.4. CVRx Reports

Table 7: CVRx Reports

Report	Submit To	Description
Unanticipated Adverse Device Effects (UADE)	Investigators, IRB (as applicable), & FDA	Notification within ten working days after the sponsor first learns of the event.
Withdrawal of IRB Approval	Investigators, FDA, & IRB	Notification within five working days after the sponsor first learns of the event.
Withdrawal of FDA Approval	Investigators & IRBs	Notification within five working days after the sponsor first learns of the event.
Progress Report	FDA	Periodic report detailing the progress of the study (as required).
Annual Report	FDA & Investigators	Report detailing the annual progress of the study.
Final Report	FDA, Investigators, & IRB	CVRx will notify the investigator(s) within 30 working days of the completion or termination of the investigation. The investigators will in turn inform their IRB/EC. A final report will be submitted to the investigator(s) after completion or termination of this study as specified by the country regulatory authority or regulations. The investigator should confirm the receipt of the final report composed by CVRx.

12. CONTACT INFORMATION

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Appendix 1. Six-Minute Hall Walk

The Six-Minute Walk Test should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface. The walking course must be 30 m in length. The length of the corridor should be marked every 3 m. The turnaround points should also be marked.

These instructions are consistent with the American Thoracic Society Guidelines for the Six-Minute Walk Test.³²

Subject Preparation

- Comfortable clothing should be worn.
- Appropriate shoes for walking should be worn.
- Subjects should use their usual walking aids during the test (cane, walker, etc.).
- The subject's usual medical regimen should be continued.
- A light meal is acceptable before early morning or early afternoon tests.
- Subjects should not have exercised vigorously within 2 hours of beginning the test.
- A "warm-up" period before the test should not be performed.
- The subject should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate.

Conducting the Test

Instruct the subject as follows:

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

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

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

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

Start now, or whenever you are ready."

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

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

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

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

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

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

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

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

If the subject stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. The subject may be allowed to rest sitting or standing, as they prefer, but they must complete the test by walking after resting. If the subject stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue) the test is considered incomplete. Note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

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

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

Appendix 2. Minnesota Living with Heart Failure Quality of Life Questionnaire

Instructions for Use

1. Patients should respond to the questionnaire prior to other assessments and interactions that may bias responses. You may tell the patient that you would like to get his or her opinion before doing other medical assessments.
2. Ample, uninterrupted time should be provided for the patient to complete the questionnaire.
3. The following instructions should be given to the patient each time the questionnaire is completed.
 - a. Read the introductory paragraph at the top of the questionnaire to the patient.
 - b. Read the first question to the patient - "Did your heart failure prevent you from living as you wanted during the past month by causing swelling in your ankles or legs"? Tell the patient, "If you did not have any ankle or leg swelling during the past month you should circle the zero after this question to indicate that swelling was not a problem during the past month". Explain to the patient that if he or she did have swelling that was caused by a sprained ankle or some other cause that was definitely not related to heart failure he or she should also circle the zero. Tell the patient, "If you are not sure why you had the swelling or think it was related to your heart condition, then rate how much the swelling prevented you from doing things you wanted to do and from feeling the way you would like to feel". In other words, how bothersome was the swelling? Show the patient how to use the 1 to 5 scale to indicate how much the swelling affected his or her life during the past month - from very little to very much
4. Let the patient read and respond to the other questions. The entire questionnaire may be read directly to the patient if one is careful not to influence responses by verbal or physical cues.
5. Check to make sure the patient has responded to each question and that there is only one answer clearly marked for each question. If a patient elects not to answer a specific question(s) indicate so on the questionnaire.
6. Score the questionnaire by summing the responses to all 21 questions. In addition, physical (items 2, 3, 4, 5, 6, 7, 12 and 13) and emotional (items 17, 18, 19, 20, and 21) dimensions of the questionnaire have been identified by factor analysis, and may be examined to further characterize the effect of heart failure on a patient's life.

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³² +ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-117.

CVRx®



Statistical Analysis Plan

Barostim NEO™

April 22, 2022

Confidential

Document Number: 360061-001 Rev. B v1.0

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1. INTRODUCTION

The purpose of this clinical investigation is to develop valid scientific evidence for the safety and effectiveness of the Barostim™ System delivered by the BATwire™ Implant Kit (BATwire Kit) in subjects with heart failure. Subjects may be enrolled if they meet the FDA approved PMA indication for use for the Barostim NEO™ device: Subjects who remain symptomatic despite treatment with guideline-directed medical therapy, are NYHA Class III or Class II (who had a recent history of Class III), have a left ventricular ejection fraction $\leq 35\%$, a NT-proBNP < 1600 pg/ml and excludes patients indicated for Cardiac Resynchronization Therapy (CRT) according to AHA/ACC/ESC guidelines.

The study is designed as a prospective, single-arm, multicenter, non-inferiority clinical investigation of Baroreflex Activation Therapy (BAT™) delivered using an ultrasound guided implanted lead versus a historical active control group that received BAT delivered using a surgically placed lead. The historical active control group consists of the 125 subjects that were implanted to receive BAT in the *Barostim NEO - Baroreflex Activation Therapy for Heart Failure (BeAT-HF)* pivotal trial that were in the Intended Use Population, a population that met the criteria of the approved device label.

Due to the lack of randomization, there is potential for differences in the patient populations to cause bias in the estimated difference in outcomes between the BATwire and BeAT-HF groups. Therefore, the study will use a two-stage “outcome-free” approach¹ to assess baseline differences and develop propensity scores, if needed, to control bias. Differences between the groups in baseline variables will be assessed without knowledge of outcome data. This SAP addresses stage 1 and specifies the historical control dataset, the endpoints, propensity score methods, blinding requirements for the stage 2 statistician, and sample size considerations.

Stage 2 of the design will take place once all baseline data has been collected. In stage 2, if important differences are observed (i.e., absolute standardized difference > 0.25) for more than 2 of 12 baseline variables to be balanced, propensity scores will be developed to achieve sufficient balance between the groups in baseline variables, conditional on the propensity score. In that case, the primary analysis for the primary endpoints is planned as a propensity score stratified analysis. In the event that there is not sufficient overlap in the propensity score distributions to include all subjects from BeAT-HF, contingency plans for alternative analyses are pre-specified for selection during the stage 2 design process. The derived propensity scores and balance achieved will be documented and outcome analysis plans finalized and submitted to FDA before outcome analyses commence. The outcomes are only made available to the analyst after completion of the stage 2 design. The balance threshold of 0.25 and the number of variables permitted to have residual imbalance (2 of 12) are informed by the 95% limits for the degree of balance expected in a randomized study with a comparable sample size.

This Statistical Analysis Plan (SAP) presents a detailed description of the statistical methods and procedures to be implemented for data analysis in the Barostim NEO™, G120010, *BATwire Implant Kit Study*. This SAP should be read in conjunction with the study clinical investigation plan (CIP) and case report forms (CRFs). This version of the SAP has been developed with respect to the *BATwire Implant Kit Study, Clinical Investigation Protocol (CIP) 360058-001*, revision D.

¹ Yue LQ, Lu N, Xu Y. Designing premarket observational comparative studies using existing data as controls: challenges and opportunities. *J Biopharm Stat.* 2014;24(5):994-1010.

Any revisions to the protocol or CRFs that impact the planned analyses may require updates to the SAP. In cases of discrepancy, the SAP supersedes the endpoint and statistical sections of the CIP. Deviations from this SAP will be considered only if there is strong statistical justification. Any deviations from these documents will be substantiated by sound rationale and documented in the final clinical report.

2. ANALYSIS POPULATIONS

2.1. Safety Population

This population consists of all subjects with a Barostim System implant attempt. An implant is considered attempted if the subject is in the operating room with anesthesia administered. Safety endpoint follow-up evaluation begins at the time of device implant or attempted implant.

2.2. Effectiveness Population

This population consists of all subjects implanted with a Barostim System using the BATwire Implant Kit (BATwire Kit). Efficacy endpoint follow-up evaluation begins at the time of device implant.

2.3. Per Protocol Population

This population consists of all subjects implanted with a Barostim System that meet eligibility criteria, are implanted using the BATwire Kit, and do not have any major deviations. Analyses limited to subjects in this patient population may be performed as sensitivity analyses to assess the potential impact of protocol deviations on the study endpoints.

3. PROPENSITY SCORES

Since the analyses planned for the BATwire study make comparisons to a historical comparison group, there is the potential for imbalance between baseline factors that may introduce bias. To limit the impact of bias on study results, a propensity score analysis will be performed if needed to adjust for observed imbalances in the BATwire and historical device subjects with respect to observed baseline characteristics if there is observed imbalance between the two groups.

A two-stage “outcome-free” approach is described in the sections below. The assessment of baseline balance is described in Section 3.1, the development of the propensity scores is described in Section 3.2, and the use of these propensity scores is described in Section 3.3.

3.1. Assessment of Baseline Balance

Baseline characteristics will be compared between BATwire and BeAT-HF subjects to determine if the groups are sufficiently balanced. Imbalance is defined as more than 2 of the pre-specified baseline variables having a between group absolute standardized difference greater than 0.25.

A bootstrap analysis of the BeAT-HF with subjects serving as a control group in the present study was performed to assess the size of difference expected due to sampling variability.

(chance) alone. Bootstrap samples matching the sample size of the BATwire group were drawn from the BeAT-HF group subjects. In 10,000 bootstrap samples, 95% of the sampled standardized differences were within approximately ± 0.25 for each variable. We adopt this threshold as providing balance for a baseline variable comparable to that expected with 95% confidence from a randomized trial with sample size matching the present study. A total of 10 out of 12 baseline variables are expected to be balanced with absolute standardized differences ≤ 0.25 with at least 95% probability in a randomized study. This conclusion is based on a binomial distribution with 12 observations (baseline variables) with each having a 5% chance of imbalance. The binomial probability is $< 5\%$ that more than 2 or more of the 12 baseline variables are unbalanced.

The standardized difference (Δ_{SD}) for continuous variables is

$$\Delta_{SD} = \frac{\bar{X}_p - \bar{X}_s}{\sqrt{(s_p^2 + s_s^2)/2}}$$

where $\bar{X}_p$ and $\bar{X}_s$ are the sample means and s_p^2 and s_s^2 are the sample variances in the BATwire and surgical (BeAT-HF) groups, respectively.

The standardized difference (Δ_{SD}) for dichotomous variables is

$$\Delta_{SD} = \frac{\hat{p}_p - \hat{p}_s}{\sqrt{[\hat{p}_p(1 - \hat{p}_p) + \hat{p}_s(1 - \hat{p}_s)]/2}}$$

where $\hat{p}_p$ and $\hat{p}_s$ are the proportion of subjects with the dichotomous baseline characteristic in the BATwire and surgical (BeAT-HF) groups, respectively. The absolute standardized difference is the absolute value of the standardized difference presented above. A weighted version of the standardized difference (Δ_{SDw}) may be calculated by substituting standard weighted estimates of sample means, standard deviations, and proportions in the formulas above (i.e., using the WEIGHT statement in SAS PROC FREQ and PROC MEANS to handle observation weights induced by full matching). For assessing balance across propensity score strata (quartiles), the average absolute standardized difference will be used:

$$\bar{\Delta}_{SD} = \sum_{i=1}^4 \frac{|\Delta_{SDi}|}{4}$$

where i indexes the 4 propensity score quartiles and Δ_{SDi} is the standardized difference calculated using data from subjects in the i^{th} propensity score quartile.

For stage 1, the 12 baseline factors to be balanced are listed below. These factors were identified as being predictive of variation in the outcome variables in the BeAT-HF subjects randomized to receive Barostim treatment, such that imbalance in these variables has the potential to bias estimated difference between BeAT-HF and BATwire groups in this study. All factors will be included in the propensity score model and will be assessed for balance regardless of whether they contribute to the final propensity score model.

- Age
- Gender

- Race (Caucasian vs non-Caucasian)
- Heart rate
- Systolic and diastolic blood pressure
- 6-minute hall walk distance
- History of coronary artery disease (CAD) and/or myocardial infarction (MI)
- Left ventricular ejection fraction (LVEF)
- History of CABG
- History of PCI
- History of atrial fibrillation
- History of CKD

3.2. Propensity Score Estimation

Propensity scores will be developed by a statistician who is blinded to the primary endpoint outcomes. A propensity score model will be developed by modeling the probability of being in the BATwire implant group as a function of the baseline variables (e.g., using logistic regression). The model may be optimized to minimize the absolute standardized difference in baseline variables between the BATwire and surgical (BeAT-HF) implant groups within propensity score quartiles. The estimated propensity scores will be fixed and documented prior to unblinding the outcome data.

3.3. Primary Endpoint Analysis Selection

The method used for the primary endpoint analysis will depend on whether there is observed imbalance in the baseline characteristics and, if imbalance is present, the steps that are necessary to achieve balance using propensity scores.

The diagram presented in Figure 1 shows an overview of the algorithm that will be used to select the final analysis method. Selection of the analysis method is part of the Stage 2 design process that will be finalized before outcome data is unblinded.

There are five steps in the algorithm that can lead to different analyses to choose from as detailed below:

1. If 2 or fewer baseline variables have absolute standardized differences greater than 0.25 between the BATwire and BeAT-HF subjects, a non-inferiority analysis that does not use propensity scores will be performed for both primary endpoints.
 - a. Details on the analysis method for the primary safety endpoint in this scenario are found in Section 4.1.3.
 - b. Details on the analysis method for the primary effectiveness endpoint in this scenario are found in Section 4.2.3.
2. If more than 2 baseline characteristics have an absolute standardized difference of more than 0.25 between the implant groups, propensity scores will be developed to balance the baseline characteristics within propensity score quartiles. If sufficient balance can be achieved (average absolute standardized difference ≤ 0.25 across

quartiles for at least 10 of 12 variables), a propensity score stratified non-inferiority analysis will be performed for both primary endpoints.

- a. Details on the analysis method for the primary safety endpoint in this scenario are found in Section 4.1.4.
 - b. Details on the analysis method for the primary effectiveness endpoint in this scenario are found in Section 4.2.4.
3. If no propensity scores can be identified that achieve balance while including all historical control BeAT-HF subjects, any BeAT-HF subjects with a propensity score outside a range of propensity score values that includes all BATwire subjects will be excluded. The range of propensity score values to include may be varied to identify a range that includes all BATwire subjects and achieves balance with BeAT-HF subjects within the range. This approach is consistent with the intent of the analysis to compare all BATwire subjects with appropriate historical controls. Propensity scores will be estimated on this subset of subjects and only these subjects will contribute to the final analysis. In this case, a propensity-score stratified non-inferiority analysis will be performed for both primary endpoints including all BATwire subjects and the subset of BeAT-HF subjects where balance was achieved.
 - a. Details on the analysis method for the primary safety endpoint in this scenario are found in Section 4.1.4.
 - b. Details on the analysis method for the primary effectiveness endpoint in this scenario are found in Section 4.2.4.
4. If no propensity scores that achieve balance through stratification into propensity score quartiles can be identified, a propensity score matching analysis that selects one or more BeAT-HF subject as a match for each BATwire subject will be employed. This is a fallback procedure in case balance cannot be achieved using stratification.

Propensity score strata may have residual imbalance due to an unequal propensity score distribution within one or more quartiles. In this case, a matching analysis will be employed as it has the potential to improve the degree of balance achieved while still including all BATwire subjects. As in #3 above, the range of propensity score values to include may be varied to identify a range that includes all BATwire subjects and achieves balance with BeAT-HF subjects within the range.

Propensity score full matching^{2,3,4,5} will be used for the propensity score matching analysis. Full matching is a sub-classification method that creates matched sets that contain at least one treatment group and one control group subject. This method has the advantage of having the capability of including all treatment and control

² Stuart EA. Matching methods for causal inference: A review and a look forward. Stat Sci. 2010;25(1):1-21. doi:10.1214/09-STS313

³ Rosenbaum PR. A characterization of optimal designs for observational studies. Journal of the Royal Statistical Society, Series B (Methodological) 1991;53(3):597–610.

⁴ Hansen, B.B. and Klopfer, S.O. (2006), 'Optimal full matching and related designs via network flows', Journal of Computational and Graphical Statistics, 15, 609–627.

⁵ Hansen BB. Full matching in an observational study of coaching for the SAT. Journal of the American Statistical Association. 2004;99(467):609–618.

subjects, an important consideration for observational studies without a large pool of control subjects to draw from for matching. Full matching is a modern matching method that avoids greedy matching of the most similar pairs and instead optimizes global criteria for the matched samples as a whole.

Full matching will be considered to have achieved sufficient balance if no more than 2 of 12 baseline covariates have an absolute standardized difference ($|\Delta_{SDw}|$) greater than 0.25.

Full matching analysis may be performed using the MatchIt package, which draws on routines from the optmatch package, in R statistical software⁶.

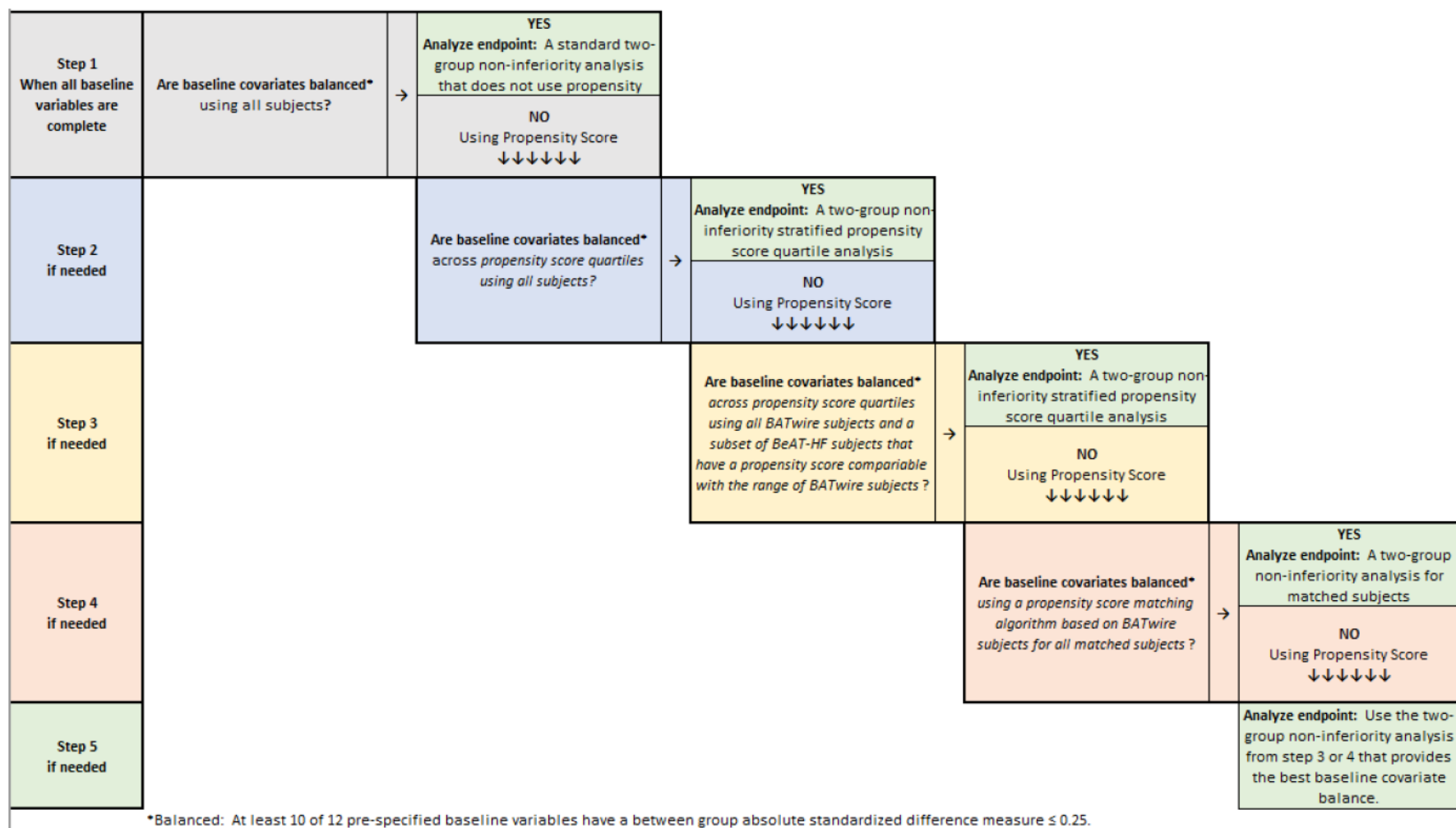
Full matching induces a weight for each observation in the analysis. Weighted analysis methods will be employed to account for the matching. Compared to inverse probability of treatment weighting (IPTW), full matching has been found to have more stable weights⁷. As with propensity score stratification, each subclass has a weight proportional to the number of subjects in the subclass in order to estimate the average treatment effect (ATE).

- Details on the analysis method for the primary safety endpoint in this scenario are found in Section 4.1.5.
 - Details on the analysis method for the primary effectiveness endpoint in this scenario are found in Section 4.2.5.
5. In the event that balance cannot be achieved through stratification or matching (e.g., if the propensity score distributions do not overlap), the method that achieved the best balance between baseline covariates across all baseline factors will be used for analysis and the degree of balance will be reported for each baseline factor. Better balance is defined as having a higher number of variables that meet the method-specific balance criteria. The method-specific standardized difference balance criteria are: $\sum_{i=1}^4 |\Delta_{SDi}|/4 \leq 0.25$ for stratification and $|\Delta_{SDw}| \leq 0.25$ for matching. In the event of a tie on the number of balanced variables, the average absolute method-specific standardized difference across the 12 variables is used as a tie breaker.

⁶ Hansen, B.B. and Klopfer, S.O. (2006), 'Optimal full matching and related designs via network flows', Journal of Computational and Graphical Statistics, 15, 609–627.

⁷ Austin PC, Stuart EA. The performance of inverse probability of treatment weighting and full matching on the propensity score in the presence of model misspecification when estimating the effect of treatment on survival outcomes. Stat Methods Med Res. 2017 Aug;26(4):1654-1670. doi: 10.1177/0962280215584401. Epub 2015 Apr 30. PMID: 25934643; PMCID: PMC5564952.

Figure 1: Primary Endpoint Analysis Choice Algorithm



4. STUDY ENDPOINTS AND HYPOTHESIS TESTS

The planned analyses will support a PMA supplement approving the BATwire Implant Kit for use with the Barostim System.

To support the evaluation of safety and efficacy of the BATwire Kit, the following safety and effectiveness endpoints will be evaluated for non-inferiority.

In the event that non-inferiority is demonstrated for both primary endpoints, the endpoints will subsequently be tested for superiority at the same one-sided alpha level as the non-inferiority tests. To account for multiplicity, a hierarchical testing procedure will be used with superiority testing for the primary effectiveness endpoint being conducted first. If superiority is demonstrated for the primary effectiveness endpoint, superiority testing will be performed for the primary safety endpoint.

4.1. Primary Safety Endpoint: Freedom from Serious Adverse Events (SAEs) related to the implantation of the lead using the BATwire Implant Kit through 30 days post implant

To demonstrate the safety of implanting the Barostim NEO lead using the BATwire Implant Kit via non-inferiority of the event free rate of Serious Adverse Events (SAEs) related to the implantation of the lead using the BATwire Implant Kit through 30 days post implant.

4.1.1. Statistical Hypothesis

The objective is to demonstrate that treatment with the Barostim System using the BATwire implanted lead results in a rate of SAEs related to the implantation of the lead that is non-inferior to the rate when using a surgically implanted lead. An equal event rate in the two groups is hypothesized.

4.1.2. Hypothesis Test

The statistical hypothesis test for the primary safety endpoint, stated in terms of a null and alternative hypothesis is:

$$H_0: p_p \leq p_s - \delta$$

$$H_a: p_p > p_s - \delta$$

where p_p is the event free rate in BATwire study subjects where the planned implant procedure is ultrasound guided placement of the lead and p_s is the event free rate in BeAT-HF treatment arm subjects in the intended use population where the planned implant procedure was surgical placement of the lead. A non-inferiority margin (δ) of 10% is specified to ensure that the event free rate is sufficiently comparable between an ultrasound guided and surgically placed lead and that only clinically acceptable outcomes lead to a conclusion of non-inferiority. This margin was chosen to account for the uncertainty and inherent variability of the event rate due to subject and procedure factors. A 10% margin maintains the consistency and degree of variation from the target that was used in the Phase III BeAT-HF event-free safety endpoint, as that study's single arm primary safety hypothesis test was based on a 10% margin from a target freedom from event rate.

The null hypothesis is rejected if the non-inferiority p-value is less than 0.05 or, equivalently, if the lower bound of the one-sided 95% confidence interval for $p_p - p_s$ is greater than $-\delta$.

Primary safety endpoint events are adjudicated by the Adverse Event Committee (AEC) as described in the committee's charter.

Determination of whether the serious adverse event is related specifically to the BATwire lead implantation is determined by the independent Adverse Event Committee (AEC). The committee determines the Type of each related adverse event:

- Type I: Related to the placement or presence of the carotid sinus lead, or the delivery of the therapy (including lead tunneling)
- Type II: Related to the implantation or presence of the IPG
- Type III: Related to the general surgical procedure
- Type IV: Due to the product labeling or training non-compliance

A list of events that should be considered related to the BATwire lead implantation are provided in the AEC Charter. This list includes all events observed in BeAT-HF within 30 days of implant that were considered in the assumptions for this endpoint:

- Infection at implant site (with or without explant)
- Stroke/TIA/CVA
- Prolonged intubation

Other events provided in the AEC Charter for consideration as related to the BATwire lead implantation are:

- Injury of carotid artery or surrounding structures
- Cranial nerve injuries
- Other vascular injury
- Need for operative or endovascular repair
- Death
- Prolonged hospitalization due to complication of lead implantation

4.1.3. Analysis Method – Without Propensity Scores

In the non-stratified test, the number of subjects (n_e) in the BATwire safety analysis population that have one or more adverse events that are adjudicated to have met the criteria for a lead-related SAE event within the first 30 days of study follow-up time (see Section 6.2) will be calculated.

The event-free proportion ($\hat{p}_p$) will be calculated as

$$\hat{p}_p = 1 - n_e/n_s$$

where n_s is the number of subjects in the BATwire safety analysis population. The hypothesis test will be evaluated with a one-sided Farrington-Manning non-inferiority hypothesis test with $\alpha = 0.05$.

This test may be performed with SAS code similar to the code presented below to compare the event free rate of primary endpoint events between subjects in the BATwire and surgical (BeAT-HF) implant groups.

```
proc freq data = BATwireSafety;  
  tables Group * SAELead30 /  
  riskdiff (noninf CL=FM method=FM margin=0.10 column=2)  
  alpha=0.05;  
run;
```

If the one-sided p-value is less than 0.05, the null hypothesis will be rejected. This rejection criteria is equivalent to the lower bound of a one-sided 95% Farrington-Manning confidence interval for the difference in proportions being greater than -10%.

In the non-stratified test, if the analysis population consists of 62 subjects with an attempted implant, then at least 58 subjects (94%) must be event-free through 30 days of study follow-up for this endpoint to be met based on the observed event free rate in BeAT-HF of 96% (120/125). Safety follow-up begins at the time of actual or attempted device implant. A one-sided 95% confidence interval for the difference in event-free rate through 30 days will be calculated using the Farrington-Manning method.

If a superiority test is performed, superiority will be demonstrated if the lower bound of the one-sided 95% Farrington-Manning confidence interval is greater than 0%.

4.1.4. Analysis Method – Propensity Score Stratified

If a propensity score stratified analysis is required, a stratified analysis will be performed with calculations presented below. The estimated difference in event-free rate will be estimated using code similar to that below:

```
proc freq data = BATwireSafety;  
  by ps_strata;  
  tables Group * SAELead30 /  
  riskdiff (noninf CL=FM method=FM margin=0.10 column=2)  
  alpha=0.05;  
run;
```

The riskdiff option results in an estimated difference ($\hat{\Delta}_j = \hat{p}_{pj} - \hat{p}_{sj}$) and its associated standard error ($\hat{\sigma}_{\hat{\Delta}_j}$) calculated by the Farrington-Manning method for each stratum. If a stratum has zero subjects in either group with a safety endpoint event, a small event rate of 0.1% is used for analysis instead of the observed value of 0% to prevent division by zero.

The overall estimated difference between groups across strata is given by

$$\hat{\Delta} = \frac{1}{4} \sum_{j=1}^4 \hat{\Delta}_j$$

which has a standard error of

$$\hat{\sigma}_{\hat{\Delta}} = \sqrt{\frac{1}{16} \sum_{j=1}^4 \hat{\sigma}_{\hat{\Delta}_j}^2}$$

The hypothesis test is passed if the lower bound of the one-sided 95% confidence interval given by $\hat{\Delta} - 1.645 \hat{\sigma}_{\hat{\Delta}}$ is greater than -10%. The one-sided non-inferiority p-value is given by $1 - \Phi^{-1}((\hat{\Delta} + 10\%)/\hat{\sigma}_{\hat{\Delta}})$.

If a superiority test is performed, superiority will be demonstrated if the lower bound of the one-sided 95% confidence interval is greater than 0%.

4.1.5. Analysis Method – Propensity Score Matching

The difference in proportions and one-sided 95% confidence interval will be estimated using a Farrington-Manning analysis with observations weighted using weights induced by propensity score full matching (weight proportion to the number of observations in the matched subclass).

This test may be performed with SAS code similar to the code presented below to compare the event free rate of primary endpoint events between subjects in the BATwire and surgical (BeAT-HF) implant groups using the weight statement to account for the weights induced by the full match.

```
proc freq data = BATwireSafety;

    weight fullmatchweight;

    tables Group * SAELead30 /

    riskdiff (noninf CL=FM method=FM margin=0.10 column=2)

    alpha=0.05;

run;
```

If the one-sided p-value is less than 0.05, the null hypothesis will be rejected. This rejection criteria is equivalent to the lower bound of a one-sided 95% Farrington-Manning confidence interval for the difference in proportions being greater than -

10%. If a superiority test is performed, superiority will be demonstrated if the lower bound one-sided 95% confidence interval is greater than 0%.

4.1.6. Analysis Population

The analysis population (denominator) is all subjects in the Safety Population defined in Section 2.

4.1.7. Sample Size

Evaluating the hypothesis test by comparing the one-sided 95% lower bound of the Farrington-Manning confidence interval to the non-inferiority margin of 10%, a sample size of 59 subjects with an attempted implant provides at least 80% power to reject the null hypothesis if the expected event-free rate is at least 96%. An expected rate of 96% matches the observed event free primary endpoint event rate in the BeAT-HF intended use population. The lowest observed event-free rate that would result in passing this study objective is approximately 94% (67/71), with the overall study sample size driven by the primary effectiveness endpoint.

The sample size calculation assumes an unstratified analysis approach and was calculated in PASS 2022 using an unconditional sample size calculation for a two-sample non-inferiority test of the difference in proportions. See Appendix I for documentation of the sample size calculation performed in PASS 2022.

To confirm that this sample size is sufficient to provide 80% power if a stratified propensity score analysis is required, propensity score quartiles were simulated by randomly allocating subjects to quartiles by arm. The sample size calculation using simulation was repeated using the stratified data analysis methods described in Section 4.1.4. The proportion of treatment and historical control subjects in each quartile was varied to assess sensitivity of the power of a stratified analysis to unequal counts of BeAT-HF and BATwire subjects in each stratum. See Section 5 for a summary of the impact of differing propensity score distributions in the BeAT-HF and BATwire groups. If the propensity score distribution is comparable in the two groups, the stratified analysis has the same sample size requirement as the unstratified analysis.

4.2. Primary Effectiveness Endpoint: Physical Function as Measured by 6 Month Change in Six-Minute Hall Walk

The six-minute hall walk (6MHW) test is used to assess functional capacity in a variety of conditions including heart failure. Baseline values of 6MHW have been shown to predict outcome in heart failure subjects with a reduced ejection fraction.⁸

4.2.1. Statistical Hypothesis

The objective is to demonstrate that treatment with the Barostim System using the BATwire implanted lead results in an improvement in 6MHW at 6 months that is non-inferior to the improvement when using a surgically implanted lead. An equal

⁸ Ingle L, Cleland JG, Clark AL. The long-term prognostic significance of 6-minute walk test distance in patients with chronic heart failure. *Biomed Res Int.* 2014;2014:505969.

improvement in the meters walked from baseline to six months in the two groups is hypothesized.

4.2.2. Hypothesis Test

The non-inferiority statistical hypothesis test for the 6MHW endpoint, stated in terms of a null and alternative hypothesis is:

$$H_0: \mu_p \leq \mu_s - \delta$$

$$H_a: \mu_p > \mu_s - \delta$$

where μ_p and μ_s are the mean improvement in 6MHW from baseline to 6 months in the BATwire and surgical (BeAT-HF) groups respectively. A non-inferiority margin (δ) of 30 meters is specified to ensure that the change in 6MHW is sufficiently comparable between a BATwire and surgically placed lead and only clinically meaningful improvements in 6MHW distance led to a conclusion of non-inferiority. In addition, a margin of 30 meters corresponds to 50% of the estimated effect size of 60 meters (treatment – control) in the BeAT-HF trial comparing BAT with medical management to medical management alone. The null hypothesis is rejected if the non-inferiority p-value is less than 0.025 or, equivalently, if the lower bound of a two-sided 95% confidence interval for $\mu_p - \mu_s$ is greater than $-\delta$.

4.2.3. Analysis Method – Without Propensity Scores

Section 3.3 describes the algorithm used to select the analysis method for the primary effectiveness endpoint.

If propensity score methods are not required, the means will be compared with an ANCOVA linear regression model that includes lead/implant group (BATwire vs BeAT-HF) and baseline 6MHW as a continuous covariate. The mean improvement in 6MHW will be compared between groups with a Wald test for the treatment group and the estimated difference and its confidence interval will be used to assess the non-inferiority hypothesis test. Success for this endpoint is determined by rejection of the null hypothesis.

Each subject's reduction in 6MHW is calculated as:

$$6MHW_{6 \text{ months}} - 6MHW_{\text{Baseline}}$$

In SAS (version 9.3 code) this model may be fit as follows:

```
proc genmod;
    model HW6D =group HWBL / dist=normal link=identity;
run;
```

where HW6D is the change in the 6MHW at 6 months, group is an indicator variable of BATwire versus BeAT-HF/surgical, HWBL is the baseline 6MHW.

The null hypothesis will be rejected if the lower bound of the two-sided 95% confidence interval for the difference between groups in mean change in 6MHW distance is greater than $-\delta$. Equivalently, a one-sided p-value will be calculated using

the Z test statistic: $Z = (\text{group} - \delta) / \text{se}(\text{group})$ where $\text{se}(\text{group})$ is the standard error of the estimate of the “group” parameter in the model. The Z test statistic will be used to calculate the non-inferiority p-value as the area under the standard normal density in the upper tail, greater than the observed test statistic. Rejection of the null hypothesis will indicate that the system using a BATwire lead implant results in a change in 6MHW distance that is non-inferior to the change in 6MHW distance observed with the system using a surgical lead implant.

If a superiority test is performed, superiority will be demonstrated if the lower bound of the one-sided 97.5% confidence interval is greater than 0 meters.

4.2.4. Analysis Method – Propensity Score Stratified

If a propensity score stratified analysis is required, a stratified analysis will be performed with calculations presented below. The estimated difference in mean change in 6-minute walk distance will be estimated using code similar to that below:

```
proc ttest data = BATwireEfficacy;
  by ps_strata;
  class Group;
  var HW6D;
run;
```

The estimated difference in mean change from baseline ($\hat{\Delta}_j = \hat{\mu}_{pj} - \hat{\mu}_{sj}$) and its associated pooled standard error estimate ($\hat{\sigma}_{\hat{\Delta}_j}$) calculated for each stratum.

The overall estimated difference between groups across strata is given by

$$\hat{\Delta} = \frac{1}{4} \sum_{j=1}^4 \hat{\Delta}_j$$

which has a standard error of

$$\hat{\sigma}_{\hat{\Delta}} = \sqrt{\frac{1}{16} \sum_{j=1}^4 \hat{\sigma}_{\hat{\Delta}_j}^2}$$

The hypothesis test is passed if the lower bound of the one-sided 97.5% confidence interval given by $\hat{\Delta} - 1.96 \hat{\sigma}_{\hat{\Delta}}$ is greater than -30 meters. The one-sided non-inferiority p-value is given by $1 - \Phi^{-1}((\hat{\Delta} + 30) / \hat{\sigma}_{\hat{\Delta}})$.

If a superiority test is performed, superiority will be demonstrated if the lower bound of the one-sided 97.5% confidence interval is greater than 0 meters.

4.2.5. Analysis Method – Propensity Score Matching

The difference in means and one-sided 97.5% confidence interval will be calculated using a weighted analysis version of the methods described in Section 4.2.3. This

analysis accounts for the propensity score full match by incorporating the weights induced by the full match (with each subclass given weight proportional to the number of observations in its subclass).

In SAS (version 9.3 code) this model may be fit as follows:

```
proc genmod;  
  
    weight fullmatchweight;  
    model HW6D =group HWBL / dist=normal link=identity;  
  
run;
```

Non-inferiority will be evaluated by comparing the confidence interval to the non-inferiority margin. If a superiority test is performed, superiority will be demonstrated if the lower bound one-sided 97.5% confidence interval is greater than 0 meters.

4.2.6. Analysis Population

The analysis population is the Efficacy Population defined in Section 2 for subjects with a valid baseline six-minute hall walk value. A 6MHW assessment that is discontinued for a non-cardiovascular reason is not valid for the endpoint analysis. A 6MHW assessment that is either not attempted, or discontinued, for site determined cardiovascular reason is valid for the endpoint analysis and is assessed in the following way, matching the methods of BeAT-HF:

- A 6MHW assessment not attempted for cardiovascular reasons is considered as 0 meters walked.
- A 6MHW assessment that is discontinued due to cardiovascular reasons is assessed as the total meters walked.

4.2.7. Sample size

The sample size is calculated assuming equal change from baseline in each group and a non-inferiority margin of 30 meters. The standard deviation of the difference in 6MHW from the BeAT-HF trial was 66.3 meters in the treatment arm. The observed standard deviation of 66.3 meters is rounded up to an assumption of 67 meters in the BATwire group for the sample size calculation. For this non-inferiority endpoint, the sample size needed for 80% power with one-sided alpha of 0.025 is 60 for the BATwire group. This sample size assumes an unstratified analysis approach and was calculated in PASS 2022 using an unconditional sample size calculation for a two-sample non-inferiority t-test of the difference in means. See Appendix I for documentation of the sample size calculation performed in PASS 2022.

To confirm that this sample size is sufficient to provide 80% power if a stratified propensity score analysis is required, propensity score quartiles were simulated by randomly allocating subjects to quartiles by arm. The sample size calculation using simulation was repeated using the stratified data analysis methods described in Section 4.2.4. The proportion of treatment and historical control subjects in each quartile was varied to assess sensitivity of the power of a stratified analysis to unequal

counts of BeAT-HF and BATwire subjects in each stratum. See Section 5.1 for a summary of the impact of differing propensity score distributions in the BeAT-HF and BATwire groups. If the propensity score distribution is comparable in the two groups, the stratified analysis has the same sample size requirement as the unstratified analysis.

It is estimated that approximately 15% of the subjects will have a missed visit or invalid 6MHW due to reasons including inability to complete the walk due to non-cardiac causes (e.g., asthma) or inability to perform the walk due to physical restrictions (e.g., physical injury) or study withdrawal. Thus, with a 15% attrition, 71 subjects would be needed to ensure 60 valid baseline and six-month results.

The observed change from baseline in BeAT-HF for BAT arm subjects in the intended use population was 48.6 meters. In order to reject the null hypothesis, a minimum mean improvement in 6-minute hall walk of approximately 40 meters in BATwire subjects is required with a sample size of 60.

4.2.8. Operational Considerations

The evaluation of a 6MHW is easily implemented and measured. Minimal site requirements to conduct this test include an indoor area that has a long, flat, straight, enclosed corridor with a hard surface of at least 30 m in length. As 6MHW is required at screening, only subjects who are physically able to complete the test are included in the study. This ensures that the collection of 6MHWs during follow-up should be feasible and that missing data should be minimized. To support a sensitivity analysis, the reasons for inability to do the test, or for stopping the test early, will be collected. Situations that could logically be imputed to have an outcome of zero meters will be identified and included in the analysis (e.g., subject who for cardiac reasons cannot, or will not, attempt a 6MHW).

Conducting the test is completed by following a clear and well-defined script that provides the site personnel with exact verbiage to use with the subject during the test. The length of the corridor should be marked every 3 meters to provide an easy way to accurately measure the distance walked.

For comparability, the 6MHW is to be performed with the identical instructions as it was in the BeAT-HF trial protocol. This includes identical instruction in the BATwire protocol under the Procedures / 6MHW section, as well as additional detailed instructions in the Appendix titled Six-Minute Hall Walk. In BeAT-HF, subjects had a screening 6MHW that determined eligibility and a second 6MHW for baseline. The average (and median) difference between these two walks was 2 meters, suggesting that a single baseline 6MHW should be an accurate baseline value. A single 6MHW reduces the burden on study subjects.

4.3. Ancillary Objectives

The following objectives will be evaluated for exploratory and supportive purposes. No formal hypotheses are provided.

4.3.1. 6- and 12-Month Change in Echocardiogram Parameters

To describe the change at 6 and 12 months in various echocardiogram parameters.

This objective includes an evaluation of left ventricular ejection fraction. Across several historical cardiac resynchronization studies that included NYHA III subjects, the average difference between CRT and no CRT in LVEF improvement was approximately 2.6%.^{9, 10, 11, 12} The CRT average improvement was approximately 4.3%. The objective would be to demonstrate that the LVEF improvement with Barostim therapy implanted using the BATwire Implant Kit is consistent with the benefit observed in CRT.

Table 1: LVEF Improvement in CRT Studies

	CRT	No CRT	Difference
CONTAK CD ⁹	6.0%	2.3%	3.7%
MIRACLE ¹⁰	4.6%	-0.2%	4.8%
MIRACLE ICD ¹¹	2.1%	1.7%	0.4%
RHYTHM ICD ¹²	4.3%	2.9%	1.4%
Estimate	4.3%	1.7%	2.6%

4.3.2. Morbidity and Mortality Outcomes

To describe the following morbidity and mortality outcomes and combination of outcomes using rates and days alive and free of morbidity:

- Hospitalization for worsening heart failure, LVAD, heart transplant, angina
- All-cause, cardiovascular and heart failure mortality
- Hospitalizations, occurrence and treatments for arrhythmias, such as atrial fibrillation, atrial flutter, ventricular fibrillation, ventricular tachycardia

4.3.3. Implantation Technique

To describe the outcomes of delivery and fixation of the CSL via BATwire Implant Kit. These will include: Guidewire delivery and placement under ultrasound guidance, dilation of tissue via the CSL BATwire Delivery Tool, mapping of electrode position, lead electrode placement verification, intraoperative therapy

⁹ Higgins SL, Hummel JD, Niazi IA, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol 2003;42:1454-9.

¹⁰ Abraham WT, Fisher WG, Smith AL, et al. CARDIAC RESYNCHRONIZATION IN CHRONIC HEART FAILURE. N Engl J Med 2002;346(24):1845-1853.

¹¹ Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD trial. JAMA 2003;289:2685-94.

¹² https://www.accessdata.fda.gov/cdrh_docs/pdf3/P030054b.pdf

response, and lead impedance. This analysis will be performed on the Safety Population.

4.3.4. 6 Month Change in Minnesota Living with Heart Failure Quality of Life Questionnaire

To describe the mean change in points in the MLWHF questionnaire. Descriptive statistics such as mean and standard deviation will be performed. This analysis will be performed on the Effectiveness Population.

4.3.5. 6 Month Change in NYHA Class

To describe the percent of subjects who improve in NYHA Class. Descriptive statistics such as frequency counts and percentages will be performed. This analysis will be performed on the Effectiveness Population.

4.3.6. 6- and 12-Month Change in Echocardiogram Parameters

To describe the change at both 6 and 12 months in various echocardiogram parameters, such as left ventricular volumes and dimensions. Descriptive statistics such as frequency counts and percentages will be performed. This analysis will be performed on the Effectiveness Population.

4.3.7. Serious Adverse Events related to the Procedure Between Implant and 30 Days Post-implant

The incidence of procedure related serious adverse events occurring between implant and 30 days post-implant will be analyzed descriptively with frequency counts and percentages. There is no formal statistical hypothesis test for this objective. This analysis will be performed on the Safety Population.

4.3.8. Serious Adverse Events related to the Procedure or Barostim System Between Implant and 6 Months Post-implant

The incidence of system or procedure related serious adverse events occurring between implant and 6 months post-implant will be analyzed descriptively with frequency counts and percentages. There is no formal statistical hypothesis test for this objective. This analysis will be performed on the Safety Population.

5. STUDY SAMPLE SIZE

The maximum number of subjects to be enrolled in this study is 300, of which up to 100 subjects will be implanted. A subject is considered enrolled when they have signed the informed consent. This sample size is derived based on the largest sample size required for 80% power among the two powered endpoints of the study, adjusting for a potential imbalance of baseline characteristics (see Section 5.1 below), 15% missing 6MHW data due to attrition/non-compliance, and an assumed screen failure rate of approximately 66%. The assumption regarding screen failure rate is based on the BeAT-HF trial, where a rate of 57% was observed, and initial screen failure rate observed in BATwire. Due to the stricter ultrasound and surgical selection criteria for this study, the BATwire screen fail rate was estimated to be 66%.

In summary, to account for potential imbalance of baseline characteristics as described in Section 5.1 below, the maximum number of subjects implanted is 100. Thus, the total number of subjects needed for the study will range from 71 (no baseline imbalance) to 100 implanted.

5.1. Sample Size Adjustment

The minimum sample sizes for each powered endpoint, as presented in detail in the endpoint descriptions above, are:

- Primary Safety Endpoint – Freedom from serious BATwire lead-related adverse events: 62 subjects with an attempted implant
- Primary Effectiveness Endpoint – 6-Minute Walk Test: 71 subjects implanted (60 subjects with baseline and follow-up data, sample size of 71 accounts for up to 15% attrition/non-compliance)

The sample size for the study is driven by the primary effectiveness endpoint. Since the sample size required for 80% power depends on the degree of imbalance in baseline characteristics between the historical BeAT-HF subjects and the prospectively enrolled BATwire subjects, the sample size may be adjusted to match the observed degree of imbalance. The sample size can range from a minimum of 71 to a maximum of 100 subjects implanted.

The sample size needed to achieve 80% power when there are equal versus unequal subject counts across propensity score quartiles is summarized in Table 2 below. The scenarios range from equal distribution (scenario #1) to increasing inequality (scenarios 2-4) with scenarios 2-4 having a shift in the distribution such that 20%, 15%, and 10% of BATwire subjects in the 4th quartile to explore a range of scenarios. The percentages shown in the table below are on a per study basis, such that each row adds to 100%. The BeAT-HF distribution is determined by the BATwire distribution, such that 25% of all subjects across both groups are in each quartile. In general, if the propensity score distribution differs between BATwire and BeAT-HF subjects, a larger sample size is required for 80% power.

Table 2: BATwire Sample Size Required for 80% Power by Propensity Score Distribution

Scenario	Group	Propensity Score Quartile				Sample Size		
		1	2	3	4	Primary Safety	Primary Efficacy	Implanted
1	BATwire	25%	25%	25%	25%	55	56	71
	BeAT-HF	25%	25%	25%	25%			
2	BATwire	30.4%	26.5%	23.1%	20.0%	57	57	71
	BeAT-HF	22.2%	24.2%	24.2%	26.0%			
3	BATwire	36.7%	27.7%	20.6%	15.0%	63	63	74
	BeAT-HF	18.1%	23.4%	27.6%	30.8%			
4	BATwire	44.7%	28.1%	17.1%	10.0%	76	83	98
	BeAT-HF	11.1%	22.8%	30.5%	35.6%			

Sample size adjustment may be performed when approximately ~57 subjects have been implanted, which is 80% of the minimum sample size of 71 implanted subjects. The timing of the sample size adjustment is planned to occur prior to implantation of 71 subjects so that enrollment may be stopped at 71 implanted in case the observed data is on track to be well balanced. The sample size adjustment is based on baseline characteristics alone. The statistician performing the sample size adjustment will not have access to study outcomes. Data provided to the statistician responsible for sample size adjustment will be limited to treatment group and pre-specified baseline characteristics.

The final sample size will be determined by a preliminary assessment of absolute standardized differences and preliminary development of propensity scores (if needed) using the analysis procedure determined by the algorithm in Figure 1. Additional details on the sample size re-estimation procedure are provided in Appendix I.

The number of subjects enrolled will range between 215 and 300 in order to provide between 71 and 100 subjects with an implant attempt (N_{implant}). Adjusting the sample size on the basis of preliminary propensity scores alone does not risk alpha inflation since no outcome data is used to inform the adjusted sample size. The stage 2 design statistician, who has no access to outcome data, performs the sample size adjustment. The adjusted sample size is binding.

The sponsor acknowledges that there is a risk of having lower power than anticipated (<80%) in the final analysis since the degree of imbalance in baseline characteristics after enrollment of all subjects may differ from the degree of imbalance at the time of sample size adjustment.

6. GENERAL STATISTICAL PRINCIPLES

6.1. Descriptive Statistics

Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, maximum and 95% confidence limits for the mean, where appropriate. Categorical variables will be summarized by frequency, percentage in the corresponding categories, and 95% exact binomial confidence limits, where appropriate.

6.2. Study Follow-up Time

For subjects with a Barostim device, the actual date of device implant will be used as the basis for calculating study follow-up time.

The days of follow-up will then be calculated as follows:

Follow-up Days = (Follow-up Date) - (Device Implant Date)

6.3. Partial Dates

In the case of adverse events with partially known dates the date of the event will be imputed. For partial dates in which the month and year is known, the day will be set to the first day of the month. For partial dates in which only the year is known, the event date will be set to January 1 of the known year. This is subject to the condition that the imputed date occurs on or after the procedure and on or before the event resolution date.

6.4. Missing Data

While missing data is a threat to the validity of clinical trials, no single method of handling missing data is ideal. Several methods may be used to assess the robustness of results to different assumptions underlying the missing data for BATwire subjects. A final assessment of the study data will depend on the amount and causes for the missing data and will need to be evaluated for the total risk/benefit profile in the context of both safety and efficacy. Subjects will be followed irrespective of their compliance with therapy and adverse event status.

The evaluation of the endpoints will be based on all available data collected on subjects in the populations defined in Section 2 describing analysis populations.

6.4.1. Multiple Imputation with Unfavorable Outcomes

In the event of missing data due to early withdrawal, the primary analysis will use multiple imputation to handle missing data. For imputation of outcome data in subjects that withdraw from the study prior to completing the 6-month visit, only subjects from the quartile with the lowest change in 6-minute hall walk distance will be used for multiple imputation. This approach imputes unfavorable outcomes for subjects that withdraw from follow-up to account for potential bias. Multiple imputation for subjects that missed the 6 month visit but remain enrolled in the study will be based on data from all subjects with a completed 6-month visit.

An MCMC multiple imputation model using the multivariate normal method that has observed values of the endpoint variable at baseline and 6 months as covariates will be used to assess the possible dependence of missing data on other observed values of

the endpoint. For the primary safety endpoint, multiple imputation with the discriminant method will be used.

For multiple imputation analyses, a total of 100 imputed datasets is planned. This number of imputations is selected to ensure accurate inference for confidence intervals and p-values. A common guideline is that the number of imputations should be greater than or equal to the percentage of data that is missing.¹³ Using 100 imputations therefore covers all possible missing data scenarios.

Additionally, sensitivity analyses will be performed to assess the impact of missing data for subjects that have withdrawn or been lost to follow-up prior to reaching study completion or have missing endpoint assessments.

6.4.2. Multiple Imputation

Multiple imputation will be used to explore potential endpoint results under the scenario that the missing data distribution depends on observed covariates (i.e., Missing at Random – MAR).

For subjects that are missing endpoint data at 6 months for the primary effectiveness endpoint, a MCMC multiple imputation model using the multivariate normal method that has observed values of the endpoint variable at baseline and 6 months as covariates will be used to assess the possible dependence of missing data on other observed values of the endpoint. Additional MCMC multiple imputation models will be explored including factors that are correlated with the missing status (i.e., the binary indicator variable of whether the endpoint is missing) or the non-missing values of the endpoint variable at 6 months.

For the primary safety endpoint, multiple imputation with the discriminant method will be used. Multiple imputation models will be explored including factors that are correlated with the missing status (i.e., the binary indicator variable of whether the endpoint is missing) or with safety endpoint status through 30 days in the observed data.

For multiple imputation analyses, a total of 100 imputed datasets is planned. This number of imputations is selected to ensure accurate inference for confidence intervals and p-values. A common guideline is that the number of imputations should be greater than or equal to the percentage of data that is missing.¹⁴ Using 100 imputations therefore covers all possible missing data scenarios.

6.4.3. Tipping Point Analysis

For each endpoint, a tipping point analysis is defined based on varying the assumed distribution of the endpoint measurement for subjects with missing data. The observed data endpoint parameter estimate by group will be used as the starting point for the tipping point analysis. The assumed distribution will be shifted away from the observed data estimate in an incremental, iterative fashion across a range of possible

¹³ Graham, John W., Allison E. Olchowski and Tamika D. Gilreath. "How many imputations are really needed? Some practical clarifications of multiple imputation theory." *Prevention Science* 8, 206-213, 2007.

¹⁴ Graham, John W., Allison E. Olchowski and Tamika D. Gilreath. "How many imputations are really needed? Some practical clarifications of multiple imputation theory." *Prevention Science* 8, 206-213, 2007.

endpoint values (e.g., from worst to best). The parameters of the missing data distribution that are least different from the observed data parameter estimates, and result in altering whether the null hypothesis is rejected, is declared the tipping point. The tipping point will be characterized by the distance from the observed data parameter estimate, both on an absolute scale and, for continuous outcomes, on a standardized scale by dividing by the standard deviation of the observed data.

6.4.4. Worst Case Analysis

For each endpoint, a worst-case analysis will be performed with the worst observed endpoint measurement among BATwire implant group subjects imputed for each BATwire implant subject with missing data. In the event that the endpoint is met under the worst-case analysis, no further missing data analyses will be performed for that endpoint. In that case, the conclusion that the endpoint was met will be considered robust to missing data.

For the primary safety endpoint, the worst-case assumption is that subjects with missing data experienced a primary safety endpoint event, thereby reducing the proportion of BATwire subjects that are event-free. For the primary effectiveness endpoint, the worst-case assumption for a subject who does not have an observed change from baseline to 6 months in the 6-Minute Hall Walk is that the change is equal to the worst observed change in BATwire subjects.

6.5. Sensitivity Analyses

Sensitivity analyses may be conducted to gain insight into the potential influence of factors that may introduce bias into the results of planned analyses. Sensitivity analyses may be conducted to assess the degree of imbalance and strength of association of additional unmeasured confounders needed to reverse the conclusions of the primary analysis¹⁵.

6.6. Assessment of Poolability

This is a multi-center clinical study with standardization of subject enrollment, data entry and adverse event reporting. All investigational sites will follow the requirements of a common protocol, data collection procedures and forms. To present the data from this clinical study in a summary form, a comparison of the endpoints across sites for BATwire subjects will be completed to determine if the generated data can be pooled.

Poolability by site will be evaluated by including a site term in the regression model for the endpoint for BATwire sites; a p-value less than 0.15 for the site term will be considered evidence of non-poolability. Reasons for non-poolability will be examined by adding covariates that vary across sites to the regression model. For example, variation in covariates across sites may explain site-to-site variation.

¹⁵ Liu W, Kuramoto SJ, Stuart EA. An introduction to sensitivity analysis for unobserved confounding in nonexperimental prevention research. *Prev Sci.* 2013;14(6):570-580. doi:10.1007/s11121-012-0339-5

6.7. Gender Analyses

Treatment differences by gender will be evaluated formally for the endpoints by including a gender term in the regression model; a p-value less than 0.15 will be considered evidence of a significant difference between gender.

6.8. Other Subgroup Analyses

Endpoint results, including statistical tests for differences, where appropriate, will be presented separately for each strata of a given subgroup as descriptive analyses.

Pre-specified subgroups include:

- Age (<65 years vs ≥ 65 years)
- Baseline NT-proBNP value
- Entreso use at baseline
- Presence of AF at baseline
- Presence of ICD at baseline
- Baseline NYHA Class
- Pre-existing medical conditions, such as history of CAD

6.9. Subject Accountability

The number of study subjects and their disposition over time will be provided by the following categories:

- Enrolled
- Implanted
- Completed the protocol required follow-up visits
- Discontinued prior to protocol required visits

6.10. Protocol Deviations

Protocol deviations in BATwire subjects will be summarized by frequency counts and percentages. Their potential impact on the primary effectiveness and safety endpoints will be assessed.

6.11. Planned Analyses

The analyses described in this Statistical Analysis Plan are consistent with those described in the BATwire Clinical Investigation Plan. Additions to the planned analyses may become necessary once the study is completed. Such additions or modifications to the SAP will be justified with supportive reasoning.

6.12. Statistical Software

Frequentist analyses will be performed using SAS v9.1.3 or higher or similar standard software package.

7. STUDY SUCCESS CRITERIA

The study will be considered successful upon successful rejection of the null hypothesis for the primary safety endpoint and primary efficacy endpoint.

8. REFERENCE DOCUMENTS

- Barostim NEO™ - BATwire™ Implant Kit Clinical Investigation Plan (#360058)
- Adverse Event Committee Charter (720077)
- Data Monitoring Committee Charter (720036)

9. SAMPLE SIZE PROGRAM

The sample size program is available on file.

10. APPENDIX I

10.1. Sample size calculation

Primary Safety:

Non-Inferiority Tests for the Difference Between Two Proportions

File View Run Procedures Tools Window Help

Reset Open Save As Report Options Home Favorites Recent Loaded Assurance Output Gallery

Calculate

Design

Solve For: Sample Size 1 = Treatment 2 = Reference

Power Calculation

Power Calculation Method: Binomial Enumeration

Binomial Enumeration Options

Maximum N1 or N2 for Binomial Enumeration: 5000

Zero Count Adjustment Method: Add to zero cells only

Zero Count Adjustment Value: 0.0001

Test

Higher Proportions Are: Better (H1: P1 - P2 > δ0)

Test Type: Likelihood Score (Farr. & Mann.)

Power and Alpha

Power: 0.8

Alpha: 0.05

Sample Size

Group Allocation: Enter N2, solve for N1

N2: 125

Effect Size

Group 1 (Treatment)

Input Type: Differences (δ0 and δ1)

δ0 (Non-Inferiority Difference): -0.10

δ1 (Actual Difference): 0

$P1.0 = P1|H0, \delta0 = P1.0 - P2$ $P1.1 = P1|H1, \delta1 = P1.1 - P2$

Group 2 (Reference)

P2 (Group 2 Proportion): 0.96

Help Center

For this procedure:

- Documentation
- Examples
- Validation Examples
- Video
- Open Example Settings File
- Validate This Procedure

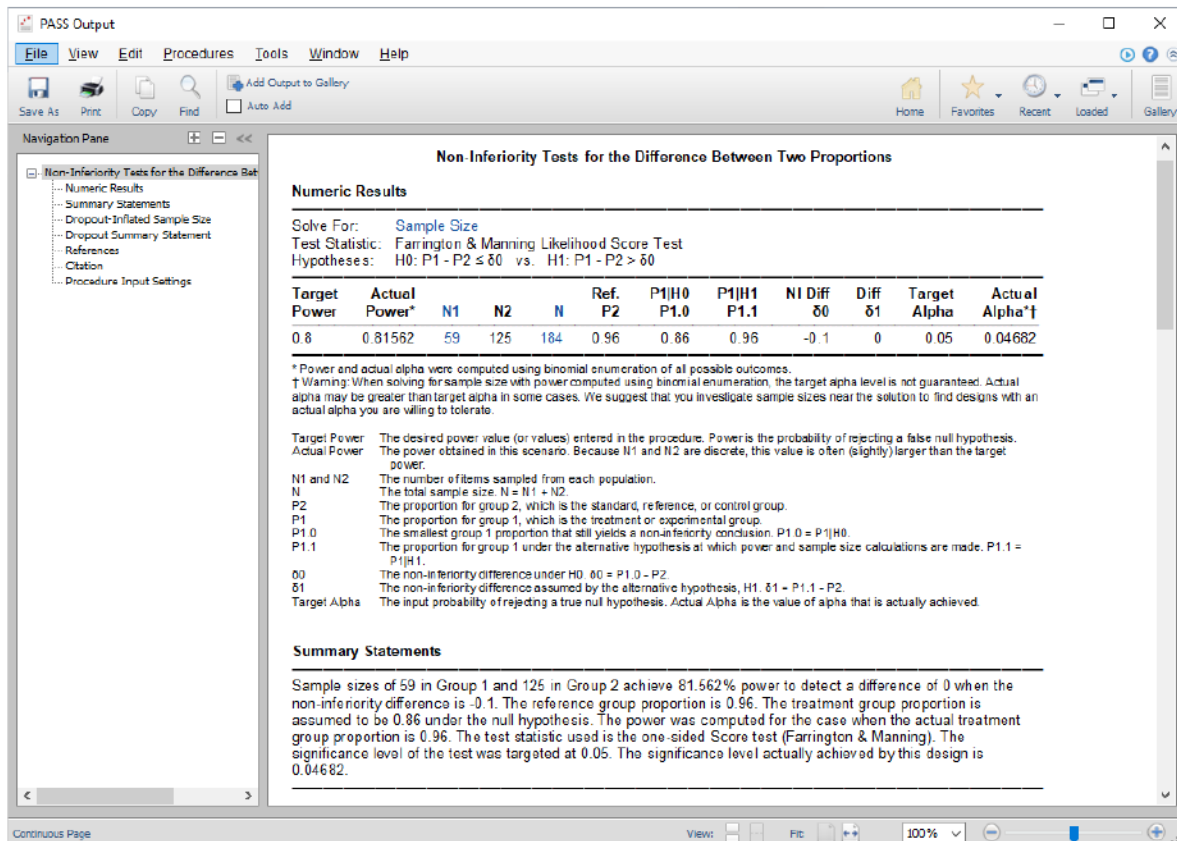
General:

- Getting Started Video
- Creating Power Curves Video

Option Info

Procedure Progress

Calculations Complete



Primary Effectiveness:

Two-Sample T-Tests for Non-Inferiority Assuming Equal Variance

File View Run Procedures Tools Window Help

Reset Open Save As Report Options Home Favorites Recent Loaded Assurance Output Gallery

Calculate

Design

Solve For: Sample Size

Test

Higher Means Are: Better (H1: $\delta > -NIM$)

Power and Alpha

Power: 0.8

Alpha: 0.025

Sample Size

Group Allocation: Enter N2, solve for N1

N2: 118

Effect Size

Mean Difference

NIM (Non-Inferiority Margin): 30

δ (Actual Difference to Detect): 0

$\delta = \mu_1 - \mu_2 = \mu_T - \mu_R$

Standard Deviation

σ (Standard Deviation): 67

Help Center

For this procedure:

- Documentation
- Examples
- Validation Examples
- Open Example Settings File
- Validate This Procedure

General:

- Getting Started Video
- Creating Power Curves Video
- All Training Videos

Option Info

Alpha

Alpha is the probability of obtaining a false positive with the statistical test. That is, it is the probability of rejecting a true null hypothesis.

Range

Since Alpha is a probability, it is bounded by 0 and 1. Commonly, it is between 0.001 and 0.10.

Recommended

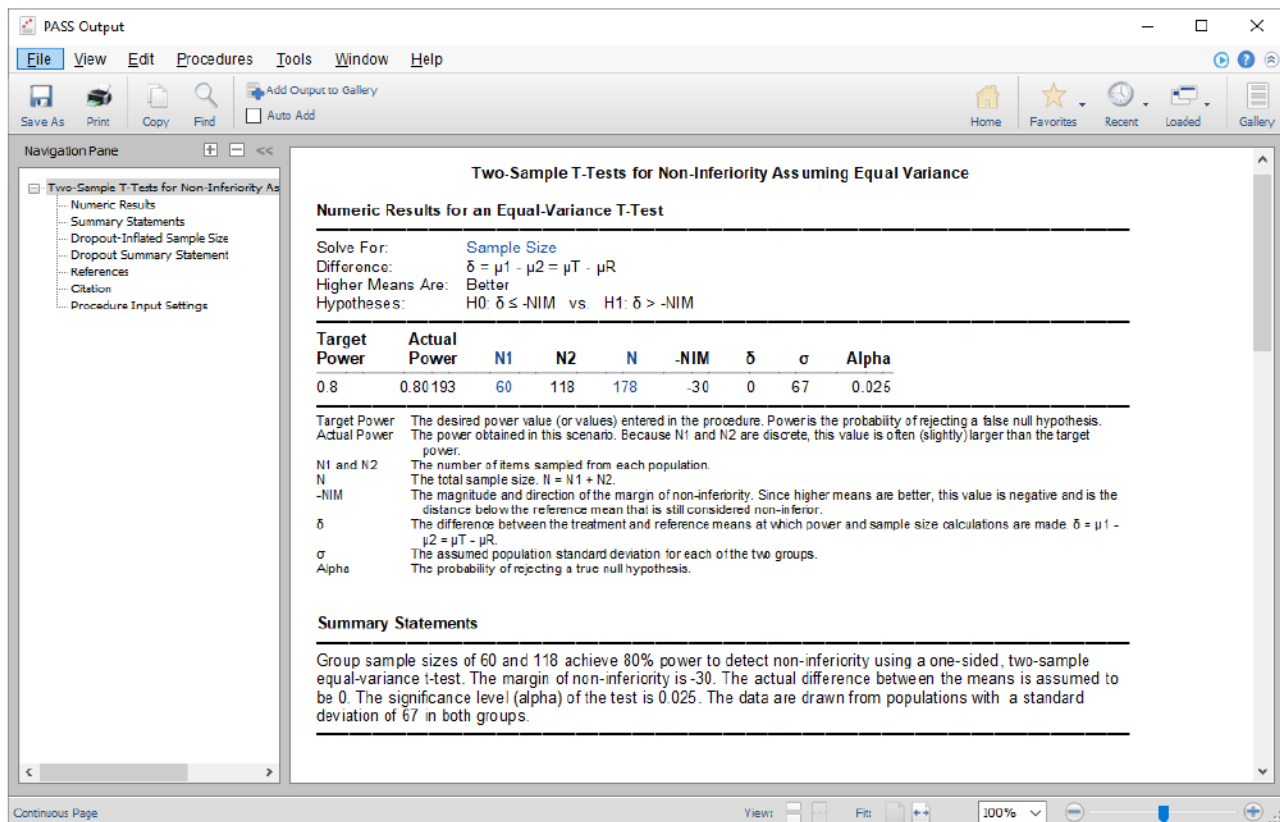
Alpha is often set to 0.05 for two-sided tests and to 0.025 for one-sided tests.

Notes

You can enter a single value such as

0.05

or a series of values such as



10.2. Sample size re-estimation procedure

A pseudo-code implementation of the sample size re-estimation procedure is provided below:

- Calculate the standard difference (Δ_{SD}) between BATwire and BeAT-HF subjects for all baseline covariates.
 - If 2 or fewer baseline covariates have $|\Delta_{SD}| > 0.25$, the baseline covariates are sufficiently balanced. The calculated 6-month sample size (N_{6month}) for 80% power is 60.
 - If more than 2 baseline covariates have $|\Delta_{SD}| > 0.25$, the baseline covariates are not sufficiently balanced. Proceed to step #2.
- If required per #1, calculate propensity scores per the SAP. Calculate the standardized difference (Δ_{SDi}) between BATwire and BeAT-HF subjects for all baseline covariates for each propensity score quartile ($i=1$ to 4).
 - If 2 or fewer baseline covariates have an average absolute standardized difference ($\sum_{i=1}^4 |\Delta_{SDi}|/4$) > 0.25 , the baseline covariates are sufficiently balanced by propensity score quartile. Proceed to step #5.
 - If more than 2 baseline covariates have an average absolute standardized difference ($\sum_{i=1}^4 |\Delta_{SDi}|/4$) > 0.25 , the baseline covariates are not sufficiently balanced by propensity score quartile and propensity score matching will be used. Proceed to step #3.
- If required per #2, perform an optimal full match using the propensity scores in #2. Calculate Δ_{SDw} , the weighted standardized difference, using the weights induced by the full match.

- a. If 2 or fewer baseline covariates have an absolute weighted standardized difference ($|\Delta_{SDw}| > 0.25$), the baseline covariates are sufficiently balanced by propensity score matching. Proceed to step #6.
- b. If more than 2 baseline covariates have an absolute weighted standardized difference ($|\Delta_{SDw}| > 0.25$), the baseline covariates are not sufficiently balanced by propensity score matching, proceed to step #4
4. If required per #3, determine whether propensity score stratification or propensity score matching provides better balance.
 - a. Count the number of variables where balance criteria are met for each method (stratification balance criteria: $\sum_{i=1}^4 |\Delta_{SDi}|/4 \leq 0.25$; matching balance criteria: $|\Delta_{SDw}| \leq 0.25$). If both methods achieve balance for the same number of covariates, the method with the lowest average balance criteria across all 12 covariates will be used. If stratification provides better balance, proceed to step #5. If matching provides better balance, proceed to step #6.
5. If required per #2 or #4, use simulation to estimate the power of the propensity score stratified analysis for each potential BATwire sample size from n=60 to 100 and select the sample size providing at least 80% power. Using the estimation procedure from Section 4.2.4 of the SAP to calculate the p-value in the simulation procedure.
6. If required per #3 or #4, use simulation to estimate the power of the propensity score matched analysis for each potential BATwire sample size from n=60 to 100 and select the sample size providing at least 80% power. Using the estimation procedure from Section 4.2.5 of the SAP to calculate the p-value in the simulation procedure.

The procedure to estimate power with sample size n (POW_n) using simulation in steps 5 and 6 is provided here:

- For s=1 to 10,000, simulate trial outcome data and calculate pvalues (the p-value for simulation #s)
 - Simulation is performed by bootstrap sampling of baseline covariates and random sampling of outcome data under the alternative hypothesis. Under the alternative hypothesis, outcomes are simulated using a normal distribution with mean of 85.5 meters and standard deviation of 67 meters for each subject from 1 to 118 for the BeAT-HF group and from 1 to n for the BATwire group.
 - pvalues is calculated using either the formula in 4.2.4 (for the propensity score stratified analysis) or 4.2.5 (for the propensity score matching analysis) of the SAP
- Estimated power for sample size n (POW_n) is the proportion of simulated trial outcomes where the null hypothesis is rejected ($POW_n = \sum_{s=1}^{10,000} I(pvalue_{s<0} < 0.025)/10,000$)

The calculated sample size is the smallest value of n for which estimated power is at least 80% for n and all sample sizes larger than n.

$$N_{6\text{month}} = \operatorname{argmin}_i \left(\prod_{n=i}^{100} I(POW_n \geq 80\%) = 1 \right)$$

The final study sample size (N_{implant}) is calculated using $N_{6\text{month}}$ and the estimated attrition rate at 6 months ($r_{\text{attrition}} = 1 - \# \text{ completed 6month visits} / \# \text{ expected 6month visits}$)

$$N_{\text{implant}} = N_{6\text{month}} / (1 - r_{\text{attrition}})$$

The final study sample size can range from 60 to 100 to account for both attrition and baseline covariate balance.