BAROSTIM NEO® - Baroreflex Activation Therapy® for Heart Failure (BeAT-HF)

CLINICAL INVESTIGATION PLAN

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REVISION HISTORY		
Revision	**Date**	**Description**
A	27-Feb-15	Initial release.
B	21-Oct-15	Revision to add Phase 1 & 2 trial structure incorporating the Expedited Access Pathway endpoints of Phase 1 supporting the PMA application
C	07-Feb-17	Updated eligibility criteria, improved operational efficiency, incorporated global requirements, updated trademark status.
D	05-May-17	Updated eligibility criteria for prior heart failure hospitalization and BNP/NT-proBNP, modified ENT evaluation, removed requirement for arrhythmia log
F	25-Jan-19	Revise eligibility criteria to baseline core lab NT-proBNP<1600 pg/ml. Updated statistical section to focus on Phase 2 morbidity and mortality data collection and analyses for subjects with a baseline NT-proBNP<1600.
G	27-May-22	Revised to include: • Updated to allow device to be left on after leaving study • Updated statistical section to include secondary endpoint. • Updated to include the new Model 2104 IPG number, Model 9020 Programmer System and MRI Conditional Use IFU

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ABBREVIATIONS AND ACRONYMS

Abbreviation	Full Text
AE	Adverse Event
AEC	Adverse Event Committee
BAT	Baroreflex Activation Therapy®
BP	Blood pressure
BNP	B-type natriuretic peptide
CA	Competent Authority
CEC	Clinical Events Committee
CRF	Case Report Form
CSNS	Carotid sinus nerve stimulation
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiography
eGFR	Estimated glomerular filtration rate
eDC	Electronic data capture
ENT	Ear, Nose and Throat
ESC	Executive Steering Committee
FDA	Food & Drug Administration
IRB	Institutional Review Board
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
mo	Month
SBP	Systolic blood pressure
UADE	Unanticipated adverse device effect

1. BACKGROUND

Heart failure (HF) is a major public health burden that is currently estimated to affect greater than 5 million patients in the United States and over 6.5 million patients in Europe.[1, 2] In the U.S. alone, each year, more than 600,000 new cases of HF are diagnosed, and over 1 million hospitalizations occur due to this disease.[3] Annual cost to the US healthcare system has been estimated at $38 billion.[3]

NYHA Class III Heart Failure is associated with poor life expectancy, as the annual mortality rate is approximately 15-20% with five-year mortality approaching 50% [4, 5] despite standard-of-care therapy. Death in these patients is an ever-present threat as they may experience acute decompensated heart failure or sudden cardiac death at any time.

Despite currently available drug and device therapies, 25% to 35% of patients with heart failure and a reduced left ventricular ejection fraction (LVEF) remain categorized in New York Heart Association (NYHA) Class III.[4] While these patients are not considered sick enough for advanced invasive heart failure therapies, such as a left ventricular assist device or cardiac transplantation, they exhibit moderate to severe heart failure symptoms, poor quality of life (QoL), and substantial limitation in exercise capacity. They are also at substantial risk for heart failure morbidity (e.g., heart failure hospitalization) and mortality, thereby incurring significant healthcare costs.[5] 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 left ventricular (LV) filling pressure, fluid retention, and exercise intolerance (Table 1). While therapies such as diuretics, β-blockers, angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB), aldosterone blockers (spironolactone, eplerenone), hydralazine, nitrates and cardiac resynchronization therapy have formed the cornerstone of HF therapy and have proven beneficial in improving outcomes over the last several decades, 5 year mortality rates and long term prognosis after confirmed HF diagnosis 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 patients[6] 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.[7] 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.[8] 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.[9] 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, hold promise for the treatment of HF.[10, 11]

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_2O 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: Potential Therapeutic Benefits of Activation of the Baroreflex

In the mid-1960s, a controlled clinical trial initiated by Eugene Braunwald and colleagues at the NIH to assess the effects of carotid sinus nerve stimulation 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. [12, 13] During the course of development of a Phase III trial, CABG surgery became widely available and thereby obviating the need for CSN 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. [14, 15]

1.2. Baroreflex Activation Therapy

Building upon the early experience with carotid sinus nerve stimulation, an implantable medical device has been developed to electrically elicit the baroreflex through stimulation of carotid baroreceptors. The CVRx BAROSTIM NEO® System, which provides Baroreflex Activation Therapy (BAT), 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. The effects of BAT are dose-dependent and can be titrated to meet the needs of each patient through interactive device programming.

1.2.1. Preclinical Evaluation

Initial pre-clinical investigations were targeted at assessing the effects of BAT on cardiac function via left ventricular pressure-volume relationships [16] measured using a conductance catheter technique in normotensive canines. Initiation of BAT increased stroke volume and maintained end-diastolic volume while reducing LV filling pressures. Cardiac output was preserved despite a reduction in heart rate of approximately 20%. The end-systolic pressure volume relationship (ESPVR, a load-independent measure of contractility) was unchanged, indicating no effect on myocardial contractile function (Figure 1B). This finding was important in that a reduction in contractility would limit the increase in stroke volume thereby resulting in a fall in cardiac output. However,

an increase in contractility would result in an increase in myocardial oxygen consumption, thereby potentially avoiding the adverse effects typically observed with positive inotropes frequently used in the treatment of systolic heart failure.

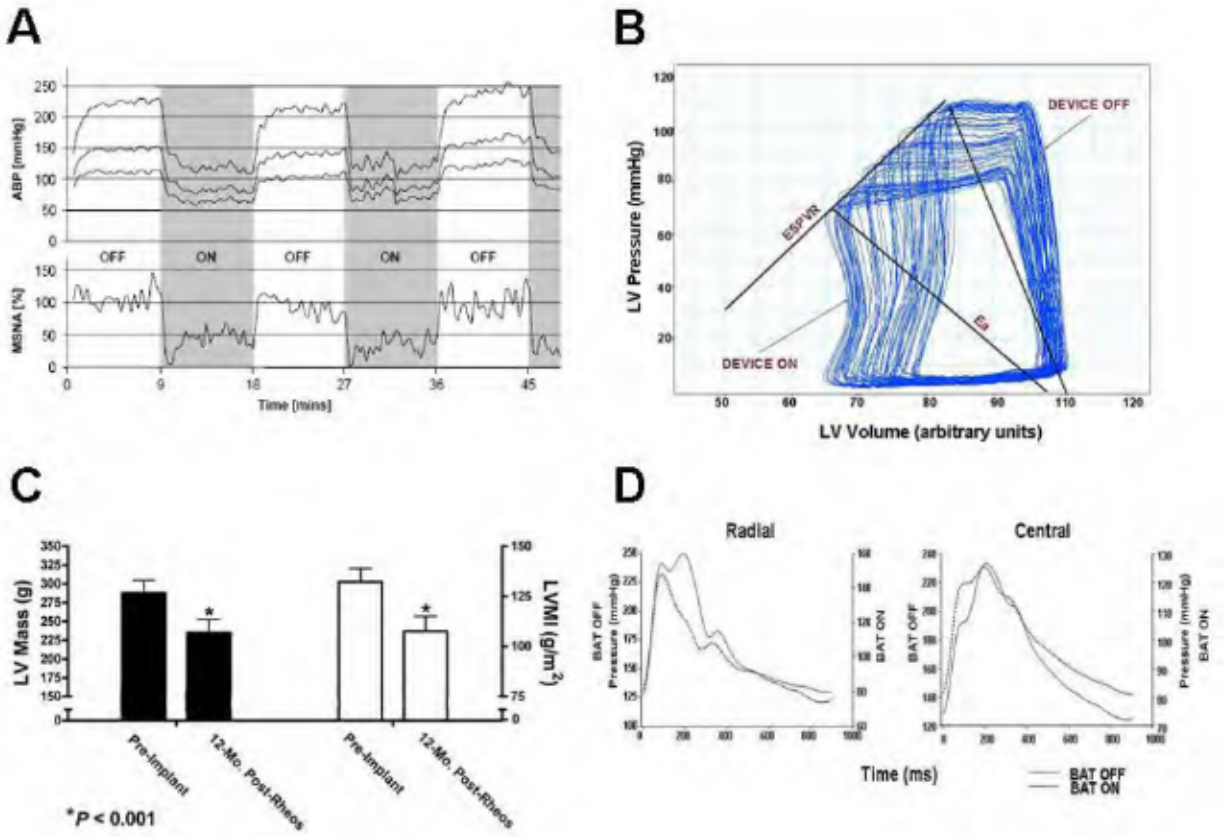


Figure 1: Baroreflex Activation Therapy™ Effects Potentially Beneficial for Heart Failure Patients

Figure 1A) **Acute impact of BAT on muscle sympathetic nerve activity in patient, showing rapid reductions in sympathetic traffic concomitant with pressure reduction induced by activation of BAT after 3 months of continuous therapy.[17]**

Figure 1B) **Acute effects of BAT on cardiac pressure-volume relationships in normotensive canines, demonstrating increased stroke volume, maintained end-diastolic volume and a large reduction in arterial resistance (Ea). No effects were observed on cardiac contractility assesses by the ESPVR.**

Figure 1C) **Chronic effects of BAT on cardiac structure in resistant hypertension patients, demonstrating significant reductions in LV mass (solid bars) and left ventricular mass index (open bars).**

Figure 1D) **Impact of acute BAT on central pressure waveform derived from radial tonometry in a patient, demonstrating reduction in augmentation index and elevated diastolic pressure despite the decrease in heart rate due to attenuation of reflected wave amplitude and timing and improved arterial stiffness. Pulse pressure amplification was also increased after BAT indicating a greater reduction in central blood pressure relative to peripheral.**

In this series of acute normotensive canines, cardiac efficiency increased due to preserved cardiac output that required less energy to accomplish as a result of reduced afterload (Figure 1B: reduction in Ea, a measure of arterial load). Specifically, the ratio of stroke work to pressure-volume area, increased by 35%. This increase was due to the maintenance of stroke work and a reduction in pressure-volume area (PVA), indicating a reduction in myocardial oxygen consumption (MVO_2) since PVA is directly correlated to MVO_2.[18] Unlike with nitrates, stroke work was preserved due to end-diastolic volume being maintained and BAT induced vasodilation, allowing extraction of potential energy available during contraction and a decrease in end-systolic volume which would have been liberated as heat. These effects are also distinct from those of β-adrenergic blockade, which acutely reduce the ESPVR (contractile function) along with heart rate, thereby reducing cardiac work at the expense of cardiac output. A study of patients receiving carotid sinus nerve stimulation has demonstrated in the clinical setting that cardiac output is unaffected by baroreflex activation.[12] Reduced heart rate is offset by increased stroke volume due to arterial vasodilation.

Neurohumoral stimulation in heart failure is the body's attempt to improve cardiac output. However, the associated decrease in venous capacitance, which would be expected to increase LV preload, is of limited value because of pericardial constraint to filling and may actually reduce LV preload by direct ventricular interaction and the increased filling pressures remain detrimental because of the pulmonary edema that frequently results. The redistribution of the venous reservoir due to increased sympathetic activity has been proposed as an aggravating mechanism for acute decompensated heart failure. Indeed, vascular capacitance is directly targeted with nitrates to ameliorate symptoms in patients with acute decompensation. Nitrates are quite effective in this setting, but therapeutic benefits cannot be chronically sustained due to tachyphylaxis and toxicity.

To investigate the potential benefits of BAT relative to venous capacitance, an acute model of advanced heart failure was studied in normal canines (data on file, CVRx). Heart failure was induced by coronary artery ligation. Effects on venous capacitance in this substrate were assessed for BAT, sodium nitroprusside (SNP) and angiotensin II (Ang II). Ang II, which simulates neurohumoral activation, produced the expected effect of reduced venous capacitance (Figure 2A). Likewise, SNP increased it as anticipated. BAT also increased venous capacitance, with an effect comparable to SNP. Additionally, in the presence of Ang II, the effects of BAT on venous capacitance were found to be dose-dependent (Figure 2B). BAT also decreased LV preload as directly assessed by left ventricular filling pressures measured by cardiac catheterization. The effects were independent of angiotensin level and were dependent on dosage of BAT.

If the large capacitance-increasing effect of BAT can be sustained, the effect may prove to be beneficial when venous capacitance is reduced in heart failure. The venous capacitance increase could work to decrease LV filling pressure and may also even increase LV preload and output by direct ventricular interaction in addition to BAT's effects on arterial conductance. Given the long-term ability of

BAT to reduce blood pressure in resistant hypertension patients, it is reasonable to postulate that similar enduring benefits may extend to heart failure. Thus, BAT may provide the first therapy to modulate venous capacitance to a similar magnitude as nitrates on a chronic basis without the associated limitations.

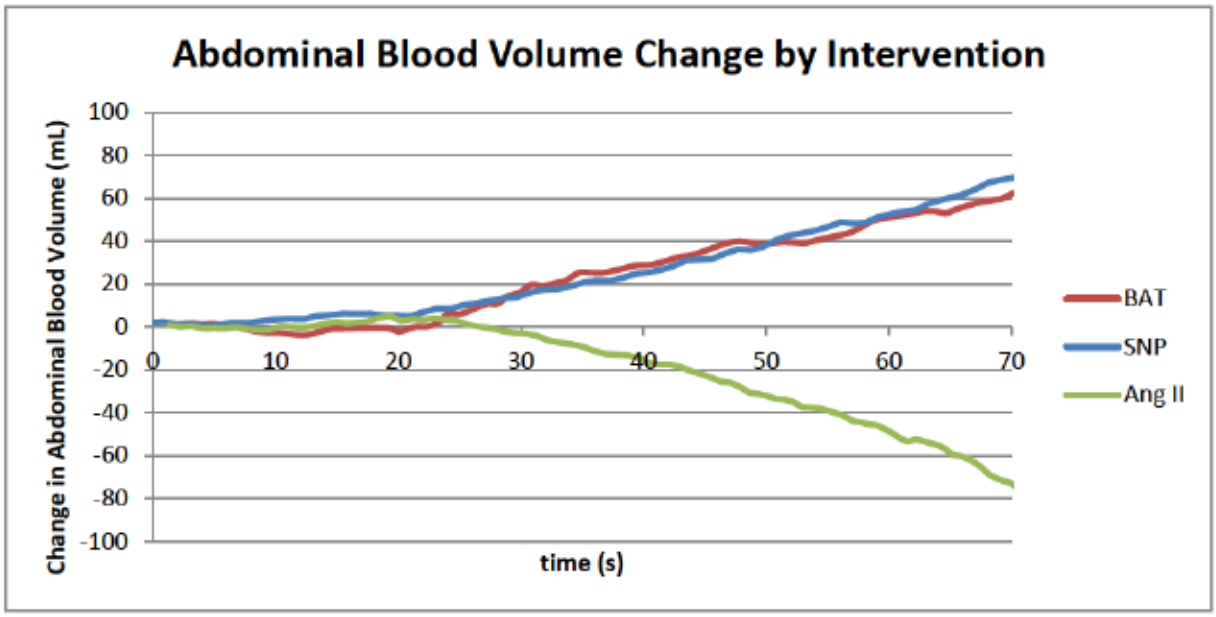


Figure 2A) **Individual effects on venous capacitance of BAT, sodium nitroprusside (SNP) and angiotensin II (Ang II) in an acute model of advanced heart failure.**

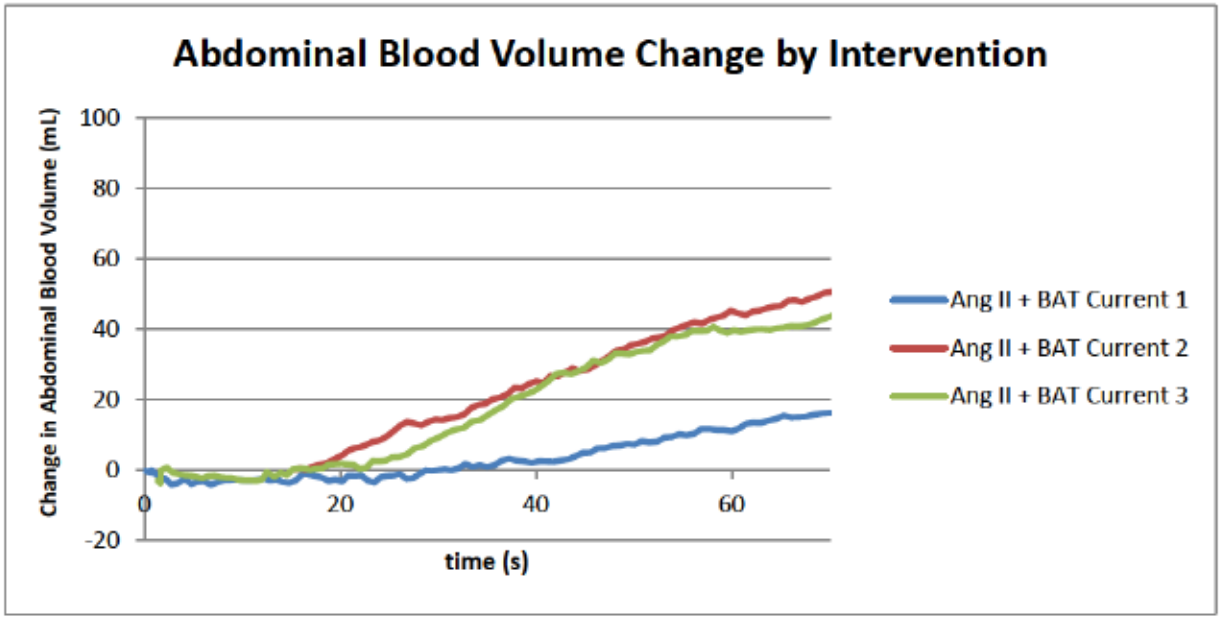


Figure 2B) **Dose-dependency of increases in venous capacitance due to BAT in the presence of angiotensin II in an acute model of advanced heart failure.**

Figure 2: Effects of Baroreflex Activation Therapy on Venous Capacitance

In another preclinical investigation of BAT in which a canine pacing model of systolic HF was utilized, LV end-diastolic pressures (filling pressures) were directly observed to be reduced by BAT versus controls not receiving BAT.[19] Similarly, increases in the levels of plasma norepinephrine and angiotensin II that occurred concomitantly with increased filling pressure were suppressed. The net result of these benefits on the pacing model was to double the survival of canines treated with BAT (68.1 ± 7.4 vs. 37.3 ± 3.2 days, mean ± SE, $p < 0.01$). Importantly, there were no differences in systolic blood pressure and the improved outcomes were independent of heart rate. In ongoing studies (N=3), the effects of stimulation on the renal blood flow and renal vascular resistance in response to graded exercise was studied. These results indicate that over the course of HF progression, BAT maintains renal blood flow and prevents the abnormal increase in resistance during treadmill running (Figure 3; data on file, Dr. I. Zucker).

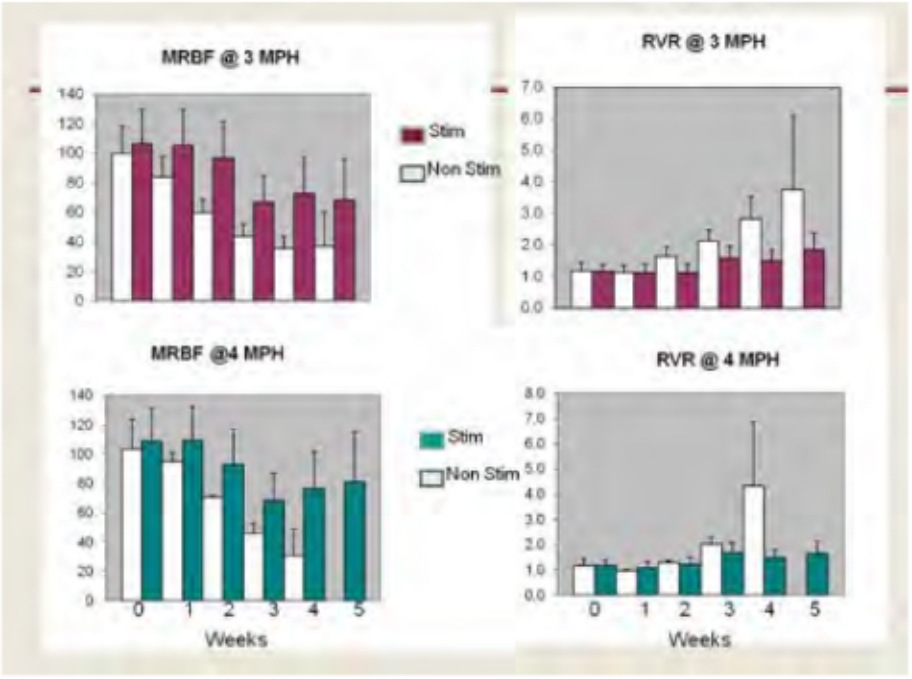


Figure 3: Renal blood flow (MRBF) and renal vascular resistance (RVR) in rapid pacing canine HF model response to graded treadmill testing.

Note the maintenance of renal blood flow and blunting of increase in resistance with HF progression. Non –stimulated animals did not survive post 4 weeks.

Significant structural remodeling was observed in a microembolization model of systolic HF when treated with BAT. Compared to control HF canines that did not receive intervention, canines treated with BAT exhibited reduced myocyte cross-sectional area, fibrosis, and LV chamber size and associated hemodynamic benefits of increased ejection fraction and reduced filling pressures.[20] Similarly, as in the pacing model, these benefits were observed without changes in blood pressure. These observations further support the notion that BAT may demonstrate clinical benefit in HF, as all therapies that have been successful in

the treatment of HF induce reverse remodeling.[21] In addition to structural benefits, molecular remodeling was also observed. BAT upregulated the levels of β1 receptor mRNA and reduced the expression of β–adrenergic kinase, which is known to desensitize β1 receptors. BAT also normalized the nitric-oxide synthase (NOS) profile by increasing expression of endothelial NOS and decreasing that for inducible NOS.[22] These effects have been shown in experimental models of HF, to improve systolic function and contractile reserve and normalize myocyte calcium handling, and has been proposed as the experimental mechanisms for the clinical benefit of β-blockers.[20]

Reduction of sympathetic activity is expected to reduce myocardial automaticity/irritability. This expectation was confirmed (Figure 4) in the microembolization model of HF, which demonstrated that chronic BAT increased the threshold to induce ventricular tachyarrhythmias versus control. The increased threshold for induction was reversed when BAT was withdrawn.[23] Clinical antiarrhythmic effects of baroreflex activation have also been documented in which patients implanted with carotid sinus nerve stimulators experienced immediate termination of supraventricular tachycardia when therapy was applied and similar to results observed with BAT.[24, 12]

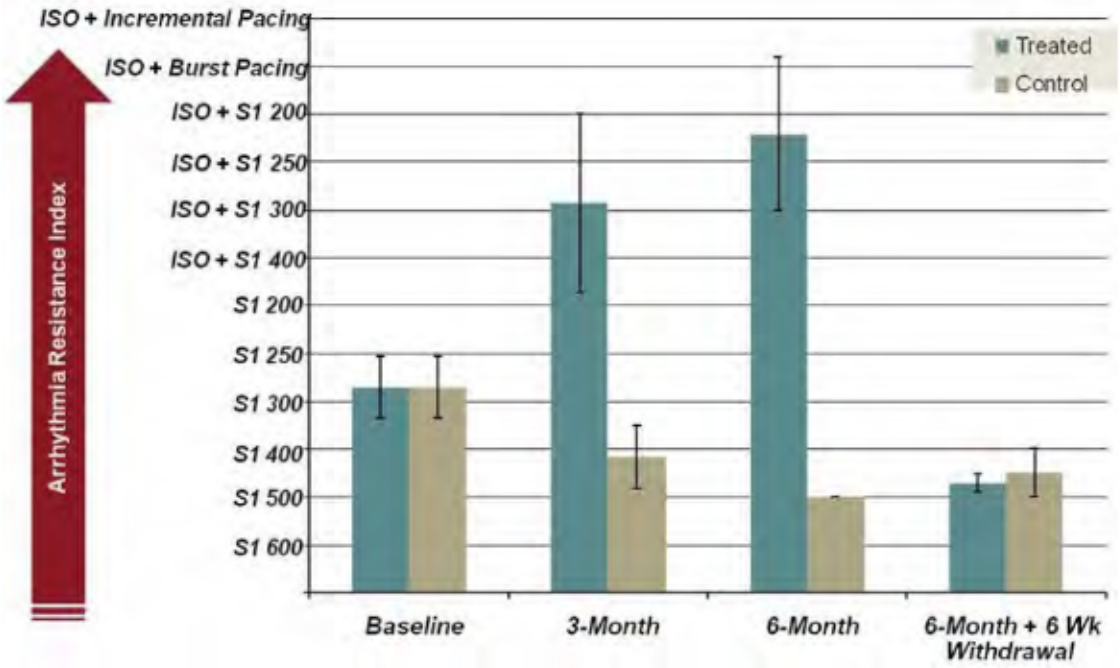


Figure 4: Arrhythmia Testing Results in Canines

Sub-studies in patients where concomitant cardiac structural and functional data were obtained have also indicated important beneficial physiological effects of BAT. In an echocardiography sub-study in which all patients had Stage II hypertension normal ejection fraction (baseline LVEF 66 ± 5%), left ventricular mass index (LVMI) decreased from a baseline of 138.8 ± 35.4 g/m^2 by 17.8 ± 16.0 g/m^2 (N=33) and 24.6 ± 17.9 g/m^2 (N=21) at 3 and 12 months, respectively ($p < 0.001$) (Figure 1C). Left atrial diameter (LAD) and mitral A wave velocity

(surrogate for late ventricular filling velocity) were also significantly reduced suggesting an improvement in LV filling pressures. Stroke work was reduced by 15% at both 3 and 12 months, while the rate-pressure product (surrogate for myocardial oxygen demand) was significantly reduced, suggesting that BAT reduced global cardiac workload. Baseline 6-minute hall walk distance (mean 6-MHW = 438 ± 153 meters) was near the clinical threshold for reduced capacity. Treatment with BAT resulted in a statistically and clinically significant improvement in 6-MHW distance (mean increase = +37 ± 60 meters).[25]

1.2.2. Related Human Clinical Evaluation

In a subset of patients in the European feasibility studies of BAT, investigators found evidence that BAT directly impacts both peripheral and central autonomic nervous system function. Wustmann et al[26] found that one year of active therapy resulted in reduced low-frequency/high-frequency ratio, corresponding to diminished sympathetic activity. Patients also developed increased heart rate turbulence, indicating increased parasympathetic activity, reduced sympathetic activity and enhanced baroreflex sensitivity (BRS). Following approximately 3 months of BAT, Heusser and colleagues observed significant increases in muscle sympathetic nerve activity (MSNA) in 12 patients when BAT was acutely turned off and a reversal of this increase when BAT was reactivated[17] (Figure 1A). Acute modulation of the renin-angiotensin-aldosterone system (RAAS) in this cohort was also observed as evidenced by a 20% reduction in plasma renin levels.

Many of the beneficial effects of BAT in HF can be seen from an invasive hemodynamic PV loop study performed in a patient indicated for a catheterization procedure with a history of hypertension and renal artery stenosis and was beginning to experience increasing frequency of hospitalizations associated with shortness of breath (Letter to editor submitted to New England Journal of Medicine). Figure 5 and Table 2 summarize the key findings. With BAT, there was a fall in peripheral resistance (R) associated with a reduction in wave reflections (P_b), confirming the non-invasive findings (Figure 1D). A novel finding from the catheterization study was a reduction in the characteristic impedance (Z_c), which has not been observed with other therapies and has been shown to be elevated in HF patients with both reduced and normal EFs.[27, 28] This indicates the potential of BAT to modulate aortic stiffness as well as resistance, and has important implications for the treatment of HF, particularly in the aged. This reduction in arterial load resulted in improved diastolic properties of the left ventricle with a reduction in filling pressures and increased early peak filling rate (PFR). The concomitant increased filling rate and reduction in end-diastolic pressures indicates improved ability of the left ventricle to act as a suction pump and fill itself, a condition which is lost or diminished in both systolic and diastolic HF.[29] Furthermore, the reduction in blood pressure and heart rate are expected to improve myocardial energetics and associated ischemia.

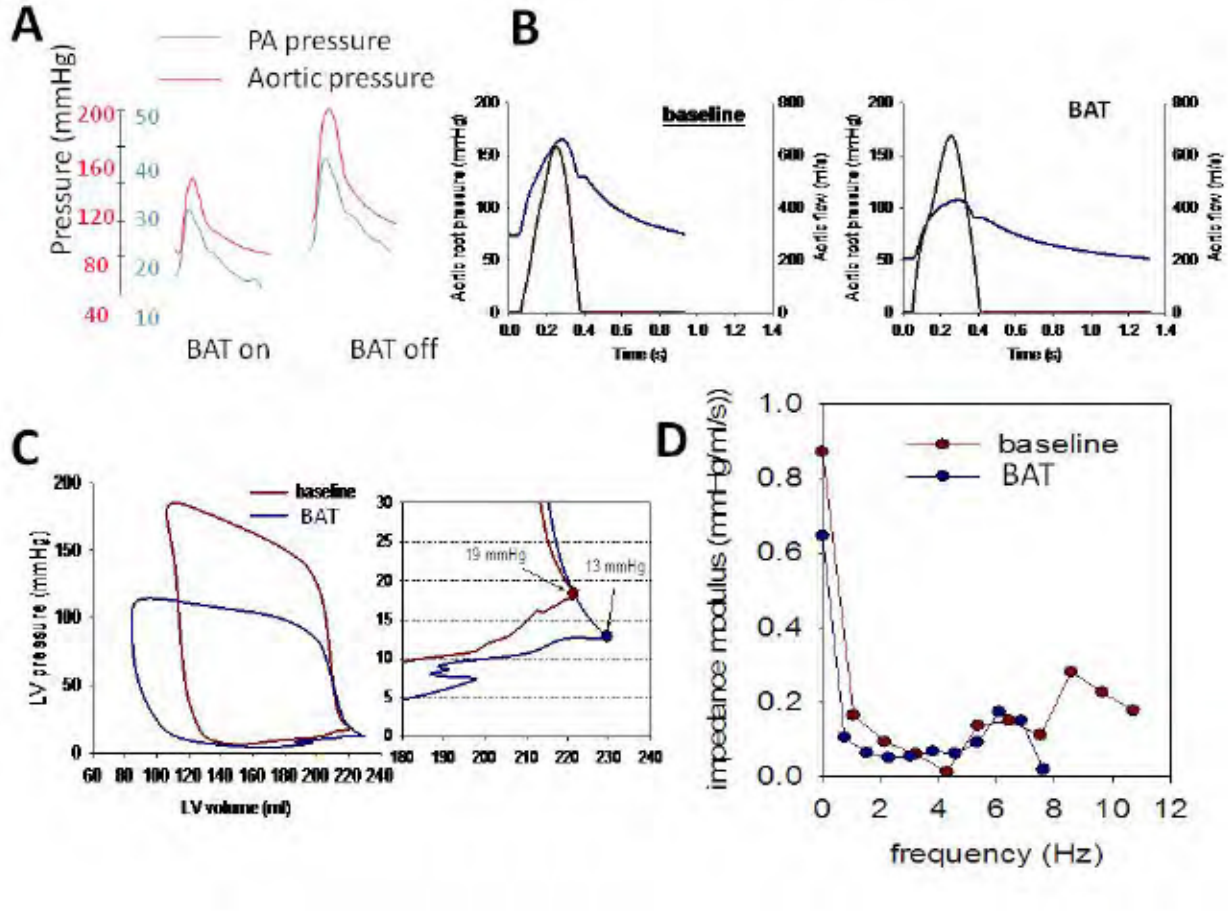


Figure 5: Summary of Key Hemodynamic Effects

Figure 5A) **BAT reduces central arterial and pulmonary artery pressures.**

Figure 5B) **Central arterial pressure and flow waveforms showing the effects of reduction in steady state and pulsatile load with a fall in pressure and increased forward flow and stroke volume.**

Figure 5C) **Pressure-volume loops with BAT showing increased stroke volume and improved diastolic function as end-diastolic pressure is reduced at similar preload.**

Figure 5D) **Arterial input impedance spectra derived from arterial pressure and flow showing reduction in resistance (0 Hz) and high frequency pulsatile components (6-12 Hz) with BAT. The latter represents a reduction in proximal aortic stiffness.**

Table 2: Summary of Hemodynamic Data from Pressure-volume Loop Study at Baseline and BAT

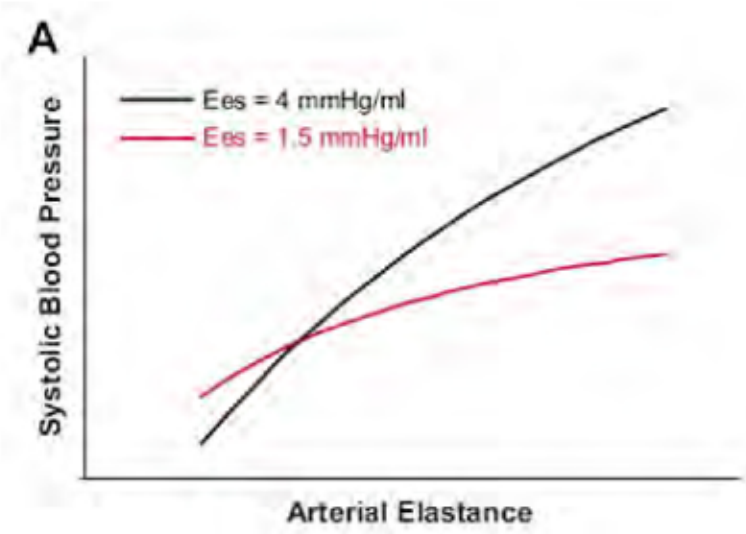
	Baseline	BAT	
SBP (mmHg)	165	107	Systolic Blood Pressure (SBP)
PP (mmHg)	92	56	Pulse Pressure (PP)
HR (/min)	64	46	Heart Rate (HR)
SV (ml)	117	147	Stroke Volume (SV)
LV EDP (mmHg)	19	13	Left Ventricular End Diastolic Pressure LV EP)
PFR (mL/s)	586	958	Peak Filling Rate (PFR)
R (mmHg/ml/s)	0.87	0.65	Resistance (R)
Z_c (mmHg/ml/s)	0.144	0.083	Characteristic impedance (Z_c)
P_f (mmHg)	90	56	Forward wave amplitude (P_f)
P_b (mmHg)	31	23	Reflected wave amplitude (Pb)

While emphasis has been placed on the afterload reduction associated with BAT in hypertensive patients, this is also applicable to HF patients with normal or reduced BP. Several clinical studies have established, along with β-blockers, vasodilators as front-line therapy for HF therapy[30] and vasodilation is the mechanism of action of most commonly used therapies. As alluded to by the HFSA Guidelines[31] and stated explicitly by the ESC Heart Failure Guidelines,[32] standard-of-care medical therapies are capable of acutely lowering blood pressure and caution should be exercised when initiating treatment in patients with systolic blood pressures of 80-90 mm Hg or lower. In patients with higher pressures, the ESC Guidelines note that hypotension is a common side effect of medical therapy that often occurs without symptoms and generally improves with time.[32] To avoid symptomatic hypotension, most drugs are up-titrated at 2-4 week intervals until the target or maximally-tolerated dose is achieved.

The reflex increase in peripheral resistance associated with sympathetic activation may appear to be compensatory, however this leads to a fall in cardiac output and further sympathetic tone creating a vicious cycle of fluid retention and increased central blood volume and cardiac filling pressures. Vasodilators in patients with reduced systolic function typically result in increased forward flow and transfer of volume from the heart and lungs to the periphery resulting in minimal or no change in systolic blood pressure, even in the presence of myocardial infarction complicated by heart failure.[33, 34] Theoretical prediction using the elastance concept predicts the systolic blood response to a change in peripheral resistance with normal and reduced systolic function (Figure 6).[35]

Unlike pharmacologic therapy, BAT can be acutely titrated to achieve target blood pressure and the mechanism of action is through ***withdrawal*** of sympathetic tone such that the therapy is effectively self-modulating and is dependent on intrinsic baseline tone and heart structure and vascular stiffness. Clinical results from the Rheos Pivotal assessing event rates of hypotension and syncope confirm this. For all patients receiving BAT for 12 months, the rate of

adverse events due to hypotension and syncope were 17% in patients achieving SBP<140mmHg (N=118) and 13% for patients with SBP>140mmHg (N=104).



Black line (Ees=4) indicates normal or elevated cardiac function as in HTN or HFpEF while red line (Ees=1.5) is reduced cardiac function.

Figure 6: Theoretical Prediction of the Response to Systolic Blood Pressure as a Function of Peripheral Resistance (Arterial Elastance)

Recently, clinical trials have been evaluating the effects of BAT in patients with HF and reduced ejection fraction. In an open-label cohort of 11 patients (data on file), it was demonstrated that BAT chronically reduced sympathetic tone by approximately one-third through direct measurement of peroneal nerve activity. Reductions were maintained for at least 6 months. Concomitant improvements were noted in 6-minute hall walk distance, quality of life and NYHA class. Two-dimensional echocardiographic assessment of LV volumes and ejection fraction did not significantly change; however, point-estimates suggested the possibility of improvement. Although not prospectively defined as an endpoint, hospitalization usage by the cohort in the 12 months after device activation was substantially less than in the 12 months prior to implant (194 vs. 29 days). As anticipated, no significant long-term changes in blood pressure were observed. The device- and procedure-related event-free rate was 91%.

Most Recent Heart Failure Studies:

US and European/Canadian randomized studies have completed six months of follow-up on 146 randomized subjects (data on file). Patients are randomized in a 1:1 fashion to BAT + optimal medical management (OMM) or to OMM alone. Consistent with the 11 non-randomized patients, results indicate significant improvement among device patients in six-minute hall walk, quality of life as measured by the Minnesota Living with Heart Failure Questionnaire (MLWHF), and NYHA class, as shown in Table 3 below. Compared to the OMM group, six-minute hall walk, quality of life, NYHA class and NT-proBNP significantly improved. In addition, there is evidence that BAT reduces the number of days spent in a hospital for heart failure six months after commencing therapy compared to six months pre-therapy within the device arm (reduction of 0.49

hospitalizations per patient per year, p=0.014) as well as between the two arms (reduction of 0.44 hospitalizations per patient per year, p=0.098).

Table 3: Outcomes at Six Months in All Subjects

	Device+ OMM		OMM		Difference
Measure	**N**	**Mean±SE**	**N**	**Mean±SE**	**Mean±SE**
Six-minute hall walk (meters)	56	59.6§ ± 14.1	43	1.5 ±13.2	58.1† ± 19.8
Quality of life (points)	64	-17.4§ ± 2.8	54	2.1 ± 3.1	-19.5† ± 4.2
New York Heart Class (% improved)	64	55%§	54	24%§	31%‡
LVEF (%)	49	2.4§ ± 1.1	40	-0.1 ± 1.3	2.5 ± 1.7
NT-proBNP (pg/ml)*	43	-69 (-504, 198)	40	129.5 (-67, 619)	-341.5‡ ± 189.8
# of HF Hosps 6M Pre/Post Randomization	57	-0.49§ ± 0.2	50	-0.05 ± 0.22	-0.44 ± 0.29

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

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%). A manuscript of the results of these studies was accepted for publication in February 2015 and will be available in March 2015 (JACC HF 2015).

1.2.3. Additional Human Clinical Analysis

In addition to the above summary results, subgroup analyses were prospectively defined in the Statistical Analysis Plan for the purposes of hypothesis generation and refinement of future clinical trial designs. An important pre-defined subgroup analysis was performed on subjects who did not have a cardiac resynchronization therapy (CRT) device at baseline. Over 2/3 (68%) of the global randomized heart failure subjects did not have a CRT device at baseline. In this large cohort, the subjects receiving BAT showed a significant improvement from baseline to six months in six-minute hall walk, quality of life measured by the MLWHF, NYHA, and left ventricular ejection fraction, as shown in Table 4. The BAT group also showed a decrease in NT-proBNP at six months. Compared to the OMM arm, the BAT arm experienced clinically relevant and statistically significant improvements in the six-minute hall walk, quality of life, left ventricular ejection fraction, and NT-proBNP. Non-significantly, the percent of subjects who improved in at least one NYHA Class was higher in the BAT arm. Similar to the full study cohort, there is evidence that BAT reduces the number of days spent in a hospital for heart failure six months after commencing therapy compared to six months pre-therapy within

the device arm (reduction of 9 day per patient per year, p=0.012) as well as between the two arms (reduction of 9 day per patient per year, p=0.057).

Table 4: Outcomes at Six Months in Subjects with No CRT at Baseline

	Device		OMM		Difference
Measure	N	Mean±SE	N	Mean±SE	Mean±SE
Six-minute hall walk (meters)	35	85.5§ ± 20.5	30	3.6 ± 16.3	81.9‡ ± 26.8
Quality of life (points)	42	-21.6§ ± 3.6	37	3.5 ± 3.7	-25.1† ± 5.2
New York Heart Class (% improved)	42	48%§	37	27%	21%
LVEF (%)	32	4.3§ ± 1.2	27	-0.1 ± 1.7	4.4‡ ± 2.0
NT-proBNP (pg/ml)*	29	-97 (-504, 93)	29	116 (-74, 700)	318‡ ± 274
HF Hosp Days 6M Pre/Post Randomization	38	-8.89§ ± 4.0	34	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 BAT subjects who did not have CRT at baseline showed consistent, and mostly significant, improvement across all efficacy endpoints. This is particularly evident when compared to the OMM only subjects, who demonstrated no improvement and even evidence of deterioration. In addition, the rate of heart failure hospitalization showed improvement in the BAT device arm six months post versus pre-enrollment, which is compared to a trend of no improvement in the OMM only arm.

1.3. Conclusions

Through the well-documented abilities of the baroreflex to modulate a host of physiologic properties, BAT targets many of the pathologies associated with HF. As previously demonstrated in patients with resistant hypertension, BAT reduces afterload, consequently reducing filling pressures, and left atrial size. Accompanying these structural changes are chronic reductions in sympathetic nerve activity and plasma norepinephrine, increased parasympathetic nerve activity, and improved heart rate variability. Dilation of arteries and veins promotes skeletal muscle and coronary perfusion, normalizes blood flow distribution, and lowers central venous pressure, a key determinant of clinical outcome. Autonomic and circulatory changes promote preservation of renal function through maintenance of renal blood flow and reduction of central venous pressure. Baroreflex-mediated changes may also ameliorate pulmonary hypertension, a common co-morbidity in HF. Results of clinical studies to date 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. The pre-specified subgroup analysis on the global

randomized heart failure subjects who do not have CRT present at baseline provides consistent and comprehensive evidence of a clinically relevant and statistically significant benefit of the BAT device in this cohort of patients. Thus, this pivotal study is intended to confirm the positive effects of the BAT device in the patient population which does not currently have and is not currently indicated for a CRT device.

1.4. Recent Information

After evaluating the pre-planned Phase 1 interim data described in previous protocol revisions, a large, important and clinically relevant population emerged. This population is characterized by having NYHA Class III heart failure, left ventricular ejection fraction (LVEF) <35% **and baseline core lab NT-proBNP < 1600 pg/ml**. To adequately evaluate this population, Revision F will actively enroll only subjects with a baseline core lab NT-proBNP < 1600. As interim data collection for the initial Phase 1 analysis is complete, Revision F will focus on the Phase 2, or morbidity and mortality extended phase, of the study. As such, the total number of subjects previously and prospectively randomized will enable the evaluation of a morbidity and mortality benefit in subjects with a baseline core lab NT-proBNP < 1600 pg/ml.

2. PURPOSE

The purpose of this clinical trial is to develop valid scientific evidence for safety and effectiveness of Baroreflex Activation Therapy® with the BAROSTIM NEO System in subjects with heart failure, defined as New York Heart Association (NYHA) functional Class III, left ventricular ejection fraction (LVEF) ≤ 35% and NT-proBNP<1600 pg/ml despite being treated with the appropriate heart failure guideline directed therapy, excluding subjects eligible for or actively receiving Cardiac Resynchronization Therapy (CRT).

The total trial 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 trial.

3. PROTOCOL

3.1. Trial Summary

The BAROSTIM NEO - Baroreflex Activation Therapy for Heart Failure is a prospective, randomized trial in subjects with reduced ejection fraction heart failure. Subjects will be randomized in a 1:1 ratio to receive Barostim Activation Therapy with an implanted BAROSTIM NEO System in addition to medical management or to receive medical management alone (no device implant). The trial will be conducted at up to 120 investigational centers in the U.S. and up to 20 investigational centers outside the U.S. These centers will enroll up to 1200 subjects to randomize approximately 480 subjects who meet the entry criteria.

A single center will not be permitted to randomize more than 15% of the total number of randomized subjects. A subject will be considered enrolled when he or she has provided written consent.

Post-consent screening measurements will be obtained only after the subject has completed a medication optimization and 4-week medication stabilization period. For all subjects, the heart failure medication regimen must remain stable during the 4-week medication stabilization period, except for minor adjustments (see inclusion criterion #5 in section 3.3.1). Subjects will be randomized when they have met all enrollment criteria and after all baseline measurements have been obtained.

Prior to randomization, site personnel will be required to provide an anticipated implant date. For subjects randomized to the Medical Management Arm, this date will be used for the timing of all other trial visits. For subjects randomized to the Device Arm, trial visits will be based on the actual date of device implant.

Device subjects will have the device activated prior to being discharged from the hospital, and should remain at the hospital for at least 2 hours post-programming for observation prior to being discharged. At the physician's discretion subjects may remain overnight for observation to evaluate programming.

For all subjects, trial visits will occur at 0.5, 1, 1.5, 2, 3, 6, 9 and 12 months post-implant (post anticipated implant for medical management). Visits will occur quarterly from 15 to 24 months and semi-annually thereafter.

Subjects are followed in an identical manner regardless of trial arm.

Figure 7 provides a schematic of the overall trial design.

Figure 7: Trial Schematic

For US study subjects only: Once the device is commercially approved by the FDA and the study has ended, CVRx may provide one BAROSTIM NEO device at no charge for each subject in the Medical Management arm that was active when the study ended; refer to the IRB approved informed consent language. CVRx has not agreed to cover any of the other costs related to implantation of the device. Subjects or their healthcare insurer must arrange for payment of all other costs such as pre-surgical physical, hospital costs, surgeon and anesthesia fees. Other conditions, as described in the consent form, must also be met.

3.2. Trial Data

All randomized subjects will complete the prescribed protocol follow-up as detailed in Table 5 Time and Events Schedule. The six month data will provide evidence of the safety and efficacy of Barostim Therapy. The accumulated morbidity and mortality

data collected will provide evidence of morbidity and mortality benefit. This trial will involve one or more interim analyses to evaluate when sufficient evidence is reached for the final morbidity and mortality analysis. Up to 1,200 subjects may be enrolled to reach the anticipated sample size of 480 randomized.

3.3. Eligibility Criteria

3.3.1. Inclusion Criteria

To be eligible for this trial, subjects must meet all of the following inclusion criteria:

1. Age 21 years or above.
2. Currently NYHA Class II or III heart failure. For NYHA Class II, must have been NYHA Class III at any point in time within 3 calendar months prior to enrollment or at time of screening (enrollment is defined as the date the subject provided written consent).
3. Left ventricular ejection fraction ≤ 35% within 45 days prior to randomization.
4. Heart failure accompanied by either:
    - Core lab NT-proBNP ≥ 400 AND <1600 pg/ml within 45 days prior to randomization **OR**
    - Core lab NT-proBNP < 400 pg/ml within 45 days prior to randomization AND a heart failure hospitalization in the past 12 months.

    Note: Heart failure hospitalization may include an overnight hospital or hospital-based observation unit stay with a primary diagnosis of heart failure or an emergency room visit with a primary diagnosis of heart failure.

    Note: Screening/Baseline core lab NT-proBNP must be collected in an outpatient setting at a time when the subject is thought to be clinically stable.
5. On optimal, stable, Guideline Directed Medical Therapy (GDMT) per country specific guidelines for the treatment of heart-failure throughout screening/baseline evaluation and for at least 4 weeks prior to obtaining any post-consent screening parameters:
    - No more than a 100% increase or a 50% decrease of the dosage of any one medication other than a diuretic.
    - Medication changes within a drug class are allowed as long as the equivalent dosage is within the limits specified above.
    - Unrestricted changes in diuretics are allowed as long as the subject remains on a diuretic.
6. Six-minute hall walk (6MHW) ≥ 150 m AND ≤ 400 m within 45 days prior to randomization.

7. The artery planned for the BAROSTIM implant must meet both of the following criteria:
    - At least one carotid bifurcation as identification by a bilateral carotid duplex ultrasound within 6 months prior to randomization that is:
        a. Below the level of the mandible AND
        b. No ulcerative carotid arterial plaques AND
        c. No carotid atherosclerosis producing a 50% or greater reduction in linear diameter in the internal carotid AND
        d. No carotid atherosclerosis producing a 50% or greater reduction in linear diameter in the distal common carotid
    - No prior surgery, radiation, or endovascular stent placement in the carotid artery or the carotid sinus region.
8. 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 trial. Women of childbearing potential must have a negative pregnancy test within 14 days prior to randomization.
9. Received a standard cardiac work up and is an appropriate candidate for the study and the surgical procedure as determined by a trial cardiologist and a trial surgeon.
10. 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.
11. Signed a CVRx-approved informed consent form for participation in this trial.

3.3.2. Exclusion Criteria

If any of the following criteria are met, subjects are not eligible for this trial.

1. Received cardiac resynchronization therapy (CRT) within six months of randomization, or is actively receiving CRT.
2. Currently have a Class I indication for a cardiac resynchronization therapy (CRT) device according to AHA/ACC/ESC guidelines for the treatment of congestive heart failure.[36, 37]
3. Known or suspected baroreflex failure or autonomic neuropathy.
4. AHA/ACC Stage D heart failure within 45 days prior to randomization.
5. Body mass index > 40.
6. Serum estimated glomerular filtration rate (eGFR) < 25 mL/min/1.73 m^2 within 45 days prior to randomization.
7. Recurring resting heart rate of either < 60 bpm or > 100 bpm via clinic measurements within 45 days prior to randomization. (Note: Heart rate

<60 bpm is not applicable to subjects with an implanted device capable of pacing.)

8. Recurring symptomatic hypotension within 45 days prior to randomization.
9. Significant uncontrolled symptomatic bradyarrhythmias or unstable ventricular arrhythmias.
10. Subjects with any surgery that has occurred, or is planned to occur, within 45 days of the BAROSTIM NEO implant procedure. This includes pacemaker or ICD implants or battery replacements.
11. Episode of NYHA class IV heart failure with acute pulmonary edema within 45 days prior to randomization.
12. Any of the following within 3 months of randomization:
    - Myocardial infarction
    - Unstable angina
    - Percutaneous coronary intervention (e.g. CABG or PTCA)
    - Cerebral vascular accident or transient ischemic attack
    - Sudden cardiac death
13. Solid organ or hematologic transplant, or currently being actively evaluated for an organ transplant.
14. Has received or is receiving LVAD therapy.
15. Has received or is receiving chronic dialysis.
16. Heart failure secondary to a reversible cause, such as cardiac structural valvular disease, acute myocarditis and pericardial constriction.
17. Primary pulmonary hypertension.
18. Infiltrative cardiomyopathy (e.g. cardiac amyloidosis).
19. Severe COPD or severe restrictive lung disease (e.g. requires chronic steroid use or home oxygen use).
20. Active malignancy.
21. Current or planned treatment with intravenous positive inotrope therapy.
22. Life expectancy less than one year.
23. Clinically significant psychological condition that in the physician's opinion would prohibit the subject's ability to meet the protocol requirements.
24. Unable or unwilling to fulfill the protocol medication compliance, testing, and follow-up requirements (e.g. recent drug abuse).
25. Enrolled and active in another (e.g. device, pharmaceutical, or biological) clinical trial unless approved by the CVRx Clinical department.
26. Subjects with known allergies to silicone and titanium.

3.4. Visit Requirements

Table 5 below outlines the procedures to be conducted at each visit and Table 6 below shows the required visit windows.

Table 5: Time and Events Schedule

Procedure					Months from Implant									
	Screen	BL	Implant	Activate/ Pre-discharge	.50	1	1.5	2	3	6	9	12	15-24*	After 24***
Subject Informed Consent	X													
Assess Enrollment Criteria	X													
Demographics/Medical History	X													
Physical Assessment	X	X			X	X	X	X	X	X	X	X	X	X
Subject Medications	X	X			X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LVEF	X													
Six Minute Hall Walk	X	X								X		X		
Core lab NT-proBNP	X									X		X		
eGFR	X													
Carotid Duplex Ultrasound†	X													
AHA/ACC Stage	X													
NYHA Classification	X	X								X		X	X**	
Voice / Eating Tool		X												
Electrocardiography (ECG)	X													
MLWHF Questionnaire		X								X		X	X**	
EQ-5D-5L Questionnaire		X								X		X	X**	
CRM Arrhythmia Log		O								O		O	O**	O
Ultrasound to Locate Bifurcation			X											
Implant Procedure Testing			X											
Device Programming Evaluation				X	X	X	X	X	X	X	X	X		

X = Required, R = If required by section 3.4.11.6; O = Optional; *Quarterly up to 24 months; **18 and 24 month visit only; *** Semi-annual

† A historical measurement may be used if within 6 months of randomization.

Red & Grey = Device Subjects Only

Table 6: Trial Visit Windows

Time Point	Date Ranges
Screening / Baseline	Date of visit
Randomization	Within 45 days from the Start of Screening* and after the completion of Baseline
Implant**	Within 14 days of randomization
Device Activation/Pre-Discharge	Activation prior to being discharged from the hospital
0.5	15 days ± 7 days post-implant±
1	30 days ± 7 days post-implant±
1.5	45 days ± 7 days post-implant±
2	60 days ± 7 days post-implant±
3	90 days ± 15 days post-implant±
6	180 days ± 45 days post-implant±
9	270 days ± 30 days post-implant±
12	360 days ± 45 days post-implant±
Quarterly (15-24 months)	At intervals of 90 ± 30 days
Semi-Annually (Long term)	At intervals of 180 ± 60 days

*Start of screening is defined as the earliest screening date for the following screening procedures: 6MHW, core lab NT-proBNP, LVEF, NYHA (see Section 3.4.8)

** Device subjects only (Note: Within 28 days of randomization if a proctor required for implant).

± Medical management subjects "Implant" is the intended device implant entered prior to randomization. Device subjects "Implant" is the actual date of the implant.

3.4.1. Important Instructions to Reduce Bias

To reduce bias and ensure the integrity of this clinical trial, the following are required:

- The subjects must be on optimized and stable background heart failure medical therapy for four weeks prior to beginning screening – see Section 3.4.7.
- Minimizing Subject Withdrawal
  - During screening, site personnel must minimize the possibility of subject withdrawal by assessing whether the subject is willing to comply with the protocol requirements, which will include discussing the possibility of the subject being randomized to the Medical Management arm. The site personnel will also discuss with the subject the importance of completing study follow-up.

- All subjects should be encouraged to remain in the clinical trial and be provided with ongoing expert medical care for their heart failure. For US study subjects only: To further encourage subjects to remain in the clinical trial, all subjects in the Medical Management arm that were active when the study ended may be offered one BAROSTIM NEO device at no charge if the subject meets the FDA indication for use, and meets the other conditions to be described in the consent form (see Section 3.1).
- Subjects should be presented with the partial withdrawal option when they express an interest in withdrawing from active follow-up in the study – see Section 3.12.

- Site personnel must follow subjects regardless of randomization assignment in an identical manner.
- Site personnel must carefully follow directions for completion of the quality of life questionnaires, six-minute hall walk, and core lab blood draw.

3.4.2. Enrollment Procedure

Subjects are enrolled in this trial when they have signed the approved informed consent form. Enrolled subjects must then meet all eligibility criteria. All enrollment criteria will be validated at the clinical site.

3.4.3. Obtaining Informed Consent

Prior to enrolling in the trial, the subject will review informed consent materials with the Principal Investigator or appointed designee. In order to obtain informed consent, each subject must be informed about the investigation and acknowledge that participation is voluntary. Documentation is required within the subject's medical record and should include the date they signed the informed consent.

3.4.4. 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, ISO 14155, and the Declaration of Helsinki). The IRB/EC for the trial site may alter or amend the text as appropriate, but the IRB/EC and CVRx must approve the final text of the informed consent before subject enrollment can begin.

After the information contained in the trial-specific informed consent document has been reviewed with each subject, the subject and the investigator (or appointed designee) 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 trial.

3.4.5. Partial Withdrawal

Partial withdrawal language may be part of the main study consent form or as a stand-alone consent. The objective of the partial withdrawal is to allow site personnel continued access to subject medical records in order to collect information for the morbidity and mortality endpoint. Subjects should be presented with the partial withdrawal option when they express an interest in withdrawing from active follow-up in the study.

Site personnel must follow instructions in Section 3.10 and Section 3.12 for subjects in the Device Arm that wish to partially withdraw. In countries where the BAROSTIM NEO is not market approved, the device must be deactivated in a Device Arm subjects who withdraw from active follow-up.

Subjects that do not wish to continue in a partial withdrawal setting will be fully terminated from the trial. For subjects that agree to be followed under the partial withdrawal, site personnel should attempt to contact the subjects to collect morbidity and mortality information in a manner consistent with the study visit schedule (Table 5) and the partial withdrawal informed consent language approved by their IRB/EC. Information collected should include any events that meet the morbidity and mortality primary endpoint: cardiovascular death, all hospitalizations (particularly heart failure hospitalization), cardiac assist device and heart transplant (definitions listed in Section 4.3.4). Every effort must be made to collect source documentation if these events are identified.

Site personnel should utilize electronic medical records in addition to attempting to contact subjects.

Missed visits or procedures following a subject's transition to a partial withdrawal status will not result in protocol deviations.

3.4.6. Subject Economic Data

Subject economic data will be collected by CVRx. In the U.S., this data will be submitted to the Centers for Medicare and Medicaid Services. The requested data includes UB04 forms and itemized bills for all trial-related medical resource utilization.

3.4.7. 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 country specific guidelines (e.g. US follows AHA/ACC guidelines, Germany follows DGK/ESC guidelines, etc.). Subjects should remain on their prescribed medication and same dosing schedule for the duration of the trial, unless investigators determine medically necessary changes are needed.

3.4.8. Screening

The Start of Screening is defined by the earliest date of evaluation for any of the following measurements: left ventricular ejection fraction (LVEF), New York

Heart Association (NYHA) Class, core lab NT-proBNP, and six-minute hall walk. All screening requirements must be assessed within 45 days of randomization.

Screening must be complete within 90 days from the date the subject provided written consent.

3.4.8.1. Screening Medical History and Physical Assessment

At the screening visit, the investigator will review and document the subject's general medical history as well as a more thorough evaluation of their cardiovascular history. This will include hospitalizations prior to enrollment.

A physical assessment will be performed at screening. This physical assessment will include the collection of weight, height, blood pressure, and heart rate. Additionally, sites will ask about any adverse events, changes in medications, or any other notable occurrences.

3.4.8.2. Screening Left Ventricular Ejection Fraction (LVEF)

An echocardiogram, or equivalent, is required at screening to confirm a LVEF $\leq$ 35% within 45 days prior to randomization. This reading will be performed locally according to the usual institutional standards.

3.4.8.3. Screening Six Minute Hall Walk Test (6MHW)

The 6MHW is required at screening and must occur within 45 days prior to randomization to confirm that the distance walked is $\geq$ 150 m AND $\leq$ 400 m. Subjects who do not complete the test are excluded from the trial. Instructions for performing the 6MHW are provided in Appendix 2 Six Minute Hall Walk Test. 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.

3.4.8.4. Screening Electrocardiography (ECG)

ECG is required at screening and must be within 45 days prior to randomization and be done locally with a minimum of three leads. There is no core laboratory for processing ECG. The following data points are required: Presence of sinus rhythm, presence of atrial fibrillation, presence of ectopic beats, QRS interval, PR interval, and cardiac conduction abnormalities.

3.4.8.5. Screening NYHA Class Assessment

The NYHA Class assessment is required to be completed at screening within 45 days prior to randomization. The NYHA Class assessment will be completed by 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 trial. This evaluation will be

used to assess the inclusion criterion of NYHA Class II or III heart failure at any point in time within 3 months prior to enrollment or at time of screening (enrollment is defined as the date the subject provided written consent).

3.4.8.6. Screening AHA/ACC Stage Assessment

The AHA/ACC stage assessment is required to be completed at screening within 45 days prior to randomization. The AHA/ACC stage assessment will be completed by the PI or as delegated by the PI to a person qualified to perform the assessment. This evaluation will be used to assess the exclusion criterion of AHA/ACC Stage D heart failure.

3.4.8.7. Screening Carotid Duplex Ultrasound

A carotid duplex ultrasound evaluation will be utilized to confirm that the artery planned for the BAROSTIM implant meets both of the following criteria:

- At least one carotid bifurcation as identification by a bilateral carotid duplex ultrasound within 6 months prior to randomization that is:
  a. Below the level of the mandible AND
  b. No ulcerative carotid arterial plaques AND
  c. No carotid atherosclerosis producing a 50% or greater reduction in linear diameter in the internal carotid AND
  d. No carotid atherosclerosis producing a 50% or greater reduction in linear diameter in the distal common carotid
- No prior surgery, radiation, or endovascular stent placement in the carotid artery or the carotid sinus region.

This assessment will be performed at a local laboratory. If the site can determine eligibility based on a carotid duplex ultrasound obtained within 6 months prior to randomization, it is not necessary to complete a screening carotid duplex ultrasound. The implanting surgeon must review the ultrasound to confirm that the subject is an appropriate surgical candidate.

3.4.8.8. Screening eGFR

A serum eGFR measurement will be obtained at screening and used to confirm the exclusion of serum eGFR < 25 ml/min/1.73 m^2 within 45 days prior to randomization. There is no core lab for eGFR therefore this analysis will be performed at a local laboratory.

3.4.8.9. Screening/Baseline Core Lab NT-proBNP

A serum NT-proBNP measurement will be collected and sent to the designated central core lab to be analyzed. This must be collected **within**

45 days prior to randomization to confirm the inclusion criterion of either:

- Core lab NT-proBNP results of ≥400 pg/ml AND <1600 pg/ml **OR**
- Core lab NT-proBNP < 400 pg/ml within 45 days prior to randomization AND a heart failure hospitalization in the past 12 months

This NT-proBNP lab sample must be collected in an outpatient setting when the subject is thought to be clinically stable. Collecting serum for NT-proBNP involves taking approximately one tablespoon of blood from the arm of the subject. A central core lab will analyze all samples in a blinded and consistent manner throughout the trial. It is important to use the shipping materials provided by the core lab and to carefully follow their instructions on how to obtain and ship the blood sample.

Note: Heart failure hospitalization may include an overnight hospital or hospital-based observation unit stay with a primary diagnosis of heart failure or an emergency room visit with a primary diagnosis of heart failure.

3.4.8.10. Assessment of Enrollment Criteria

Following completion of the screening requirements, all eligibility criteria should be assessed and entered into the trial database. Most screening criteria must be assessed within 45 days of randomization.

3.4.8.11. Re-testing During Screening

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

Exemption: One (1) redraw of the screening/baseline core lab NT-proBNP will be permitted without prior approval during the 45-day screening window due to the variability of this assay.

3.4.8.12. Re-screening Subjects

Re-screening of subjects who previous failed the eligibility criteria are permitted with CVRx Clinical department approval.

3.4.9. Baseline Visit

For each assessment that occurs for both Screening and Baseline (e.g. Physical Assessment, Subject Medications, Adverse Event, Six Minute Hall Walk and NYHA Class Assessment), the Screening and Baseline assessments must be completed on separate days. For example, the Screening and Baseline six-minute hall walk must not be done on the same day.

3.4.9.1. Baseline Physical Assessment

A physical assessment will be performed at baseline. This physical assessment will include the collection of weight, blood pressure, and heart rate. Additionally, sites will ask about any adverse events, changes in medications, or any other notable occurrences.

3.4.9.2. Baseline Six Minute Hall Walk Test (6MHW)

A 6MHW will be performed at baseline. It is very important that each subject attempts to complete the 6MHW assessment. The reasons for inability to do the test, or for stopping the test early, will be collected.

Instructions for performing the 6MHW are provided in Appendix 2 Six Minute Hall Walk Test. These instructions include a clear and well-defined script that provides 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.

3.4.9.3. Baseline NYHA Class Assessment

The NYHA Class assessment is required to be completed at baseline after the screening NYHA. 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 trial.

3.4.9.4. Voice Handicap Index and Eating Assessment Tool

At the baseline visits, subjects will be asked to complete a Voice Handicap Index and Eating Assessment Tool to evaluate if there are any previously existing neurological deficits. If the Voice Handicap Index contains any responses that include a 2 ("Sometimes") or higher for any question OR the Eating Assessment Tool contains any responses that include a 1 or higher for any question, it is recommended that an ENT physician (or clinician with ENT training) is consulted prior to the scheduled implant (or intended implant for medical management subjects) regardless of randomized arm.

3.4.9.5. Baseline Questionnaires

At the baseline visit, subjects will be asked to complete both the Minnesota Living with Heart Failure quality of life (MLWHF) and the EuroQol 5-Dimension (EQ-5D-5L) questionnaires.

Both questionnaires are designed to be self-administered. It is recommended that they be 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 questionnaires are 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 questionnaires to the subject. If possible, the same clinician should instruct the subject throughout the course of the trial. If the subject has questions regarding the questionnaires, 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 questionnaires, the investigator or designee may choose to read the materials to the subject and record their responses.

3.4.9.6. Baseline CRM Arrhythmia Log

At the baseline visit, the Arrhythmia Log may be collected from all subjects with an existing Cardiac Rhythm Management device. If the Log is collected, a copy of this Log must be redacted, re-marked with the subject ID number, and sent to CVRx. The maximum information available for arrhythmias for at least the prior 12 months should be provided. This may require consulting the CRM device physician/clinic to obtain episodes that have been shortened or overwritten with more recent arrhythmias so a full 12 months of data is provided.

3.4.10. Randomization

Once the subject has been determined to meet all eligibility criteria and all baseline measurements have been obtained, subjects may be randomized. Subjects will be randomized 1:1 to either medical management or device and medical management. The randomization assignment will be stratified by site and obtained via the electronic data capture (eDC) system.

Prior to obtaining the randomization assignment, an intended device implant date must be entered into the eDC system. This will be used as the date for the timing of follow-up visits for those randomized to the medical management arm. The actual implant date will be used as the date for the timing of follow-up visits for those randomized to the device arm.

Details on the Implant Procedure Testing and Data for subjects randomized to device may be found in Section 3.4.12 Implant Procedure Testing and Data.

3.4.11. Follow-up Visits

All visits must be completed at the site with the subject physically present. However, after completion of the 12-month visit, an exception may be made if the subject is physically unable to attend a trial visit (e.g. hospitalized or physically unable to travel to the site). In this unique circumstance, this visit may be completed by phone. The specific reason for the inability of the subject to be physically present must be documented.

3.4.11.1. Follow-up Physical Assessment

A physical assessment will be performed at each scheduled follow up visit per the time and events table (see Table 5). This physical assessment will include the collection of weight, blood pressure, and heart rate.

Additionally, sites will ask about any adverse events, changes in medications, or any other notable occurrences.

3.4.11.2. Follow-up Six Minute Hall Walk Test (6MHW)

A 6MHW will be performed at the 6- and 12-month follow-up visits. It is very important that each subject attempts to complete the 6MHW assessment. The reasons for inability to do the test, or for stopping the test early, will be collected.

Instructions for performing the 6MHW are provided in Appendix 2 Six Minute Hall Walk Test. These instructions include a clear and well-defined script that provides 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.

3.4.11.3. Follow-up Core Lab NT-proBNP

A serum NT-proBNP measurement will be performed at the 6- and 12-month follow-up visit. This NT-proBNP must be collected in an outpatient setting when the subject is thought to be clinically stable. Collecting serum for NT-proBNP involves taking approximately one tablespoon of blood from the arm of the subject. A central core lab will analyze all samples in a blinded and consistent manner. It is important to use the shipping materials provided by the core lab and to carefully follow their instructions on how to obtain and ship the blood sample.

3.4.11.4. Follow-up NYHA Class Assessment

The NYHA Class assessment is required to be completed at 6-, 12-, 18-, and 24-month follow up visits. 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 trial.

3.4.11.5. Follow-up Questionnaires

At the 6-, 12-, 18-, and 24-month visits, subjects will be asked to complete both the Minnesota Living with Heart Failure quality of life (MLWHF) and the EuroQol 5-Dimension (EQ-5D-5L) questionnaires.

Both questionnaires are designed to be self-administered. It is recommended that they be provided to the subject at the beginning of each visit prior to any subject interaction, in an effort to minimize the potential influence of healthcare providers. The questionnaires are 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 questionnaires to the subject. If possible, the same

clinician should instruct the subject throughout the course of the trial. If the subject has questions regarding the questionnaires, 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 questionnaires, the investigator or designee may choose to read the materials to the subject and record their responses.

3.4.11.6. Follow-Up ENT Consult

An ENT consult is recommended for any subjects, regardless of randomized arm, with 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.

3.4.11.7. Follow-up CRM Arrhythmia Log

If the CRM Arrhythmia Log was provided at baseline, the Arrhythmia Log may also be collected during follow-up from all subjects with existing cardiac rhythm management devices at an interval of 6 months. If a Log is provided, a copy of the Log must be redacted, re-marked with the subject ID number, and sent to CVRx. The maximum information available for arrhythmias for at least the prior 6 months should be provided. This may require consulting the CRM device physician/clinic to obtain episodes that have been shortened or overwritten with more recent arrhythmias, so a full 6 months of data is provided.

3.4.12. Implant Procedure Testing and Data

3.4.12.1. Locating the Bifurcation

At the beginning of the implant procedure prior to the skin incision, a carotid ultrasound (duplex not required) must be utilized to clearly mark the location of the bifurcation. This will be used to locate the placement of the skin incision.

3.4.12.2. System Implantation

The system implant procedure will be performed with a single lead. It is recommended that the surgeon place the carotid sinus lead on the right side through a transverse incision located directly over the carotid bifurcation; however, the lead may be placed on the left side if factors such as subject anatomy indicate that the left side would be preferable providing the artery meets inclusion criteria #7 (see Section 3.3.1).

The procedures for system implantation and recommended anesthetic regimen are included in the System Reference Guide, which is provided to all clinical sites. All surgeons must be appropriately trained and proctored

to implant the BAROSTIM NEO System. The procedures for surgeon training are described in Section 3.8.

In a continuous effort to reduce potential risks associated with the implantation of the BAROSTIM NEO System, please see the following important items:

- Only a surgeon investigator will perform the surgical procedure.
- Omni-Tract products and other self-retaining retractor systems are NOT recommended since the degree of traction is difficult to assess and has resulted in cranial nerve traction injuries in the past.
- Cephalad traction against the mandible with hand held retractors should be monitored since marginal mandibular nerve injury has occurred with excessive retraction.
- If the subject has a prior cardiac rhythm management device implanted, testing should be completed during the procedure to ensure that the BAROSTIM NEO System does not interfere with the therapy being delivered by the other device.
- Subjects on anticoagulation therapy should be managed according to the ACC/AHA/ESC Guidelines for the Management of Atrial Fibrillation.

3.4.12.3. Anesthetic and Medication Management

The surgery may be performed under general anesthesia or cervical regional block (at the approval of the sponsor). 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 recommended that subjects continue their pre-operative therapy with beta-blockers and aspirin to minimize the potential risks of peri-operative stroke, or myocardial infarction. Other medications that may interfere with the baroreflex or cause hemodynamic instability are to be withheld during the pre-operative period.

3.4.13. Device Programming Evaluation

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 should assess symptoms at rest and walking 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 must be adjusted to alleviate any adverse reactions.

Programming decisions will primarily be evaluated through heart rate and blood pressure. Optionally, blood pressure waveforms reflecting changes in vascular resistance may be used for optimization.

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. Duration of stay after initial device activation will be determined on a patient-by-patient basis at the discretion of the investigational site staff. The principal investigator must be included in the decision to discharge the patient before the recommended 2-hour post-programming time point. At the physician's discretion, subjects may remain overnight after the device has been activated to evaluate programmed settings. The physician should 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 trial.
- 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).

CVRx personnel will only interact with the subject for programming purposes and will not interact during collection of other trial measures such as QOL or NYHA.

3.4.14. System Replacement

The Implantable Pulse Generator (IPG) may need to be replaced during the trial 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 System Reference Guide. The replacement procedure may be performed under local anesthesia.

3.5. Adverse Events

3.5.1. 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 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.

3.5.2. Adverse Event Reporting

Once a subject is enrolled (enrolled is defined as the date the subject provided written consent), all adverse events must be reported until the subject is withdrawn or is terminated from the trial. All reported events regardless of geography will be reported in study reports (e.g. annual reports).

In addition, all adverse events that occur in OUS subjects will also be reported according to ISO 14155:2011, while recognizing and following the requirements including reporting timelines specified in other specific laws, regulations, directives, standards and/or guidelines as appropriate.

3.5.3. Adverse Event Relatedness

Investigators will be asked to assess the potential relationship of the adverse event to the BAROSTIM NEO 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 replacement.
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 peri-operative hypotension.

3.5.4. Cardiovascular Adverse Event

Investigators will be asked to assess if the event was cardiovascular or not. A cardiovascular event is any event related to the heart or vascular system.

3.5.5. Serious Adverse Events

All adverse events will be further classified whether Serious or not according to the definition below.

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.

Note: 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.

Note: 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. If the required timeline for reporting SAEs in other geographies is sooner, then these country regulations must also be followed. For example, in Germany SAEs must be reported to CVRx immediately, within 24 hours after the event is recorded in the test center. CVRx will report SAEs in accordance with the German SAE Reporting work instruction (740070-001).

Note: For reporting in the US, the SAE definition is as defined above. For reporting in other geographies, the Serious Adverse Event definition may be modified to accommodate country specific laws and regulations. For example, for Germany a Serious Adverse Event is defined as an adverse event that lead or could have lead directly or indirectly to death, serious deterioration in the health of the subject, user or other person 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.

3.5.6. Observations and Complications

Adverse events will be further classified as a Complication or an Observation as defined below.

Complication: A complication is defined as an adverse event that results in death, permanent injury, or requires an invasive intervention to prevent death or permanent injury. Blood transfusions are classified as complications. An invasive procedure is not considered a complication if it is performed solely for the purpose of diagnosis.

Observation: An adverse event that does not result in death, permanent injury, or require an invasive intervention to correct.

3.5.7. Adverse Event Organ System Affected

Investigators will be asked to select one of the following organ systems affected by the adverse event. Adverse events that affect multiple systems should be classified as "General disorders".

- Blood and lymphatic system disorders
- Cardiac disorders
- Congenital, familial and genetic disorders
- Ear and labyrinth disorders
- Endocrine disorders
- Eye disorders
- Gastrointestinal disorders
- General disorders
- Hepatobiliary disorders
- Immune system disorders
- Infections and infestations
- Injury, poisoning and procedural complications
- Investigations
- Metabolism and nutrition disorders
- Musculoskeletal and connective tissue disorders
- Neoplasms benign, malignant and unspecified (including cysts and polyps)
- Nervous system disorders
- Pregnancy, puerperium and perinatal conditions
- Psychiatric disorders
- Renal and urinary disorders

- Reproductive system and breast disorders
- Respiratory, thoracic and mediastinal disorders
- Skin and subcutaneous tissue disorders
- Social circumstances
- Surgical and medical procedures
- Vascular disorders

3.5.8. Major Neurological and Cardiovascular Events (MANCE)

Investigators will be asked to determine whether an adverse event is a Major Neurological and Cardiovascular Event (MANCE) which includes: cardiovascular-related death, stroke, cardiac arrest, acute myocardial infarction, acute decompensated heart failure, hypertensive crisis, severe complications of heart failure treatment, systemic and pulmonary thromboembolism, infection requiring explantation of any portion of the BAROSTIM NEO System, functional cranial nerve damage that is either permanent (not resolved within 12 months from onset) or requires an invasive intervention to correct, and events requiring non-elective major restorative procedures (specific to the placement of the BAROSTIM NEO System e.g. operation for wound hematoma at the surgical site).

To provide more clarity around any suspected cranial nerve damage, these events will be classified as to the presence or absence of an associated functional neurological deficit. A functional neurological deficit is defined as related to either the placement of the carotid sinus lead or the delivery of the therapy that cannot be programmed around, and resulting in difficulty swallowing, difficulty speaking or facial droop with drooling or difficulty eating that impacts the subject's daily lifestyle. Functional neurological deficit events must be confirmed by an ENT specialist.

MANCE will be adjudicated by independent adjudication committees (AEC/CEC). If multiple MANCE events in the same subject are adjudicated as causally or temporally linked, such linked events shall be counted as one event. For example, a subject with acute myocardial infarction complicated during the same hospitalization by acute heart failure and cardiovascular-related death would be counted as a single MANCE event, i.e. cardiovascular death linked to acute heart failure and acute MI dated from the time of the inciting event.

3.5.9. Unanticipated Adverse Device Effect (UADE)

For the US study subjects, per 21 CFR 812.3(s) "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.

For other geographies, ISO 14155 defines an Unanticipated Serious Adverse Device Effect (USADE) as a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. Reporting of USADEs must follow country regulations.

3.6. Equipment, Instrumentation and Support

CVRx will provide the following:

- Carotid Sinus Lead(s)
- Implant Tool
- Implant Adapters
- Implantable Pulse Generator
- Programmer System
- Magnet
- Accessory Kit
- CSL Repair Kit
- System Reference Guide
- All required Forms and Agreements
- Shipping materials to return investigational devices and trial data
- Support for implants and follow-ups as available
- Protocol, implantation and device operation training
- Subject identification cards
- Electronic Data Capture (eDC) database and support
- Blood corelab materials

The Participating Institution will provide the following:

- Expertise in the care and management of subjects with heart failure
- All facilities, equipment and expertise required for CSL and IPG implantation
- Capabilities and facilities to collect all required data
- Appropriately trained personnel to handle and ship blood

3.7. Investigator Certification

All investigators participating in this trial are expected to fully execute the CVRx Investigator Agreement for the trial. Investigational devices will not be provided to any investigator prior to the receipt of the signed agreement.

3.8. Surgeon Training

Surgeon Investigators must be trained in order to implant the BAROSTIM NEO System. The training process will require:

- Training on implant procedure, anesthesia, and BAROSTIM NEO System operation.
- A minimum of two proctored implants of the BAROSTIM NEO System with a CVRx-certified proctor (inclusive of any prior BAROSTIM NEO System implant experience).

3.9. Device Accountability, Handling and Storage

This trial will utilize CVRx Implantable Pulse Generators (IPGs) and Carotid Sinus Leads (CSLs). These devices will be labeled as Investigational Devices and will require special handling and storage controls. All IPGs, CSLs, Programmers, CSL Repair Kits, and accessory kits delivered to the institution will be recorded by serial number on a Device Accountability Log. 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.

All IPGs and leads utilized in the trial will be recorded in the trial database. Upon conclusion of the trial all unused and any explanted IPGs and CSLs will be returned to CVRx in the device shipment materials provided.

3.10. Termination of Therapy

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. It is recommended to wait at least 30 days following termination of therapy prior to explanting the device to allow for an assessment of the subject status. If the decision is made by the subject or clinician to withdraw or partially withdraw from the trial, the Baroreflex Activation Therapy can continue outside the study. The investigator should discuss the options for following routine care of the system, turning off the device or explanting the IPG including the potential risks of each. It is recommended that the Carotid Sinus Leads should not be explanted, and the leads should be left implanted with the leads capped.

If any portion of the system 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 system- or procedure-related 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 trial database. A trial termination form should be completed.

3.11. Final Trial Visit

If the subject has any ongoing system- or procedure-related adverse events at the time of the final trial visit, these events will be listed as unresolved. If the subject decides not to continue to receive therapy, please refer to Section 3.10 Termination of Therapy. A trial termination form should be completed indicating the "subject completed trial per protocol" and the date of the final trial visit.

3.12. Withdrawal of a Subject

A subject may be withdrawn or partially withdrawn from the trial at any time by the investigator for a variety of reasons including, but not limited to, the subject not following trial-related directions, or a serious reaction develops or implantation of the BAROSTIM NEO System in countries where the device is market approved. A subject may also choose to voluntarily withdraw consent for the trial or from receiving further trial treatment at any time. The subject's eligibility for continuing medical care will not be affected by his/her withdrawal from the trial.

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. Note the non-US PIs will make every effort to encourage the subjects to stay in the trial to their assigned randomization before opting out to a BAROSTIM NEO implant.

Should a subject express the desire to withdraw from the study, the subject should be made aware of the option to partially withdraw from the study. This may be done through a consent form for subjects who wish to discontinue active follow-up in the trial, but not fully withdraw. The objective of the partial withdrawal is to allow site personnel continued access to subject medical records in order to collect information for the morbidity and mortality endpoint. Please refer to Section 3.4.5 Partial Withdrawal

For subjects who progress in their heart failure status to receive either a cardiac assist device or a heart transplant, see Section 3.15.

3.13. Lost to Follow-Up

It is strongly recommended that multiple telephone numbers should be obtained from the subject to ensure the ability to contact him or her for the required follow-up visits. These phone numbers should include all home/mobile numbers, work numbers (if applicable) and their primary physician numbers. A phone number of a relative or friend should also be requested.

If a subject cannot be reached for a follow-up visit, the site will complete a protocol Deviation Case Report Form. The efforts undertaken to contact the subject, family members, or other alternate contacts should be noted in the subject's records. These efforts should include at least 2 attempts of telephone contact on separate dates, and at least two weeks of non-response after a certified letter sent to the last known address.

If two consecutive protocol-required visits meet the above criteria, a subject is considered lost to follow-up. As the subject has not withdrawn consent, the subject may remain active in the database to collect any available data. At the end of the study they will be considered permanently lost-to-follow.

3.14. Discontinuation of Therapy

Circumstances may arise during the trial that require the device to be temporarily or permanently turned off for a subject. This may include an adverse event, an intercurrent illness or other medical condition where continued therapy would not be in the best interest of the subject, or subject's wish.

If the device is turned off temporarily, the reason should be clearly noted in the subject's medical records and a Programming CRF should be completed to document the date.

3.15. Cardiac Assist Device or Heart Transplant

Subjects in either treatment arm who progress in their heart failure status to receive either a cardiac assist device or a heart transplant must be withdrawn from the study. For subjects with an active BAROSTIM NEO device in geographies where the device is not approved, the device must be permanently turned off prior to the cardiac assist device or heart transplant procedure (see Section 3.10). 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 Leads should not be explanted, and the leads should be left implanted with the leads capped. These device subjects must be followed for 30 days after the termination of device therapy or after the explanting of any of the BAROSTIM NEO System.

4. ENDPOINTS, STATISTICAL METHODS AND DATA ANALYSIS

4.1. General Principles

The primary analysis for all baseline characteristics and trial outcomes will include all randomized subjects, unless specified otherwise. Standard summary statistics will be calculated for all trial variables. For continuous variables, statistics will include means, standard deviations, medians and ranges. Categorical variables will be summarized in frequency distributions.

For effectiveness outcomes, primary analyses will be conducted on an intent-to-treat (ITT) basis, for which subjects are analyzed according to their randomized assignment irrespective of the treatment received. The safety analysis will include all subjects where an implant has been attempted.

Statistical analyses will be conducted in SAS version 9.3 or above (SAS Institute, Cary, N.C.) or another validated statistical software.

Details on the analyses defined below, as well as supportive and ancillary analyses, will be provided in a Statistical Analysis Plan (SAP). Any deviation from the protocol or the SAP will be discussed and based on sound statistical rationale. Endpoints and analyses defined in a Statistical Analysis Plan supersede the definitions in this protocol.

4.2. Experimental Design

This is a prospective, randomized trial demonstrating the safety and efficacy of the BAROSTIM NEO System in the indicated trial population.

4.3. Primary Morbidity and Mortality Endpoint

The primary morbidity and mortality (M&M) analyses will support a supplemental PMA submission for the following Indication for Use statement:

The BAROSTIM NEO System is indicated for patients with heart failure. Heart failure is defined as:

New York Heart Association (NYHA) functional Class III, left ventricular ejection fraction (LVEF) ≤ 35% and NT-proBNP<1600 pg/ml despite being treated with the appropriate heart failure guideline-directed therapy, excluding subjects eligible for or actively receiving Cardiac Resynchronization Therapy (CRT).

4.3.1. Rate of Cardiovascular Mortality and Heart Failure Morbidity

The endpoint is to demonstrate that treatment with the BAROSTIM NEO System, relative to medical management, reduces the rate of cardiovascular mortality or worsening heart failure that leads to hospitalization or emergency room visit, cardiac assist device or heart transplant.

Subjects will be censored at the time of a terminal event (i.e., death, permanent cardiac assist device, heart transplant, or novel implantation of a device to receive Cardiac Contractility Modulation) or end of follow-up, whichever occurs first. Subjects who progress in their heart failure status to receive either a cardiac assist device or a heart transplant must be withdrawn from the study within 60 days of the assist device procedure or heart transplant (see Section 3.15).

Definitions for the endpoint components can be found in Section 4.3.4. The events will be adjudicated in a blinded manner by an independent Clinical Events Committee (CEC). The CEC Charter definitions supersede any definitions in this protocol.

4.3.2. Statistical Hypothesis Test

The rate of endpoint events will be compared between the two groups using a negative binomial model. The model will be adjusted for the number of heart failure hospitalizations 12 months prior to enrollment to adjust for any potential imbalance between the two arms.

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

Ho: $\beta_1 = 0$

Ha: $\beta_1 < 0$

where β_1 is the natural log of the ratio of events per patient-year between groups (treatment/control).

Success for this endpoint is determined by rejection of the null hypothesis with a lower rate of events in the treatment arm compared to the control arm.

4.3.3. Sample Size and Power

The total sample size is based on having an adequate number of events to evaluate the morbidity and mortality endpoint in subjects with NT-proBNP <

1600. The simulations are based on a frequentist design using a fixed sample size assuming three interim analyses and a final analysis, a 35% relative reduction in morbidity and mortality, and a control arm rate of 0.4 events per patient year. Under these assumptions, a total of 320 events provide 87% conditional power and a one-sided conditional type I error of 5%.

The total number of randomized subjects with an NT-proBNP < 1600 needed to reach 320 events is approximately 331. A total of 259 subjects with an NT-proBNP < 1600 have been randomized and are accruing events. A total of 72 new subjects with an NT-proBNP < 1600 will be randomized (approximately 240 new enrollments) to accrue the planned number of events. The final trial sample size will result in 480 subjects randomized, with approximately 331 of these randomized subjects with a baseline NT-proBNP < 1600.

Assuming up to 70% of subjects enrolled were not randomized (e.g., failure to meet all inclusion/exclusion criteria), a total of up to 1200 subjects may need to be enrolled.

The average follow-up time for the M&M endpoint is expected to be 2.3 years.

Full details regarding the planned analysis and statistical details are defined in a Statistical Analysis Plan supplement.

4.3.4. Cardiovascular Death and Heart Failure Hospitalization Definitions

The CEC Charter definitions supersede all definitions below.

Cardiovascular Death

Deaths are considered cardiovascular unless a specific non-cardiovascular cause is identified. Deaths classified as "Unknown" are considered cardiovascular.

Heart Failure Hospitalization

A heart failure hospitalization for worsening heart failure is defined as a non-elective hospitalization that includes at least two of the following: Increased signs (e.g., Jugular venous distention, pulmonary rales, S3, edema), symptoms (e.g., dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, fatigue) or laboratory evidence [e.g., Chest x-ray - PVR, interstitial edema, effusions, significantly increased BNP, NT-proBNP, new onset or worsening prerenal azotemia (BUN/CR)] of worsening heart failure. The administration or augmentation of parenteral agents (e.g., inotropes, diuretics, and/or vasodilators), mechanical heart failure therapy or use of ultrafiltration and/or paracentesis is required.

Cardiac Assist Device

A mechanical circulatory device used to partially or completely replace the function of a failing heart.

Heart Transplant

A surgical transplant procedure that is performed due to end-stage heart failure or severe coronary artery disease.

4.3.5. Morbidity and Mortality Interim Analyses

The cadence and details regarding pre-specified interim analyses is detailed in a Statistical Analysis Plan. The purpose of the morbidity and mortality interim analyses are for the evaluation of a successful morbidity and mortality endpoint, and will be based on a frequentist negative binomial analysis.

4.4. Secondary Morbidity and Mortality Endpoint

The secondary objective is to demonstrate that treatment with the BAROSTIM NEO System, relative to medical management, reduces the rate of cardiovascular mortality or worsening heart failure that leads to hospitalization (expanded definition) or emergency room visit (expanded definition), cardiac assist device or heart transplant.

As this endpoint may include additional events due to the expanded definition, and the planned censoring, statistical hypothesis, analysis method and population is the same as the primary endpoint, the endpoint should have at least the power of the primary endpoint. The expanded definition is defined in the CEC Charter and includes hospitalizations that are determined to be heart failure hospitalizations by a CEC consensus yet may not have all of the documentation available.

4.5. Poolability Across Investigational Sites

This is a multi-center clinical trial 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 trial in a summary form, a comparison of the primary endpoint across sites will be completed to determine if the generated data can be pooled. Any center which implanted fewer than ten (10) subjects will be combined to facilitate modeling and comparisons.

Poolability by site will be evaluated by including a site term and a treatment-by-site interaction term in the regression model for the primary endpoint; a p-value less than 0.15 for the interaction term will be considered evidence of non-poolability.

4.6. Gender Analysis

Treatment differences by gender will be evaluated formally for the primary endpoint by including a gender term and treatment-by-gender interaction term in the regression model; a p-value less than 0.15 for the interaction term will be considered evidence of a significant interaction between the treatment arms and gender

5. TRIAL OVERSIGHT AND COMMITTEES

5.1. Executive Steering Committee (ESC)

The Heart Failure ESC will be responsible for general oversight of the trial. A list of the members can be found in APPENDIX 1: Executive Steering Committee Members.

5.2. Adverse Events Committee (AEC)

An Adverse Events Committee (AEC) will review and adjudicate adverse events per the AEC Charter. The AEC is not blinded to treatment arm. The definitions in the AEC charter will supersede the 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.

5.3. Clinical Event Committee (CEC)

A Clinical Events Committee (CEC) will adjudicate events such as hospitalizations and deaths. The primary role of the CEC is to adjudicate hospitalizations and deaths to determine if the event is a primary efficacy endpoint event according to the definitions in the CEC charter. The CEC is blinded to treatment arm. The CEC charter definitions supersede any definitions in this protocol.

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

5.4. Data Monitoring Committee (DMC)

A Data Monitoring Committee (DMC) will provide independent oversight of the trial. As part of this oversight, the DMC will ensure protocol adherence, proper protocol conduct, data quality, and subject safety and efficacy.

Members of the DMC will be independent in that they are not involved in the conduct of the trial except through their role on the DMC, have no financial or other important connections to CVRx or CVRx affiliates and will confirm that they have no other conflicts that would prevent them from completing their charter in an unbiased, objective manner.

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

The sponsor will:

- Provide to the FDA a copy of any written communication from the DMC to the Sponsor related to safety concerns, or changes to the trial protocol, procedures or informed consent document.
- Provide to the DMC a copy of any written letter from the FDA to the Sponsor related to safety concerns, or changes to the trial protocol, procedure or informed consent document.

6. RISK ANALYSIS

6.1. Benefits

All subjects enrolled in the trial will receive nominal compensation for their time and travel expenses and will also receive medical care from physicians who are experts in the treatment of heart failure. They will be seen at frequent visits throughout trial follow-up and will receive ongoing care throughout the duration of the trial.

Subjects randomized to the Device Group will also receive Baroreflex Activation Therapy (BAT). At this time, the benefit of BAT is unproven in a heart failure population. It is anticipated that BAT in subjects with heart failure will reduce subject symptoms and increase subject quality of life by improving cardiac and vascular function. These improvements are expected to result in fewer hospital stays and possibly provide a survival benefit to subjects. These anticipated effects are supported by preclinical and clinical evaluations conducted by CVRx.

6.2. Risks and Minimization of Risks

It is anticipated that subjects who are 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 or anesthetic complications
- Infection – the need for antibiotics or possible removal of the BAROSTIM NEO System
- Wound complication – including hematoma (i.e. bruising and/or swelling)
- Arterial damage – including carotid artery rupture or hemorrhage (sudden and significant blood loss at a site of blood vessel rupture that may require reoperation or transfusion)
- Pain – an unpleasant sensory experience
- Nerve damage/stimulation – including injury to or stimulation of Cranial, Marginal Mandibular, Glossopharyngeal, Recurrent Laryngeal, Vagus and Hypoglossal Nerves (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
- Hypertensive crisis – uncontrolled rise in blood pressure
- Respiratory – including low oxygen saturation, respiratory distress, shortness of breath
- 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 subject – may be due to surgical procedure, device use, or interaction with other devices
- Need for reoperation – operation to explant/replace IPG or CSLs 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
- Exacerbation of heart failure
- Cardiac arrhythmias
- Death

These risks can be minimized through selection and training of qualified investigators, use of strict aseptic technique, compliance with the trial 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.

7. DESCRIPTION OF DEVICE

A complete description of the device 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 BeAT-HF 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 BAROSTIM NEO System includes the following components:

- Implantable Pulse Generator, Model 2102 or 2104
- Carotid Sinus Lead, Models 1036 or 1037

- CSL Repair Kit, Model 5010
- Programmer System Model 9010 or 9020

The primary components of the BAROSTIM NEO System are shown in Figure 8.

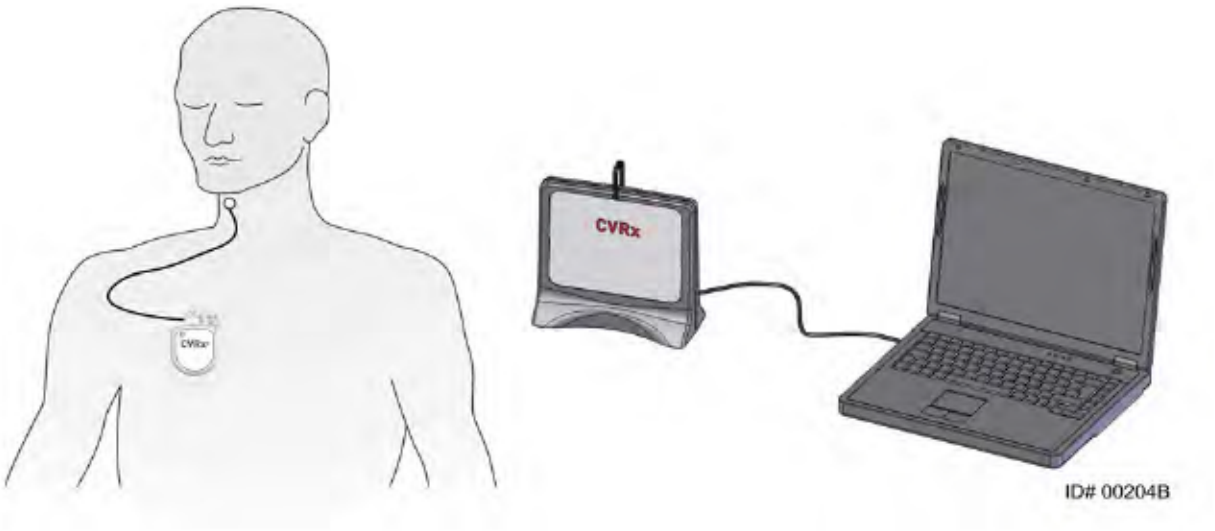


Figure 8: BAROSTIM NEO System

8. MONITORING

Each clinical site will be monitored to ensure that the trial is conducted in full compliance with the trial 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 trial. 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

9. LABELING

Copies of the instructions for use (IFU) pertaining to this protocol are provided in the Barostim System IFUs, 900133-001 to -005 will be provided to all participating sites as part of the site initiation process. Copies of all device package labeling are available and will be provided to the sites upon request.

Copies of all labeling for the device including the System Reference Guide and device package labeling were provided to FDA in the IDE application.

10. CONSENT MATERIALS

Copies of all forms and informational materials to be provided to subjects to obtain informed consent will be provided to all participating clinical sites.

11. INSTITUTIONAL REVIEW BOARD/ETHNICS COMMITTEE INFORMATION

All investigational sites will be required to have IRB or EC approval, as required by country specific regulations, and investigator agreements approved before they will be allowed to enroll subjects into the trial.

12. OTHER INSTITUTIONS

CVRx will only conduct the investigation at institutions that meet the requirements noted in Section 11 above.

13. RECORDS AND REPORTS

13.1. 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 the investigator must maintain the records required during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

An investigator may withdraw from the responsibility to maintain records and transfer custody of the records to any other person, including the sponsor, who will accept responsibility for them. Notice of a transfer shall be given to the sponsor not later than 10 working days after transfer occurs.

Records may include (not all inclusive):

- All significant 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; 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
- EC/IRB Approval and discourse documentation. A copy of the IRB/EC Approval must be submitted to CVRx.

13.2. Investigator Reports

Table 7: Investigator Reports

Report	Submit To	Description
Unanticipated Adverse Device Effects (UADE) or Unanticipated Serious Adverse Device Effect (USADE)	EC/ IRB (as applicable) & CVRx	In the US, UADEs must be reported to CVRx within 10 working days after the site first learns of the event. For other geographies, reporting is required as specified by country regulations.
Serious Adverse Events (SAE)	CVRx	In the US, SAEs must be reported to CVRx within 10 working days after the site first learns of the event, other geographies as specified by country regulations.
Withdrawal of IRB/EC Approval	CVRx	Notification within five working days
Progress Report	CVRx, IRB	Periodic report detailing the progress of the trial, occurring at least annually.
Deviations from Investigational Plan	IRB/EC & 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.

13.3. 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 trial visit reports
- CVRx will own and store the clinical data generated under this protocol
- CVRx will maintain these records according to country requirements

13.4. CVRx Reports

Table 8: CVRx Reports

Report	Submit To	Description
Unanticipated Adverse Device Effects (UADE) or Unanticipated Serious Adverse Device Effect (USADE)	Investigators, IRB/ECs (as applicable), & FDA/CA	In the US, Notification within ten working days after the sponsor first learns of the event. For other geographies, reporting is required as specified by country regulations.
Withdrawal of IRB/EC Approval	Investigators, FDA/CA, & IRB/ECs	Notification within five working days after the sponsor first learns of the event.
Withdrawal of FDA Approval	Investigators, CA & IRB/ECs	Notification within five working days after the sponsor first learns of the event.
Progress Report	FDA	Periodic report detailing the progress of the trial (as required).
Annual Report	FDA & Investigators	Report detailing the annual progress of the trial.
Final Report	FDA/CA, Investigators, & IRB/ECs	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 trial as specified by the country regulatory authority or regulations. The investigator should confirm the receipt of the final report composed by CVRx.

14. PUBLICATION POLICY

A multi-center manuscript summarizing the trial results will be prepared for publication at the end of the trial. Single-center publications summarizing primary endpoint data are not allowed until after the publication of the primary manuscript.

15. CONTACT INFORMATION

CVRx
9201 West Broadway Avenue North, Suite 650
Minneapolis, MN 55445
Telephone: +1 763-416-2840
Facsimile: +1 763-416-8402

APPENDIX 1: Executive Steering Committee Members

Michael Zile, M.D. (Chair)	Medical University of South Carolina
William Abraham, M.D.	The Ohio State University
JoAnn Lindenfeld, M.D.	Vanderbilt Heart and Vascular Institute
Fred Weaver, M.D.	University of Southern California
Faiez Zannad, M.D.	Université de Lorraine, CHU de Nancy

Appendix 2: Six Minute Hall Walk Test

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.[38]

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.

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