A PHASE II STUDY TESTING THE FEASABILITY AND EFFICACY OF CORONARY SINUS NARROWING IN PATIENTS WITH CORONARY MICROVASCULAR DYSFUNCTION

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Study Device:	The Reducer (Neovasc Inc., Richmond, B.C., Canada)
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Study synopsis

Title	A Phase II Study Testing the Feasibility and Efficacy of Coronary Sinus Narrowing in Patients with Coronary Microvascular Dysfunction
Study objective	To evaluate the impact of the Neovasc Reducer ™ device implantation on coronary microvascular function assessed invasively by measurement of coronary flow reserve (CFR) and the hyperemic myocardial resistance (HMR) in patients with angina but no-obstructive coronary artery disease (ANOCA) and documented coronary microvascular dysfunction (CMD) [CFR≤2.5 and/or HMR≥2.5] or coronary blood flow (CBF) response to acetylcholine ≤ 50%.
Study hypothesis	In patients with ANOCA and documented CMD, narrowing of the CS by Reducer implantation will improve microvascular function as measured by CFR and HMR, and quality of life
Device	The Neovasc Reducer™ System (Neovasc Inc., Richmond, B.C., Canada)
Study design	• Prospective, single center, single arm, clinical trial • Patients with chronic refractory angina (Canadian Cardiovascular Society (CCS) grade II-IV, no obstructive CAD (<50% stenosis in epicardial vessels and/or iFR>0.89 or FFR>0.8 in vessels with 50 to 70% stenosis), and documented CMD (CFR≤2.5 and/or HMR≥2.5) or coronary blood flow (CBF) response to acetylcholine ≤ 50% on clinically indicated coronary angiography and invasive coronary reactivity testing which uses Adenosine, Acetylcholine & Nitroglycerin as standard clinical practice will be eligible for enrolment.

	• After a full clinically indicated coronary flow evaluation is performed in the left anterior descending artery (LAD) as standard of care using an intracoronary combined Doppler-flow and pressure wire (ComboWire XT, Philips Volcano Corporation, Del Mar, California) that provides iFR/FFR, HMR and CFR measurements, patients will be determined eligible. • Baseline clinical evaluations of eligible patients will include clinical characteristics, medication profiles including antianginals, evaluation of angina severity and frequency by CCS angina class and Seattle Angina Questionnaire (SAQ), in addition to ischemia, exercise capacity, and left ventricular diastolic function and filling pressures at peak exercise on an exercise bike echocardiographic stress test (EBEST) using a supine bike protocol starting at 25 Watts and increasing by 25 Watts every 2 minutes. • Eligible patients will undergo percutaneous CS Reducer implantation for the treatment of CMD. • Adverse events will be collected during the 4 months study period and monthly follow-up phone calls with study participants will be conducted at 1, 2, and 3 months post CS reducer implant • Study participants will undergo full repeat invasive evaluation of coronary blood flow and microvascular resistance (CFR and HMR) as well as repeat clinical evaluation (including CCS class, SAQ, antianginal medication use, adverse events, and EBEST) at 4 months following Reducer implantation.
Number of subjects	30

Population	Patients with chronic refractory angina (CCS class II-IV), no obstructive CAD (<50% stenosis in epicardial vessels and/or iFR>0.89 or FFR>0.8 in vessels with 50 to 70% stenosis), and documented CMD (CFR≤2.5 and/or HMR≥2.5) & or coronary blood flow (CBF) response to acetylcholine ≤ 50% on clinically indicated coronary angiography and invasive coronary reactivity testing which uses Adenosine, Acetylcholine & Nitroglycerin as standard clinical practice
Inclusion criteria	• Age ≥18 • Able to provide written informed consent and willing to participate in all required study follow-up assessments • Symptomatic CAD with refractory angina defined as CCS class II to IV, despite optimal tolerated medical therapy • Abnormal coronary microvascular function indices: CFR≤2.5 and/or HMR≥2.5 & o or coronary blood flow (CBF) response to acetylcholine ≤ 50%
Exclusion criteria	• Recent (within 3 months) acute coronary syndrome • • Patients with prior coronary artery bypass surgery • Unstable angina (recent onset angina, crescendo angina, or rest angina with ECG changes) during the last 30 days • Subjects in cardiogenic shock (systolic pressure < 80mm/Hg, on vasopressors or intraaortic counter pulsation) at the time of consenting. Subjects who recover from cardiogenic shock by the time of consenting are eligible. • Obstructive CAD on coronary angiography (>70% stenosis or 50-70% stenosis with iFR≤0.89 or FFR≤0.8 in epicardial artery)

	• Inability to perform invasive coronary flow evaluation and/or measure CFR and HMR in the LAD • Severe valvular heart disease • LVEF<30% • Decompensated congestive heart failure (CHF) or hospitalization due to CHF during the last 3 months • Patient with a pacemaker electrode in the CS • Mean right atrial pressure >15 mmHg • Anomalous or abnormal CS anatomy (e.g., tortuosity, aberrant branch, persistent left superior vena cava (SVC) as demonstrated on angiogram • CS diameter at the site of planned implantation greater than 13mm or less than 9.5 mm as measured by angiogram • Severe chronic obstructive pulmonary disease (COPD) indicated by a forced expiratory volume in one second that is less than 55 percent of the predicted value • Tricuspid valve replacement or repair (tissue or mechanical) • Chronic renal failure (serum creatinine >2mg/dL), and or on chronic hemodialysis • Moribund, or with comorbidities limiting life expectancy to less than one year • Known severe reaction to required procedural medication • Known allergy to stainless steel or nickel • Magnetic Resonance Imaging (MRI) within 8 weeks of Reducer implantation • Participation in another ongoing investigational trial • Additional factors deemed unsuitable for trial enrollment per discretion of principal investigator • Inmates
Primary endpoint	Change in CFR and HMR measurements at 4 months post Reducer implantation compared to baseline

Secondary endpoints	• Change in CCS angina class • Change in the score of all 5 domains of the Seattle Angina Questionnaire for assessing quality of life • Change in short acting nitrates (spray or sublingual consumption frequency • Change in EBEST parameters at 4 months compared with baseline (total exercise duration, time to 1 mm ST segment depression, evidence of ischemia, peak exercise stage, peak exercise diastolic function and filling pressures as measured by echocardiographic E/e', and exercise-induced symptoms) • Procedural-related Major Adverse Cardiac Events defined as: death, myocardial infarction, perforation of the CS, CS total occlusion, or need for urgent dilatation of the Reducer within 4 months of follow-up
Statistical considerations	The effect of the CS Reducer implantation on microvascular function will be evaluated by the change in measured CFR and HMR at 4 months follow-up compared to baseline pre-CS Reducer implantation. Statistical analysis of the absolute and percent change in CFR and HMR measurements at follow-up will be done. Analysis of the delta change in CFR and HMR will also be performed. Change in angina intensity and frequency, and quality of life, will be evaluated by analyzing the change in CCS angina class, SAQ score in all five domains, and antianginals need and frequency rom baseline to follow-up. Change in functional capacity will be evaluated as the change in baseline to follow-up EBEST total exercise duration, peak exercise stage, exercise-induced symptoms, and ischemic ECG and echocardiographic findings. Change in diastolic function and filling pressures

	will be evaluated as baseline to follow-up change in resting and peak exercise echocardiographic E/e' ratio.

Project Summary/Abstract

The estimated patient population that suffers from coronary microvascular dysfunction (CMD) is high with limited current available therapeutic strategies. At least 40-50% of symptomatic patients referred for a clinically indicated coronary angiography have non-obstructive coronary artery disease (CAD) and among those, more than 60% have CMD by invasive diagnostic coronary reactivity testing. Currently there is no established effective treatment for symptomatic patients with CMD, and therefore a novel effective CMD treatment remains an important unmet clinical need. Previous studies have demonstrated that narrowing of the coronary sinus (CS) using The Neovasc Reducer™ System (Neovasc Inc., Richmond, B.C., Canada), has demonstrated to be safe with promising therapeutic results in patients with severe refractory angina secondary to obstructive CAD with no revascularization options. Procedural success of CS Reducer implantation has been shown to be very high in the COSIRA randomized controlled trial, in interim analysis of the largest European prospective registry with up to 2 years follow-up and in many smaller observational studies. CS narrowing leads to increased backwards pressure that causes slight dilatation and a consequent reduction in the resistance to flow in the microvasculature (resistance arterioles) of the ischemic sub-endocardial myocardium. This subsequently causes a redistribution of blood from the less ischemic sub-epicardium to the more ischemic sub-endocardium accompanied by symptomatic improvement. A small observational study and few case reports have recently suggested that CS narrowing may be effective in improving angina, quality of life, functional capacity and reduction in myocardial ischemia in patients with angina but no obstructive CAD. The potential benefit of an effective therapy which will improve CMD is far-reaching. Considering the already established efficacy of the Reducer in improving symptoms of angina and reducing ischemic burden, its beneficial effect on ischemia in patients without obstructive

CAD, the evidence that increased CS pressure improve microvascular function, and bearing in mind the presumed mechanism of action of the CS Reducer, it is plausible that this treatment can be effective in this patient population.

Approximately, 30 subjects with angina, no obstructive CAD, and CMD invasively diagnosed by abnormal coronary flow reserve (CFR) and/or hyperemic microvascular resistance (HMR) will be enrolled in this single arm study. The primary objective is to evaluate the effect of CS narrowing using the Neovasc Reducer™ System on CFR and HMR at 4 months post Reducer implantation. Additional data will be collected on the adverse events and procedural success of the Reducer implantation procedure; as well as 4-months post-implant symptomatic and quality of life improvement as measured by the Canadian Cardiovascular Society (CCS) angina class, Seattle Angina Questionnaire short acting nitrates consumption frequency, functional capacity, intracardiac filling pressures, and ischemia as measured by exercise bicycle echocardiogram stress testing.

We hope that this study, the first of its kind in the USA using the CS Reducer as potential therapy for angina with no obstructive CAD (ANOCA) will address the therapeutic potential of CS narrowing for the treatment of CMD, an important unmet clinical need, and generate preliminary data for larger randomized phase 2 and 3 trials.

Study protocol

1- Introduction

This document is a human research study protocol. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

2- Background

2.1 Coronary microvascular dysfunction: Magnitude of the problem

Coronary microvascular dysfunction is not uncommon. The prevalence of non-obstructive coronary artery disease (CAD) in patients suffering from angina pectoris undergoing clinically indicated coronary angiography is 30-50% [1, 2]. Of those patients with angina and non-obstructive coronary artery disease (ANOCA), 90% have identifiable abnormal coronary physiology [3] and 50-60% have coronary microvascular dysfunction (CMD) [3, 4].

2.2 Coronary microvascular dysfunction: Symptoms and adverse outcomes

Coronary microvascular dysfunction contributes to myocardial perfusion abnormalities and ischemia [5] and leads to poor outcomes. In addition to disabling angina and severely limited quality of life [3], CMD has been associated with a 6-fold increase in adjusted mortality and higher risk of major adverse cardiovascular events (MACE), including diastolic heart failure, acute coronary syndrome, myocardial infarction, and sudden cardiac death [5-10].

2.3 Coronary microvascular dysfunction: Pathophysiology of ischemia and angina

Coronary microvascular dysfunction (CMD) refers to the subset of disorders affecting the structure and function of the coronary microcirculation. It is prevalent in patients across a broad spectrum of cardiovascular conditions such as left ventricular diastolic dysfunction, cardiomyopathies, coronary atherosclerosis, hypertensive heart disease, and diabetes mellitus.

The coronary arterial system represents a continuous network of functionally distinct vessel segments of decreasing size and diameter. The epicardial arteries (>400 μm) have a primary conductance function and exhibit minimal resistance to coronary flow under normal conditions, with their diameters regulated by shear stress and endothelial function. In contrast, the pre-arterioles (100 to 400 μm) and arterioles (<100 μm) make up most of the resistance circuit of the heart and are responsible for regulation and distribution of blood flow to match the dynamic needs of local tissue metabolism via the coronary capillaries bed (<10 μm) [5]. In healthy arteries, coronary blood flow and myocardial perfusion are regulated by coronary arteriolar tone. Coronary blood flow remains constant over a wide range of coronary perfusion pressures through dynamic changes in resistance vessel tone. These dynamic changes result from a series of mechanisms, including adrenergic stimuli, changes in local oxygen tension, and the response to changes in transmural pressure [5]. Such control of coronary blood flow helps to mitigate myocardial ischemia during the development and progression of epicardial atherosclerosis. In the heart, oxygen extraction is near-maximal at rest; therefore, myocardial oxygen delivery is almost completely dependent on coronary blood flow [11]. Consequently, an increase in myocardial oxygen demand must be matched by a proportional increase in coronary blood flow to prevent myocardial ischemia. CMD attenuates coronary flow augmentation in response to stress, and, if severe enough to lead to demand-supply mismatch, may lead to myocardial ischemia and to angina [12].

A number of structural and functional changes have been linked to CMD. Structural changes include microvascular obstruction with intramural arteriolar luminal narrowing/obliteration and capillary rarefaction [13], and is known to be magnified by the presence of atherosclerosis, particularly in patients with CV risk factors including diabetes, hypertension, and renal impairment, or evidence of diffuse epicardial atherosclerosis.

Functional abnormalities of the microcirculation regulating arteriolar tone are present in the majority of patients with CMD. Attenuated vasodilator responses to papaverine, adenosine, or dipyridamole, which are largely mediated by vascular smooth muscle relaxation of resistive vessels, have been documented in patients with diabetes, metabolic syndrome and other cardiovascular risk factors [12]. Thus, assessing microvascular function is essential for the diagnosis and risk stratification of patients with angina or myocardial ischemia and non-obstructive CAD [14, 15].

2.4 Coronary microvascular dysfunction: Diagnosis

Visualization of the coronary microcirculation is beyond the resolution of both invasive angiography and noninvasive coronary imaging modalities. Therefore, direct interrogation of coronary microvascular function is necessary to establish the diagnosis of CMD. Coronary flow reserve (CFR), calculated as the ratio of hyperemic to rest coronary blood flow, is a measure of coronary vasomotor function that integrates the hemodynamic effects of not only focal and/or diffuse epicardial disease but also small vessel disease on coronary blood flow in response to hyperemic pharmacologic (such as adenosine) or physiologic (exercise) stimuli. Therefore, in the absence of the obstructive epicardial disease, abnormal CFR is diagnostic of CMD. CFR can be measured by invasive coronary reactivity testing [11] and non-invasive imaging modalities such as positron emission tomography (PET), cardiac magnetic resonance imaging and transthoracic echocardiography [12]. However, while these non-invasive imaging modalities are able to identify impaired CFR, they are not able to reliably evaluate the hemodynamic significance of a moderate or severe epicardial lesion and thus rule out the presence of concomitant obstructive CAD. On the hand, invasive angiography by combining the ability to exclude obstructive epicardial CAD, with complementary catheter-based

techniques to probe epicardial [by fractional flow reserve (FFR) or instantaneous flow reserve (iFR)] and microvascular coronary physiology [by CFR and hyperemic microvascular resistance (HMR)], is an accurate, comprehensive, and reproducible approach to evaluate patients with CMD. Accordingly (Figure 1):

- FFR (the ratio between coronary pressure distal to a stenosis and aortic pressure during maximal hyperemia, normal > 0.8) and iFR (the ratio between coronary pressure distal to a stenosis and aortic pressure during diastolic wave-free phase of the cardiac cycle, normal >0.89) are used to rule out flow limiting lesions in epicardial arteries [16-19]. Both FFR and iFR are assessed using a pressure guidewire.
- CFR (the ratio of hyperemic over rest coronary blood flow) ≤2.5 is diagnostic of CMD in the absence of obstructive epicardial disease [11]. It is most commonly assessed using an intracoronary Doppler-tipped guidewire or thermodilution techniques.

3 HMR (the ratio of distal coronary pressure divided by coronary blood flow at maximal hyperemia using a combined pressure-flow intracoronary guidewire), similar to the index of microvascular resistance (IMR) [ratio of distal coronary pressure divided by the inverse of the mean transit time during maximal hyperemia using a pressure-thermodilution intracoronary guidewire and commercially available software], is a direct measure of microcirculatory resistance and is independent of epicardial vascular function. Using a combined pressure-flow wire, HMR ≥2.5 mHg/cm/s is diagnostic of CMD in the absence of obstructive epicardial disease and significant collateral coronary flow [12, 20, 21].

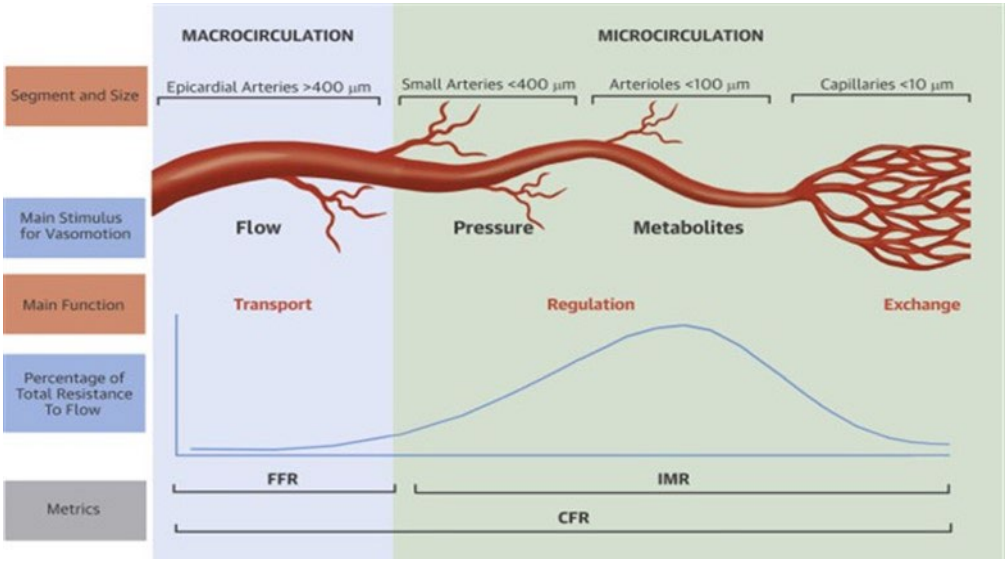

Figure 1: CFR: Coronary flow reserve; FFR: Fractional flow reserve; IMR: Index of microvascular resistance

2.5 Coronary microvascular dysfunction: Current limited treatment options and unmet clinical need

Small, short-term studies of symptomatic patients with ischemia but no obstructive CAD using anti-atherosclerotic and/or anti-ischemic agents have produced limited symptomatic, ischemic, or functional improvement. Accordingly, in the absence of large randomized controlled trials demonstrating effective therapies for CMD, existing guidelines focus on reassurance and symptom management [22, 23] with current standard therapy mostly extrapolated from obstructive epicardial coronary artery disease and consisting of cardiovascular risk factors control, statins and traditional antianginal therapies, such as beta-blockers, calcium channel blockers, and long-acting nitroglycerine [24, 25]. Angiotensin converting enzyme inhibitors, L-arginine and aspirin may also sometimes be used for treatment of CMD [24-26]. CORMICA, a randomized controlled blinded clinical trial of stratified medical therapy versus standard care in patients with angina and non-obstructive angiographic CAD, showed that invasive assessment of the microvascular function at the time of the coronary angiogram as a

mechanism of ischemia, and stratified medical treatment of CMD improves symptoms and quality of life in this patient population [14]. However, current traditional antianginal drugs were shown to be effective in only about half of patients with CMD. This is suboptimal and hence the growing need for more research to investigate novel therapies addressing this unmet clinical need. A personalized approach is therefore needed with follow-up of individual patients to tailor therapy according to symptom relief and side-effects [24].

2.6 Coronary Sinus Narrowing: A potential treatment for microvascular dysfunction in patients with ANOCA

Augmentation of coronary sinus (CS) pressure for the treatment of chronic angina is a long-standing concept**.** In the 1950's and 1960's, surgical narrowing of the CS by Claude Beck for treatment of angina by redistribution of myocardial blood flow into ischemic myocardial territories showed remarkable success [27, 28]. In the 1980's, Mohl and colleagues used a closed loop CS balloon system to automatically occlude and release the CS to elevate CS pressure [29, 30]. In 2015, Verheye and colleagues showed, in the COSIRA double-blind, sham-controlled, multicenter trial, that CS Reducer (Neovasc Inc) improves Canadian Cardiovascular Society (CCS) angina class and quality of life with a trend to reduction in ischemic burden in patients with refractory angina and obstructive CAD with no revascularization options [31]. More recently, a small observational study (n= 8) by Giannini and colleagues showed that CS Reducer also improved CCS class, myocardial ischemia by perfusion cardiac MRI, all domains of the Seattle Angina Questionnaire (SAQ), and 6-minute walk test (6MWT) in patients with angina and no obstructive CAD [32]. Most recently, De Maria and colleagues demonstrated that CS pressure elevation using the pressure-controlled intermittent CS occlusion (PICSO) system in patients presenting with first anterior STEMI, not only improves microvascular function evaluated by

IMR, but also reduces infarct size (OxAMI-PISCO study) [33]. It has been suggested that CS narrowing leads to increased backwards pressure that causes slight dilatation and a consequent reduction in the resistance to flow in the arterioles of the ischemic sub-endocardial myocardium. This subsequently causes a redistribution of blood from the less ischemic subepicardium to the more ischemic subendocardium [34]. The enhancement of blood flow within the ischemic subendocardial layers of the myocardium reduces ischemia and leads to symptoms relief and improved quality of life.

3- The Coronary Sinus Reducer

The Neovasc Reducer™ System (Neovasc Inc., Richmond, B.C., Canada), hereby referred to as the CS Reducer in this protocol, is a CE marked, balloon-mounted, hourglass-shaped stainless steel mesh for percutaneous transvenous implantation into the coronary sinus. The CE Mark indication for use is in patients with refractory angina pectoris and objective evidence of reversible myocardial ischemia, who have limited treatment options and are thus referred to as 'no-option' patients. These patients are either not amenable to, or are high risk for, revascularization by coronary artery bypass grafting (CABG) or by percutaneous coronary intervention (PCI). The Reducer System is intended to create a permanent and controlled narrowing of the coronary sinus (CS), to improve perfusion to ischemic myocardium. As discussed above, CS Reducer is emerging as a potentially effective therapy for disabling angina in patients (n=104) with obstructive CAD and no revascularization options [31] with objective evidence to support reduction in myocardial ischemia on MRI, SPECT and dobutamine stress echocardiography [35-37] and improvement in diastolic left ventricular function [38]. However, the role of the CS Reducer in patients with microvascular angina and no obstructive CAD remains unclear. Observational data from a first-in-human

(n=8) preliminary study of compassionate CS Reducer implantation for presumed refractory microvascular angina post at least one PCI procedure and no residual epicardial obstructive disease demonstrated improvement in CCS class, SAQ score, and 6MWT at 4 months post implant [32], with improved myocardial perfusion reserve index in a subgroup of patients (n=3) suggestive of improved microvascular function (Figure 2). Yet, CS Reducer has not yet been specifically tested in ANOCA patients with invasively documented microvascular dysfunction.

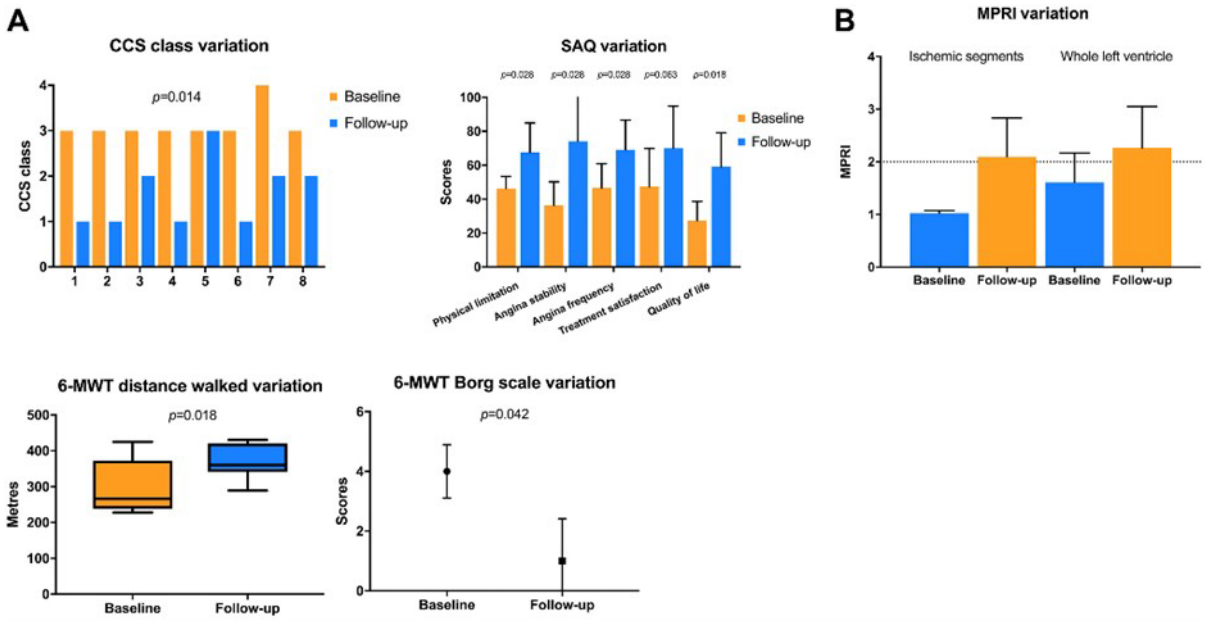

Figure 2: A) Improvement in Canadian Cardiovascular Society (CCS) class, Seattle Angina Questionnaire (SAQ) score, and 6 minute walk test (6MWT) at 4 months post CS Reducer implantation. B) Improved myocardial perfusion reserve index in a subgroup of patients. Adapted from Giannini F et al., JACC Cardiovascular Interventions [32].

More supportive data for the concept that increased CS pressure might improve microvascular function can be found in a very recent case presented by Tommaso Gori [39] of a 61 year old man who presented with severe (CCS class 4) angina, non-obstructive CAD and elevated IMR. This patient was treated with Reducer implantation with consequent resolution of angina and dramatic reduction in IMR. Also, CS pressure elevation using pressure-controlled

intermittent CS occlusion (PICSO) in patients presenting with first anterior STEMI, resulted in improves microvascular function (reduction in IMR values) as well as reduction of infarct size (OxAMI-PISCO study) [33].

Safety and Procedural Success of CS Reducer System and Implantation Procedure

The safety and procedural success of CS Reducer implantation has been demonstrated in one randomized clinical trial and numerous observational studies done in Europe and Canada [36, 37, 40, 41]. To date, no feasibility and efficacy studies have been done in the United States. Potential complications of the procedure include dissection or perforation of the CS and device migration. However, as demonstrated in previous studies (COSIRA, n=52 and REDUCER-I, n=204) and non-published post-marketing commercial use in more than 1800 patients worldwide, no cases of mortality has been recorded and the rates of aforementioned complications, including myocardial infarction or permanent damage related to the device or procedure such as perforation, are very low (Table 1). Moreover, implantation procedure has very high success rates. The largest multicenter Italian registry reports 98.6% (n=139) procedural success with 2 patients (1.4%) failing due to unfavorable anatomy of the coronary sinus [41]. Summary of technical success data of CS Reducer implantation procedure from four previous studies is summarized in Table 2.

Table 1: Safety Data of CS Reducer System and Implantation Procedure[3]

Potential Complications (REDIFU-002 Reducer IFUCE Mark REV K)	Pre-Market Event Rate (COSIRA) N=52 n(%)	Post-Market Event Rate (REDUCER-I) N=204 n(%)	Post-Market Event Rate (Commercial Use) N=1840 n(%)
Allergic reaction	0(0.00)	0(0.00)	0(0.00)

Arrhythmias (e.g. ventricular tachycardia (VT) or ventricular fibrillation (VF)	1(1.92)	4(1.96)	0(0.00)
Dissection (e.g. coronary sinus)	0(0.00)	4(1.96)	2(0.11)
Embolism (e.g. pulmonary or vessel)	0(0.00)	0(0.00)	0(0.00)
Conduction Disturbances	0(0.00)	0(0.00)	0(0.00)
Hypotension/hypertension	0(0.00)	0(0.00)	1(0.05)
Infection	0(0.00)	0(0.00)	0(0.00)
Access site complications	1(1.92)	1(0.49)[2]	0(0.00)
Access site hematoma (not SAE)	Not reported	8(3.92)	Not reported
Access site minor bleed (not SAE)	Not reported	4(1.96)	Not reported
Ischemic events (e.g. myocardial infarction (MI) or unstable angina)	1(1.92)	0(0.00)	0(0.00)
Minor or major bleeding events (e.g. hemorrhage, cardiac tamponade, or pericardial effusion)	1(1.92)	1(0.49)	1(0.05)
Vascular event (e.g. pseudoaneurysm or thrombus)	0(0.00)	0(0.00)	0(0.00)
Perforation/rupture of coronary sinus, right atrium (RA), or internal jugular vein	0(0.00)	1(0.49)	3(0.16)
Pulmonary edema	0(0.00)	0(0.00)	0(0.00)
Reducer and/or coronary sinus occlusion (e.g. thrombus)	0(0.00)	0(0.00)	0(0.00)
Reducer fracture	0(0.00)	0(0.00)	0(0.00)
Reducer malposition, migration or embolization	2(3.85)	2(0.98)	10(0.54)
Respiratory failure	0(0.00)	0(0.00)	0(0.00)
Spasm of CS or jugular vein	0(0.00)	0(0.00)	0(0.00)
Cardiac valve injury (tricuspid)	0(0.00)	0(0.00)	0(0.00)
Myocardial damage	0(0.00)	0(0.00)	0(0.00)
Pyrogenic immunological or toxicological reaction	0(0.00)	0(0.00)	0(0.00)
Angina	0(0.00)	3(1.47)	0(0.00)
Chest pain[1]	1(1.92)	1(0.49)	0(0.00)

Minor neurologic event, including dysphagia, blurred vision, or TIA	0(0.00)	3(1.47)	0(0.00)

[1]Chest pain has previously been categorized as angina and is therefore not currently included as an independent complication in the IFU
[2]Access Site Complications: one (1) access site complication due to device retrieval via the femoral vein
[3]Source: 022-CLN-012-2019 Rev A

Table 2: Technical Success of CS Reducer Implantation Procedure

Study	N	Technical Success % (n)
COSIRA Treatment Arm	52	96.2 (50/52)[1]
FIM	15	93.3 (14/15)[2]
REDUCER-I Overall	211	96.6 (204/211)[3]
REDUCER-I Arm 1	161	95.6 (154/161)[3]

[1] Two subjects were not implanted – one due to inability to cannulate the CS and one due to inability to advance the guide catheter in the CS to the intended implant location

[2] One subject experienced a migration post-implantation. The Reducer was noted to have moved during insertion but was inflated. As a result, the position of the deployed Reducer device was more proximal than desired. The dislodged Reducer then migrated and a 2nd Reducer was implanted without complications

[3] Seven subjects were not implanted – 2 for CS dissection, 2 for tortuous anatomy, 1 for CS too small, 1 for inability to advance the guiding catheter, and 1 for movement of the Reducer while retracting the guidewire

Accordingly, in this Phase-1 study we aim to evaluate the feasibility of CS Reducer implantation and its efficacy on invasively assessed microvascular function in ANOCA patients with CMD.

4- Study Hypothesis

In patients with ANOCA and invasive evidence of CMD, CS Reducer implantation is safe and will improve microvascular function as measured by CFR and HMR.

5- Aims

5.1 To evaluate the potential efficacy of CS Reducer implantation in ANOCA patients with CMD on microvascular function using invasive CFR and HMR assessments

5.2 To evaluate the potential efficacy of CS Reducer implantation in ANOCA patients with CMD on angina severity and frequency as assessed by CCS angina class and short-acting nitrates use, ischemia and exercise capacity as assessed by exercise bike echocardiographic stress test (EBEST), and quality of life as assessed by SAQ score.

5.3 To evaluate the potential efficacy of CS Reducer on left ventricular diastolic function and filling pressures as assessed by transthoracic echocardiographic parameters at peak exercise

5.4 To confirm the safety and feasibility of CS Reducer implantation patients with ANOCA and invasively documented CMD.

5.5 A successful demonstration in the proposed trial that CS Reducer implantation can be beneficial to patients with CMD will significantly advance the field of research aimed at FDA approval of the CS Reducer for treatment of ANOCA patients with CMD and opening the door to commercialization of CS Reducer for treatment of CMD, which is a critical unmet clinical need. If successful, the next stage of investigation will be the conduct of one or more pivotal registration studies to support FDA approval, and the proposed trial will provide information necessary to design these studies.

6- Study design

6.1 General Study Design:

- Prospective, single center, open label, single arm, clinical trial
- Number of participants: 30 subjects
- Duration of study: 4 months
- Patients with chronic refractory angina (CCS class II-IV), no obstructive CAD (<50% stenosis in epicardial vessels and/or iFR>0.89 or FFR>0.8 in vessels with 50 to 70% stenosis), and documented CMD (CFR≤2.5 and/or HMR≥2.5) & or coronary blood flow (CBF) response to acetylcholine ≤ 50%.on clinically indicated coronary angiography and invasive coronary reactivity testing which uses Adenosine, Acetylcholine & Nitroglycerin as standard clinical practice will be eligible for enrolment.
- A full clinically indicated coronary flow evaluation will be performed in the left anterior descending artery (LAD) as standard of care using an intracoronary combined Doppler-flow and pressure wire (ComboWire XT, Philips Volcano Corporation, Del Mar, California) that provides iFR/FFR, HMR and CFR measurements. This will determine patient eligibility. If patients are deemed eligible, and wish to participate, they will go through the informed consent process to enroll in the study after their procedure.
- Baseline clinical evaluations of eligible patients will include clinical characteristics, medication profiles including antianginals, evaluation of angina severity and frequency by CCS angina class and Seattle Angina Questionnaire (SAQ), in addition to ischemia, exercise capacity, and left ventricular diastolic function and filling pressures at peak exercise on an exercise bike echocardiographic stress test (EBEST)

using a supine bike protocol starting at 25 Watts and increasing by 25 Watts every 2 minutes.

- Eligible patients will undergo percutaneous implantation of The Neovasc Reducer™ System (Neovasc Inc., Richmond, B.C., Canada) for the treatment of CMD.
- Adverse events will be collected during the 4 months study period and monthly follow-up phone calls with study participants will be conducted at 1, 2, and 3 months post CS reducer implant
- Study participants will undergo full repeat invasive evaluation of coronary blood flow and microvascular resistance (CFR and HMR) as well as repeat clinical evaluation (including CCS class, SAQ, antianginal medication use, adverse events, and EBEST) at 4 months following Reducer implantation.

6.2 Primary Endpoint

Change in CFR and HMR measurements at 4 months post CS Reducer implantation compared to baseline

6.3 Secondary Endpoints

- Change in CCS angina class
- Change in the score of all 5 domains of the Seattle Angina Questionnaire for assessing quality of life
- Change in the consumption and frequency of short acting nitrates (spray or sublingual tablets)
- Change in EBEST parameters at 4 months compared with baseline (total exercise duration, time to 1 mm ST segment depression, evidence of ischemia, peak exercise stage, peak exercise diastolic function and filling pressures as measured by echocardiographic E/e', and exercise-induced symptoms)

- Procedural-related Major Adverse Cardiac Events (MACE) defined as: death, myocardial infarction, perforation of the CS, CS total occlusion, or need for urgent dilatation of the Reducer within 4 months of follow-up

7- Study Population:

Patients with chronic refractory angina (CCS class II-IV), no obstructive CAD (<50% stenosis in epicardial vessels and/or iFR>0.89 or FFR>0.8 in vessels with 50 to 70% stenosis), and documented CMD (CFR≤2.5 and/or HMR≥2.5) & or coronary blood flow (CBF) response to acetylcholine ≤ 50%. on clinically indicated coronary angiography and invasive coronary reactivity testing which uses Adenosine, Acetylcholine & Nitroglycerin as standard clinical practice

7.1 Inclusion Criteria:

- Age ≥18
- Able to provide written informed consent and willing to participate in all required study follow-up assessments
- Symptomatic CAD with refractory angina defined as CCS class II to IV, despite optimal tolerated medical therapy for more than 3 months.
- Abnormal coronary microvascular function indices: CFR≤2.5 and/or HMR≥2.5 & or coronary blood flow (CBF) response to acetylcholine ≤ 50%.

7.2 Exclusion Criteria:

- Recent (within 3 months) acute coronary syndrome
- Recent (within 6 months) percutaneous coronary intervention revascularization by stent
- Patients with prior coronary artery bypass surgery

- Unstable angina (recent onset angina, crescendo angina, or rest angina with ECG changes) during the last 30 days
- Subjects in cardiogenic shock (systolic pressure < 80mm/Hg, on vasopressors or intraaortic counter pulsation) at the time of consenting. Subjects who recover from cardiogenic shock by the time of consenting are eligible.
- Obstructive CAD on coronary angiography (>70% stenosis or 50-70% stenosis with iFR≤0.89 or FFR≤0.8 in epicardial artery)
- Inability to perform invasive coronary flow evaluation and/or measure CFR and HMR in the LAD
- Severe valvular heart disease
- LVEF<30%
- Decompensated congestive heart failure (CHF) or hospitalization due to CHF during the last 3 months
- Patient with a pacemaker electrode in the CS
- Mean right atrial pressure >15 mmHg
- Anomalous or abnormal CS anatomy (e.g., tortuosity, aberrant branch, persistent left superior vena cava (SVC) as demonstrated on angiogram
- CS diameter at the site of planned implantation greater than 13mm or less than 9.5 mm as measure by angiogram
- Severe chronic obstructive pulmonary disease (COPD) indicated by a forced expiratory volume in one second that is less than 55 percent of the predicted value
- Tricuspid valve replacement or repair
- Chronic renal failure (serum creatinine >2mg/dL), and or on chronic hemodialysis
- Moribund, or with comorbidities limiting life expectancy to less than one year

- Known severe reaction to required procedural medication
- Known allergy to stainless steel or nickel
- Magnetic Resonance Imaging (MRI) within 8 weeks of Reducer implantation
- Participation in another ongoing investigational trial
- Additional factors deemed unsuitable for trial enrollment per discretion of principal investigators
- Inmates

7.3 Subject Recruitment, Enrollment and Screening:

The first six patients will be sequentially enrolled, and subsequent enrollment will be held until one-month follow-up. Provided there are no safety concerns at this time, enrollment will continue. Staggered enrollment will help ensure that subsequent patients are not enrolled until there is adequate follow-up and safety of initial patients. The patients for this study will be recruited through the outpatient clinics in the Department of cardiology, including the Chest Pain and Coronary Physiology Clinic and the Coronary Artery Disease Clinic at Mayo Clinic. There have been over 35,000 patients seen in the Cardiovascular Division at Mayo Clinic yearly. There are over 6,000 cardiac catheterizations performed yearly in the cardiac catheterization lab. As a part of our clinical practice, patients with angina referred to the catheterization laboratory for a clinically indicated coronary angiography and found to have non-obstructive CAD are undergoing a comprehensive coronary reactivity testing including assessment of microvascular function with CFR and HMR. Typically, 8-10 patients per month undergo this comprehensive coronary physiology study. This will be mediated through referring physicians. Patients that meet inclusion and exclusion criteria will be considered for recruitment in the study.

7.4 When and How to Withdraw Subjects:

Subjects will be withdrawn from the study prior to completion of all study related procedures if 1 of 5 consecutive patients have serious adverse safety events.

7.5 Data Collection and Follow-up for Withdrawn Subjects:

Even though a subject has withdrawn from the study, it may be important to collect some follow-up or survival data on such subjects throughout the protocol defined follow-up period. Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study device and/or implantation procedure. If a subject withdraws consent to participate in the study, for subject safety reasons, we will make attempts to obtain permission to collect follow up information whenever possible.

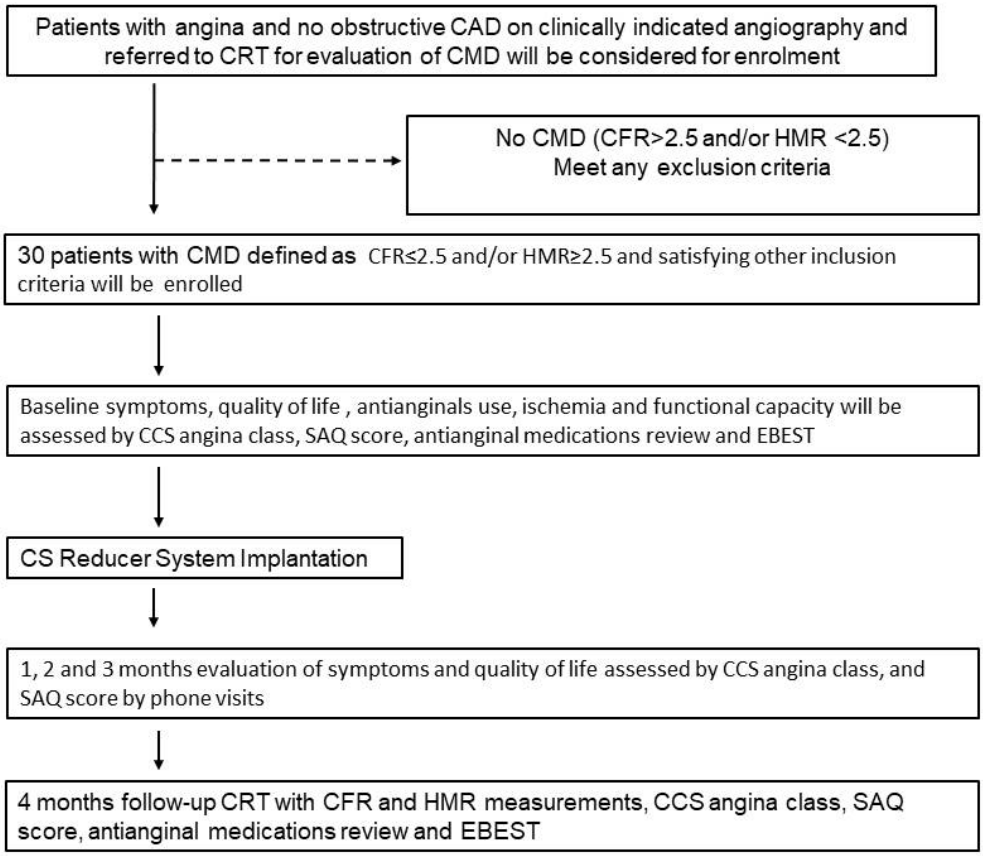

Figure 3: Flow chart of the study design. CAD: coronary artery disease; CMD: coronary microvascular dysfunction; CRT: coronary reactivity testing; CFR: coronary flow reserve; HMR: Hyperemic microvascular resistance; CCS: Canadian cardiovascular society; SAQ: Seattle angina questionnaire; EBEST: Exercise bike echocardiographic stress test.

8- Study Device, Implantation Procedure, and Subject Compliance Monitoring

8.1 Study Device:

The Neovasc Reducer™ System (Neovasc Inc., Richmond, B.C., Canada) is a stainless-steel mesh pre-mounted on a customized hourglass shaped balloon catheter, is designed to create a focal narrowing in the lumen of the CS to generate a pressure gradient across it [42] (Figure 4). When inflated, the expanded balloon gives the metal mesh its final hourglass configuration. The narrowing within the CS, and the pressure gradient across the device are established 4–6 weeks after implantation, when the metal mesh should be covered by tissue ingrowth. The semi-compliant delivery balloon is available in one single size, and the final expanded diameters are dependent on the inflation pressure. The proximal and distal portions of the device are configured to different diameters, based on balloon expansion, allowing the device to conform to the tapered configuration of the anatomy of the CS, with a central narrowing of 3 mm in diameter.

Importantly, since the narrow central part of the device is not in direct contact with the vessel wall, and does not cause any vessel wall injury, there is no trigger for tissue growth at this point, and therefore, the vessel lumen at the center of the device remains patent. Moreover, acceleration of venous blood flow through the narrowed center of the device prevents thrombosis at that site.

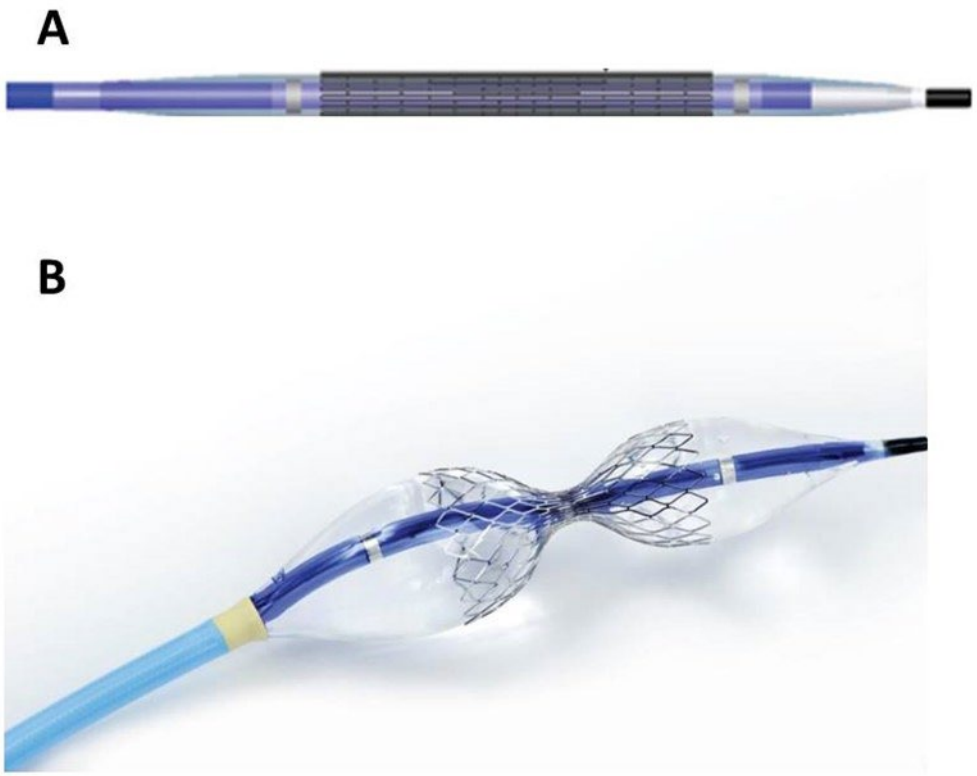

Figure 4: Neovasc Reducer™ System. A) Coronary sinus Reducer pre-mounted on the Reducer Balloon. B) Expanded Reducer over the Reducer Balloon.

8.2 Implantation Procedure:

The Reducer is implanted in the CS through a 9F guiding catheter from the right (or left) internal jugular vein as was previously described [42]. Use instructions of the Neovasc Reducer System and implantation procedure steps are detailed in the accompanying confidential 'Instructions For Use' document. In brief, the Reducer system is advanced over a wire inside a 9 F guiding catheter and located within the designated implanting location. When proper location is confirmed, the guiding catheter is withdrawn, exposing the Reducer, which is held in the landing zone previously identified. The balloon is inflated to 4–6 atm to achieve 10–20% oversize of the vessel . Oversizing is important and helps to achieve two goals: (1) to

anchor into the elastic vessel wall to help prevent migration and (2) to trigger a process of injury-induced tissue proliferation [43-45].

8.3 Subject Compliance Monitoring:

There will be no assessment of compliance as the device will be implanted in the cath lab, and there are no further drugs that need to be administered.

9- Coronary Reactivity Testing

A full clinically indicated coronary flow evaluation will be performed in the left anterior descending artery (LAD) as standard of care to determine study eligibility using an intracoronary combined Doppler-flow and pressure wire (ComboWire XT, Philips Volcano Corporation, Del Mar, California) that provides iFR/FFR, HMR and CFR measurements. In cases in which assessment cannot be performed in the LAD, coronary reactivity testing may be done in the left circumflex (LCx) artery. In brief, after engaging the coronary artery of interest with a guiding catheter, FFR or iFR will first be done in case of moderate (>50 to <70%) epicardial disease to document non-obstructive CAD (FFR>0.8 or iFR>0.89) as was previously described in section 2.4. In cases of mild (<40%) epicardial disease by angiography, FFR/iFR is not recommended but may be done at the discretion of the operator. After confirming non-obstructive epicardial CAD (no CAD, mild CAD<40% or negative FFR/iFR for moderate CAD >50 but <70%), the ComboWire XT will be inserted and parked in the mid LAD for measurement of CFR and HMR. Intracoronary bolus injections of incremental doses (36, 60 and 72 μg) of adenosine will be administered until maximal hyperemia is achieved or the largest dose was given [11]. CFR will be measured as the average hyperemic blood velocity post adenosine/average baseline velocity. Highest achieved CFR

will be used for analysis. A cine image of the LAD will be obtained after each adenosine administration. Coronary artery diameter will then be measured offline by an independent investigator in the segment 5 mm distal to the tip of the pressure-flow wire with a quantitative coronary angiography program (Medis Corp, Leiden, the Netherlands) as described previously [46, 47] and coronary blood flow (CBF) will then be calculated from the Doppler-derived time velocity integral and vessel diameter, where CBF=π×(coronary artery diameter/2)^2×(average peak hyperemic velocity/2) [48]. HMR will then be calculated as distal coronary pressure divided by coronary blood flow at maximal hyperemia. For binary analysis, CMD will be defined as CFR≤2.5 and/or HMR≥2.5[11, 12, 20, 21].

10- Prior and Concomitant Therapy

CS Reducer is being tested as an add-on therapy for ANOCA patients with microvascular dysfunction and ongoing refractory angina despite optimal tolerated conventional medical therapy. Any previously ongoing therapy for CMD or other conditions, prior to CS Reducer implantation, can be continued during the study.

11- Study Procedures

11.1 Visit 1: Screening Visit

The screening visit will take place within 30 days before CS Reducer implantation, primary safety endpoints and secondary endpoints. Information on safety will be captured between visits on a diary card.

Screening Visit:

- Informed consent

- Demographic data
- Medical and surgical history
- Medication history
- Concomitant medication
- Concomitant procedures
- Vital signs, including height and weight
- 12 Lead ECG
- Physical exam
- Pregnancy test (blood) in reproductive-age woman

Based on results of screening test and review of eligibility criteria, PI will assess subject's eligibility for study inclusion. If deemed eligible, the patient will be enrolled in an open study cohort. Screening visit results will be recorded in the subjects electronic case report form and the subject will be scheduled for CS Reducer implantation procedure.

11.2 Pre-Implant Days -21 to -1

- Vital signs
- 12-lead ECG
- Recording of concomitant medications
- Recording of adverse events
- Evaluation of angina severity and frequency by CCS angina class
- Evaluation of quality of life by SAQ
- Standard pre-procedural laboratory tests including hematology and blood chemistry.
- Evaluation of ischemia, exercise capacity, and left ventricular diastolic function and filling pressures at peak exercise on EBEST

11.3 Implant day 0

- Vital signs
- 12-lead ECG
- Limited physical examination
- CS Reducer implantation
- Recording of adverse events
- Recording of concomitant medications

11.4 Post-Implant day 30 (±4 Days)

- Phone call to assess:
    - CCS angina class assessment
    - SAQ assessment
    - Adverse events
    - Concomitant medications

11.5 Post-Implant day 60 (±7 Days)

- Phone call to assess:
    - CCS angina class assessment
    - SAQ assessment
    - Adverse events
    - Concomitant medications

11.6 Post-Implant day 90 (± 7 Days)

- Phone call to assess:
    - CCS angina class assessment

- SAQ assessment
- Adverse events
- Concomitant medications

11.7 Post-Implant day 120 (± 14 days)

- Vital signs
- 12-lead ECG
- CCS angina class assessment
- SAQ assessment
- Adverse events
- Concomitant medications
- Limited physical exam
- Standard laboratory tests including hematology, blood chemistry, liver function tests, CRP and creatinine, urinalysis
- Evaluation of ischemia, exercise capacity, and left ventricular diastolic function and filling pressures at peak exercise on EBEST
- Coronary angiography and reactivity testing to measure CFR and HMR

11.8 Schedule of Study Procedures and Assessments

Study Procedure/ Assessment	**Screening**	**Enrolment/ Pre-Implant**	**Implant Day**	**Post-Implant**			
Days	**-30**	**-5 to -1**	**0**	**30**	**60**	**90**	**120**

Windows				**± 4**	**±7**	**±7**	**±14**
Eligibility criteria	**X**						
Informed consent	**X**						
Medical history	**X**						
Vital signs	**X**	**X**	**X**				**X**
12-lead ECG	**X**	**X**	**X**				**X**
Standard laboratory tests including hematology, blood chemistry, liver function tests, CRP and creatinine, urinalysis.		**X***					**X**
EBEST		**X**					**X**
CS Reducer Implant			**X**				
CCS Angina Class		**X**		**X**	**X**	**X**	**X**
SAQ		**X**		**X**	**X**	**X**	**X**
Coronary angiography to measure CFR and HMR							**X**
Physical exam	**X**						
Limited physical exam			**X**				
Adverse events	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Concomitant medications	**X**	**X**	**X**	**X**	**X**	**X**	**X**

a. CS Reducer will be implanted in the coronary sinus through right (preferably, or left internal jugular venous access)
b. The patient will receive a phone call from the study coordinator to collect information on adverse events, angina class, SAQ, and concomitant medications.
c. Vital signs will be measured prior to implant and every 8 hours until discharge
   * Standard pre-procedural laboratory tests including hematology and blood chemistry including creatinine. Liver function tests, CRP, and urinalysis only at Day 120.

12- Statistical Plan

The effect of the CS Reducer implantation on microvascular function will be evaluated by the change in measured CFR and HMR at 4 months follow-up compared to baseline pre-CS Reducer implantation. Statistical analysis of the absolute and percent change in CFR and HMR measurements at follow-up will be done. Analysis of the delta change in CFR and HMR will also be performed. Change in angina intensity and frequency, and quality of life, will be evaluated by analyzing the change in CCS angina class, SAQ score in all five domains, and antianginals need and frequency rom baseline to follow-up. Change in functional capacity will be evaluated as the change in baseline to follow-up EBEST total exercise duration, peak exercise stage, exercise-induced symptoms, and ischemic ECG and echocardiographic findings. Change in diastolic function and filling pressures will be evaluated as baseline to follow-up change in resting and peak exercise echocardiographic E/e' ratio.

All-completed population: Only subjects who completed ALL study related procedures and follow-up will be included in analysis.

13- Safety and Adverse Events

The investigator will be responsible for the detection and documentation of any adverse events or serious adverse events as defined by this protocol. During the study there will be several safety evaluations and the investigator and/or site staff will be responsible for

detecting, documenting and reporting both adverse events and serious adverse events as defined by this protocol. These will be reported from the signing of the informed consent through the 4-month visit. Serious adverse events will be reported from the signing of the informed consent through the 4 month visit as well. Investigators will report any procedure or hospitalization to the Sponsor-Investigator to ensure any event needing adjudication can be done so in a timely fashion.

13.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, and consent document, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND

- Related: A problem or event is "related" if it is possibly related to the research procedures.
- Unanticipated Adverse Device Effect:

  Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. In the event of attempted device implant with circumstances that prevent implant due to malfunction or deficiency the unused devices will be retained until arrangements for its collection are made and can be returned to Neovasc for further analysis and investigation.

There are several inherent risks associated with this protocol that must be considered. There are risks associated with the various study procedures including cardiac catheterization, CS Reducer implantation, invasive coronary reactivity testing, and exercise testing.

Contemporary overall rates of major complications (death/ myocardial infarction/ stroke/ unplanned coronary bypass grafting/ pericardial effusion) related to diagnostic cardiac catheterization procedures at our institution are extremely low (<1 per 1000 left heart catheterization) [49]. Second, coronary reactivity testing is a safe procedure with <1/100 risk of severe adverse events (coronary artery dissection and myocardial infarction) [50]. Third, in the largest available database (REDUCE study), CS Reducer implantation procedure was also shown to be a safe procedure with no CS perforations, cardiac tamponade, peri-procedural

death or myocardial infarction reported in the largest database available at 14 months median follow-up [41]. Lastly, exercise testing may pose a minimal risk to patients if they were to develop arrhythmias during the testing. This risk is minimal, and the room in which EBEST is performed, and personnel performing testing will be equipped to handle any potential complications.

13.2 Adverse Event

An adverse event will be defined as any medical occurrence in a subject or clinical investigation subject that is temporally associated with use of the medicinal product, whether or not it is considered related to the medicinal product. This is thus any unfavorable or unintended sign, such as abnormal symptoms, laboratory values, or new disease, which can be associated with the CS Reducer implantation by temporal association.

13.3 Serious Adverse Event

Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- Death
- Myocardial infarction
- Stroke
- Life threatening adverse procedural or periprocedural complications
- Any hospitalizations post CS Reducer implantation
- Inpatient, new, or prolonged; disability/incapacity

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data. Serious adverse events are ones that may result in death or can be life-threatening, requires extended hospitalization, significant disability, meaning a substantial disruption to the person's ability to conduct normal life functions. This excludes experiences of minor medical significance such as headache, nausea, vomiting, influenza, diarrhea, accidental trauma, which may disrupt daily functions but is not substantial. Medical or scientific judgment should be exercised when deciding whether reporting is appropriate in situations.

All adverse events that do not meet any of the criteria for serious, should be regarded as non-serious adverse events.

13.4 Adverse Event Reporting Period

Serious adverse events should be reported using the Serious Adverse Event Report Form within 24 hours of study personnel becoming aware of an event. This data must be entered into the electronic capture system within 24 hours as well.

If serious adverse event results in death or is considered to be related to the study device, then the medical monitor must be contacted immediately.

The follow-up period is defined as 4 months following CS Reducer implant. This is the study period during which adverse events must be reported.

13.5 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

13.6 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

13.7 Post-study Adverse Event

All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

13.8 Patients on Anticoagulants and Antiplatelets

Patients on warfarin will hold their medication prior to procedure or reduce their dose as directed by their primary provider. They will then have an INR checked on evaluation. Patients with an INR less than 1.4 will undergo CS Reducer implantation and invasive coronary reactivity testing. Those with an INR >1.4, will be asked to hold their warfarin for additional time until the INR is less than 1.4, and then the procedure will be undertaken.

Novel anticoagulant medications will be held 3-5 days prior to procedure as mandated by laboratory protocol.

While antiplatelet therapy may increase the bleeding risk, it will not preclude enrollment in the study. Given the nature of patients seen in the cardiac catheterization laboratory, many are on antiplatelet therapy, and it is preferred that patients have antiplatelet therapy prior to initiation of the procedure. For these reasons we will plan on continuing antiplatelet therapy.

13.9 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances. Hospitalizations that do not necessitate reporting as adverse events, including those that are scheduled as a part of the study or as a part of the predetermined care of the patient, or hospitalization for preexisting conditions, including elective surgical procedures. These include:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

13.10 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF) or in a separate adverse event worksheet. All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should be recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study device or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

13.11 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

13.12 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures. All serious adverse events must be reported in writing to both the Institutional Review Board by the investigator himself as institutional policies mandate. The investigator must then provide a summary describing the SAE in detail and his assessment of how related the event is to the study device. The documentation related to the SAE must follow the initial SAE report immediately as available. As new information becomes available to the investigator, the investigator must continue to collect and forward this information,and provide a corresponding follow-up summary.

Information collected on the adverse event worksheet (*and entered in the research database)*:

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (device, procedure):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

13.13 Sponsor-Investigator reporting: Notifying the FDA

The sponsor-investigator will report to the FDA any unanticipated adverse device events and the reviewing IRB as well as all participating investigators within 10 working days after the Sponsor-Investigator is aware of the occurrence.

The sponsor-investigator will submit annual progress reports to FDA which will include a summary of progress to date, a summary of results, a summary of anticipated and unanticipated adverse effects, any deviation from the protocol, any minor change to the protocol, and any changes to the risk analysis. State any future plans including any anticipated changes to the investigation and include any resulting publications from the study.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to both the Institutional Review Board by the investigator himself as institutional policies mandate after the sponsor-investigator's initial receipt of the information about the event.

13.14 Stopping Rules

The principal investigator will review all serious adverse events and be involved in the decision to stop the study. The study will be stopped if 3/5 patients experience serious adverse events deemed secondary to the study device, including death, cardiovascular mortality, bleeding, stroke or sepsis thought to be secondary to CS Reducer implantation. Given that the CS Reducer has no FDA approved indication yet, and to ensure independent review and reporting of adverse events and determine if study stopping criteria have been met, a DSMB committee will be formed. The committee will be formed of 3 independent members: Dr. Charanjit S. Rihal, an independent interventional and structural heart disease expert will be a member and chair the committee, and the remaining 2 members will be an independent cardiologist who evaluates and manages patients with coronary microvascular dysfunction at Mayo Chest Pain Clinic, and an independent Mayo Clinic statistician. These members will be named prior to initiation of the study.

13.15 Medical Monitoring

It is the responsibility of the sponsor-investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 17 below; Study Monitoring, Auditing, and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

14- Data Handling and Record Keeping

The data collection tool for this study will be sponsor-investigator defined case report forms. The investigator will maintain complete and accurate study documentation in a separate file. Study documentation may include medical records, records detailing the progress of the study for each subject, signed informed consent forms, study device disposition records, correspondence with the study coordinator study monitor/sponsor, screening and consent information, severe adverse event reports, laboratory reports, subject diaries, data clarifications requested by the sponsor, and any other documentation deemed relevant and pertinent to the study and the study subjects. Subject data necessary for analysis and reporting will be entered into a validated database or data system in accordance. Clinical data management will be performed in accordance with applicable data management vendor standards and data cleaning procedures. The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. The handling of data by the sponsor-investigator, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor.

14.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

14.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

14.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it.

All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

15- Data Management

15.1 Data Quality Assurance

There will be computerized checks that ensure data integrity. These will be reviewed by a clinical research coordinator for fidelity. Source document verification will be performed to ensure data fidelity as well. To ensure compliance with GCP and all applicable regulatory requirements, the sponsor-investigator or designee may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study.

Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

15.2 Data Clarification Process

All data queries will be recorded by the clinical study coordinator and reviewed by the study investigator.

15.3 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents. These will

be in the form of locked excel files and on a secure server that is password protected. Subject names or other directly identifiable information will not appear on any reports, publications or other disclosures of clinical study outcomes. These materials will be coded by a subject identification code list, and will be stored on a single secure server, to protect the subjects' confidentiality.

The sponsor-investigator will retain the specified records and reports for;

1. Up to 2 years after the marketing application is approved for the device; or, if a marketing application is not submitted or approved for the device, until 2 years after shipment and delivery of the device for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717

16- Study Monitoring, Auditing, and Inspecting

16.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. catheterization laboratory, etc.), and has adequate space to conduct the monitoring visit.

All SAEs will be reported to the IRB within 24 hours. Based on our previous studies we anticipate rate of approximately 1% risk of mainly a reversible coronary spasm and

hematomas and less than 1% for bleeding. Screening and application of exclusion criteria will minimize potential risks.

As a service to the sponsor-investigator, this study may be monitored during the conduct of the trial by staff from the Mayo Clinic Office of Research Regulatory Support. Clinical trial monitoring may include review of the study documents and data generated throughout the duration of the study to help ensure the validity and integrity of the data along with the protection of human research subjects. This will assist sponsor-investigators in complying with Food and Drug Administration regulations.

16.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, , and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. catheterization laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

17- Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

18- Study Finances

18.1 Funding Source

This study is financed by a Small Business Innovation Research Grant through the National Institute of Health.

18.2 Conflict of Interest

Royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

19- Publication Plan

There are no specific publication policy requirements of the sponsor-investigator, other investigators or funding agency. The primary responsibility for publication of the results of the study belongs to the Principal Investigator. Any information from this study can be used or passed onto a third party only after approval from the principal investigator. The registration of the study to ClinicalTrials.gov will occur prior to subject recruitment and enrollment. Posting of results to ClinicalTrials.gov will be done within 12 months of final data collection for the primary outcome.

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