IDE PROTOCOL
IDE# G130013

CALM-FIM_US –CONTROLLING AND LOWERING BLOOD PRESSURE WITH THE MOBIUSHD™
A PROSPECTIVE MULTICENTER SAFETY STUDY

STUDY SPONSOR:

VASCULAR DYNAMICS, INC.
2134 OLD MIDDLEFIELD WAY
SUITE J
MOUNTAIN VIEW, CA 94043

VERSION 1 – JANUARY 2013
VERSION 2 – MARCH 2013
VERSION 3 – SEPTEMBER 2013
VERSION 4 – DECEMBER 2013
VERSION 5 – OCTOBER 2014

INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE:	**CALM-FIM_US –CONTROLLING AND LOWERING BLOOD PRESSURE WITH THE MOBIUSHD™ - A PROSPECTIVE MULTICENTER SAFETY STUDY**
PROTOCOL NUMBER:	**CRD0152**
DATE:	**08 OCTOBER 2014**
STUDY SPONSOR:	**VASCULAR DYNAMICS, INC.** **2134 OLD MIDDLEFIELD WAY** **SUITE J** **MOUNTAIN VIEW, CALIFORNIA 94043** **(650) 963-9370**

DECLARATION OF INVESTIGATOR

I have read the above Protocol and agree to adhere to the requirements. I will provide copies of this Protocol and all pertinent information to the study personnel. I will discuss this material with them and ensure they are fully informed regarding the investigational device and the conduct of the study. I will work according to the principles of Good Clinical Practice (GCP) according to 21 CFR Parts 50, 54, 56, and 812, to other applicable regulations, to applicable laws and to hospital Institutional Review Board / Ethics Committee (IRB/EC) requirements.

Investigator Signature
I have read and understand the contents of the Protocol. I agree to follow and abide by the guidelines set forth in this document.

Principal Investigator Signature: _____ Date: _____
DD/MM/YY

Principal Investigator Printed Name:_____

Investigational Site: _____

APPROVALS:

Sujith Shetty MBBS
Vice President, Clinical, Regulatory, and Quality
Vascular Dynamics, Inc.

08 OCT 14
Date

Robert A. Stern
President and CEO
Vascular Dynamics, Inc.
(Signature of business representative indicates understanding of study design)

10-8-14
Date

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TABLE OF CONTENTS

ACRONYMS

ABPM	Ambulatory Blood Pressure Monitoring
ABS	Acrylonitrile butadiene styrene
AE	Adverse Event
BMI	Body Mass Index
BP	Blood Pressure
CAS	Carotid Artery Stenting
CBC	Complete Blood Count
CEA	Carotid Endarterectomy
CCA	Common Carotid Artery
CRF	Case Report Form
CVA	Cerebrovascular Accident
DBP	Diastolic Blood Pressure
DVT	Deep Venus Thrombosis
DC	Delivery Catheter
DSMB	Data Safety Monitoring Board
ECA	External Carotid Artery
EF	Ejection Fraction
GFR	Glomerular filtration rate
ICA	Internal Carotid Artery
ICD	Informed Consent Document
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
PEEK	Polyetheretherketone
PTFE	Polytetrafluoroethylene
PI	Principal Investigator
SBP	Systolic Blood Pressure
TIA	Transient Ischemic Attack

DEFINITIONS

Cerebrovascular accident (CVA) or stroke: Focal irreversible brain injury with neuron cell death most commonly caused by compromise of end-organ oxygen supply due to parenchymal hemorrhage from loss of arterial vascular integrity or flow interruption from intracranial arterial occlusion.

Transient ischemic attack (TIA): Focal neurological symptoms that resolve spontaneously within 24 hours without evidence of cerebral infarction.

Secondary hypertension: High blood pressure that is caused by an identifiable secondary medical condition or exogenous substrate. Secondary hypertension differs from the usual type of high blood pressure (essential hypertension), which is often referred to simply as high blood pressure. Essential hypertension, also known as primary hypertension, has no clear cause and is thought to be linked to genetics, poor diet, lack of exercise and obesity. Secondary hypertension has been linked to conditions that affect kidney function, as well as sleep apnea, renal circulation compromise, congenital aortic abnormalities, unusual adrenalin secreting tumors, and endocrine system abnormalities. In addition, the aggravating factor for secondary hypertension could also be medications like NSAIDs.

Vulnerable plaque: An atheromatous plaque in an arterial wall that has abundant macrophages, prominent lipid pool, and is usually covered by a thin fibrous cap that is providing a limiting protective barrier from rupture. The repeated cycle of rupture and healing is regarded as one of the key mechanisms of arterial stenosis progression in atherosclerotic heart disease, myocardial infarction and strokes.

Clinical significant structural valvular cardiac disease: For the purpose of this study we define a "significant" valvular condition as any structural heart abnormality that increases the patient's risks for a stroke or adverse event during the follow-up period. For example, patients with hemodynamically significant aortic stenosis as defined by a mean gradient of > 30mmHg and/or symptoms of dyspnea, chest pain or syncope. In addition, this includes patients with moderate to severe mitral stenosis based on contemporary echo or hemodynamic guidelines.

Moderate to severe reactive airway disease:

> Moderate persistent asthma: Documented primary reactive airway disease with symptoms that occur daily. In addition, flare-ups can occur, increasing the symptoms from moderate to severe, which often last several days. Thus any patient with chronic daily symptoms and or documented flair-ups over the last year falls in this exclusion definition. Coughing and wheezing may disrupt the normal activities and make it difficult to sleep. Nighttime flare-ups may occur more than once a week. In moderate persistent asthma, lung function is roughly between 60% and 80% of normal, without treatment.
>
> Severe persistent asthma: With severe persistent asthma, symptoms occur daily and often. They also frequently curtail the patient's activities or disrupt his/her sleep. Lung function is generally less than 60% of the normal level without treatment. History of hospitalization within the preceding year for an asthmatic attack is also consistent with severe asthma.

Moderate to severe COPD:

Moderate COPD: For the purpose of this study, moderate COPD will be defined as any patient with documented chronic lung disease that experiences daily dyspnea symptoms and requires daily medical treatment in order to maintain normal daily activities.

Severe COPD: Any patient with documented COPD on lung function and/or X-ray studies that has persistent limiting symptoms due to dyspnea. In addition these patients frequently have orthopnea that would prohibit them from lying flat during the needed imaging and transcatheter study device placement. This will also include any patient who has been hospitalized with acute exacerbation of COPD in the preceding year.

Moderate to severe primary pulmonary hypertension: Any patient with symptoms of dyspnea and known pulmonary hypertension without secondary cause of recurrent pulmonary embolism, sleep apnea, left sided heart failure, chronic lung disease or other primary substrate. Objectively this can be defined as NYHA II or III symptoms with mPAP >41mmhg, or PASP >49 in the absence of a secondary cause.

1.0 PROTOCOL SYNOPSIS

TITLE	CALM-FIM _US - Controlling and Lowering Blood Pressure with the MobiusHD™ - A Prospective Multicenter Safety Study
STUDY OBJECTIVE	To evaluate the safety and performance of the MobiusHD system in subjects with resistant hypertension.
STUDY DESIGN	This is an open-label, multicenter, first-in-man clinical trial to be conducted inside the United States. Eligible subjects with stage 2 resistant systemic arterial hypertension currently being treated with a minimum of three (3) anti-hypertensive drugs, who consent to study participation will be assigned to treatment with the MobiusHD system. Potential study participants will be consented and then screened at two (2) baseline visits beginning at least 30 days prior to MobiusHD placement. Qualified patients will undergo placement of the MobiusHD under angiographic visualization, and will then be followed for 36 months. Subjects will be enrolled in two (2) phases, as follows: ▪ Ten subjects will be implanted unilaterally and followed for seven (7) days. ▪ Based on consensus following 7-day clinical outcome analysis by an independent data safety monitoring board (DSMB), 10 additional subjects will be enrolled and implanted bilaterally.
PATIENT POPULATION	Subjects with resistant hypertension receiving at least three (3) anti-hypertensive medications including a diuretic and with no evidence of extracranial carotid disease or significant great vessel/aortic arch atherosclerotic disease.
NUMBER OF PATIENTS	Twenty subjects are to be enrolled at two (2) to ten (10) U.S. clinical sites.
PRIMARY OUTCOME	Safety: Incidence of serious adverse events (SAEs) and unanticipated adverse device effects (UADE) reported for the study population from implantation through six (6) months of follow-up.
SECONDARY OUTCOME	Performance: Decrease in office cuff blood pressure (BP).
ADDITIONAL OUTCOMES	Change in heart rate Reduction of medication post 6-month follow-up 365-Day safety and efficacy Long term safety and efficacy – one (1) to three (3) years

INCLUSION CRITERIA	**Baseline Screening Visit 1 – (Day 0 – 14) – Assessed on Day 14** 1. Provided written informed consent; 2. ≥ 18 years of age and ≤ 80 years of age; 3. Office cuff SBP ≥ 160 mmHg measured per protocol instructions (Appendix IV) following at least one (1) month of maximally tolerated therapy with at least three (3) anti-hypertensive medications, of which at least one (1) must be a diuretic. Any combination medications will be counted per the active ingredient. (For example, Zestoretic (Lisinopril +HCTZ) equals two (2) anti-hypertensive medications); 4. Renal artery imaging performed within the last 12 months showing no evidence of renal artery stenosis. Acceptable imaging modalities include renal duplex, magnetic resonance angiography, CT angiography, and selective or nonselective renal angiography depending on trial site diagnostic standards. In the absence of adequate imaging testing this inclusion criteria could also be met by obtaining a renal duplex prior to enrollment, or by performing nonselective renal angiography at the time of device implantation. 5. Compliant with medications (self-reported) and daily blood pressure readings – Subject must be minimum 80% complaint with diary entries; and 6. For females (with child-bearing potential), a negative pregnancy test, and the use of a medically accepted method of birth control for the duration of the trial. **Baseline Screening Visit 2 – (Day 15 – 30) - Assessed on Day 30** 1. No significant obstructive vascular disease or plaque on CTA or MRA of the aortic arch and great vessels; 2. Carotid duplex studies demonstrating no obstructive carotid disease or plaque; 3. Continued adherence to hypertension medications without anticipated changes and daily blood pressure readings – Subject must be a minimum 80% compliant with diary entries; and 4. Continued office cuff SBP ≥ 160 mmHg despite at least one (1) month of maximally tolerated therapy with at least three (3) anti-hypertensive medications, of which at least one (1) must be a diuretic. Any combination medications will be counted per the active ingredient. (For example, Zestoretic (Lisinopril+HCTZ) equals two (2) anti-hypertensive medications). **Day of Procedure -** 1. Continued adherence to hypertension medications without anticipated changes and daily blood pressure readings – Subject must be a minimum 80% compliant with diary entries.

EXCLUSION CRITERIA	**Baseline Screening Visit 1 – (Day 0 – 14) – Assessed on Day 14** 1. Known or clinically suspected baroreflex failure or autonomic neuropathy; 2. Hypertension secondary to an identifiable and treatable cause other than sleep apnea (e.g., hyperaldosteronism, renal artery stenosis, pheochromocytoma, Cushing's disease, coarctation of the aorta, hyperparathyroidism and intracranial tumor); 3. Treatable cause of resistant hypertension including, but not limited to, improper BP measurement, volume overload and pseudotolerance (excessive sodium intake, volume retention from kidney disease, inadequate diuretic therapy), drug-induced or other causes (non-adherence, inadequate doses, inappropriate combinations, NSAIDs, COX-2 inhibitors, cocaine, amphetamines, or other drugs, sympathomemetics, oral contraceptives (confirmed cause of resistant hypertension), adrenal steroids, cyclosporine, and tacrolimus, erythropoietin, licorice (including some chewing tobacco), ephedra, ma haung, bitter orange); and excessive alcohol intake; 4. Arm circumference greater than 46cm and/or BMI ≥ 40; 5. Chronic atrial fibrillation or recurrent atrial fibrillation with episode within the last 12 months; 6. Vulnerable plaque or ulceration of any size in the carotid artery or aortic arch; 7. History of bleeding complications with dual anti-platelet therapy in the past or has known uncorrectable bleeding diathesis; 8. Current use of additional anticoagulation therapy. Examples include vitamin K antagonists like warfarin, direct thrombin inhibitors, direct factor Xa inhibitors, thrombin IIa inhibitors like apixaban, rivaroxaban, dabigatran and etexilate; 9. Peptic ulcer disease with documented active ulcer or bleeding within the last year. 10. History of allergy to contrast dye that cannot be managed medically; 11. History of orthostatic hypotension; 12. History of syncope within the last six (6) months; 13. History of myocardial infarction or unstable angina within the past three (3) months; 14. History of cerebral vascular accident (stroke or TIA) within the past year; 15. Severe chronic kidney disease (calculated GFR < 45 ml/min); 16. Prior surgery, radiation, or endovascular stent placement in either

carotid region;

17. Clinically significant structural valvular cardiac disease;
18. Moderate to severe reactive airway disease, chronic obstructive pulmonary disease, or primary pulmonary hypertension;
19. Uncompensated congestive heart failure or known severe reduction in left ventricular function (EF < 30%);
20. Uncontrolled co-morbid medical condition that would adversely affect participation in the trial;
21. Non-controlled diabetes mellitus;
22. Active infection within the last month;
23. Co-morbid condition that reduces life expectancy to less than one (1) year;
24. Mental health issues that would prohibit the subject's availability to meet the Protocol requirements;
25. Currently taking an imidazoline receptor agonist or central sympathetic treatment;
26. Enrolled in a concurrent clinical trial;
27. Unable or unwilling to fulfill the protocol follow-up requirements;
28. Subject is a prisoner or member of other protected population;
29. Planned surgery or other procedure within the next six (6) months;
30. Deep venous thrombosis (DVT) within the last year or documented recurrent DVT.

Baseline Screening Visit 2 – (Day 15 – 30) - Assessed on Day 30

1. ICA lumen diameters < 5 mm or > 11.75 mm within the planned location of the device placement via CTA or MRA;
2. Carotid hypersensitivity detected by carotid massage or typical history, as described in the Protocol (Appendix V); or
3. Significant aortoiliac or common femoral artery disease that will prohibit safe femoral access.

Day of Procedure – Angiographic

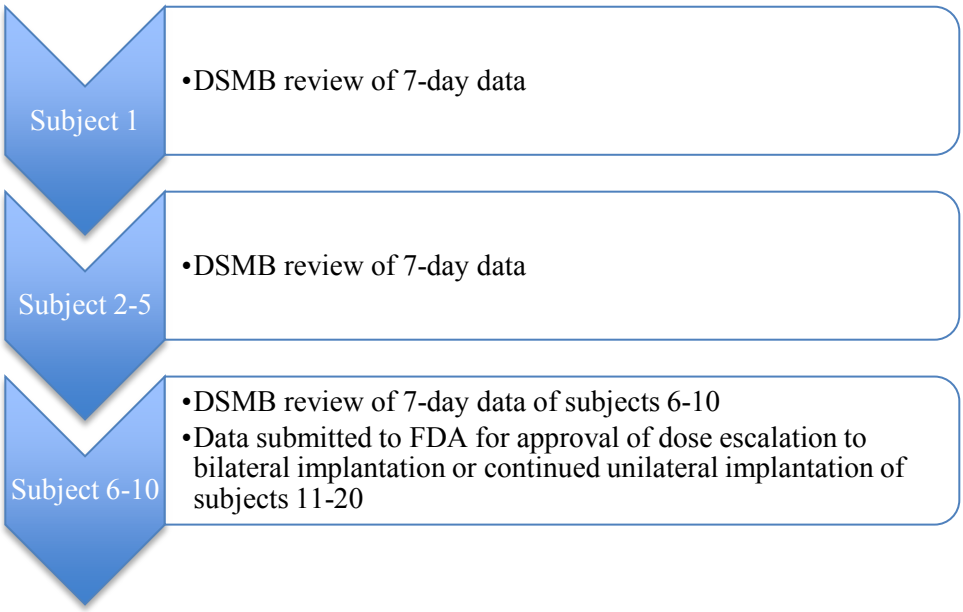
1. Evidence of plaque, ulceration or any stenosis on selective carotid angiography performed in orthogonal views. Lumen diameters will be assessed to exclude subjects with ICA lumen diameters smaller than 5 mm or larger than 11.75 mm within the planned location of the device placement;
2. Any angiographic evidence of plaque or ulceration in the aortic arch and/or the supra aortic vasculature;

	3. Inappropriate anatomy of the carotid bifurcation for deployment of the MobiusHD, including, but not limited to, tortuosity of the extracranial vessels and significant angulation of the common carotid artery bifurcation; or 4. Type III arch or horizontal takeoff of the left carotid from the innominate and any calcification of the carotid bulb.

STUDY ENROLLMENT

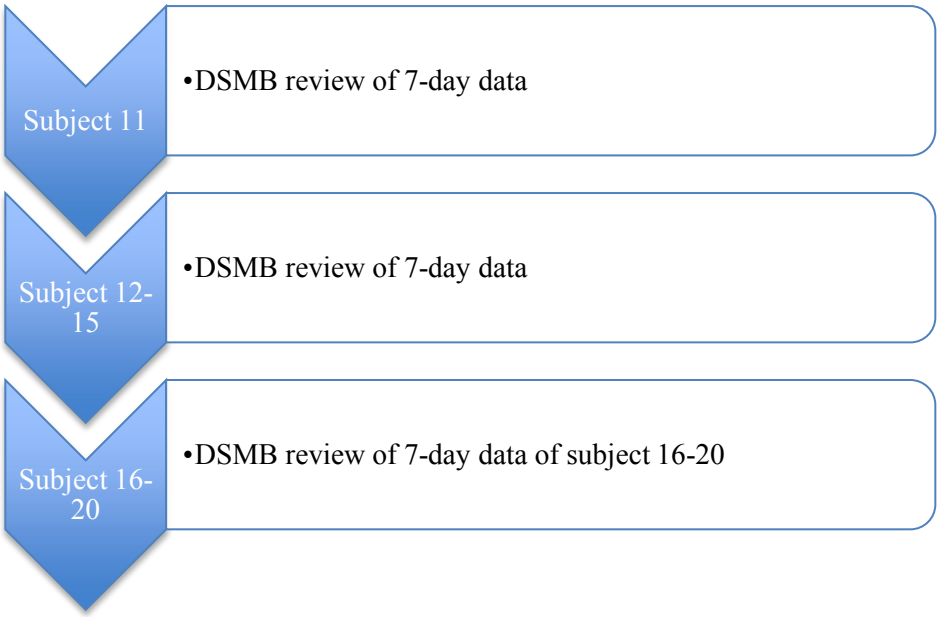
This study will be enrolled based on the following matrix with review of Data Safety Monitoring Board (DSMB) and FDA:

Unilateral study safety design:



Following enrollment of the initial 10 subjects, based on DSMB review of available data, a determination will be made on whether the safety of the MobiusHD is adequate to support bilateral placement. If the DSMB determines that bilateral treatment is warranted, an interim report with all available clinical data will be submitted to FDA with a request for initiation of bilateral treatment in the remaining 10 study subjects.

Bilateral study design: (if approved by DSMB and FDA)



2.0 BACKGROUND AND INTRODUCTION

Normal or optimal blood pressure (BP) is defined as the level at which minimal vascular damage occurs. The Joint National Committee 7 (JNC 7) defines normal BP as a systolic BP (SBP) less than 120 mmHg and diastolic BP (DBP) less than 80 mmHg.[1]

An estimated 76 million adults above the age of 20 have high blood pressure in the United States. Data from NHANES 1999-2006 found that approximately 8% of US adults have undiagnosed hypertension. Approximately 30% of adults are unaware of their hypertension, greater than 40% are not on any treatment and two-thirds of hypertensive patients are not being controlled to BP levels <140/90 mmHg.[1] The highest prevalence of hypertension in the US is noted in African Americans.

Worldwide prevalence estimates indicate that hypertension may affect as many as 1 billion individuals, and approximately 7.1 million deaths per year may be attributable to hypertension.[1] The World Health Organization reports that suboptimal BP (>115 mmHg SBP) is responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease (IHD), with little variation by sex. In addition, suboptimal BP is the number one attributable risk factor for death throughout the world.[1]

Blood pressure control rate is recognized to be suboptimal in those who have serious comorbid conditions like chronic kidney disease. In a survey of patients in the United States with chronic kidney disease, BP control was found to be a dismal 13.2%.[2] On a global level, hypertension is an even greater problem, with 13.5% of all deaths attributed to BP-related diseases. A majority of those who carry this disease burden belong to lower economic strata.[3]

It is clearly recognized that increased BP is associated with a greater risk of heart attack, stroke, and kidney disease. In fact, for persons aged 40 to 70 years, each increment of 20 mmHg in SBP or 10 mmHg in DBP actually doubles the risk of cardiovascular disease across the entire range of BP, from 115/75 to 185/115 mmHg.[4]

TABLE 1: CLASSIFICATION OF BLOOD PRESSURE (BP)

Classification	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal	<120	*And* <80
Prehypertension	120-139	*Or* 80-89
Stage 1 hypertension	140-159	*Or* 90-99
Stage 2 hypertension	>160	*Or* >100

BP, blood pressure data from http://www.nhlbi.nih.gov/guidelines/hypertension/index.htm (accessed April 12, 2012).

Based on JNC 7, patients with sustained hypertension are further divided into stage 1 hypertension (SBP 140-159 mmHg or DBP 90-99 mmHg), stage 2 hypertension (SBP >160 mmHg or DBP >100 mmHg), and those with compelling indications that include diabetes, cardiovascular disease, and renal disease. Each BP increase of 20/10 mmHg doubles the risk of cardiovascular death.

Hypertension remains uncontrolled in the majority of treated patients, especially those with multiple cardiovascular risk factors. This was demonstrated by a French study that showed that 70% of treated hypertensive patients are not controlled to the target level of 140/90 mmHg. This proportion reached 84% in hypertensive patients with diabetes (target level 130/85 mmHg).

Resistant hypertension is a widely prevalent condition, estimated to affect approximately 30% of the population in the United States. Resistant hypertension is defined as elevated BP that remains despite treatment with at least three (3) anti-hypertensive agents at optimal doses. The morbidity and mortality risks associated with hypertension support the need for evaluation of new therapies that can reduce or eliminate the challenges of side effects and poor long-term compliance associated with commercially available blood pressure-lowering medications.

2.1 CURRENT HYPERTENSION TREATMENT

2.1.1 Lifestyle Modification

Educating patients regarding the importance of non-pharmacologic interventions for effective BP control is an important component of reducing cardiovascular risk in the general population. This is particularly true for the pre-hypertensive and hypertensive patient. Aggressive efforts, however, are needed to ensure optimal adherence to recommendations.

Lifestyle modifications include limiting alcohol intake, increasing physical activity, and reducing sodium intake to less than 6 g of sodium chloride daily. Results from the long-term follow-up of the Trials of Hypertension Prevention (TOHP) study demonstrated that patients who were randomized to a low-salt diet (sodium <1800 mg/24 hr) had a 25% risk reduction in cardiovascular events.[5]

Weight reduction of as little as 10 to 12 pounds in the obese hypertensive patient can have a considerable impact on elevated BP. Appropriate nutritional counseling can encourage a diet with reduced total fat and cholesterol intake, in addition to providing an adequate daily intake of potassium, calcium, and magnesium. The Dietary Approaches to Stop Hypertension (DASH) trial has provided substantial data that a diet rich in fruits, nuts, vegetables and low-fat dairy products, with an emphasis on fish and chicken rather than red meat, contributed to lowered BP, even without weight reduction. This dietary approach was particularly effective for participants who also restricted sodium chloride intake.[6] Dietary recommendations must be made on an individualized basis and should be well supported with continued educational and counseling efforts.

Cigarette smoking is a recognized accelerator of cardiovascular disease. Smoking cessation should, therefore, be strongly encouraged for all patients, and education, counseling, and medication should be provided as needed.

The effects of implementing these modifications are both dose-dependent and time-dependent and could be greater for some patients than for others. Also, a combination of two or more lifestyle modifications can lead to even better results. Lifestyle modifications not only reduce BP but also enhance the efficacy of antihypertensive drugs and decrease cardiovascular risk.

2.1.2 Medical Treatment for Stage 1 and Stage 2 Hypertension

Based on Antihypertensive and Lipid Lowering to Reduce Heart Attack Trial (ALLHAT) data, JNC 7 recommends diuretics as first-line therapy for the management of stage 1 hypertension, and a combination of two (2) drugs as initial therapy for stage 2 hypertension, preferably with a diuretic as one (1) of these two (2) drugs.[1]

It was concluded from this trial that diuretic therapy is as effective as a calcium channel blocker (CCB) or an angiotensin-converting enzyme (ACE) inhibitor from the standpoint of the primary outcome of the trial, and diuretic therapy is superior for select subgroup analyses. A critical look at the trial design suggests a more prudent conclusion that diuretics should be part of all antihypertensive regimens unless they are clearly contraindicated.

In addition, there was a concern that diuretics might worsen glucose tolerance and insulin resistance. Recent data demonstrates that the higher incidence of diabetes mellitus related to thiazides does not appear to be responsible for the increase in risk for coronary heart disease.5 In addition to thiazide diuretics, JNC 7 guidelines also recommend ACE inhibitors, angiotensin receptor blockers (ARBs), beta-blockers (BBs), and CCBs as first-line therapy for hypertension. Since the publication of JNC 7 guidelines, studies have shown that beta-blocker therapy might not be effective and in fact might increase the risk of stroke.1,4 In the newer guidelines published by various national societies, BBs have been removed as first-line therapy and are recommended only with a compelling indication in those with cardiac disease.

Based on evidence of improved outcomes, JNC 7 has recommended several medications for compelling indications (Tables 2 and 3). These include BBs and aldosterone antagonists in those with cardiac disease, ACE inhibitors and ARBs in those with chronic kidney disease, and diuretics and CCBs in those with isolated systolic hypertension. A combination of ACE inhibitors and diuretics instead of ACE inhibitors alone is recommended for preventing recurrence of stroke based on findings of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), which showed a 42% stroke reduction in those treated with this combination of therapy.[7]

TABLE 2: CLASSIFICATION AND MANAGEMENT OF BLOOD PRESSURE FOR ADULTS

				Initial Drug Therapy	
BP Classification	**SBP,* mmHg**	**DBP,* mmHg**	**Lifestyle Modifications**	**With Compelling Indications**	**Without Compelling Indications**
Normal	<120	and <80	Encourage		
Prehypertension	120-139	*Or* 80-89	Yes	No antihypertensive drug indicated	Drug(s) for compelling indications†
Stage 1 Hypertension	140-159	*Or* 90-99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination	Drug(s) for the compelling indications.‡ Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed
Stage 2 Hypertension	>160	*Or* >100	Yes	Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB)	

Data from Chobanian AV, Bakris GL, Black HR, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42(6):1206-1252. Available at http://www.nhlbi.nih.gov/guidelines/hypertension/index.htm (accessed April 12, 2012).

**Treatment determined by highest blood pressure category. †Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension. ‡Treat patients with chronic kidney disease or diabetes to blood pressure goal of;130/80 mmHg. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure, SBP, systolic blood pressure.*

TABLE 3: CLINICAL TRIAL AND GUIDELINE BASIS FOR COMPELLING INDICATIONS FOR INDIVIDUAL DRUG CLASSES

	Recommended Drugs						
Compelling Indication*	**Diuretic**	**BB**	**ACEI**	**ARB**	**CCB**	**Aldo ANT**	**Clinical Trial Basis†**
Heart failure	√	√	√	√		√	ACC/AHA heart failure guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES
Post-myocardial infarction		√	√			√	ACC/AHA post-MI guideline, BHAT, SAVE, Capricorn, EPHESUS
High coronary disease risk	√	√	√		√		ALLHAT, HOPE, ANBP2, LIFE, CONVINCE
Diabetes	√	√	√	√	√		NKF-ADA guideline, UKPDS, ALLHAT
Chronic kidney disease			√	√			NKF guideline, captopril trial, RENAAL, IDNT, REIN, AASK
Recurrent stroke prevention	√		√				PROGRESS

Data from Chobanian AV, Bakris GL, Black HR, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42(6):1206-1252. Available at http://www.nhlbi.nih.gov/guidelines/hypertension/index.htm (accessed *April 12, 2012).*

**Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the BP.*

†Conditions for which clinical trials have demonstrated benefit of specific classes of antihypertensive drugs. ACEI, angiotensin-converting enzyme inhibitor; Aldo ANT, aldosterone antagonist; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker.

2.1.3 Baroreceptor Modulation for Hypertension

The pivotal role of the autonomic nervous system in the pathogenesis of hypertension is well established. However, pharmacological therapies that block sympathetic activity have not achieved the desired outcomes.

In the past few years, there have been efforts to develop medical devices and techniques that influence sympathetic nervous system activity. These include endovascular renal sympathetic denervation and continuous electrical baroreceptor nerve pacing.

Vascular Dynamics' approach is to modulate the baroreflex using a simple, passive, implantable device as a means for inhibiting sympathetic activity and lowering BP. The application of localized mechanical forces to the arterial wall of the carotid sinus changes its geometric shape to increase baroreceptor signaling, while preserving arterial pulsatility and blood flow.

The effect of a change in the morphology of the carotid sinus on systemic BP has been studied in dogs, both acutely by Bagshaw, et. al. (1987)[8], and chronically by Fadali, et. al. (1969).[9] In both studies, the canine carotid sinuses were surgically enlarged using a vein patch. Bagshaw measured the effect this "patchplasty" had on systemic BP and found that the increase in carotid baroreceptor sensitivity correlated with the increase in the diameter of the sinus. In the chronic study by Fadali, the dogs' systemic BP was lowered significantly over a follow-up period of six (6) months.

Although the exact change in carotid sinus morphology in the studies described above is different from the one produced by the MobiusHD, these studies clearly demonstrate that an artificial increase in the diameter of the carotid sinus, which preserves the pulsatile nature of the input to the baroreceptors, increases the strain measured by the baroreceptors and ultimately reduces systemic BP. This is especially relevant to the MobiusHD's mechanism of action since the enlarged diameter in these studies was produced by a surgical change rather than as a result of mere over-inflation of the sinus by increased internal pressure.

A study in human subjects by McKevitt, et. al. (2003)[10] investigated the short and long term effects of carotid endarterectomy (CEA) and carotid artery stenting (CAS) on systemic arterial BP. A statistically significant decrease in SBP was found at one and six months only in the surgical group (37 subjects) but not in the CAS group (40 subjects). Acute hypotension was observed in both groups. These findings support our hypothesis that traditional carotid stents cause only transient hypotension due to an exaggerated stretching of the arterial wall, which reduces pulsatility and ultimately induces baroreceptor resetting.

In a CEA the diameter of the carotid sinus is enlarged by use of a patch, and the cross section of the artery becomes non-circular, resulting in short-term hypotension[11]. Implantation of the MobiusHD also results in a change to the cross-sectional shape of the carotid sinus, but unlike a carotid stent or CEA, the MobiusHD maintains pulsatility.

Knowledge derived from NASA's research on the baroreflex in humans using the Variable Pressure Neck Chamber is described by Fadel, et. al.(2003).[12] These experiments demonstrate the significant impact that mechanical modulation of the carotid sinus has on systemic BP in humans, and that this effect is mostly exerted through a change of systemic vascular resistance by the sympathetic nervous system.

Based on data suggesting the potential utility of mechanical modulation of the baroreflex for lowering BP, Vascular Dynamics has developed the MobiusHD for the treatment of resistant hypertension.[13] The MobiusHD, the subject of this protocol (Protocol), is a sterile self-expanding nitinol implant, delivered through a disposable catheter, the Delivery Catheter. Together, the MobiusHD and Delivery Catheter make up the MobiusHD system. The MobiusHD is designed to treat drug-resistant hypertension by amplifying carotid sinus baroreceptor afferent signaling.

3.0 MOBIUSHD™ SYSTEM

3.1 DETAILED DESCRIPTION OF MOBIUSHD

The MobiusHD system consists of two parts: (1) the implant (MobiusHD); and (2) the Delivery Catheter (DC). The implant is a thin, flexible, open metal cage that is implanted in the carotid sinus. It is made of a nickel-titanium alloy (nitinol) tubing and laser-cut into a cage shape. Two radiopaque markers made of tantalum are welded at each end of the implant to help with visualization and positioning under fluoroscopy. The implant is mounted in a long, thin, tube-like device called a catheter, which together with the delivery handle, constitutes the Delivery Catheter.

The MobiusHD system is compatible with appropriately sized commercially available guidewires and guiding catheters and/or sheaths. The MobiusHD system is introduced into the femoral artery in the groin, and advanced through the length of the guiding catheter or sheath over a guidewire into the carotid sinus using fluoroscopic guidance.

Once the Delivery Catheter has been guided to the desired location, the implant is partially deployed by holding the delivery handle stationary, while moving the lever to a secondary locked position. At this point, the operator has the opportunity to review the position and recapture the device if repositioning is needed. The recapture is performed by simply advancing the lever forward back to the closed position. Alternatively, if the operator is pleased with the position, a second release maneuver is performed and with a final short lever retraction, the remaining constrained portion of the implant is allowed to expand and is released from the delivery system. The implant is designed to expand to a programmed size after being released from the delivery catheter.

3.2 COMPONENTS

The MobiusHD system consists of two parts: (1) the implant (MobiusHD); and (2) the Delivery Catheter.

- Implant – A super-elastic self-expanding nitinol open metal cage with two radiopaque markers on each end. The implant expands as it is deployed from the delivery catheter. The implant may be partially deployed and still be retracted back into its delivery catheter. The implant is preloaded in the Delivery Catheter.
- Delivery Catheter – A soft, atraumatically tipped delivery catheter with a delivery handle attached to its proximal end. The delivery handle has stops that allow for partial deployment without risk of unintended release of the implant. In addition there are locks that prevent premature unsheathing or device release. When release is desired, the delivery handle must be further actuated to release the implant from the delivery catheter.

The MobiusHD system is designed to track easily within the guiding catheter or sheath through the vasculature to the left or right carotid sinus located in the ICA just distal to the common carotid bifurcation.

3.2.1 MobiusHD (implant)

The MobiusHD is laser cut from a tube of superelastic nitinol. This is the same material used in most self-expanding stents. After laser cutting, the implant is heat set to its final shape. Radiopaque tantalum markers are swaged and welded into marker holes previously cut into the implant. Finally, the implant is electropolished to create a smooth surface. The design consists of four "windows," which amplify carotid sinus baroreceptor afferent signaling, while maintaining pulsatility of the vessel. The "crowns" at each end of the windows generate the radial force necessary for the implant to self-expand and allow the struts of the implant in the mid-body to maintain proper wall apposition, thus creating the wide "windows" necessary to amplify pulsatility. To minimize the force per area, the struts along the main body of the implant are doubled to increase the surface area in order to distribute the radial force. The implant design is illustrated in Figures 1 and 2 and its characteristics are presented in Table 4.

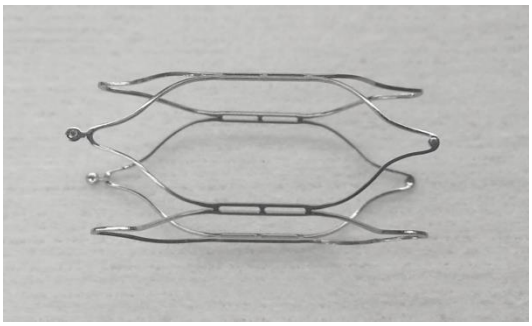


FIGURE 1: MOBIUSHD™

TABLE 4: MOBIUSHD IMPLANT CHARACTERISTICS

Characteristic	Specification
Length (unconstrained)	17.00 to 19.30 mm
Expanded Diameter	5.00 to 11.75 mm
Implant Coverage (%Surface Area)	≤ 10.25% for all models

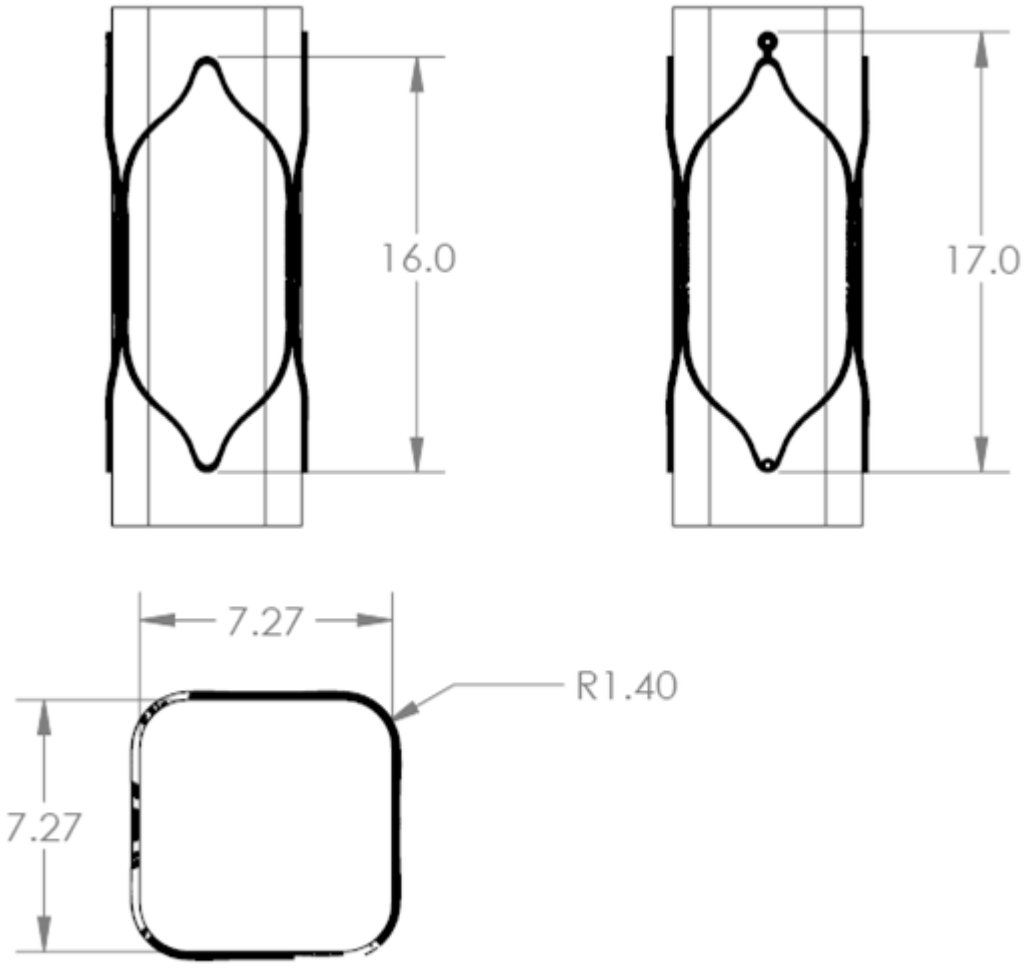


FIGURE 2: MOBIUSHD SIZE A, AS EXAMPLE

3.2.2 Delivery Catheter

The Delivery Catheter (DC) is designed to enable the physician to navigate to the desired deployment location and accurately unsheathe the implant in a controlled fashion. Similar to other commercially available devices, the DC is designed with a truncated central guidewire lumen (i.e. rapid exchange) to allow introduction over a standard length 0.014" guidewire. The DC is comprised of an inner body and an outer body. The delivery handle connects these two components and allows the user to controllably retract the outer body while maintaining the position of the implant in the desired deployment location. This enables the implant to gently expand to meet the interior luminal vessel wall. The additional control provided by the delivery handle reduces the risk associated with advancing the implant rather than retracting the outer body.

In order to avoid unintentional deployment, the delivery handle incorporates features that require additional action on the part of the user to move from the partial deployment position to full deployment. Additionally, the DC allows the physician to re-sheath and reposition the implant to ensure the desired placement is achieved. The actuation of the Delivery Catheter is illustrated in Figure 3.

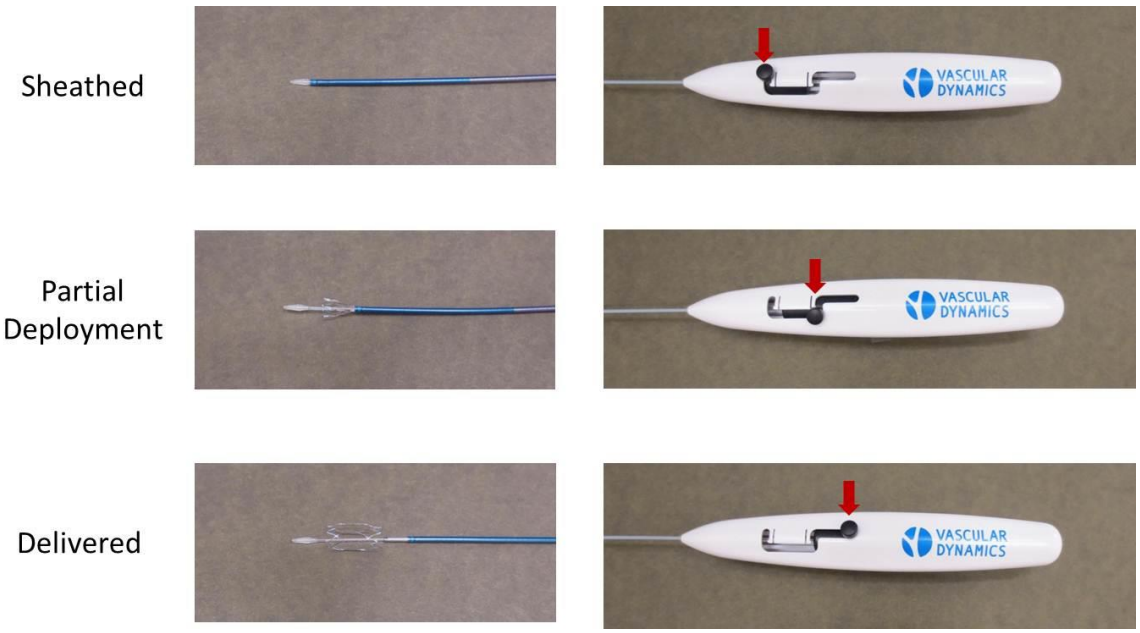


FIGURE 3: ACTUATION OF DELIVERY CATHETER

Materials standard to commercially available medical devices have been employed in the construction of the Delivery Catheter. These materials include Nylon-12, PEEK, Pebax, high density polyethylene (HDPE), 90% Platinum/10% Iridium, stainless steel (in the form of wire, tubing and machined components), ABS, and medical grade adhesives. Similarly, common processes are used for construction of the DC, including extrusion, thermal and adhesive bonding, conventional machining, injection molding and braiding. Components of the Delivery Catheter are listed in Table 5. Key measurements are presented in Table 6 and Figure 4.

TABLE 5: COMPONENTS AND MATERIALS IN THE DELIVERY CATHETER

Catheter Component	Material	Patient Contact?
Inner Extrusion	PEEK	Yes
Atraumatic Tip	Pebax	Yes
Support Coil	Stainless Steel	No
Retractor	Stainless Steel	Yes
Hypotube, Proximal	Stainless Steel	Yes
Hypotube Cover	HDPE	Yes
RX Adaptor	Stainless Steel	Yes
Outer Shaft, Braided	PTFE, Stainless Steel, Nylon-12, Pebax, Pt/Ir, PET	Yes
Handle, Top	ABS, Ink	No
Handle, Bottom	ABS	No
RHV Sheath	PEEK	No
Shuttle, Handle	ABS	No
Screw, Handle	Stainless Steel	No
Standoff, Handle	Stainless Steel	No
Cap, Handle	ABS	No
Crimp Tube & Block	Stainless Steel, Ag Solder	No

TABLE 6: DELIVERY CATHETER KEY MEASUREMENTS

Characteristic	Specification*
RX Section Length	35 cm
Tri-Axial Section Length	30 cm
Working Length	135 cm
Guidewire Compatibility	.014”
Crossing Profile	.078” Max
Guide Catheter/Sheath Compatibility	8 Fr Guide Catheter / 6 Fr Sheath with minimum inner diameter of .086”/2.18mm
*All dimensions nominal	

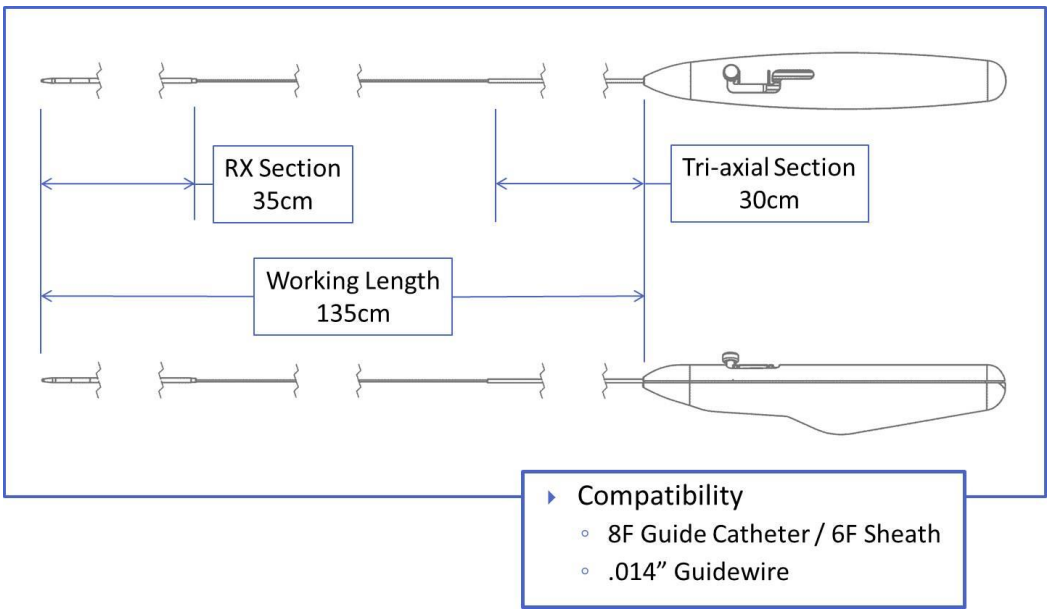


FIGURE 4: DELIVERY CATHETER KEY MEASUREMENTS

3.3 PRINCIPLE OF OPERATION

The MobiusHD is placed in the target carotid sinus by advancing the catheter to the target site through the femoral artery, through an appropriate guiding catheter or sheath, and over a .014 inch guidewire. This catheter houses the MobiusHD implant. The catheter is precisely positioned in the carotid sinus using the marker bands on the DC and implant as a guide. When properly positioned, the DC protective sheath is pulled back by manipulation of the handle, to allow expansion of the implant and apposition with the vessel intima. The catheter is then withdrawn, leaving the implant at the site of the carotid sinus.

4.0 STUDY OBJECTIVES

The objective of the present study is to prospectively evaluate the safety of the MobiusHD system in subjects with resistant hypertension in a multi-center, open-label, first-in-man clinical trial.

Additional goals of this study are to evaluate the effect of MobiusHD device on systemic blood pressure, diastolic blood pressure, and heart rate.

5.0 CLINICAL STUDY DESIGN

This is an open-label, multicenter, first-in-man clinical trial to be conducted inside the United States. Up to 20 patients with stage 2 resistant hypertension (i.e., inadequate blood pressure control with a minimum of three (3) anti-hypertensive drugs), who meet the protocol eligibility criteria and consent to study participation will undergo placement of the MobiusHD implant in the carotid sinus and will be followed for 36 months.

The first 10 patients enrolled will undergo unilateral placement of a single MobiusHD implant. Enrollment of this group of 10 subjects will be staggered based on review of clinical outcomes by the Data Safety Monitoring Board (DSMB) and by FDA, as shown in Figure 5.

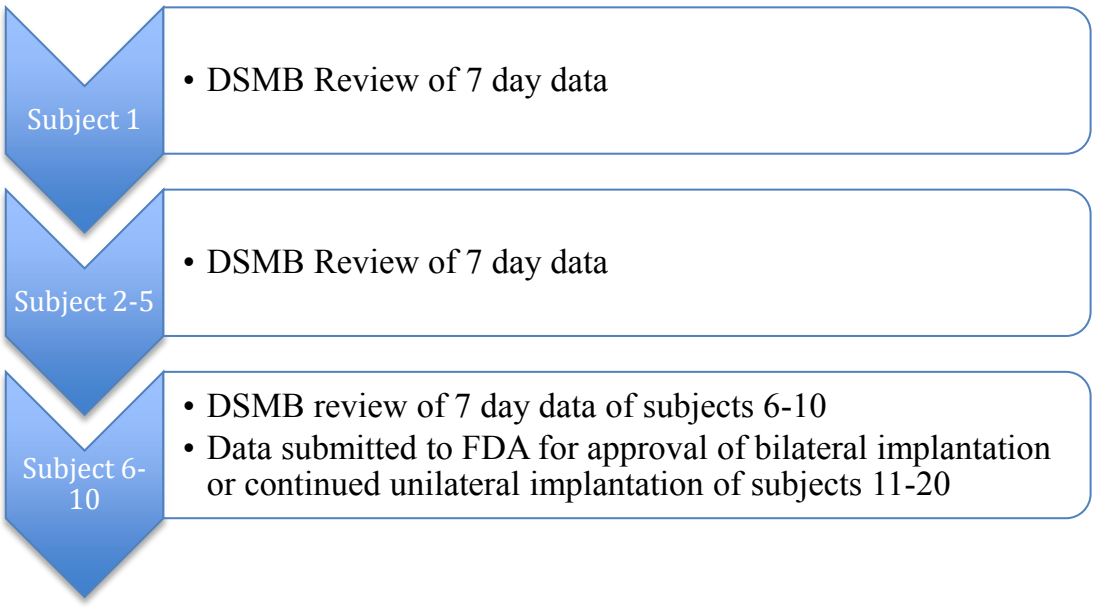


FIGURE 5: ENROLLMENT SCHEDULE FOR FIRST 10 STUDY SUBJECTS (UNILATERAL TREATMENT)

Following enrollment of the initial 10 subjects, based on DSMB review of available data, a determination will be made on whether the safety of the MobiusHD is adequate to support bilateral placement. If the DSMB determines that bilateral treatment is warranted, an interim report with all available clinical data will be submitted to FDA with a request for initiation of bilateral treatment in the remaining 10 study subjects.

If bilateral placement of the MobiusHD is recommended by the DSMB and approved by FDA, enrollment will again be staggered as shown in Figure 6.

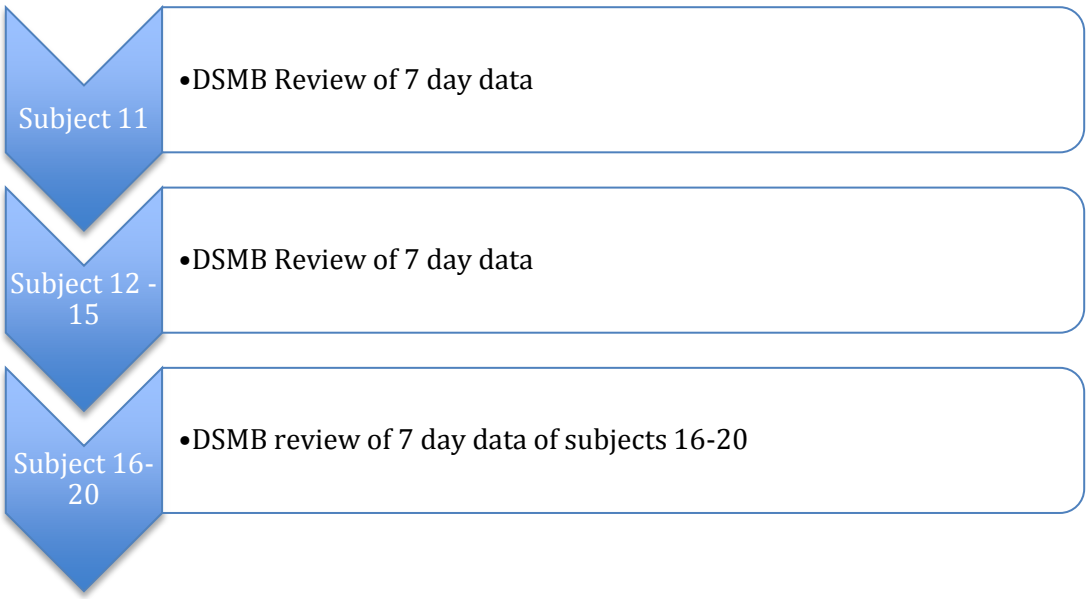


FIGURE 6: ENROLLMENT SCHEDULE FOR AN ADDITIONAL 10 STUDY SUBJECTS (BILATERAL TREATMENT)

Flow charts for patient screening and enrollment are provided in Figure 7 and Figure 8, for the 10 subjects to be treated with a single device (Unilateral Cohort) and for the next 10 subjects to receive devices bilaterally (Bilateral Cohort), respectively. As shown, study subjects have two (2) screening visits for determination of eligibility, an initial screening visit (Day 0 to 14) and a second screening visit (Day 15 to 30), followed by a baseline visit. All study subjects will be examined on days 7, 30, 90, 180, 360, 1 year 6 months, 2 years, 2 years 6 months, and 3 years.

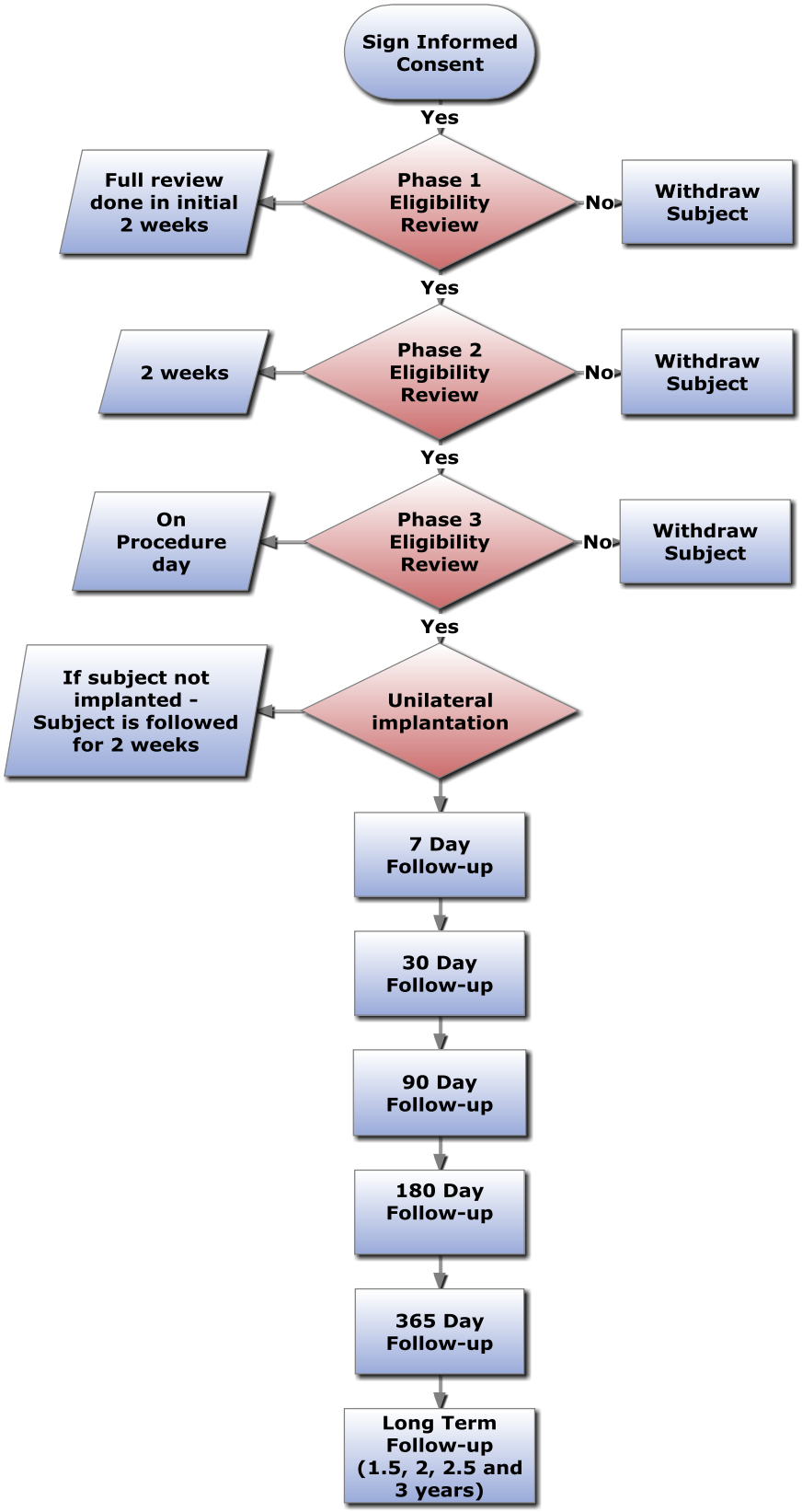


FIGURE 7: STUDY FLOW CHART UNILATERAL COHORT (N = 10 SUBJECTS)

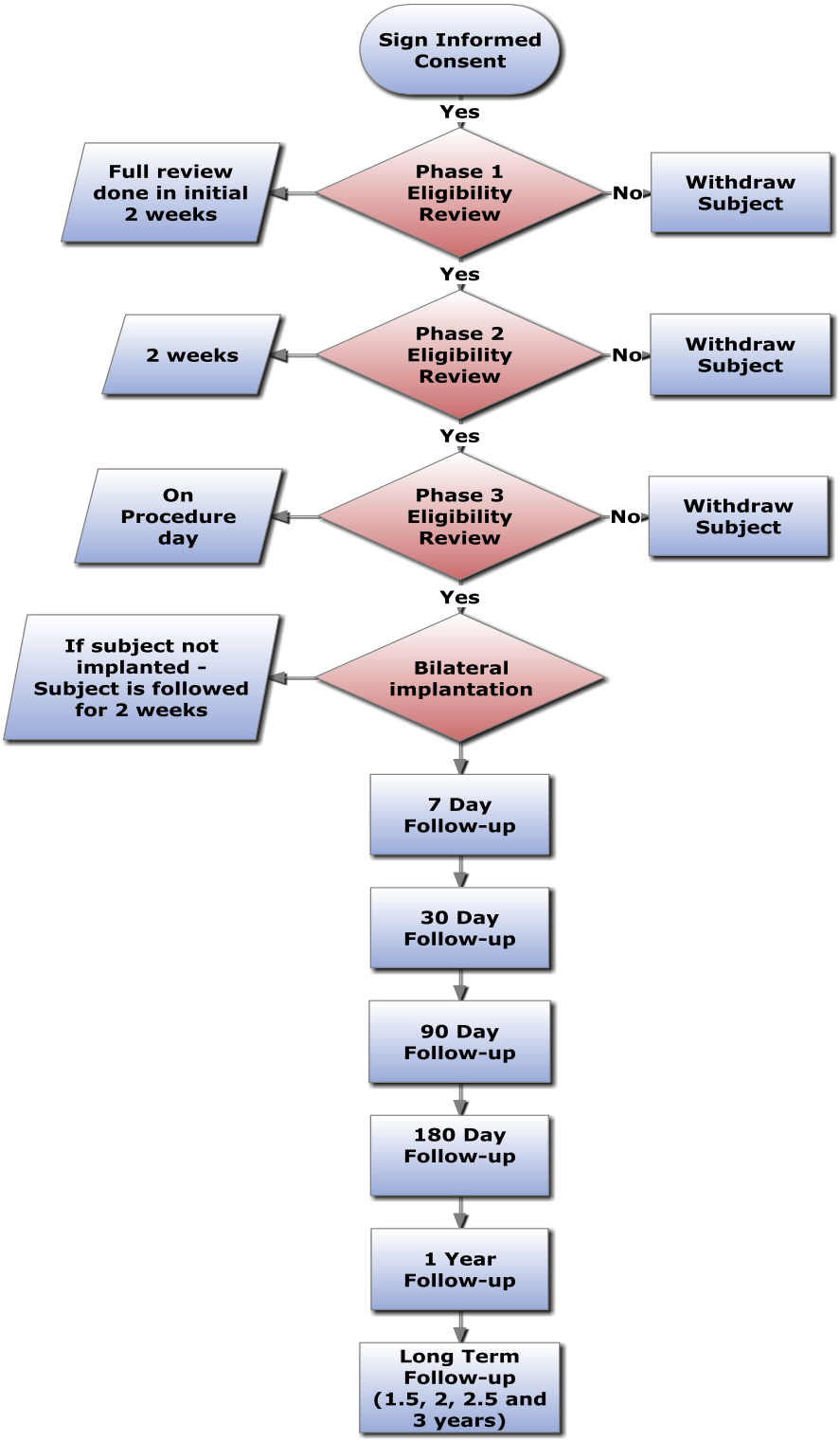


FIGURE 8: STUDY FLOW CHART BILATERAL COHORT (N = 10 SUBJECTS)

6.0 STUDY POPULATION

The study population for this clinical trial consists of male and female adults who have been diagnosed with stage 2 resistant hypertension, on at least three (3) anti-hypertensive medications of which one is a diuretic. All potential study participants must meet all of the following eligibility criteria to qualify for enrollment in the study.

6.1 INCLUSION CRITERIA

Candidates for this study must meet the following criteria to be enrolled in the study, as determined in the following screening and baseline visits:

Baseline Screening Visit 1 – (Day 0 – 14) – Assessed on Day 14

1. Provided written informed consent;
2. ≥ 18 years of age and ≤ 80 years of age;
3. Office cuff SBP ≥ 160 mmHg measured per protocol instructions (Appendix VI) following at least one (1) month of maximally tolerated therapy with at least three (3) anti-hypertensive medications, of which at least one (1) must be a diuretic. Any combination medications will be counted per the active ingredient (for example, Zestoretic (Lisinopril +HCTZ) equals two (2) anti-hypertensive medications);
4. Renal artery imaging performed within the last 12 months showing no evidence of renal artery stenosis. Acceptable imaging modalities include renal duplex, magnetic resonance angiography, CT angiography, and selective or nonselective renal angiography depending on investigator site diagnostic standards. In the absence of adequate imaging testing this inclusion criteria could also be met by obtaining a renal duplex prior to enrollment or by performing nonselective renal angiography at the time of device implantation.
5. Compliant with medications (self-reported) and daily blood pressure readings – Subject must be a minimum 80% compliant with diary entries; and
6. For females (with child-bearing potential), a negative pregnancy test and the use of a medically accepted method of birth control for the duration of the trial.

Baseline Screening Visit 2 – (Day 15 – 30) - Assessed on Day 30

1. No significant obstructive vascular disease on CTA or MRA of the aortic arch and great vessels;
2. Carotid duplex studies demonstrating no obstructive carotid disease;
3. Continued adherence to hypertension medications without anticipated changes and daily blood pressure readings – Subject must be a minimum 80% compliant with diary entries;
4. Continued office cuff SBP ≥ 160 mmHg despite at least one (1) month of therapy at maximally tolerated therapy with at least three (3) anti-hypertensive medications, of which at least one (1) must be a diuretic. Any combination medications will be counted per the active ingredient (for example, Zestoretic (Lisinopril +HCTZ) equals two (2) anti-hypertensive medications).

Day of Procedure -

1. Continued adherence to hypertension medications without anticipated changes and daily blood pressure readings – Subject must be a minimum 80% compliant with diary entries.

6.2 EXCLUSION CRITERIA

Candidates will be ineligible for enrollment in the study if any of the following conditions are identified at the screening or baseline visits:

Baseline Screening Visit 1 – (Day 0 – 14) – Assessed on Day 14

1. Known or clinically suspected baroreflex failure or autonomic neuropathy;
2. Hypertension secondary to an identifiable and treatable cause other than sleep apnea (e.g., hyperaldosteronism, renal artery stenosis, pheochromocytoma, Cushing's disease, coarctation of the aorta, hyperparathyroidism and intracranial tumor);
3. Treatable cause of resistant hypertension including, but not limited to, improper BP measurement, volume overload and pseudotolerance (excessive sodium intake, volume retention from kidney disease, inadequate diuretic therapy), drug-induced or other causes (non-adherence, inadequate doses, inappropriate combinations, NSAIDs, COX-2 inhibitors, cocaine, amphetamines, or other drugs, sympathomemetics, oral contraceptives (confirmed cause of resistant hypertension), adrenal steroids, cyclosporine, and tacrolimus, erythropoietin , licorice (including some chewing tobacco), ephedra, ma haung, bitter orange); and excessive alcohol intake;
4. Arm circumference greater than 46 cm and/or BMI $\geq$ 40;
5. Chronic atrial fibrillation;
6. Vulnerable plaque or ulceration of any size in the carotid artery or aortic arch;
7. History of bleeding complications with dual anti-platelet therapy in the past or has known uncorrectable bleeding diathesis;
8. Current use of additional anticoagulation therapy. Examples include vitamin K antagonists like warfarin, direct thrombin inhibitors, direct factor Xa inhibitors, thrombin IIa inhibitors like apixaban, rivaroxaban, dabigatran and etexilate;
9. Peptic ulcer disease with documented active ulcer or bleeding within the last year;
10. History of allergy to contrast dye that cannot be managed medically;
11. History of orthostatic hypotension;
12. History of syncope within the last six (6) months;
13. History of myocardial infarction or unstable angina within the past three (3) months;
14. History of cerebral vascular accident (stroke or TIA) within the past year;
15. Severe chronic kidney disease (calculated GFR < 45 ml/min);
16. Prior surgery, radiation, or endovascular stent placement in either carotid region;

17. Clinically significant structural valvular cardiac disease;
18. Moderate to severe reactive airway disease, chronic obstructive pulmonary disease, or primary pulmonary hypertension;
19. Uncompensated congestive heart failure or known severe reduction in left ventricular function (EF < 30%);
20. Uncontrolled co-morbid medical condition that would adversely affect participation in the trial;
21. Non-controlled diabetes mellitus;
22. Active infection within the last month;
23. Co-morbid condition that reduces life expectancy to less than one (1) year;
24. Mental health issues that would prohibit the subject's ability to meet the protocol requirements;
25. Currently taking an imidazoline receptor agonist or receiving central sympathetic treatment;
26. Enrolled in a concurrent clinical trial;
27. Unable or unwilling to fulfill the protocol follow-up requirements;
28. Subject is a prisoner or member of other protected population;
29. Planned surgery or other procedure within the next six (6) months; or
30. Deep venous thrombosis (DVT) within the last year or documented recurrent DVT.

Baseline Screening Visit 2 – (Day 15 – 30) - Assessed on Day 30

1. ICA lumen diameters < 5 mm or > 11.75 mm within the planned location of the device placement via CTA or MRA;
2. Carotid hypersensitivity detected by carotid massage or typical history, as described in the study protocol; and
3. Significant aortoiliac or common femoral artery disease that will prohibit safe femoral access.

Day of Procedure – Angiographic

1. Evidence of plaque, ulceration or any stenosis by angiographic evaluation in orthogonal views of the carotid artery. Lumen diameters will be assessed to exclude subjects with ICA lumen diameters smaller than 5 mm or larger than 11.75 mm within the planned location of the device placement;
2. Any plaque or ulceration on the arch angiogram involving the aortic arch and/or the origin of the great vessels;
3. Inappropriate anatomy of the carotid bifurcation for deployment of the MobiusHD, including, but not limited to, tortuosity of the extracranial vessels and significant angulation of the common carotid artery bifurcation; and

4. Type III arch or horizontal takeoff of the left carotid from the innominate and calcification of the carotid bulb.

7.0 SUBJECT ENROLLMENT

Clinical site personnel will review the patient's medical history for eligibility. Potential candidates will be fully informed of the purpose of the study and the nature of the implantation procedure. The implantation procedure will be described and its potential risks and benefits will be explained in detail. Once the patient's potential eligibility has been determined, the Investigator will discuss the study and ask the patient if they are interested in participating in the study. Patients who voluntarily agree to participate in the trial will be asked to sign and date the written Informed Consent Document (ICD). The study will be explained to the patient in lay terms. The ICD, approved by the site Institutional Review Board (IRB), must be signed by the potential study participant before he or she undergoes any study specific assessments. A copy of the signed and dated ICD should be provided to the subject. Failure to obtain a signed ICD prior to the procedure constitutes a protocol deviation. Subjects must be informed that they may withdraw from the study at any time, and for any reason, and will continue to receive therapy as indicated by their physician.

All subjects who meet the eligibility criteria and give written informed consent are considered enrolled in the study and must be entered into the electronic database for assignment of subject identification number. This unique number identifies each Case Report Form (CRF) and should be used on all source documents so that study data is reported in anonymous form to protect subject confidentiality.

A screen-failed subject refers to a subject who signed the approved ICD but failed to meet all the eligibility criteria. There are no follow-up requirements for subjects who electively withdraw from the study prior to treatment. The original ICD and a screening log will be maintained in the clinical site's study files. No CRFs are required to be completed for screen failure patients and these patients will not be followed per the Investigational Plan requirements.

If the Investigator is unable to place a MobiusHD implant in a subject, the subject will be followed to the 30-Day visit and will then be exited from the study in the absence of any ongoing adverse events. If an adverse event is ongoing or not stabilized, the subject will continue to be followed until complete resolution or stabilization of the AE with no expectation or need for further treatment. The reason(s) for failure to place the implant will be documented on the Procedure CRF.

8.0 STUDY METHODS

The study assessments, beginning with the baseline assessments used for screening potential study participants, are described below by visit.

8.1 MEDICAL THERAPY REGIMEN – ALL SUBJECTS

All participants in the study will be on a minimum of three (3) anti-hypertensive drugs such as, but not limited to, the following:

Diuretics			
Class	**Generic name**	**Brand name**	**Side effects**
Thiazide diuretics	chlorothiazide	Diuril	Weakness, confusion, potassium depletion, gout, fatigue, thirst, frequent urination, lightheadedness, muscle cramps, diarrhea or constipation, increased sensitivity to sunlight, allergic reaction in people allergic to sulfa drugs, impotence.
	chlorthalidone	Hygroton	
	hydrochlorothiazide	Esidrix, HydroDiuril, Microzide	
	indapamide	Lozol	
	metolazone	Mykrox, Zaroxolyn	
Loop diuretics	bumetanide	Bumex	Weakness, confusion, potassium depletion, gout, fatigue, thirst, diarrhea or constipation, increased sensitivity to sunlight, allergic reaction in people allergic to sulfa drugs, impotence.
	ethacrynic acid	Edecrin	
	furosemide	Lasix	
	torsemide	Demadex	
Potassium-sparing diuretics/ aldosterone-receptor blockers*	amiloride	Midamor	Excessive potassium levels, especially in patients with kidney disease; breast enlargement and erectile dysfunction in men; menstrual irregularities in women.
	spironolactone	Aldactone	
	triamterene	Dyrenium	
	eplerenone	Inspra	Headache, dizziness, diarrhea, fatigue, upset stomach, and breast enlargement or tenderness.

*Note: Potassium-sparing diuretics also directly or indirectly block aldosterone, a hormone that raises blood pressure by causing the kidneys to conserve sodium and water. As a result, these four medications are sometimes also known as aldosterone-receptor blockers. Amiloride (Midamor), spironolactone (Aldactone), and triamterene (Dyrenium) also affect other hormones and thus carry some unwanted side effects, such as breast enlargement and impotence in men and menstrual irregularities in women. Eplerenone (Inspra) is the only one of these medications that affects solely aldosterone and not other hormones.

Anti-adrenergic drugs			
Class	**Generic name**	**Brand name**	**Side effects**
Beta blockers (cardioselective)	atenolol	Tenormin	Wheezing, dizziness, depression, impotence, fatigue, insomnia, decreased HDL cholesterol levels, lower exercise tolerance. Can worsen peripheral vascular disease and heart failure. Abrupt withdrawal may trigger angina or a heart attack in patients with heart disease.
	metoprolol	Lopressor	
	metoprolol extended release	Toprol-XL	
	nebivolol	Bystolic	
Beta blockers (nonselective)	nadolol	Corgard	
	pindolol	Visken	
	propranolol	Inderal, Inderal LA	
	sotalol	Betapace	
	timolol	Blocadren	
Alpha-1 blockers	doxazosin	Cardura	A drop in blood pressure upon standing up, fainting, weakness, heart palpitations, headache, nasal congestion, dry mouth.
	prazosin	Minipress	
	terazosin	Hytrin	
Alpha and beta blockers	carvedilol	Coreg	Wheezing, depression, insomnia, diarrhea, lightheadedness, dizziness, unusual tiredness or weakness, drying of the eyes, erectile dysfunction, headache, dry mouth, nasal congestion, decreased HDL cholesterol levels, lower exercise tolerance, a drop in blood pressure upon standing up, fainting, heart palpitations. Can worsen peripheral vascular disease and heart failure. Abrupt withdrawal may trigger angina or a heart attack in patients with heart disease.
	labetalol	Normodyne, Trandate	
Peripheral nerve–acting agents	guanethidine	Ismelin	A drop in blood pressure upon standing up, depression, nasal stuffiness, nightmares. Guanethidine may slow heart rate and reserpine may cause indigestion.
	reserpine	Serpalan	

Direct-acting vasodilators		
Generic name	**Brand name**	**Side effects**
hydralazine	Apresoline	Headaches, palpitations, weakness, flushing, nausea. Minoxidil may cause hair growth, fluid retention, and increased blood sugar.
minoxidil	Loniten	
Calcium-channel blockers		
Generic name	**Brand name**	**Side effects**
amlodipine	Norvasc	Headache, dizziness, edema, and heartburn. Nifedipine can cause palpitations. Diltiazem and verapamil can cause constipation and a slowed heartbeat.
diltiazem	Cardizem, Dilacor, others	
felodipine	Plendil	
isradipine	DynaCirc	
nicardipine	Cardene, Cardene SR	
nifedipine	Adalat CC, Procardia XL	
verapamil	Calan, Isoptin, others	
ACE inhibitors		
Generic name	**Brand name**	**Side effects**
benazepril	Lotensin	Cough, rash, fluid retention, high potassium levels, and loss of taste. May cause low blood pressure and fainting. Can worsen kidney impairment if narrowed arteries feed both kidneys. May cause fetal abnormalities.
captopril	Capoten	
enalapril	Vasotec	
fosinopril	Monopril	
lisinopril	Prinivil, Zestril	
quinapril	Accupril	
ramipril	Altace	

Angiotensin-receptor blockers (ARB)		
Generic name	**Brand name**	**Side effects**
candesartan	Atacand	Muscle cramps, dizziness.
eprosartan	Teveten	
irbesartan	Avapro	
losartan	Cozaar	
olmesartan	Benicar	
telmisartan	Micardis	
valsartan	Diovan	

Combination antihypertensive drugs		
Class	**Generic name**	**Brand name**
Potassium-sparing and thiazide diuretics	amiloride + HCTZ*	Moduretic
	spironolactone + HCTZ	Aldactazide, Spironazide, Spirozide
	triamterene + HCTZ	Dyazide, Maxzide
Alpha blocker and diuretic	prazosin + polythiazide	Minizide
Beta blocker and diuretic	atenolol + chlorthalidone	Tenoretic
	bisoprolol + HCTZ	Ziac
	metoprolol + HCTZ	Lopressor HCT
	nadolol + bendroflumethiazide	Corzide
	propranolol + HCTZ	Inderide, Inderide LA
	timolol + HCTZ	Timolide
ACE inhibitor and diuretic	benazepril +HCTZ	Lotensin HCT
	captopril + HCTZ	Capozide
	enalapril + HCTZ	Vaseretic
	fosinopril + HCTZ	Monopril HCT

Class	Generic name	Brand name
ACE inhibitor and diuretic (continued)	lisinopril + HCTZ	Prinzide, Zestoretic
	moexipril + HCTZ	Uniretic
	quinapril + HCTZ	Accuretic
ARB and diuretic	candesartan + HCTZ	Atacand HCT
	eprosartan + HCTZ	Teveten HCT
	irbesartan + HCTZ	Avalide
	losartan + HCTZ	Hyzaar
	telmisartan + HCTZ	Micardis HCT
	valsartan + HCTZ	Diovan HCT
Calcium-channel blocker and ACE inhibitor	amlodipine + benazepril	Lotrel
	diltiazem + enalapril	Teczem
	felodipine + enalapril	Lexxel
	verapamil + trandolapril	Tarka
Other combinations	methyldopa + HCTZ	Aldoril
	reserpine + chlorothiazide	Diupres
	reserpine + HCTZ	Hydropres
	aliskiren + HCTZ	Tekturna HCT
Calcium-channel blocker and ARB	amlodipine + valsartan	Exforge
	amlodipine + olmesartan	Azor
*HCTZ=hydrochlorothiazide		

Medications for treating hypertension
http://www.health.harvard.edu/newsletters/Harvard_Womens_Health_Watch/2009/August/Medications-for-treating-hypertension
(downloaded on 7/3/2012)

All subjects that are implanted with the MobiusHD will be required to be on duel antiplatelet therapy (ie. aspirin 81-325 mg daily and clopidogrel 75 mg daily; substitutes can be used but should be equivalent) for three (3) days prior to the implant procedure as well as three (3) months post-procedure. Aspirin will continue for the duration of study.

Management of subject's individual risk factors as appropriate, e.g., statins, smoking cessation, nutritionist, diabetes management, etc., will remain as standard of care and any changes to this regimen will be documented by the study team.

Subjects should be advised of the importance of not stopping their medical therapy regimen before first consulting with the study center. In the absence of changes initiated by the study physician in response to severe symptomatic drops in blood pressure, subjects should not reduce or stop their anti-hypertensive medication dosage until the 6-month time point, at which time the Principle Investigator may decide to reduce medication use.

8.2 STUDY ENROLLMENT

The number of subjects to be enrolled in the study is up to 20. This sample size is estimated to be sufficient to yield acceptable, first-in-man, safety and effectiveness data for initial analysis and to support future regulatory submissions. It is anticipated that up to ten (10) centers inside the United States will be needed to enroll this study in a timely fashion. Each investigational site will be expected to enroll at least two (2) and up to eight (8) subjects.

8.3 INVESTIGATOR QUALIFICATION AND TRAINING

The MobiusHD system should only be used by interventionists with expertise in the navigation of catheter systems and stenting procedures. Qualified potential Investigators for this clinical trial will have successfully placed carotid stents in at least 10 patients in the 12 months prior to Site Initiation and 100 carotid stents during their careers.

Qualified study centers will be expected to work in research teams that include the appropriate specialties for the proper conduct of the study (e.g., interventional cardiologist(s) or neurointerventionalist(s) experienced in carotid stenting, internists, and study coordinator(s)). Qualified interventionists will have successfully performed carotid stenting in at least 10 patients in the last calendar year and 100 patients in their careers.

All Investigators and those to whom the Investigator delegates study responsibilities (see Investigator Agreement), will be trained on the Protocol by a representative of the Sponsor. Interventional Investigators using the investigational device will be trained on the Instructions For Use of the MobiusHD system. Additional training such as preparation and table-top deployment of a demonstration device, animal lab, and/or case support will be offered by Sponsor, as appropriate, to meet the needs of the site Investigators. In addition, training on topics such as Medical Imaging Guidelines ("Core Lab", Appendix I), internet-based CRF (iCRF) data entry procedures, and investigational device inventory management will be conducted at Investigator meetings and during site visits. All training completed will be appropriately documented. Research staff responsible for assessing neurological status using the NIHSS must be certified in the proper administration of this assessment tool. Training and Certification on administration of the NIHSS, if such documentation is not already available, can be obtained by taking a web-based accredited course such as: http://nihss-english.trainingcampus.net/uas/modules/trees/windex.aspx

8.4 SELECTION AND SCREENING OF SUBJECTS

Prior to subject participation in this study, the study team must obtain written IRB/EC approval for the Protocol and the ICF. The study population for this clinical trial will be comprised of adult patients who have been diagnosed with stage 2 resistant hypertension. In addition, these patients must satisfy the inclusion and exclusion criteria. The trial will prospectively enroll up to 20 subjects. Patients presenting with stage 2 resistant hypertension must be on a minimum of three (3) anti-hypertensive medications. Clinical site personnel will review the patient's medical history for eligibility. Potential candidates will be fully informed by a member of the research team as to the purpose of the study and the nature of the implantation procedure. The implantation procedure will be described and its potential risks and benefits will be explained in detail. Patients who voluntarily agree to participate in the trial will be asked to sign and date the written Informed Consent Form (ICF). If approved by the reviewing IRB/EC, subjects may indicate verbal, witnessed consent with the signature of a patient representative not associated with the study team if cognition is intact but the subject is unable to sign (e.g., the subject has inhibited hand function or visual disturbance).

The approved ICF must be signed for study enrollment prior to performing study related assessments. A copy of the signed and dated ICF should be provided to the subject. Subjects must be informed that they may withdraw from the study at any time, and for any reason, and will continue to receive therapy as indicated by their physician. Internet-based Case Report Forms must be completed for each subject who consents to study participation.

8.5 BASELINE ASSESSMENT: VISIT 1 (DAY 0-14) – ASSESSED DAY 14

The following information will be assessed and the documentation will be maintained as source records at the study site:

- Medical history;
- Office cuff blood pressure (Note: Office cuff BP recordings must be performed as detailed in Appendix IV);
- Check for orthostatic blood pressure and orthostatic pulse assessments;
- Daily patient diary assessments of blood pressure and medication compliance;
- Assessment for renal artery stenosis. If duplex, renal MRA, renal angiography or renal CTA has been performed in the 12 months preceding screening, and in the absence of evidence of renal artery stenosis, no further work-up is needed. Otherwise, an abdominal angiogram in the 20-degree LAO projection will be performed prior to device placement.;
- Current medication history including all hypertensive medication;
- Physical examination;
- NIH Stroke Scale (NIHSS); and
- Laboratory testing, including hemoglobin (Hg), platelet count (Plt), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), high-density lipoprotein (HDL), low-density lipoprotein (LDL-C), creatinine (Cr), glucose, and pregnancy test (if subject is a female with child-bearing potential).

Local laboratories with appropriate certifications will be used for all laboratory testing.

- 12 lead electrocardiogram.

To avoid repeat testing, any of the testing listed above, performed within 90 days prior to presentation for the initial baseline assessment, may be used as baseline data.

8.6 BASELINE ASSESSMENT: VISIT 2 (DAY 15-30) – (+45 DAYS)

- Assessment of patient diary;
- Office cuff blood pressure (Note: Office cuff BP recordings must be performed as detailed in Appendix IV);
- Check for orthostatic blood pressure and orthostatic pulse assessments;
- Changes of medication regimen;
- Review and assessment of adverse events;
- CTA scan or MRA to assess exclusion criteria, from root of Aortic artery to intracranial vessels;
- Duplex imaging of the carotid artery;
- Assessment for carotid hypersensitivity;
- 24 hour ambulatory blood pressure measurement (24hr ABPM); and

8.7 BASELINE ASSESSMENTS VISIT 3 (DAY OF PROCEDURE) – ASSESSED ON DAY OF PROCEDURE

- Physical examination;
- Assessment of patient diary;
- Changes of medication regimen;
- Review and assessment of adverse events;
- Office cuff blood pressure (Note: Office cuff BP recordings must be performed as detailed in Appendix IV);
- Digital subtraction angiography – Inclusion/Exclusion criteria;
- Assessment of all Inclusion/Exclusion criteria; and
- Implantation of MobiusHD.

8.8 BASELINE ANGIOGRAM

After consent, all subjects should complete the baseline assessments outlined in Sections 8.5 – 8.7 and the Schedule of Study Visits and Assessments (Table 7). Subjects who meet all Inclusion/Exclusion criteria should then undergo angiogram according to imaging guidelines to measure and check the remaining Inclusion/Exclusion criteria. If renal duplex, renal MRA, renal CTA or renal angiography was performed in the 12 months preceding screening and showed no evidence of renal artery stenosis then no further work-up is needed. If no workup has been done then an abdominal angiogram in the 20 degree

LAO projection will be done prior to device implantation. During this angiogram procedure, if all Inclusion/Exclusion criteria are met, then the subject may be treated with the MobiusHD.

8.9 MOBIUSHD PROCEDURE

Prior to implantation, all assessment data should be entered into the eDC and there should be documentation that the patient has taken the dual antiplatelet regimen for the three (3) days. Also, diabetic subjects taking drugs containing metformin should be switched to insulin management the night before the implant procedure and should not be restarted on metformin until 48 hours after the last injection of contrast dye.

The patient will be placed in the standard supine position on the imaging table and prepped and draped as with any standard carotid transcatheter therapeutic or diagnostic study. Use of a head-stabilizing device is optional for this study and depends on physician preference. Light sedation and local anesthesia is recommended to allow for clinical neurological assessment, as needed.

In patients without adequate pre-procedure work-up for renal artery stenosis, non-selective renal angiography should be performed based on local technique preferences. In the absence of a local preference, begin with placement of the pigtail or lateral spray (i.e., tennis racket) catheter at the level of L-1. Make certain the catheter is easily movable and can rotate to ensure the tip is not inadvertently positioned in a thoracic or lumbar branch. Place the image intensifier at 20 degrees left anterior oblique and inject 15 cc/sec for 2 seconds under breath-hold conditions with digital subtraction. Different obliquity images may be needed if the renal ostia are eclipsed by overlying mesenteric vessels.

Heparin is given during the angiogram and implantation procedures (100 I.U./kg). ACT > 250 must be documented before implantation and measurement of platelet function is recommended according to local carotid stent protocols.

The aortic arch is defined by baseline angiography in the left anterior oblique projection. Selective carotid angiography of the target vessel for implant is performed in orthogonal views. If the aortic arch and carotid meet the study inclusion criteria then the operator will proceed with the implant.

The target common carotid is accessed with a 6 Fr kink-resistant sheath or an 8 Fr guiding catheter using the external carotid anchor-wire, telescoping technique or whatever approach the operator typically uses for carotid stenting. The guide or sheath tip should be in a stable position within the common carotid prior to removal of the .035 or .038 inch wire.

Once the guiding catheter or sheath is in position and the ACT is above 250 seconds, the ICA is accessed with a .014 inch guidewire. The implant delivery catheter is then prepared and introduced over the guidewire. Carotid imaging and roadmaps may be useful at this time. Selection of the implant size should be based on the angiographic measurements of the carotid sinus and these should coincide with the non-invasive (Duplex and or CTA) measurements. To select an appropriate implant size, select the size that correlates to the measurement made of the diameter of the carotid sinus.

Some degree of distal embolization likely occurs during all transcatheter interventional procedures. The clinical sequela is defined by the sensitivity of the target organ to segmental ischemia and the burden of embolic load.[14] Due to the low burden of embolic load expected in this procedure due to the inclusion and exclusion criteria the use of a protection device is based on operator preference. Distal protection may be used with any FDA-approved distal protection device but is not mandatory. Precise placement of the implant within the sinus is required and should be controlled by road map or contrast injections. Gentle forward and backward movements may be needed as with a carotid stent, to release tension and eliminate redundancy within the delivery catheter. Implant delivery is performed by very slow retraction of the implant delivery catheter sheath and this is performed by releasing the initial lock, then sliding the control knob proximally. The device will flower open and during this maneuver movement of the delivery catheter must be strictly avoided. The operator has the opportunity to re-sheath and reposition or release the second lock and deploy the implant, depending on his or her satisfaction with the implant position and apposition. Following implantation, the delivery catheter is removed; fluoroscopic guidance should be used until the nosecone is retracted past the implant. Post procedure angiography should be performed to evaluate proper implant positioning, apposition, and maintenance of the vessel lumen. Completion angiograms should display the implanted site and the dependent territory in at least two (2) orthogonal planes.

Refer to the IFU (Appendix VI) for detailed preparation procedures and detailed sizing and placement of the device.

8.10 POST-PROCEDURE CARE

Following the angiogram and procedure, the subjects will be asked to lie flat with a pressure bandage over the groin puncture site according to the local standard of care (e.g., assess for bleeding, hematoma, pedal pulses). A post-implant carotid duplex imaging study is required prior to discharge. The subject will be monitored closely for significant change in status (peri-procedural adverse events).

Implanted subjects should be monitored in an intensive care or intermediate care unit; with emphasis on meticulous blood pressure monitoring over the first 12 hours for recognition and/or prevention of severe hypotension (symptomatic drop in BP bellow 90/50) or severe hypertension (rise in BP above 180/100 mmHg with or without symptoms). If blood pressure drops below 90/50 with clinical symptoms or the subject has symptoms with a relative drop from baseline pressure due to past compensatory changes, then aggressive rescue (may include pressors, fluids, placement in trendelenburg position, withdrawal of blood pressure medications, etc.) should be provided to increase blood pressure to a point where the symptoms are alleviated. Blood pressure medications can be withdrawn if there is an abrupt drop in blood pressure from baseline, and should be documented as an adverse event and logged in the medication log. Aggressive use of protamine sulfate to antagonize the total dose of heparin should be avoided due to risk of implant thrombosis. Take vital signs once an hour for three (3) hours and enter data in the post-procedure iCRF. Standard post-procedure labs should be taken prior to discharge. These labs should include CBC, Chem 7, and Hematologic labs.

Prior to release from the hospital the subject's lying and standing bedside blood pressure should be measured and analyzed for orthostatic changes. In addition, the subject must be ambulatory, without dizziness or other symptoms.

If a new neurological deficit or a significant change in neurological status is determined using the NIHSS during post-procedure monitoring, assess for intracranial thrombus or hemorrhage using CT scan or MRI, if deemed appropriate by the Investigator under standard of care, and treat accordingly.

Body temperature >38˚C should be investigated, and testing performed per the standard of medical care (e.g., blood cultures, urinalysis, chest X-ray, phlebitis source), to allow appropriate treatment to be implemented.

8.11 SUBJECT DISCHARGE

On the day of discharge, clinical and neurological assessment of the subject is completed. Duplex imaging is done to visualize the carotid sinus and to assess for complications. Office cuff blood pressure should be taken and documented on the discharge iCRF. Orthostatic blood pressure measurement and orthostatic pulse assessments should be taken (sitting and standing). Assessment for any new or unresolved adverse events will be made and any changes in medication regimen will be recorded.

8.12 7-DAY FOLLOW-UP VISIT (+2 / -3 DAYS)

During the 7-Day follow-up visit, clinical assessment of the subject and evaluation of neurological symptoms will be performed by the study team. Office cuff blood pressure will be taken and assessment of the subject diary will be reviewed. A six minute walk test will be done following the March 2002 ATS Statement: Guidelines for the Six-Minute Walk Test, and orthostatic assessment should be done following this test. Orthostatic blood pressure measurement and orthostatic pulse assessments should be taken (sitting and standing). The neurological examinations are classified by NIHSS. Duplex imaging is done to visual carotid sinus and to assess for complications. Assessment for any new or unresolved adverse events will be made and any changes in medication regimen will be recorded.

8.13 30-DAY FOLLOW-UP VISIT (+7 / -7 DAYS)

During the 30-Day follow-up visit, clinical assessment of the subject and evaluation of neurological symptoms will be performed by the study team. Duplex imaging is done to visualize the carotid sinus and to assess for complications. Office cuff blood pressure will be taken and assessment of the subject diary will be reviewed. A six minute walk test will be done following the March 2002 ATS Statement: Guidelines for the Six-Minute Walk Test and orthostatic assessment should be done following this test. Orthostatic blood pressure measurement and orthostatic pulse assessments should be taken (sitting and standing). The neurological examinations are classified by NIHSS. Assessment for any new or unresolved adverse events will be made and any changes in medication regimen will be recorded.

8.14 90-DAY FOLLOW-UP VISIT (+14 / -14 DAYS)

During the 90-Day follow-up visit, clinical assessment of the subject and evaluation of neurological symptoms will be performed by the study team. Office cuff blood pressure will

be taken and assessment of the subject diary will be reviewed.
24-hour ambulatory blood pressure monitoring will be assessed. The neurological examinations are classified by NIHSS. Assessment for any new or unresolved adverse events will be made and any changes in medication regimen will be recorded.

8.15 180-DAY FOLLOW-UP VISIT (+14 / -14 DAYS)

During the 180-Day follow-up visit, clinical assessment of the subject and evaluation of neurological symptoms will be performed by the study team. Office cuff blood pressure will be taken and assessment of the subject diary will be reviewed. 24-hour ambulatory blood pressure monitoring will be assessed. The neurological examinations are classified by NIHSS. Duplex imaging is done to visualize the sinus and to assess for complications. Assess for any new or unresolved adverse events and record any changes in medication regimen. Assessment for any new or unresolved adverse events will be made and any changes in medication regimen will be recorded.

8.16 365-DAY FOLLOW-UP VISIT (+14 / -14 DAYS)

During the 365-Day follow-up visit, clinical assessment of the subject and evaluation of neurological symptoms will be performed by the study team. Office cuff blood pressure will be taken. The neurological examinations are classified by NIHSS. Assessment for any new or unresolved adverse events will be made and any changes in medication regimen will be recorded.

8.17 LONG TERM FOLLOW-UP VISITS - 18, 24, 30, AND 36-MONTH FOLLOW-UP VISIT (+14 / -14 DAYS)

During the long term follow-up visits after the angiogram/implantation procedure, clinical assessment of the subject and evaluation of neurological symptoms will be performed by the study team. Office cuff blood pressure will be taken. The neurological examinations are classified by NIHSS. Assessment for any new or unresolved adverse events will be made and any changes in medication regimen will be recorded.

8.18 UNSCHEDULED FOLLOW-UP VISIT

If an unscheduled follow-up visit is required, the study subject should be assessed for new or unresolved adverse events. Any testing required, including imaging studies, should be provided to the study Sponsor for DSMB adjudication. Office cuff blood pressure will be taken and assessment of the subject diary will be reviewed. Change of medications, diagnostic test results, or interventions should be documented.

8.19 SCHEDULE OF STUDY VISITS AND ASSESSMENTS

A summary of the study related assessments as outlined above is described in Table 7.

TABLE 7: SCHEDULE OF STUDY VISITS AND ASSESSMENTS

	Follow-up									Long Term Follow-up
Visit	**Visit 1**	**Visit 2**	**Visit 3/ Procedure**	**Discharge**	**7 Days (+2/-3 days)**	**30 Days (+/- 7 days)**	**90 Days (+/- 14 days)**	**180 Days (+/- 14 days)**	**365 Days (+/- 14 days)**	**18, 24, 30 and 36 Months (+/- 14 days)**
Eligibility	✓	✓	✓							
Informed Consent	✓									
Medical History	✓									
Physical	✓		✓		✓	✓	✓	✓	✓	✓
Neurological Exam	✓		✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medications	✓	✓	✓		✓	✓	✓	✓	✓	✓
Baseline 12 lead ECG	✓									
Blood Testing	✓			✓						
Patient Diary	✓	✓	✓		✓	✓	✓	✓		
Duplex Imaging		✓		✓	✓	✓		✓		
CT or MR Angiography		✓								
Renal Artery CTA/MRA or Duplex*	✓									
24 hour ABPM		✓					✓	✓		
Assessment for Carotid		✓								
6MWT					✓	✓				
MobiusHD Placement			✓							
Office cuff BP Measurement	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Discharge				✓						
Adverse Events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

* If not performed in the 12 months preceding screening

9.0 STUDY COMPLETION

After the subject has completed the 3-Year follow-up visit, a Subject Termination iCRF must be completed. During the course of the study, it is possible that subjects will be withdrawn from the study early. Factors leading to subject withdrawal may include, but are not limited to, the following:

- **Subject Withdrawal** - A subject may voluntarily withdraw from the study at any time without affecting his or her future medical treatment or benefits. In addition, the Investigator may withdraw a subject from the study if the subject refuses further testing or follow-up evaluations, or for any other reason as determined by the Investigator.

- **Subject Lost to Follow-Up** – If the Investigator has attempted to contact a subject at least three (3) times and receives no response, the subject may be lost to follow-up. The research staff should document at minimum three (3) attempts to contact the subject prior to terminating the subject from the trial.

- **Subject Death** - When a subject expires, the Serious Adverse Event and Subject Termination iCRFs must be completed promptly. Source documents such as death summary, autopsy report (if done), and a copy of the death certificate should be redacted of personal identifiers and provided to the designated clinical monitor and DSMB to describe the cause of the subject's death. The Investigator will notify the IRB/EC and Sponsor within 24 hours of learning of the event.

The Termination iCRF should be completed for each study subject, to record date and reason for early termination (if subject does not complete the study) or at the final visit (if subject completes all study time points).

10.0 CONCOMITANT MEDICATIONS

To be eligible for enrollment, study participants must require a minimum of three (3) anti-hypertensive medications at the time of entry into the study. Additionally, all subjects will remain on at least three (3) anti-hypertensive medications for the duration of the study.

In addition to the required regimen of hypertensive medications, all study subjects will be required to adhere to a regimen of duel antiplatelet therapy consisting of aspirin (81-325 mg daily) and clopidogrel (75 mg daily), or equivalent medications. If alternative equivalent medications are used, these should be initiated at least three (3) days prior to the implant procedure and continued for at least three (3) months post-procedure. Use of aspirin is required for the duration of study.

Appropriate management of subject's individual risk factors such as statins, smoking cessation, nutrition, diabetes will remain as standard of care and any changes to this regimen will be documented by the study team.

Subjects should be advised of the importance of continuing their medical therapy regimen without consulting with the study center. Subjects should not reduce or stop their anti-hypertensive medication dosage until the 6-month time point, at which time the Principle Investigator may decide to reduce medication as per the site's protocol.

All medications will be recorded on the Concomitant Medication log.

11.0 ADVERSE EVENTS

Safety assessments include adverse events and serious adverse events. The reporting period is from the initial treatment through the last study visit (Month 36).

11.1 DEFINITIONS OF ADVERSE EVENTS

An adverse event is any untoward and unintended sign, symptom or disease temporally associated with the use of an investigational device/drug/biologic or other protocol-imposed intervention, regardless of the suspected cause. Conditions or diseases that are chronic but stable should not be recorded on AE pages of the CRF. Changes in a chronic condition of disease that are consistent with natural disease progression are NOT adverse events and also should not be recorded on the AE pages of the CRF.

11.1.1 Serious Adverse Events (SAE)

An AE should be classified as an SAE and reported as such, if it meets one or more of the following criteria:

- It results in death (i.e., the AE actually causes or leads to death)
- It is life threatening (i.e., the AE places the subject at immediate risk of death)
- It requires or prolongs inpatient hospitalization
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be recorded as the event. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass.

Hospitalizations for the following reasons will not be recorded as SAEs:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow outcome measurement for the study
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

11.1.2 Unanticipated Adverse Device Effects (UADE) (where applicable)

An unanticipated adverse device effect (UADE) is 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. Anticipated adverse events are identified in Section 11.3.

11.2 ADVERSE EVENT ASSESSMENT AND DOCUMENTATION

All subjects who have been exposed to the study treatment will be evaluated for adverse events. All adverse events, regardless of severity and whether or not they are ascribed to the study treatment, will be recorded in the source documents and CRF using standard medical terminology.

All adverse events will be evaluated beginning with onset, and evaluation will continue until resolution is noted, or until the investigator determines that the subject's condition is stable. The investigator will take appropriate and necessary therapeutic measures required for resolution of the adverse event. Any medication necessary for the treatment of an adverse event must be recorded on the concomitant medication case report form.

All AEs will be characterized by the following criteria:

- Event term
- Intensity or severity
- Expectedness
- Relationship to study treatment
- Outcome
- Treatment or action taken.

Whenever possible, recognized medical terms should be used when recording AEs. Colloquialisms and/or abbreviations should not be used. Only one medical concept, preferably a diagnosis instead of individual symptoms, should be recorded as the event.

If more than one distinct adverse event occurs, each event should be recorded separately. However, if known at the time of reporting, a diagnosis (i.e., disease or syndrome) should be recorded on the CRF rather than individual signs and symptoms (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as a separate AE. A diagnosis that is subsequently established should be reported as follow-up information. However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE).

Adverse events occurring secondary to other events (e.g., sequelae) should be identified by the primary cause; a "primary" event, if clearly identifiable, should represent the most accurate clinical term to record as the AE event term. For example:

Orthostatic hypotension ⇒fainting and fall to floor ⇒head trauma ⇒neck pain

The primary event is orthostatic hypotension and the sequelae are head trauma and neck pain.

11.2.1 Classification of Adverse Events by Intensity/Severity

All adverse events should be graded on a four-point scale (mild, moderate, marked, severe) for intensity/severity. These definitions are as follows:

Mild:	Transient discomfort; no medical intervention/therapy required and does not interfere with daily activities.
Moderate:	Low level of discomfort or concern with mild to moderate limitation in daily activities; some assistance may be needed; minimal or no medical intervention/therapy required.
Marked:	Considerable discomfort with limitation in daily activities, some assistance usually required; medical intervention/therapy usually required.
Severe:	Extreme discomfort and limitation in daily activities, significant assistance required; ***significant*** medical intervention/therapy required.

There is a distinction between the severity and the seriousness of an adverse event. Severity is a measurement of intensity; thus, a severe reaction is not necessarily a serious adverse event (SAE). For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for serious adverse events.

11.2.2 Expectedness

All AEs will be evaluated as to whether they are expected or unexpected.

Expected (anticipated):	An adverse event is expected when the nature, severity, or degree of incidence was previously described.
Unexpected (unanticipated):	An adverse event is unexpected when the nature, severity, or degree of incidence was not previously described.

11.2.3 Relatedness

The study investigator will evaluate if the AE is related to the MobiusHD system. Relationship is defined in the following manner:

Not related: Evidence indicates no plausible direct relationship to the study device, such that:

- A clinically plausible temporal sequence is inconsistent with the onset of the AE and device administration; and/or
- A causal relationship is considered biologically implausible
- The AE can be attributed to concurrent/underlying illness, other drugs, or procedures.

Related: Evidence indicates a reasonable temporal sequence of the event with the study device administration exists, or that the association of the event with study device administration is unknown and the event is not reasonably supported by other conditions, such that:

- There is a clinically plausible time sequence between onset of the AE and study treatment administration; and/or
- There is a biologically plausible mechanism for study treatment causing or contributing to the AE; and
- The AE cannot be reasonably attributed to concurrent/underlying illness, other drugs, or procedures.

11.2.4 Outcome

The clinical outcome of an AE will be characterized as follows:

- Resolved without sequelae
- Resolved with sequelae (specify)
- Ongoing (i.e. continuing at time of study discontinuation)
- Death.

11.2.5 Treatment or Action Taken

- None
- Medical Intervention
- Surgical Intervention
- Other.

11.3 ANTICIPATED ADVERSE EVENTS

Adverse events that are anticipated to occur during the study are listed below.

- Death;
- stroke/CVA, TIA or seizure;
- vessel damage, dissection, occlusion, aneurysm, perforation, Post-Procedure neck pain, guidewire perforation, rupture or injury;

- damage to, fracture, fragmentation, or dislocation of the implanted device;
- embolization of air, thrombus, or other embolic debris;
- end organ ischemia, vessel thrombosis, or spasm;
- hypotension/hypertension (acute/subacute to 30 days);
- hypotension/hypertension (chronic>30 days);
- hypertension recurrent;
- infection (local or systemic);
- myocardial infarction;
- puncture site complications (i.e. vessel occlusion, hemorrhage; hematoma, pseudoaneurysm or arteriovenous fistula, excessive blood loss);
- renal insufficiency, kidney failure, hematuria;
- bleeding complications;
- bradycardia or arrhythmias including ventricular fibrillation of tachycardia;
- unintentional detachment or implantation of a component of the system, inappropriate sizing of the device;
- drug reaction;
- allergic reaction to contrast media, medications or device materials; and
- emergent surgery.

11.4 SERIOUS ADVERSE EVENT AND UNANTICIPATED ADVERSE DEVICE EFFECT REPORTING

Serious Adverse Events (SAE) and unanticipated adverse device effects (UADE) must be reported to the study sponsor as soon as possible and no later than 2 days after the investigator first learns of the event.

For initial reports, investigators should record all case details that can be gathered within the reporting timeframe. The contact information for Vascular Dynamics Inc. is below:

VASCULAR DYNAMICS, INC.
2134 OLD MIDDLEFIELD WAY
SUITE J
MOUNTAIN VIEW, CALIFORNIA 94043
Phone: (650) 963-9370
Fax: (650) 963-9029
clinical@vasculardynamics.com

Relevant follow-up information should be submitted to Vascular Dynamics, Inc. as soon as it becomes available and/or upon request. For some events, the sponsor or its designee or the medical monitor may follow up with the site by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the event (e.g., hospital discharge summary, consultant report, or autopsy report). Reports relating to the subject's subsequent medical course must be submitted to the study sponsor

until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

11.5 INDEPENDENT ADJUDICATION OF CLINICAL OUTCOME EVENTS BY DSMB

All SAEs and UADEs will be reviewed and adjudicated by the DSMB. Clinical event summaries and relevant imaging studies will be reviewed by the DSMB, which includes an interventional cardiologist, a neurologist, an internist, and a biostatistician.

12.0 ETHICS AND REGULATORY CONSIDERATIONS

12.1 SUBJECT INFORMATION AND CONSENT PROCEDURES

The Investigator, or designee, will obtain written informed consent from the subject prior to performing study assessments. The subject will be informed that the Sponsor and regulatory authorities will have access to personally identifiable information for the purposes of monitoring data against source documentation. However, all data entered in the database, filed, and presented by the Sponsor will be in anonymous form.

The site-customized ICF (see sample ICF provided by Sponsor), must be approved by Vascular Dynamics, Inc. and the IRB/EC before use. Each investigational Site will provide Vascular Dynamics, Inc. with a copy of the IRB/EC approved ICF and renewed approvals and consents as appropriate for the duration of the study.

The original, signed and dated ICF should be retained in the subject's study records, and a copy provided to the subject. The consent completion will be monitored by the Sponsor or designee.

12.2 IRB/EC APPROVAL

The Investigator, or designee, is responsible for submitting the clinical protocol and any amendments to the IRB/EC for approval prior to any subject being enrolled and for obtaining renewals at periods determined by the IRB/EC for the duration of the study.

13.0 STATISTICAL METHODS

Since this is a pilot study designed to evaluate the initial safety of the MobiusHD in subjects with stage 2 hypertension, no formal hypothesis testing is planned. Complete data for each study subject will be presented in an individual patient profile consisting of all CRF fields and a narrative summary. Additionally, where appropriate, descriptive statistics will be used to tabulate and summarize study outcomes. Background and demographic characteristics will be presented. Continuous variables will be summarized by descriptive statistics (sample size, mean and standard deviation, median, minimum and maximum). Discrete variables will be summarized by frequencies and percentages. Adverse events will be summarized by presenting the number and percentage of patients having any adverse event. Any other information collected (such as severity or relationship to study device) will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

14.0 RECORDS AND REPORTS

14.1 RECORDS

The investigational site will maintain iCRF and source study records for monitoring and audit purposes for the latter of:

- At least two (2) years after study completion
- At least two (2) years after Sponsor receives approval from the local governing regulatory authority
- For the period required by the local governing authority and reviewing IRB/EC

Sponsor is to be advised prior to destruction of study records and notified if study records are moved to an off-site location for archiving.

14.2 REPORTS

Investigators at participating sites are required to submit reports in conformance with all applicable regulations.

15.0 DATA MANAGEMENT

All required data for this study will be collected on appropriate source medical records and study forms and entered into a secure, 21 CFR Part 11 compliant, web-based database (MedNet Solutions, Inc.).

16.0 MONITORING OF THE STUDY AND QUALITY CONTROL

16.1 DSMB

All SAEs will be evaluated by the DSMB for potential relationship to the investigational device or procedure. All AEs will be evaluated by Sponsor for significance and relevance with respect to trends that may represent a previously unknown or unanticipated risk that may relate to the investigational device or procedure.

16.2 DATA COLLECTION AND MONITORING

The Research Coordinator will collect and document data in hospital and clinic charts and on source document forms prepared for the study. iCRF data will be entered in anonymous form into the secure web-based, password protected database. Passwords will not be issued by the Sponsor until Site Initiation and database training has been conducted for all personnel to whom Investigator has delegated data entry responsibilities. Hardcopy blank CRFs may be reproduced as needed and may be used as source documents; these should be signed and dated by the person collecting the data. Completed iCRFs in final form (with queries resolved) may be printed and filed in hardcopy for archiving if required by local governing authority. All data will be exported and stored on appropriate electronic media by Sponsor and to biostatistician for analysis.

The Sponsor will designate and train monitors to review iCRF data against source documents for completeness and accuracy. Discrepant data will be queried; the electronic

database will maintain audit trails of all queried and corrected data. The Investigator is responsible for data integrity at the site and will review and electronically sign all Inclusion/Exclusion, Adverse Event, Deviation, and Terminations iCRFs.

16.3 SOURCE DOCUMENTATION

Regulations require that Investigators maintain information in the study subject's medical records that corroborate data reported in the iCRFs. In order to comply with these regulatory requirements, at a minimum, the following information should be maintained:

- Sufficient medical history/physical condition of the study subject before involvement in the study to verify protocol entry criteria;
- Dated and signed notes on the day of entry into the study including a statement regarding the consent process that was followed;
- A log that maps the key to subject identity for monitors and auditors showing subject name and assigned identification number. This record will not be collected by Sponsor but should be maintained at the study site so that the appropriate medical records are compared to study iCRF data;
- Dated and signed progress notes, procedure reports, assessments, and diagnostic results as appropriate to each study subject visit to confirm iCRF data;
- Investigator / site radiologist assessment of medical imaging;
- Evaluate clinical significance of abnormal lab results;
- Records following adverse events reported, results of diagnostic tests ordered, treatment given, and clinical outcome at resolution or stabilization;
- Dictated procedure report;
- Dictated discharge summary;
- Notes regarding medications taken during the study; and
- Study subject's condition upon completion of, or withdrawal from, the study.

16.4 SITE COMPLIANCE / DEVIATIONS

The clinical site will be monitored routinely for adequate enrollment, timeliness of data submission, and compliance with the Investigational Plan and local regulations. Consistent pattern of non-compliance with respect to the above will require a corrective action plan to be negotiated with the Investigator. If corrective actions are not effective in resolving site compliance, the Sponsor may withdraw the clinical site from the study.

Significant deviation from the protocol will be reported to the Sponsor via the Deviation iCRF which may be completed by the site or the Sponsor. The Sponsor will categorize and report deviations (e.g., improper informed consent, inappropriate use of investigational device, visit outside window, assessment missed).

In the event that the Investigator identifies a potential subject that meets all but one (1) Inclusion/Exclusion criterion and expresses a medical opinion regarding why it is appropriate to consider the patient for the study, this documentation may be submitted to the

Sponsor for consideration. If the Sponsor agrees, then a prospective deviation may be approved to allow the subject to be enrolled in the study.

16.5 MONITORING PLAN

Study monitoring activities will include Site Initiation Visits, interim Site Monitoring Visits and a Site Close-Out Visit.

- The Site Initiation Visit enables the Sponsor to thoroughly review the study protocol and CRFs with the Investigator's staff, in order to assure that the Investigator understands the Protocol. This includes (1) assessing required records and reports; (2) verifying the staff has sufficient background, facilities, subject load, time, and willingness to comply with the study requirements; is able to submit the Protocol to the IRB/EC for review and approval; and can maintain all correspondence, the Protocol, and all required records on file; and (3) verifying that the Principal Investigator can submit required reports, assumes responsibility for the investigation at his or her institution (which may include supervision of some tasks), and has sufficient experience with the study population.

- Site Monitoring Visits will be scheduled depending on the rate of subject enrollment. During the Site Monitoring Visit, the monitor will review the CRFs of each subject in the study to make certain that the data provided are accurate and obtained in the manner specified in the Protocol. The subjects' clinical records will be reviewed to confirm that the case report form data are consistent with the Investigator's clinical records, the background data and concurrent medication are documented in the CRFs, and that there is an accurate account of the use of the investigational device in the treatment. The Site Study Binder and other study documents will be reviewed. The subjects' clinical records will be reviewed to determine whether recording of adverse events has been omitted in the CRFs. If this is found to be so, the CRFs will be returned to the Investigator and corrected to include this information. During the course of the study, the Sponsor shall be available to discuss, in person or by telephone, questions regarding adverse effects, removal of subjects from the study, conduct of the study, etc.

- At the completion or termination of this study a Site Close-Out Visit will be conducted.

17.0 DATA MANAGEMENT

17.1 RECORD RETENTION

It is required that a copy of all records (e.g., informed consent documents, source documents, safety reports, study device dispensing record, etc.) which support CRFs for this study, be retained in the files of the responsible Investigator for the latter of the following:

- At least two (2) years after study completion
- At least two (2) years after Sponsor receives approval from the local governing regulatory authority
- For the period required by the local governing authority and reviewing IRB/EC.

Sponsor is to be advised prior to destruction of study records and notified if study records are moved to an off-site location for archiving.

If the Principal Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Vascular Dynamics, Inc. must be notified in writing of the name and address of the new custodian.

18.0 PROTOCOL AMENDMENTS

An amendment to the Protocol may be proposed by the Sponsor, or by an Investigator with prior Sponsor approval. The amendment must be submitted to the IRB/EC and its implementation can take place only after IRB/EC approval.

19.0 PROTOCOL DEVIATIONS

The Investigator will not deviate from the Investigational Plan without the prior written approval of Vascular Dynamics, Inc., except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the subject's risk or affect the validity of the investigation. In medical emergencies, prior approval for Investigational Plan deviations will not be required, but Vascular Dynamics, Inc.'s clinical research personnel must be notified within five (5) days of the incident.

All deviations from the Protocol that occur during the study will be captured and the impact of the Protocol deviations on the validity of the clinical study reports will be discussed in the final clinical study report.

20.0 DEVICE ACCOUNTABILITY

Complete traceability records will be kept of all investigational devices during the study. The MobiusHD system and the applicable accessories will be provided by Vascular Dynamics, Inc. The device number will be documented in subject medical records, CRFs and in the center's logs.

Each Investigator will be responsible for the safe storage with restricted access of the investigational materials in their possession, to prevent use of investigational materials by any persons not participating in the study.

After completion of the study, all unused investigational devices must be returned in their original packaging to Vascular Dynamics, Inc., 2134 Old Middlefield Way, Suite J, Mountain View, CA 94043.

All Investigators will be responsible for using the investigational device according to the IFU and Protocol and for maintaining product inventory and records.

21.0 INFORMED CONSENT PROCESS

Informed consent shall be obtained in writing from each study subject or legal guardian and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject.

The subject will be asked to read the Informed Consent Form (ICF) and to sign the form to indicate consent to participate in the study.

The research nature of the study will be explained carefully to the subject. The scope and aims of the research will be described together with known or foreseeable benefits, risks and discomforts that subjects may experience. Appropriate alternative treatments will be discussed so that the subject may determine whether or not he or she wishes to participate in the study. The subject must understand that throughout the study his or her participation remains voluntary and protected by the Declaration of Helsinki. The Investigator is responsible for obtaining written (or witnessed) informed consent from potential subjects prior to study entry. Subjects will be given time to read the ICF consent and ask any questions before being asked to sign the form. The ICF (approved by the Sponsor and the IRB/EC) must be signed and dated by the subject and the Investigator. The Investigator will retain the original signed ICF, give one copy to the subject, and send a second copy to the referring Investigator (if applicable).

Subjects may withdraw their consent to participate in the study at any time without prejudice. The Investigator may withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject, or if the subject cannot comply with the protocol. Attempts should be made to complete any examinations and the Sponsor must be notified of all withdrawals.

Should a Protocol amendment be made, the subject's consent form may be revised to reflect the changes of the Protocol. It is the responsibility of the Investigator to ensure that an amended ICF is approved or reviewed by the IRB/EC, and that it is signed by all subjects subsequently entered in the study, and those currently in the study, if they are affected by the amendment.

If new information becomes available that could significantly affect a subject's future health and medical care, the information shall be provided to the subject in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

22.0 PREMATURE STUDY TERMINATION

A subject should be removed from the study whenever considered necessary for his or her welfare or when a subject expresses a desire to withdraw from the study. Non-compliance with the Protocol, the occurrence of a SAE or any medical condition that, in the opinion of the Investigator, warrants discontinuation from the study for the safety of the subject, may necessitate discontinuing a subject. If a subject is discontinued, the reason must be entered on the CRF and signed by the Investigator. In case of any questionable situation, the study monitor or Vascular Dynamics, Inc. personnel should be consulted. When a subject is removed from the study as a result of SAE, a final physical examination must be performed. Subjects removed from the study because of an AE will be followed-up until the adverse event has been resolved.

In the case that the occurrence of AEs is greater than anticipated, the clinical investigation will be suspended; in such a case, a safety committee will be arranged to decide if the study

could be continued. The IRB/EC will be notified and the results of the safety committee discussions will be brought to the IRB/EC for review and decision.

Vascular Dynamics, Inc. reserves the right to discontinue any study at any time for administrative reasons including, but not limited to, a decision to discontinue further clinical investigation of the device, improper conduct of the study by the Investigator, and inability to obtain the number of subjects required by the Protocol. Reimbursements for reasonable expenses will be made if such an action is necessary.

23.0 REGULATORY AND HEALTH AUTHORITY AUDITS

The U.S. Food and Drug Administration (FDA), European authorities, and the local state health authorities may request access to all study records, including source documents, for inspection. The Investigator and hospital staff are requested to cooperate with these audits. The Investigator must notify the Sponsor of any health authority audit as soon as notification of such audit is made. A representative or designee of the Sponsor may also conduct similar audits and may be present during health authority audit.

24.0 SUBJECT PRIVACY AND CONFIDENTIALITY

The subject's name and personal data will remain confidential and will not be published in any way. However, the Sponsor's monitor or representative and regulatory representatives, auditors and inspectors may have access to medical files in order to verify authenticity of data collected.

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APPENDIX I: IMAGING GUIDELINES

APPENDIX II: SAMPLE INFORMED CONSENT

APPENDIX III: SAMPLE CASE REPORT FORMS

APPENDIX IV: BP MEASUREMENT INSTRUCTIONS

APPENDIX V: CAROTID SINUS MASSAGE INSTRUCTIONS

APPENDIX VI: INSTRUCTIONS FOR USE

APPENDIX VII: GUIDELINES FOR THE SIX-MINUTE WALK TEST