CLAUDICATION: EXERCISE VS. ENDOLUMINAL REVASCULARIZATION

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PROTOCOL SYNOPSIS

Title: **CL**audication **E**xercise **V**s. **E**ndoluminal **R**evascularization

Description: The CLEVER trial is a prospective**,** multicenter, three-arm clinical trial with unbalanced randomization, testing the following 3 key hypotheses:

Primary Endpoint

1.) Aortoiliac revascularization with stent (ST) combined with optimal medical care improves maximum walking duration compared to optimal medical care (OMC) alone in patients with claudication and peripheral arterial disease (PAD) who are amenable to peripheral stenting.

2.) Regular supervised exercise (SE) combined with optimal medical care improves maximum walking duration compared to optimal medical care alone (OMC) in patients with claudication and PAD who are amenable to peripheral stenting.

3.) Aortoiliac revascularization with stent (ST) combined with optimal medical care improves maximum walking duration compared to supervised exercise (SE) combined with optimal medical care in patients with claudication and PAD who are amenable to peripheral stenting.

The sequential testing of these hypotheses yields 80% power to observe 30% difference in improvement in the primary endpoint of maximum walking duration (MWD).

Secondary Endpoints:

1. To evaluate the mid-term durability of any treatment effect by performing pair-wise comparisons of change in MWD between baseline and 18 month time points among all three treatment groups of primary interest.

2. To assess a treatment effect on free-living daily activity levels of any treatment group, comparing baseline electronic step monitors values with those obtained at both follow up intervals (6 and 18 months).

3. To examine treatment effects on patient-perceived health-related quality of life (physical function) between all groups at 6 and 18 months.

4. To examine inpatient and outpatient costs associated with the three treatment strategies, and to evaluate the relative cost-benefit by calculating incremental cost-effectiveness

and cost effectiveness acceptability curves using health utility change in the denominator.

5. To evaluate the impact of cardiovascular disease risk factors by comparing these values at baseline, 6 months, and 18 months.
6. To evaluate the interaction effect, if any, of gender or race on improvements in MWD, improvement in free-living daily activities, and quality-of-life.
7. To track major adverse peripheral events (MAPEs) associated with aortoiliac stenting and femoropopliteal endovascular intervention.
8. Rate of major complication defined as any occurrence of death, myocardial infarction, amputation of the target limb (limb treated in this study), or occurrence of critical limb ischemia or repeat target limb revascularization (TLiR).

Over three years, about 30 clinical sites will recruit approximately 130-150 participants with claudication and PAD who are amenable to aortoiliac revascularization with stenting. Subjects will provide written informed consent and be randomized to one of three study arms: OMC, ST, or SE and followed at six and eighteen months. The efficacy of these potential therapies and their mechanisms of benefit observed in the CLEVER trial are certain to inform future choices of therapy and thereby extend and improve the quality of life of millions of patients who now suffer from claudication and PAD.

Enrollment: Approximately 130-150 participants from about 30 U.S. and Canadian study sites will be enrolled in this study.

Timelines:

First patient enrolled:	February 2007
Last patient enrolled:	December 2010
Last 18 month follow-up:	June 2012

PROTOCOL SYNOPSIS (continued)

Patient Population:

Patients with:

- Moderate to severe claudication
- Hemodynamically significant lower extremity arterial stenoses, including the aortoiliac segment
- Rutherford Grade 1 symptoms

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ABBREVIATIONS AND ACRONYMS

ACRONYM	DEFINITION
ABI	Ankle-brachial index
ACR	American College of Radiology
AE	Adverse Event
AHA/ACC	American Heart Association/American College of Cardiology
ANCOVA	Analysis of Covariance
ARDMS	American Registry of Diagnostic Medical Sonographers
ATP	Adult Treatment Panel
BMI	Body Mass Index
CAP	College of American Pathologists
CCC	Clinical Coordinating Center
CE	Cost Effectiveness
CEC	Clinical Events Committee
CFA	Common Femoral Artery
CK-MB	Creatine Kinase MB Isoenzyme
CHD	Coronary Heart Disease
CLEVER	Claudication Exercise vs Endoluminal Revascularization
CLIA 88	Clinical Laboratory Improvement Amendments of 1988
eCRF	Electronic Case Report Form
CV	Cardiovascular
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GEE	Generalized Estimating Equation
HCRI	Harvard Clinical Research Institute
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
ICAVL	Intersocietal Commission for the Accreditation of Vascular Laboratories
ICH	International Committee on Harmonization
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ITT	Intent-to-treat
JNC	Joint National Committee
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
MAPE	Major Adverse Peripheral Events
MAR	Missing at random
MCAR	Missing completely at random

ABBREVIATIONS AND ACRONYMS continued

ACRONYM	DEFINITION
MNAR	Missing not at random
MOP	Manuel of Operations
MWD	Maximum Walking Duration
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
OMC	Optimal Medical Care
PAD	Peripheral Arterial Disease
PAQ	Peripheral Arterial Questionnaire
PI	Principal Investigator
PT	Pharmacotherapy
PTA	Percutaneous Transluminal Angioplasty
QALY	Quality-adjusted life year
QoL	Quality of Life
RC	Research Coordinator
RFR	Risk Factor Reduction
SAE	Serious adverse event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Supervised Exercise
SF-12	Short Form 12
ST	Stenting
SUAE	Serious unanticipated adverse event
Thigh-BI	Thigh-brachial index
TSR	Target Site Revascularization
TLiR	Target Limb Revascularization
UADE	Unanticipated Adverse Device Experience
UC	Usual Care
WIQ	Walking Impairment Questionnaire

1.0 INTRODUCTION

1.1 BACKGROUND

1.1.1 Impact of Claudication on Cardiovascular Health

Peripheral arterial disease (PAD) is common, affecting up to 12% to 29% of the elderly [1,2]. Intermittent claudication is its most frequent symptom of PAD[3-6]. The incidence of PAD is expected to increase as our population ages[7]. Those with claudication experience an increased relative risk of total mortality that is 2 to 4 fold greater than those without claudication[8-12], and have 6-year survival of only 55%[13], and 10 year survival of only 37%[14].

Intermittent claudication profoundly limits physical functioning[15,16]. Reduced physical activity in older individuals is associated with increased markers of cardiovascular disease risk, such as: high blood pressure[17], diabetes[18], obesity[19], oxidative stress[17], systemic inflammation[20], tendency to thrombosis[21], and unhealthy plasma lipid profile[22]. The prevalence of these factors have been studied in populations with intermittent claudication, confirming the presence of adverse atherosclerosis risk profiles in individuals with claudication[21,23]. Physical activity is known to be inversely associated with cardiovascular events in men[24] and in women[25]. Lack of physical activity is a contributing factor to obesity, which is associated with increased cardiovascular disease risk[19,26,27]. Obesity in adults is associated with the presence of physical disability[28], and is specifically strongly correlated with lower extremity mobility difficulty[28]. Walking disability caused by PAD results in a sedentary lifestyle[29], self-perceived ambulatory dysfunction[30], and lower health-related quality of life[31]. In summary, intermittent claudication precludes an active, healthy life-style in many older individuals that may contribute to the observed excess mortality in this population.

1.1.2 Management Options for Intermittent Claudication

Treatment options for those with intermittent claudication include modification of systemic risk of atherosclerotic ischemic events and treatments directed at improving physical functioning. These latter options include medications, exercise training, angioplasty/stent placement, or bypass surgery.

The “de facto” standard of care in most primary care and specialty practices for individuals with claudication symptoms is for the physician to advise patients to “stop smoking and keep walking”[32]. Revascularization for those with intermittent claudication is controversial[33,34]. Although effective for many patients in improving walking ability, the procedures are invasive and expensive. The option to not revascularize individuals with claudication has been justified by excellent improvement in maximum walking distance with supervised exercise training[35], low risk of disease progression or amputation[8] without revascularization[36,33,34,37], and a lack of epidemiological evidence of effect of angioplasty and bypass surgery on amputation rates[34,38-41].

"Optimal medical care" for intermittent claudication for most patients in the U.S. includes risk-factor modification and recommendations to exercise three to five times a week for an hour or more[42], perhaps with the addition of a claudication medication[4]. Cilostazol and pentoxyfilline improve maximum walking distance by 40-60% and 20-25%, respectively, on constant-load exercise tests[35]. Recently, pharmacotherapy has been established as effective in improving claudication symptoms, and cilostazol is increasingly being used for claudication due to its proven efficacy[35]. Its use among patients with claudication continues to grow as costs of generic versions are now much lower.

The first randomized control trial of exercise training in patients with peripheral arterial occlusive disease demonstrating improvement was done in 1966[43]. Numerous clinical trials have demonstrated that supervised exercise training[30,44-48] and medications[49,50] can significantly improve walking performance and quality of life in patients with intermittent claudication. On average, individuals enrolled in supervised exercise training programs improve maximum walking duration between 74% and 240% on a continuous-load treadmill protocol[51]. Most comparisons of supervised exercise training and unsupervised exercise show no improvement in MWD for unsupervised exercise[45,52,53], or at best modest improvement[44].

Functional benefits have been demonstrated in individuals with claudication treated with surgery[54-56]. Peak treadmill walking time improved by 190% in one study of patients with intermittent claudication treated surgically [54]. However, for those with aortoiliac PAD, surgery entails substantially more morbidity than angioplasty or stent placement, with a 3.3% 30-day mortality rate[41,57]. In contrast, aortoiliac stent placement has a mortality of 0.5% in all patients, including those with more advanced ischemic symptoms[58]. Bypass surgery is usually reserved for more advanced symptoms (Rutherford Grade II or III[59]; rest pain, ischemic ulcer, gangrene).

The roles of angioplasty and exercise training for intermittent claudication have been the subject of a Cochrane Database Review[42]. This review presented data from two studies that randomized claudication patients to angioplasty or other treatment. In these series, most patients were treated for femoropopliteal PAD, and stents were not used only balloon angioplasty[60] was performed[61,62]. Results between the two studies were not consistent at 6 months. The Edinburgh study showed better exercise performance in the angioplasty group[62], and the Oxford experience showed better results from exercise training[60]. A subgroup analysis of the Oxford experience, however, showed better exercise performance with angioplasty for those with aortoiliac PAD at baseline, as opposed to femoropopliteal PAD[60]. It has been reported that individuals with claudication with aortoiliac arterial obstruction have more severe ischemia while walking than those with more distal obstruction[63], and stents are very effective in these arteries (in contrast to the femoropopliteal arteries), and thus the aortoiliac PAD population is most appropriate subset of claudicators for this study.

Supervised exercise training has been clearly shown to improve exercise performance[30,45,52]. However, as a medical treatment it has some drawbacks. First, the

commitment to exercise training is considerable[52], and there is opportunity cost of the time involved[64]. The long-term benefits are not clear[65], and there is a suggestion that the benefits of exercise training can wane over time[66]. It is rare in studies of exercise training for patients to be asymptomatic on followup[44,45,52]. Since supervised exercise training requires time commitment and is expensive, it can not be administered indefinitely.

1.2 PRELIMINARY STUDIES

Pilot outcomes data on patients with intermittent claudication treated with aortoiliac stent placement were collected at Rhode Island Hospital. One hundred and six (106) consecutive individuals with claudication were screened and referred for consideration of revascularization. Most (n=67) were found to be ineligible by history or available prior testing and were not recruited; 3 others were found ineligible by treadmill tests. Of the 36 patients enrolled based on noninvasive tests, 35 of 36 had significant aortoiliac disease at arteriography. These 35 subjects were all treated with stents and outcomes data obtained and compared to baseline results. We prospectively collected baseline and follow-up data from these 35 patients, and 47 iliac arteries were stented (12 bilaterally), including 16 chronic iliac artery occlusions. The mean ankle-brachial index in the 47 lower extremities was 0.65 ± 0.16, and the mean thigh-brachial index was 0.83 ± 0.25. The average time to onset of claudication in 35 patients by treadmill testing using the Hiatt protocol was 1.7 ± 1 minutes, and the average maximum walking time was 3.3 ± 1.8 minutes. The average ABI decreased to 0.35 ± 0.26 immediately after exercise (n=47). Patients underwent exercise testing at baseline and during follow-up to one year using a graded treadmill protocol (Hiatt protocol[67]). They completed generic and disease-specific health-status questionnaires at baseline and during follow-up, including the SF-36[68] and the Walking Impairment Questionnaire, developed by Regensteiner et al[67].

Improvement in exercise performance for this cohort of claudicants treated with aortoiliac stenting is presented below. The treadmill test protocol used was the Hiatt protocol, which starts at a speed of 2 miles per hour with 0% grade, increasing the grade by 3.5% every 3 minutes[67]. Thus, the increase in work over time is not linear.

TABLE 1. PRELIMINARY EXERCISE DATA FOR AORTOILIAC STENT PATIENTS, GRADED (HIATT) TREADMILL PROTOCOL.

Reference	N	Therapy	Entry MWD (minutes)	Exit MWD (minutes)	Increase (%)
Murphy (Preliminary Data)	26	Aortoiliac Stent	3.3	8.7	164

An increase of 164% in the maximum walking duration on the Hiatt treadmill test compared to baseline performance was observed on average after aortoiliac stent placement (baseline s.d. 1.8 minutes). These results in 26 patients with the 12 month

follow-up visit were similar to those achieved with the entire cohort when "last outcome carried forward" was used for missing data at 12 months. And although complete relief of symptoms is rare with exercise training, this was observed in 29% of patients in our series.

There is evidence that supervised exercise training, the "gold standard" of conservative therapy for intermittent claudication, also improves exercise performance compared with baseline results. In 3 trials that used the Hiatt (graded) protocol, improvement in exercise performance with exercise training is presented below:

TABLE 2. PUBLISHED RESULTS OF SUPERVISED EXERCISE TRAINING, GRADED (HIATT) PROTOCOL

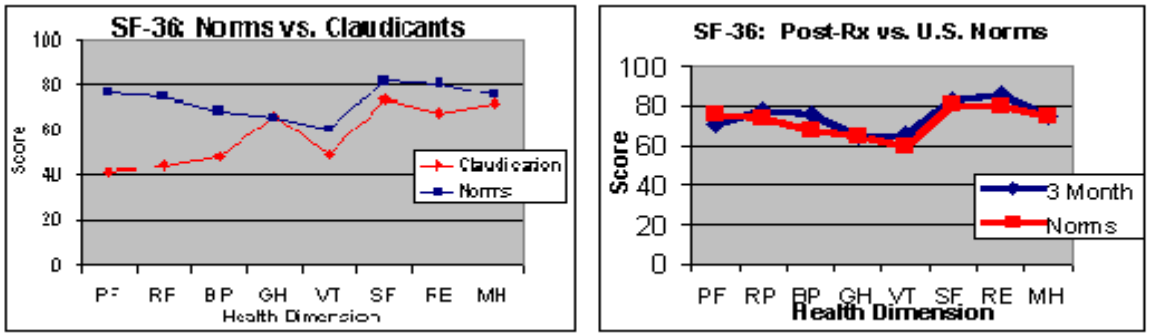
Reference	Treadmill protocol	"N"	Baseline (minutes)	Follow-up (minutes)	% Increase
Hiatt, Regensteiner, et al. 1990	Hiatt	10	6.4	13.9	117%
Regensteiner, Meyer, et al. 1997	Hiatt	10	4.6	10.9	137%
Regensteiner, Steiner, et al. 1996	Hiatt	10	9.6	17.2	79%

The mean improvement, 113%, appears to be toward the lower end of the range of 74% to 240% described in a Cochrane Database Review of exercise training results[51], but, unlike most studies where a constant-load treadmill test is done, these 3 studies used a graded treadmill protocol in which the level of work increases every 3 minutes.

Of the two frequently-used graded treadmill test protocols for claudication, the Gardner protocol has probably been used in more published research and will therefore be the protocol used for exercise testing of MWD for this trial. Both protocols are similar, but the Gardner protocol increases the grade more frequently and by smaller amounts than the Hiatt protocol.

Data from SF-36 questionnaires in claudicants treated with exercise training and stents are also informative. Baseline data in our stent cohort demonstrate much lower health-related quality of life compared with age-matched norms[68]. The baseline data in our population of claudicants are similar to those obtained in one study of exercise training at baseline[45]. After stent placement, our cohort reported SF-36 responses comparable to age-matched norms in each health dimension.

Figure 1. On the left, SF-36 baseline results for our population, mean age 61±10 years, graphed with the published norms for U.S. population sample age range 55-64 years [68]. On the right, after iliac artery stent placement, SF-36 results compared with U.S. norms for people of similar age[68]. QoL results after stent placement closely reflects results obtained in a cross-section of the population of similar age. (PF=physical functioning, RP=role physical, BP=bodily pain, GH=general health, VT=vitality, SF=social functioning, RE=role-emotional, MH=mental health).



We have previously reported our experience with aortoiliac stent placement in general[69], as well as the results observed in those treated for intermittent claudication[70]. These data are valuable as they give us an idea of the success of the intervention as well as the risk associated with the procedure. Over the last 10 years we have accumulated a database including 218 patients {312 procedures (94 bilateral)} who presented with a complaint of intermittent claudication and were treated with aortoiliac stent placement. During that time 147 other patients were treated with aortoiliac stents for limb-threatening ischemia. Therefore, 60% of aortoiliac stent placement procedures at our institution are performed for intermittent claudication. Technical success (<5 mm Hg trans-stenotic gradient after stenting) was achieved in 97%. There were 302 limbs (97%) in which the trans-lesion gradient was satisfactory after stent placement (≤5 mm Hg mean). Ankle-brachial indexes improved from 0.58 at baseline to 0.83 after stent placement. Major complications (defined as those for which patients underwent any therapy to address) were observed in 6.9% of patients. Types of major complications are presented in the table below:

TABLE 3. COMPLICATIONS OF AORTOILIAC STENT PLACEMENT.

Complication type	"N" (out of 218)
Distal embolization	5
Iliac artery rupture	3
Acute thrombosis	4
Stent/artery infection	2
Significant hematoma	1

One amputation occurred in this group in the peri-procedure period, which was the only amputation to occur overall (<0.5%) in almost three years mean follow-up. Patients were followed for a mean of 33.5±27.9 months. There were no 30 day deaths in our series of patients treated for claudication. Primary patency at 3 years was 78% (standard error {S.E.} 3%), assisted patency 84% (S.E. 3%), and secondary patency 87% (S.E. 2%), with 93 patients having follow-up at least that long.

1.3 EXPERIMENTAL STRATEGIES

In this study participants in each treatment group will receive both risk factor modification and pharmacologic therapy. All subjects enrolled in the CLEVER Study who can tolerate it will receive cilostazol without charge for the duration of the study. Participants who previously did not tolerate cilostazol therapy due to side effects such as headache or who have contraindications such as congestive heart failure may still be eligible to be enrolled but should not start cilostazol. Cilostazol is a drug for the treatment of intermittent claudication, and allows people with this condition to walk longer before they must stop because of their pain. Cilostazol's mechanism of action is not clear. It is an inhibitor of phosphodiesterase III (PDE III), and acts as a vasodilator and inhibitor of platelet aggregation, and these actions may contribute to its effect. The standard dose for cilostazol use in this study is 100 mg twice a day by mouth. The protocol allows for full, partial, and no cilostazol use depending upon patient tolerance of the drug. However, the goal for all patients should be 100 mg twice a day. For participants not currently medicated with cilostazol at study enrollment, cilostazol dose-toleration will be assessed over a 2 week treatment interval after randomization. If the 100 mg twice daily dose is not tolerated, subjects will be down-titrated to 50 mg twice daily. If this dose is not tolerated, then cilostazol will be discontinued, but subjects will continue in the study. Subjects receiving the lower 50 mg bid dose will be continued at this dose for three weeks and then increased to the full dosage of 100 mg bid. If this dose is then tolerated, then the increased dose will be maintained. Participants who only tolerate 50 mg twice daily will receive pill cutters and instructions on how to cut the 100 mg pills in half. Study participants will receive cilostazol at enrollment and at quarterly visits with research coordinators therafter, and coordinators will conduct pill counts with subjects at their quarterly visits to measure compliance. Cilastozol compliance is defined as greater than 80% monthly usage of prescribed medication.

1.3.1 "Optimal Medical Care" (OMC): Home-based Exercise plus Pharmacotherapy

"Optimal medical care" in this study will be representative of the medical care that most patients with claudication receive when they go to their doctor: they will be advised to "stop smoking and keep walking"[32], with the addition of cilostazol therapy for those who can tolerate it. Subjects enrolled in the "optimal medical care" arm will be advised verbally to perform a home exercise program based on similar criteria as participants receiving supervised exercise training and will receive a brochure with exercise regimen recommendations. They will be advised that they should walk at least three to five times a week up to their claudication threshold, then stop, and begin a repeat bout of exercise, continuing the exercise-rest-exercise bouts as tolerated[52]. They will be advised that they should try to exercise at each session for a total duration of at least 35 minutes including time for rest, increasing the total duration of exercise each week until they are able to exercise for up to 50 minutes[52]. Patients will be instructed to stop walking and rest when pain is moderate, and then to begin walking again immediately upon relief of pain[52]. For patients who do not have a treadmill at home, they will be instructed to perform their exercise outdoors or indoors where extensive walking is possible, such as at shopping malls.

Participants in this group will be responsible for maintaining their exercise regimen on their own. At baseline, 6 months, and 18 months they will receive a brochure with exercise regimen recommendations. Participants allocated to this treatment group will not receive exercise logs. All study participants will receive telephone calls at least monthly to encourage study retention as outlined in section 4.4 but in this study group those calls will not include exercise education.

1.3.2 Stent Group (ST)

This study is designed as a study of patients with claudication and aortoiliac arterial insufficiency. As such, the goal will be to revascularize most symptomatic aortoiliac lesions. It is recognized that many patients will also have femoropopliteal arterial insufficiency. Although this is not a study of femoropopliteal interventions, this protocol will include interventions on those patients in the stent groups found to have femoropopliteal lesions on the symptomatic side if they are generally accepted as amenable to balloon angioplasty (AHA type 1 (focal < 3 cm long, concentric, not calcified, see section 4.4.3, "Revascularization").

Aortoiliac revascularization will be performed with self-expandable or balloon-expanding stents. Aortoiliac stents will be placed primarily, without pre-dilatation, with an angioplasty balloon, if possible (see section 4.4.3, Revascularization). Balloon-expandable stents will be indicated for focal ($\leq$3 cm long), ostial, eccentric, or heavily-calcified lesions, whereas self-expanding stents will be used for lengthy lesions (>3cm) or concentric non-ostial stenoses[69]. Stent lengths will be chosen to match the length of hemodynamically-significant plaque ($\geq$50% by diameter by visual estimate confirmed to have a mean trans-stenotic gradient of >5 mm Hg without pharmacologic augmentation), and stents will be dilated to increase the diameter of the diseased segment to 100% of the non-diseased contiguous segment, or the contralateral artery if the entire artery is involved. No more than two stents should be used for each flow-limiting lesion.

Technical endpoints for aorto-iliac artery stent procedures are a reduction in the trans-stenotic gradient to 5 mm Hg mean or less by simultaneous pressure readings with <30% stenosis by angiography. For management of bilateral aortoilic disease and/or femoropopliteal artery occlusive disease in participants with at least one qualifying leg, please refer to section 4.4.3.1, "*Procedures for Aortoiliac and Femoropopliteal Revascularization*".

Patients with total aortoiliac obstruction should not undergo attempted revascularization. Therefore, if the aorta is occluded from the renals through to the aortic bifurcation, with or without iliac artery disease, revascularization should not be attempted. Patients who are found to have total aortic occlusion will remain in their assigned treatment group. Focal aortic lesions, occlusions or stenoses, and total iliac (common and external iliac artery) occlusions or stenoses should be treated. Patients who have mild or no aortoiliac obstruction by angiography and catheter pressure measurements should not undergo stent placement.

Drug-eluting stents have shown great improvement in patency in the coronary arteries[71], where restenosis is a significant problem. However, the aortoiliac segment is not prone to restenosis and therefore drug-eluting stents will not be utilized in the conduct of this study. Also, bypass surgery is not a treatment arm in this study and bypass surgery at any level will not be performed as an experimental intervention for claudication under this protocol.

During routine clinical follow-up, decreases in the ankle-brachial index of >0.10 compared with post-treatment ABI will indicate possible loss of primary patency. If the thigh-brachial index is normal and not more than 0.10 less than the post-stent value, this result will be considered evidence of continued stent patency. If the thigh-BI is also abnormal (<1.3) or >0.10 less than a post-stent thigh-bi, participants will undergo a repeat evaluation by either duplex ultrasound or by arteriography to assess restenosis. If restenosis is present a repeat intervention by either angioplasty or stent placement will be performed. If restenosis cannot be managed percutaneously and symptoms or signs of progression to limb-threatening categories are evident, patients will be considered for bypass surgery. Subjects in this cohort will be analyzed in the stent group according to intention to treat methods.

At baseline, 6 months, and 18 months ST group participants also will receive a brochure with exercise regimen recommendations. Participants allocated to this treatment group will not receive exercise logs. All study participants will receive telephone calls at least monthly to encourage study retention as outlined in section 4.4 but in this study group those calls will not include exercise education.

1.3.3. Supervised Exercise Training/Adherence to Physical Activity (SE)

Management for participants randomized to the Supervised Exercise/Adherence to Physical Activity group will be similar to the "optimal medical care" cohort, with the

addition of supervised exercise training and behavioral medicine to foster exercise adoption. Supervised exercise training will be done in accordance with guidelines of the American College of Sports Medicine[72], and American College of Cardiology/American Heart Association[73,74]. Supervised exercise training will be conducted at designated rehabilitation centers associated with each study site, i.e., exercise training will be administered locally. Rehabilitation centers will be established in dedicated vascular medicine PAD rehabilitation centers or in cardiac rehabilitation centers, i.e., training centers will be clinically operational and will not be established for this study only.

Supervised exercise training will be conducted for 26 weeks for participants randomized to that treatment group. Starting in month 5 and continuing through month 18, adherence to physical activity will be optimized by using state-of-the-art behavioral medicine techniques under the direction of the Adherence to Physical Activity Committee (as outlined in Appendix E).

1.4 RATIONALE

Intermittent claudication is a common chronic disease in older individuals that severely limits physical activity levels. Lack of reimbursement inhibits access to supervised exercise training for intermittent claudication. In the sequential primary analyses of this study, we will compare stenting to optimal medical care and supervised exercise training to optimal medical care. If both of those analyses are positive, we will challenge the existing paradigm for the management of intermittent claudication by directly comparing stenting to supervised exercise training.

This investigation will assess the efficacy, quality-of-life, and health economic impact of three treatment strategies for patients with aortoiliac PAD and claudication. The relative benefits and costs of each of these experimental strategies are poorly understood. The secondary endpoints will put the relative treatment effect, if any, in the context of the effectiveness of combination therapy on MWD, safety, cost-effectiveness and quality of life. The results of this trial could have a significant impact on coverage decisions for supervised exercise training for people with claudication. Indeed, we may find that the noninvasive, unreimbursed service (supervised exercise training) has equivalent efficacy and is more affordable than stenting, or has inferior efficacy but superior cost-effectiveness; the implications of either result could support insurance coverage for supervised exercise training for claudication, depending on the magnitude of the result.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE AND ENDPOINT

The primary comparisons to be made in this study are to contrast the relative superiority of aortoiliac stenting (ST) and supervised exercise therapy (SE) to optimal medical care (OMC) — as measured by maximum walking duration (MWD) at 6 months in patients with claudication due to aortoiliac peripheral arterial disease (PAD). If these comparisons are positive, we will then compare stenting with supervised exercise training by sequential analysis.

By sequential testing, the primary endpoints to be evaluated in this study are intended to demonstrate a 30% difference in improvement in MWD at 6 months in subjects undergoing either:

1.) Optimal medical care alone (OMC) versus optimal medical care and aortoiliac revascularization by stent placement (ST)

2.) Optimal medical care alone (OMC) versus optimal medical care and supervised exercise training (SE).

3.) Optimal medical care and supervised exercise training (SE) versus optimal medical care and aortoiliac revascularization by stent placement (ST).

2.2 SECONDARY OBJECTIVES AND ENDPOINTS

The secondary objectives in this study are to evaluate the safety and effectiveness, quality of life and cost effectiveness of each of the three treatment strategies. These secondary comparisons will help assess the effectiveness of combination therapy on MWD, and the cost, durability, and magnitude of the treatment effect of each group. The comparison of supervised exercise training and stent placement is of particular interest because reimbursed access to supervised exercise is generally unavailable in the U.S.

Specifically, the secondary endpoints will assess:

1. The mid-term durability of any treatment effect by performing pair-wise comparisons of change in MWD between baseline and 18 month time points among all three treatment groups.
3. Treatment effect on free-living daily activity levels of any treatment group, comparing baseline electronic step monitors values with those obtained at both follow up intervals of 6 and 18 months.
4. Treatment effects on patient-perceived health-related quality of life (physical function) between all groups at 6 and 18 months.
5. Inpatient and outpatient costs associated with the three treatment strategies, and the evaluation of the relative cost-benefit by calculating incremental cost-

effectiveness and cost-effectiveness acceptability curves using health utility change in the denominator.

6. The impact on cardiovascular disease risk factors by comparing these values at baseline, 6 months, and 18 months.
7. The interaction effect, if any, of gender or race on improvements in MWD, improvement in free-living daily activities, and quality-of-life.
8. Major adverse peripheral events (MAPEs) associated with aortoiliac stenting and femoropopliteal endovascular intervention.
9. Rate of major complication defined as any occurrence of death, myocardial infarction, amputation of the target limb (limb treated in this study), or occurrence of critical limb ischemia or repeat target limb revascularization (TLiR).

3.0 STUDY DESIGN

3.1 STUDY POPULATION

This study is conducted under an investigational device exemption (IDE). The study population will consist of men and women at least 40 years of age with moderate to severe exercise-induced lower extremity atherosclerotic aortoiliac peripheral arterial occlusive disease. Patients with limb-threatening ischemia (Rutherford Grade II or III) will not be eligible and should be referred for consideration for revascularization. Patients will be screened for leg claudication symptoms attributable to peripheral arterial disease (PAD) and clinical suspicion of significant aortoiliac disease. It is anticipated that 130-150 study subjects will be randomized. The comparison of each treatment strategy will be performed using sequential hypothesis testing methods.

For study eligibility, objective evidence of significant claudication and associated arterial insufficiency is required, as well as hemodynamically significant anatomic occlusive disease located in the aortoiliac segment, as demonstrated by noninvasive vascular laboratory methods and/or imaging tests. Inclusion criteria are designed to enroll patients with hemodynamically significant, not mild, aortoiliac obstruction, and study participants will be enrolled based upon noninvasive examinations without requiring catheter arteriograms on all patients (Refer to Eligibility Criteria Section, 3.3). This approach is desirable since arteriography is expensive, invasive, and results in complications (4-7% of patients). The point of clinical decision-making to offer revascularization to individuals with claudication typically occurs prior to catheter arteriography. With this approach, the normal routine of clinical decision-making will be closely followed when randomization occurs after noninvasive tests and prior to arteriography, and also avoids invasive arteriography for patients randomized to noninvasive treatment groups.

Vascular noninvasive tests (e.g., Doppler ultrasound, Exercise Treadmill Testing) are required to be performed by vascular labs accredited by national organizations such as the Intersocietal Commission for the Accreditation of Vascular Laboratories (ICAVL) or the American College of Radiology (ACR), and will require that tests are performed by Registered Vascular Technologists, certified by the American Registry of Diagnostic Medical Sonographers (ARDMS). Prior to activating study sites and vascular laboratories, participating vascular staff at all study sites will be trained and credentialed in methods according to those accepted by the Intersocietal Commission for the Accreditation of Vascular Laboratories (ICAVL). ABI/Thigh-BI may be performed by site staff trained in these procedures.

Study sites and their participating exercise training staff will also be required to undergo training for the supervised exercise intervention prior to site activation and randomization of study subjects. Training will occur at the investigator's meeting prior to study initiation and at all sites prior to study initiation. Completion of this training will be required prior to certification of each site for enrollment in CLEVER. Additionally, sites will provide data from all supervised exercise visits for all supervised exercise group

participants throughout the study. The Exercise Training Committee will review the subjects' data to monitor progress and appropriate advancement of exercise prescription (as described in Appendix E) to ensure that the improvement in MWD is optimized. Missing data or incorrect implementation of the exercise regimen will be apparent on weekly review by the Exercise Training Committee, and sites who are not implementing the exercise training protocol correctly will be told to stop enrollment.

In order to ensure uniformity of stenting technique, credentialing of interventionalists will be performed at each treatment site. Interventionalists eligible to perform stent procedures at each site will be named and will have a minimum experience of 25 prior aortoiliac stent procedures, and have privileges at their hospital to perform aortoiliac arteriography and stent placement. All participating interventionalists are required to submit two retrospective cases of aortoiliac stenting for review, including anonymized reports of arteriograms, waveform tracings, and CRFs, and be approved by the Site Selection Committee prior to enrolling subjects.

Refer to figure in Section 4.2 that illustrates the flow of initial subject screening, eligibility by phase of screening and subject enrollment.

3.2 PROJECTED TIMELINE

Study enrollment began in February 2007. Study recruitment is expected to end in December 2010, and followed by 18 months of follow-up (June 2012), with study close out in December 2012.

3.3 ELIGIBILITY CRITERIA

3.3.1 Inclusion Criteria

1. Subject has symptoms suggestive of intermittent claudication, such as exercise-induced pain, cramps, fatigue, or other equivalent discomfort, involving large muscle groups of the leg(s) (calf, thigh, buttocks), relieved by rest.
2. Subject is ≥ 40 years old.
3. Claudication score consistent with “Rose”, “atypical”, or “noncalf” claudication by San Diego Claudication Questionnaire *(see Appendix A for acceptable responses)*

4. Positive noninvasive evaluation for significant aortoiliac PAD on the most symptomatic side(s) (bilaterally if symptoms are equal):
   a. **Contrast Arteriography**: Contrast arteriogram showing at least 50% stenosis in the aorta, common iliac artery, or external iliac artery, **OR**
   b. **CTA or MRA**: At least 60% stenosis in the aorta, common iliac artery, external iliac artery, accompanied by a biphasic or monophasic Doppler wave form at the common femoral artery (loss of early diastolic flow reversal or loss of forward flow during diastole), **OR**
   c. Duplex Ultrasound: Occlusion or focal doubling of peak systolic velocity in the aorta, common iliac artery, or external iliac artery, accompanied by a biphasic or monophasic Doppler wave form at the common femoral artery (loss of early diastolic flow reversal or loss of forward flow during diastole), **OR**
   d. Vascular Noninvasive Physiologic Tests: Ankle-brachial index <=0.9 (or abnormal ankle PVR waveform at ankle if arteries are incompressible*) with resting thigh-brachial index (thigh-BI) < 1.1, and common femoral artery Doppler systolic acceleration time >140 msec [these tests may be ordered for study screening].

   *Abnormal PVR waveform must lack augmentation at the ankle, have a delayed, rounded systolic peak, and straight or convex downslope, and must be reviewed by the core lab.

   Note: MRA/CTA, and contrast arteriogram images images must be submitted to the Clinical Coordinating Center and Doppler waveform tracings to the Noninvasive Test Committee for over read pre- or post-randomization.

5. Highest ankle pressure reduced by at least 25 mm Hg after exercise compared to resting pressure (or loss of previously present Doppler signal for both the posterior tibial and anterior tibial arteries immediately after exercise if arteries were incompressible).

   Note: The highest ankle pressure result is determined by using the higher result of either the dorsalis pedis or posterior tibial artery measurement.
6. Subject has moderate to severe claudication symptoms, defined as less than 11 minutes MWD at baseline (initial) Gardner treadmill test (see Appendix B).
7. Performance on a second Gardner treadmill test within 25% of the initial baseline MWD test result.

3.3.2. Exclusion Criteria

1. Presence of critical limb ischemia (Rutherford Grade II or III[59] PAD, defined as pain at rest, ischemic ulceration, gangrene) or acute limb ischemia (pain, pallor, pulselessness, paresthesias, paralysis) in either leg.
2. Common femoral artery (CFA) occlusion or >=50% stenosis by angiography, MRA, CTA, or duplex ultrasound or doubling of systolic velocity in the ipsilateral common femoral artery by duplex ultrasound, or 50% diameter stenosis by

visual estimate in the CFA by angiography, MRA, or CTA, (inadequate outflow for iliac stent intervention), if available pre-randomization

3. Known total aortoiliac occlusion from the renal arteries to the common iliac arteries (all other occlusions ARE eligible)
4. Participant has bilateral claudication symptoms and the limb that is more symptomatic does not show evidence of aortoiliac insufficiency as described in inclusion criterion number 4.
5. Participant has bilateral claudication symptoms, but both limbs are equally symptomatic and one side does not show evidence of aortoiliac insufficiency as described in inclusion criterion number 4.
6. Subject meets the following exclusions based upon modified American College of Sports Medicine criteria for exercise training:
    i. Ambulation limited by co-morbid condition other than claudication, for example:
        1. severe coronary artery disease
        2. angina pectoris
        3. chronic lung disease
        4. neurological disorder such as hemiparesis
        5. arthritis, or other musculoskeletal conditions including amputation
    ii. Poorly-controlled hypertension (SBP>180 mm Hg)
    iii. Poorly-controlled diabetes mellitus
    iv. Other active significant medical problems such as cancer, known chronic renal disease (serum creatinine >2.0 mg/dl within 60 days or renal replacement therapy), known chronic liver disease or anemia, active substance abuse, or known history of dementia.
7. Contraindication to exercise testing according to AHA/ACC guideline, specifically: Acute myocardial infarction (within 3-5 days), unstable angina, uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise, active endocarditis, symptomatic severe aortic stenosis, acute pulmonary embolus or pulmonary infarction, acute noncardiac disorder that may affect exercise performance or be aggravated by exercise such as infection, thyrotoxicosis, acute myocarditis or pericarditis, known physical disability that would preclude safe and adequate test performance, known thrombosis of the lower extremity, known left main coronary stenosis or its equivalent, moderate stenotic valvular heart disease, electrolyte abnormalities, known pulmonary hypertension, tachyarrhythmias or bradyarrhythmias, hypertrophic cardiomyopathy, mental impairment leading to inability to cooperate, or high degree atrioventricular block
8. Arterial insufficiency of target lesion due to restenosis of an angioplasty/stent or bypass is not eligible.
9. Recent (<3 months) infrainguinal revascularization (surgery or endovascular intervention).
10. Recent major surgery in the last 3 months.
11. Abdominal aortic aneurysm > 4 cm or iliac artery aneurysm >1.5 cm is present.
12. Patients who are pregnant, planning to become pregnant, or lactating.

13. Unwilling or unable to attend regular (3 times a week) supervised exercise sessions. *{Please review this commitment carefully with each prospective participant}*
14. Weight >350 lbs or 159 kg (may exceed treadmill and angiography table limits).
15. Language barrier exists for primary QoL instruments (available in English and Spanish).
16. Inability to understand and sign informed consent forms due to cognitive or language barriers (interpreter permitted).
17. Absolute contraindication to iodinated contrast due to prior near-fatal anaphylactoid reaction (laryngospasm, bronchospasm, cardiorespiratory collapse, or equivalent) and which would preclude patient from participation in angiographic procedures.
18. Allergy to stainless steel or nitinol.
19. Nonatherosclerotic cause of PAD (fibromuscular dysplasia, dissection, trauma, etc).
20. Inability to walk on a treadmill without grade at a speed of at least 2 mph for at least 2 minutes on the first treadmill test.
21. ST-segment depression >1 mm in any of the standard 12 ECG leads or sustained (>30 seconds) arrhythmia other than tachycardia or occasional premature atrial or ventricular contractions during exercise testing.
22. Post-exercise systolic blood pressure within the first five minutes after eligibility treadmill test lower than pre-exercise systolic blood pressure.
23. A peak heart rate $\geq$80% of maximum (calculated by subtracting age from 220) while reporting ”onset” of claudication symptoms during the second baseline examination.
24. Repeat treadmill test shows a MWD result that is >25% different than the subject’s initial Gardner treadmill test result.
25. Current active involvement in a supervised exercise program (e.g., with a trainer, exercise protocol, and goals, such as in cardiac or pulmonary rehabilitation) for more than 2 weeks within the prior 6 weeks.

3.4 RANDOMIZATION

Randomization will occur as follows using a web-based randomization system. Randomization will be unbalanced in a 2:2:1 ratio (ST:SE:OMC). Randomization must occur within 24 hours of the second baseline treadmill test to preserve the timing of the follow-up assessments (see appendix F, “Schedule of Assessments”).

Study region along with cilostazol use at baseline were selected as the stratification factors. Cilostazol was chosen from other factors because the interaction effect between cilostazol use and treatment group is unknown. It was determined that requiring either a washout period (for those on cilostazol) or an induction period (for those not on cilostazol) prior to eligibility treadmill testing was not practical. Study region was chosen instead of study site due to the anticipated small numbers of participants enrolled per site which might result in potential bias in treatment assignment. Other baseline variables (current smoking status, use of statin medications,

presence of diabetes) were considered for stratification; however, these factors were associated with modest beneficial effect on exercise performance[75]. Active cigarette smoking may be associated with reduced MWD[76]; however, given the relatively small sample size in this study, randomization based upon other multiple stratified factors is not practical. It is expected that these additional stratification variables will be uniformly distributed throughout the treatment groups and will be monitored.

The DCC will generate the randomization scheme to be used for the CLEVER study. Randomization will only be performed after the subject's eligibility is confirmed based upon results of the second Gardner treadmill test. The study site investigator must review and approved subject enrollment prior to randomization.

After randomization, subjects should begin assigned treatment within 14 days; the coordinator should be informed if this cannot be achieved. If randomized treatment intervention is not performed within 60 days then repeat treadmill tests must be performed.

3.5 EXPERIMENTAL STRATEGIES AND INTERVENTIONS

Three (3) treatment groups will be evaluated in this study: (a) Optimal Medical Care (OMC), (b) OMC plus Aortoiliac Revascularization with Stent (ST), and (c) OMC plus Supervised Exercise Training (SE). A fourth treatment group, Stent plus Supervised Exercise (ST+SE) has been terminated due to slow enrollment. Participants enrolled in ST+SE will continue to be treated and followed in the ST+SE treatment group. All study participants who can tolerate it will receive cilostazol medication without charge and risk factor reduction recommendations, as described below. Initiation of treatment in all cases should start as soon after randomization as possible to minimize deregistration, and at most within 60 days of randomization.

Risk Factor Reduction

For all three treatment groups, atherosclerotic cardiovascular disease risk factor modification is an expected standard of care, and includes smoking cessation counseling, lipid and blood pressure lowering treatments, and antiplatelet medication administration appropriate to the high-risk status of patients enrolled in this study. As an exploration into the effects of treatment allocation on Framingham Coronary Heart Disease Risk, obesity, blood pressure, lipid profiles, and glycemic control will be monitored for all treatment groups at baseline and 6 and 18 month follow-up intervals.

It is recommended that all participants in this study be managed according to the most recent treatment guidelines available. In this regard, the goals available from the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[96], Adult Treatment Panel (ATP) III[99] and the ACC/AHA 2001 guidelines for secondary prevention[100] will be expected targets for patients in CLEVER, regardless of randomized treatment assignment (see Appendix J).

Study investigators will be provided with a laminated reference of current recommendations for cardiovascular disease risk factor reduction developed by the Risk

Factor Reduction (RFR) Committee. This will include a summary of guideline recommendations for blood pressure and LDL cholesterol targets, current smoking, and specific anti-platelet pharmacologic management. A Risk Factor Management electronic case report form (eCRF) will capture data regarding the major risk factor goals in binary fashion to indicate if the target goal was achieved and will be utilized for baseline and follow-up visits. When received at the DCC for the baseline and 6-month follow-up visits, the DCC will note any management that is not in accordance with CLEVER recommendations and forward those to the CCC. The CCC will work with the RFR Committee to provide feedback, gather information about mitigating circumstances, and reinforce the recommendations. Contact will be continued at the discretion of the CCC and RFR Committee until compliance with recommendations is achieved, or the inability to achieve recommended targets is accepted by the CCC and RFR Committee. Exercise education will not be performed outside of the baseline and follow-up intervals for patients randomized to optimal medical care or stent plus optimal medical care. The Supervised Exercise Training plus OMC group and the exploratory stent plus supervised exercise with OMC group will be the only groups to receive behavioral medicine counseling designed to promote exercise adoption.

Cilostazol

Cilostazol has shown a modest but statistically significant effect in improving MWD in patients with claudication when studied with constant-load treadmill tests[35]. It is not known whether this effect applies to graded treadmill test results; however, given the possibility of uneven usage among treatment groups, all participants in this study who do not have a contraindication or history of intolerance to it will be standardized to receive cilostazol (without charge) at the usual dose of 100 mg twice daily (bid) by mouth, if tolerated. Cilostazol will be distributed from the pharmacy at Rhode Island Hospital labeled with the standard dosage and the annotation, “For CLEVER Study Use Only”, and will be shipped to the site research coordinators for distribution to patients. Study coordinators will record the study subject’s name in the space provided on the label.

For participants not medicated with cilostazol at study enrollment and without a contraindication or history of intolerance, cilostazol dose-toleration will be assessed over a 2 week treatment interval after randomization. If the 100 mg twice daily dose is not tolerated, subjects will be down-titrated to 50 mg twice daily. If this dose is not tolerated, then cilostazol will be discontinued, but subjects will continue in the study. Subjects receiving the lower 50 mg bid dose will be continued at this dose for three weeks and then increased to the full dosage of 100 mg bid. If this dose is then tolerated, the increased dose will be maintained. Participants who only tolerate 50 mg twice daily will receive pill cutters and instructions on how to cut the 100 mg pills in half. Study participants will receive cilostazol at enrollment and at quarterly visits with the research coordinators thereafter, and coordinators will conduct pill counts with subjects at their quartlery visits to measure compliance. Cilastozol compliance is defined as greater than 80% monthly usage of prescribed medication.

Investigators will adhere to the contraindications as defined in the drug information label for cilastozol. Since cilostazol is extensively metabolized by cytochrome P-450 isoenzymes, caution should be exercised when cilostazol is co-administered with inhibitors of C.P.A. such as ketoconazole and erythromycin or inhibitors of CYP2C19 such as omeprazole. Pharmacokinetic studies have demonstrated that omeprazole and erythromycin significantly increased the systemic exposure of cilostazol and/or its major metabolites. Population pharmacokinetic studies showed higher concentrations of cilostazol among patients concurrently treated with diltiazem, an inhibitor of C.P.A. Concomitant medications will be collected and specific information about the use of ketoconazole, erythromycin, omeprazole, and diltiazem will be gathered. If a study participant develops congestive heart failure during the study, cilostazol is contraindicated and should be immediately discontinued by the study investigator.

Concomitant medications will be collected and targeted to the classes of Medications outlined in Appendix G.

3.5.1 "Optimal Medical Care" (OMC) Group: Home-based Exercise and Pharmacotherapy and Risk Factor Reduction

Optimal medical care (OMC) in this study will represent the standard of care that most patients with claudication receive when they visit their doctor: they are advised to "stop smoking and keep walking" and receive pharmacotherapy with cilostazol if tolerated, which is now increasingly used in individuals with claudication. As mentioned previously, all study participants who tolerate it will receive cilostazol throughout the study without charge, and all study participants will receive telephone calls from local research coordinators monthly to encourage study retention as outlined previously. The date of randomization, which in many cases should be the date of the second baseline treadmill test is considered "day zero" for calculating the dates of the follow-up visits (see appendix F, "Schedule of Assessments"). Subjects enrolled in the "optimal medical care" arm will be verbally advised at baseline and at 6 month follow-up visits to perform home exercise based on similar criteria as supervised exercise subjects. They will receive written exercise instructions including a description of optimal exercise regimens given their age and ability. Monthly calls in this group will not include exercise education.

3.5.2 Stent (ST) Group: Aortoiliac Stent and OMC

Management for participants randomized to the Aortoiliac Stent Group will reflect closely that of the "optimal medical care" cohort, plus the addition of revascularization with stenting. In this trial, subjects will be treated with bare metal stents suitable for treatment of aortoiliac stenosis using standard angiographic and interventional methods. For a discussion of management of different anatomic presentations of occlusive disease, as well as technical details of the revascularization procedure, please see section 4.4.3.1, "Procedures for Aortoiliac and Femoropopliteal Revascularization".

Bypass surgery is not an experimental intervention or treatment arm in this study. Bypass surgery at any level will not be performed for claudication under this protocol, unless a subject is discontinued from the study because he/she meets the pre-defined endpoint of critical limb ischemia and requires bypass surgery for treatment of this severe disease progression.

Study participants in the stent group will receive telephone calls at least monthly in order to promote study retention, but they will not receive adherence to physical activity counseling or adherence to physical activity materials. In a manner identical to the "optimal medical care" group, they will receive exercise training recommendations in the office setting at baseline, 6 months, and 18 months.

During routine clinical follow-up, decreases in the ABI of >0.10 compared with post-treatment ABI will indicate possible loss of primary patency of the stent intervention. If the thigh-brachial index is normal (>=1.3) or not more than 0.10 less than the post-stent value, this result will be considered evidence of continued stent patency. If the thigh-BI is also decreased, patients will undergo a repeat evaluation by either duplex ultrasound or by arteriography (catheter angiography or CTA) to assess restenosis. If restenosis is present, a repeat intervention by either angioplasty or stent placement will be performed. If restenosis can not be managed percutaneously and there are symptoms or signs of progression to limb-threatening categories, patients will be considered for bypass surgery. Subjects in this cohort will be analyzed in the stent group according to intention-to-treat methods.

The day of randomization is considered "day zero" for calculating the dates of the follow-up visits (see appendix F, "Schedule of Assessments"). For many participants, that will be the same day as the second baseline treadmill test. Ideally, the duration between the second treadmill test and randomization will be minimized to ensure that supervised exercise participants get a full 26 week course of supervised exercise therapy.

3.5.3. Supervised Exercise Training (SE): Supervised Exercise Training/Adherence to Physical Activity Group and OMC

Participants randomized to the Supervised Exercise Training/Adherence to Physical Activity group will receive similar management as the "optimal medical care" cohort. In addition to "optimal medical care", they will receive supervised exercise training for the first 26 weeks and behavioral medicine interventions to foster long-term adoption of ongoing exercise between months 5 and 18. Supervised exercise training will be performed in accordance with American College of Sports Medicine, and American College of Cardiology/American Heart Association guidelines[74]. Supervised exercise therapy will be conducted at designated rehabilitation centers associated with each study site to ensure exercise training is administered locally, and all sessions will be conducted under the guidance and direction of trained exercise rehabilitation staff.

Supervised exercise training will be implemented using an individualized regimen for each patient prescribed based on baseline treadmill test results. The regimen will be established centrally by the Exercise Training Committee and conducted according to the procedures outlined in Appendix E.

For purposes of timing of the follow-up assessments, the treatment "day zero" is the day of randomization (see Appendix F, Schedule of Assessments). Usually, supervised exercise should begin within 14 days of randomization. Initiation of supervised exercise can be delayed for a total of up to 60 days, but this should be as minimized as much as possible to ensure that they get as much supervised exercise training as they can before the 6 month endpoint. Participants will stop supervised exercise training at 6 months regardless of the number of supervised sessions they undergo. They will be analyzed in this treatment group according to intention-to-treat.

Individual regimens will be implemented by the research coordinator according to the algorithm outlined in Appendix E. Supervised exercise training will occur three times a week. The research coordinator will record attendance and the start time of exercise, the finish time, the number and duration of walking episode, the duration of each episode of rest, and the treadmill grade and speed that day. This information will be forwarded to the DCC on eCRFs and will be accessible in real time by the Exercise Training Committee. The Exercise Training Committee will track the progress of each participant in the SE group weekly and advance their exercise prescription as tolerated. Exercise prescriptions will be recorded in the DCC database. The Exercise Training Committee will advance the exercise program according to methods outlined in the Appendix E, and confirm the prescription every two weeks for each participant with each site. Sites will keep dated copies of prescriptions in a binder for each participant for review by the Clinical Coordinating Center.

Adherence to physical activity will be optimized for this group from month 5 through month 18 under the direction of the Adherence to Physical Activity Committee.

3.6 RETENTION OF STUDY SUBJECTS

A number of motivating factors will be utilized to promote continued subject participation in this study over time. First, telephone contact will be performed at least monthly to keep participants engaged and enthusiastic about the study. Participants will be reminded about their next visit date, thanked for their continued participation in the study, and any questions will be answered during that call. All study subjects will receive pedometers, which they will be told they can keep if they continue to participate in the study. Study participants randomized into either supervised exercise training group will be told of the relative cost of care or a gym membership, and counseled about the benefits of attending exercise sessions with regards to achieving and maintaining event-free cardiovascular health. Study participants will also be reimbursed for time and travel, including additional reimbursement for those randomized to attend exercise sessions. The total will be $250 for each study participant, plus up to $15 per session for those in the supervised exercise group up to $1,170.

During monthly calls, the research coordinator will ask general medical questions concerning the subject's condition and try to keep the subject engaged and enthusiastic about the study. If a research coordinator detects symptoms that indicate progression of limb-threatening disease (Rutherford II or III category), the patient will be assessed and referred for consideration of alternative treatment (if warranted). Coordinators must make every effort to schedule a study cross-over visit data collection visit, including graded treadmill test if the patient remains ambulatory, prior to any alternative treatment procedure.

3.7. POTENTIAL FOR CROSSOVER BETWEEN STUDY ARMS

Several potential cross-over scenarios may occur in this study that will result in participants not receiving their allocated treatment or receiving treatment other than that outlined for their treatment group. One possible scenario may occur with false-positive noninvasive tests results for subjects allocated to the stent group who will then not undergo stent placement. Similarly, a participant allocated to the stent strategy may have anatomy that precludes a successful revascularization procedure. Another possible scenario may include patients allocated to stent or optimal medical care groups who enroll themselves in supervised exercise programs outside of the context of this study. Finally, a participant allocated to optimal medical care or supervised exercise training could possibly undergo stenting during follow-up.

It is expected in this trial that all participating investigators accept that no treatment in this study has demonstrated superiority for claudication and, therefore, there can be no justification for crossing patients from one treatment group to another without clinical progression of disease into limb-threatening categories. Progression to limb-threatening ischemia is not common in patients with intermittent claudication, and it is expected that this occurrence will be rare and unusual. At the time of consent subjects and their referring physicians will be informed that crossover treatment will not occur, except as mandated and documented by the development of limb threatening ischemia, which is expected to occur rarely in this study.

Several efforts must be made to keep such crossover between strategies to a minimum. First, all false-positive screenings will be tracked and pre-randomization data for quality assurance and quality improvement review will be performed for each false positive finding. Since each site will enroll only on average 5 patients per treatment arm, if more than one false positive occurs per site, the site may be terminated as an enrollment center.

Only one legitimate reason for crossover between treatment strategies or alternative medical therapy is justified: progression of disease to limb-threatening status. This progression will be signaled by the presence of rest pain, ischemic ulceration, or gangrene. Although an investigator's first responsibility is to the patient, there should be no medical reason to cross-over individuals with claudication to an alternative treatment strategy or other medical therapy without a diagnosis of limb-

threatening ischemia. Crossovers for patients with claudication who have not progressed to limb-threatening status are not sanctioned in this study.

When any patient does experience progression to limb-threatening status and cross-over is requested, Investigators are required to submit clinical data including noninvasive test results (ABI results, segmental limb pressures, pulse-volume recordings, and arteriograms, if available). These results will be reviewed by an ad hoc cross-over committee using study leadership and enrolling center investigators. This committee may also review photographs (digital or hard copy) of ischemic lesions or gangrene, if that is the reason cited for the requested crossover. Investigators planning on crossing-over participants for refractory or worsening claudication will also be asked to submit this data to the CCC and will generally be discouraged from this type of cross-over. For all planned cross-over procedures, study endpoints, including walking treadmill performance, obtained after the cross-over and as close to the scheduled evaluation time as possible, will be used for analysis to preserve the intention to treat approach. Other methods to impute data at time intervals after cross-over will also be used for secondary analysis (see "Statistical Analysis Plan", section 6.0). Study participants who cross over to a treatment group to which they were not randomized will continue to be followed at regularly scheduled intervals and all possible data will be collected, including treadmill tests. Such patients will be analyzed as randomized for the intention to treat analysis.

Stenting that is performed in a patient randomized to "optimal medical care" or "supervised exercise training" without progression to limb-threatening status and without approval of the cross-over committee will be considered a major protocol violation. Depending upon the circumstances, the enrollment center may be terminated from the study.

In the unlikely event that an angiogram performed on a patient allocated to the stent treatment group reveals no significant arterial occlusive disease, the patient will receive treatment identical to the OMC group, but will be analyzed under intention to treat as in the stent group.

3.8 SUBJECT WITHDRAWAL OR TERMINATION

Subjects will be terminated from the study if they die or withdraw from the study during the follow-up period. Subjects will not be terminated if they progress to limb-threatening ischemia (Rutherford Grade II or III; rest pain, ischemic ulceration, gangrene) during the follow-up period but rather will undergo necessary treatment and will continue to be followed in their assigned treatment group. Patients who die will have zero imputed as their MWD and other patients will be handled statistically using a multiple imputation. The Crossover Management Policy described above will be strictly enforced. If it is determined retrospectively that any enrolled study participant did not meet inclusion/exclusion criteria a protocol deviation will be documented and they will be followed according to the protocol for the intent-to-treat analysis. Upon completion of all follow-up requirements a Study Exit Form is completed for each subject. This form is

also completed for those that have died, withdrawn, or are lost to follow-up. Subjects who miss the 6 month visit by more than two months will be counted as missing a visit and data for that time point; they will be recruited for their 18 month data collection visit. Subjects who die or are lost-to follow-up will be censored in the survival analysis.

4.0 PROCEDURES AND EVALUATION SCHEDULE

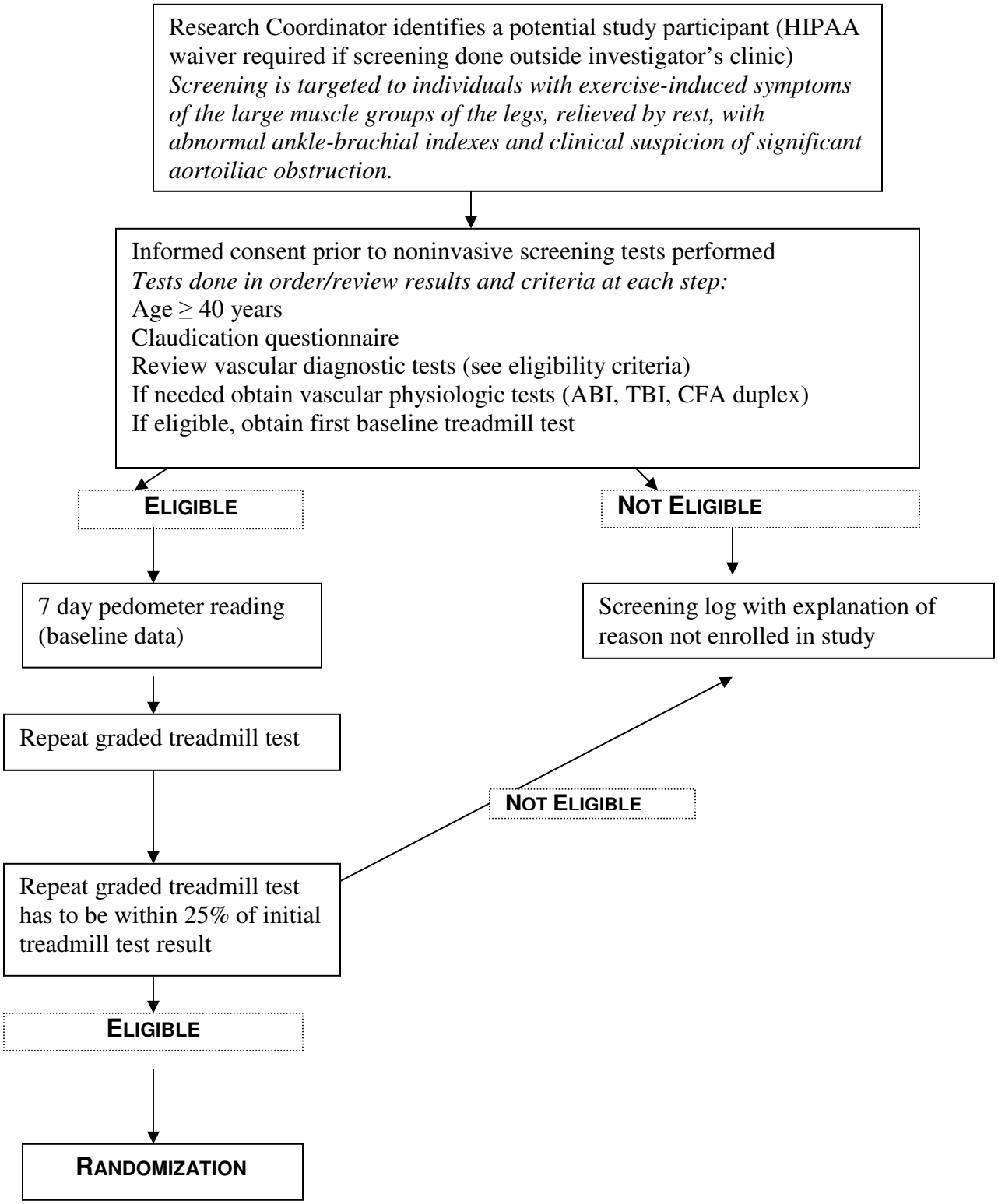
4.1 SUBJECT INFORMED CONSENT PROCEDURES

In general, suitable patients to consider for informed consent for this study are those with exercise-induced symptoms of the large muscle groups of the legs, relieved by rest, with abnormal ankle-brachial index and clinical suspicion of significant aortoiliac obstruction. Upon patient referral for consideration for the study, the research coordinator will review the clinical inclusion and exclusion criteria for each potential subject. HIPAA waivers in accordance with 45 CFR 164.512(i)(1)(i) will be required from local IRBs for all investigators who plan to screen clinical data at their institutions for patients not directly under their care. If vascular diagnostic tests were conducted prior to referral, the results of these should be reviewed by the research coordinator and investigator with attention to contrast arteriograms, MRA, CTA, ABI, thigh-BI, and common femoral artery systolic acceleration time, if available.

Informed consent will be obtained by enrolling center investigators or site research coordinators. All sites will develop and perform informed consent in accordance with the NIH 7 Elements of Conformance. Informed consent will occur in a non-coercive environment and with patients whose judgments are not impaired by sedative or narcotic medications. Both verbal and written consent will be obtained. Inability of the study participant to understand the informed consent forms is an exclusion criterion for this study. The original consent form will be kept with the study records. Patients will receive copies of eligibility and enrollment consent forms and copies will be placed in the medical record. No patient will undergo a research-related procedure until informed consent applicable to that procedure has been obtained.

Screening logs will be maintained via the web for all patients who sign informed consent and will include demographic information, subsequent enrollment or reason for screen failure (either specific inclusion/exclusion criteria failure or patient refusal and reason). The screening log will be completed online on a monthly basis. The DCC will review and provide information to study leadership regarding study screening and enrollment percentages based upon these logs at intervals to be determined by study leadership.

4.2 STUDY PARTICIPANT SCREENING PROCEDURES



4.2.1 Identifying Patients for Screening

The following data will likely be available from the medical record for most patients with suspected lower extremity arterial disease. If you screen patients not under your direct care, a HIPAA waiver must be obtained prior to reviewing these data.

To identify patients for screening for CLEVER, obtain the following data based upon medical history review and *prior* to any non-invasive or invasive vascular assessment, exercise testing, Quality of Life Assessments or other survey or exam. Patients with these criteria would be good candidates for screening:

1. Age ≥40
2. Medical history of exercise-induced symptoms of the large muscle groups of the legs (usually the calf), relieved by rest
3. Absence of rest pain, ischemic tissue loss, or gangrene
4. Signs or symptoms of significant aortoiliac insufficiency, such as buttock or thigh claudication, OR decreased femoral pulses, OR impotence in males (note that these are for purposes of narrowing the screening population only and that most patients with significant inflow disease complain of calf claudication primarily)

4.2.2 Review of Non-invasive and Invasive Testing Requirements:

Much of the data used to evaluate participant eligibility (section 3.3) may be available in the medical record.Listed below are the tests involved in determining eligibility. Not all of them need to be done in for each participant as there are a number of combinations, for example, or noninvasive tests that can be used to determine aortoiliac insufficiency for this study. If the medical record is incomplete with regard to these evaluations, additional study-driven tests can be undertaken after suitable study participants are identified and signed informed consent for the study is obtained.

Tests performed on subjects passing initial screening criteria above will have the following assessments performed:

1. San Diego Claudication questionnaire results consistent with “Rose”, “atypical”, or “noncalf” claudication *(see Appendix A for scoring combinations that meet study inclusion criteria)*
2. Confirmatory evidence of significant aortoiliac PAD (see inclusion criterion 4, section 3.3.1).

Once a study participant has passed the screening evaluation, including the noninvasive and/or invasive test review, they can proceed to the first baseline treadmill test.

4.3. BASELINE EVALUATION AND ENROLLMENT (DAY -8)

Baseline Visit 1 (Day minus 8)

Baseline data collection will include classic variables associated with coronary heart disease (CHD) risk using Framingham Heart Study Prediction Scores. They include:

1. Demographics and risk factors
   - Age
   - Gender
   - Smoking status
   - History of hypertension, hyperlipidemia, diabetes, and renal failure
   - Risk Factor Reduction checklist
   - Height (recorded from a stadiometer)
   - Body weight (recorded from a balance beam scale), and body mass index will be calculated as weight in kg/height in m^2.
   - Waist circumference
   - Blood pressure (systolic, diastolic, pulse pressure), seated upright at least 15 minutes prior to blood pressure measurement. Blood pressure will be measured using an automated blood pressure cuff.
   - Resting ABI

2. Brief physical exam targeted to evidence of rest pain, ischemic ulcer, and gangrene.
3. First baseline treadmill test using the Gardner graded protocol (performed as described in Appendix B).

   Note: For at least 2 hours prior to undergoing treadmill testing, subjects are required to have fasted and to have not smoked.

4. Participant must walk >=2 minutes and <11 minutes on the Gardner protocol to be eligible (see eligibility section 3.3), and the ankle pressure post exercise decreased by at least 25 mm Hg.

5. If participant is eligible after the baseline 1 treadmill test, they should be given an Omron pedometer and instructed in its use (see instructions in pedometer box), and an appointment for the baseline 2 treadmill test at least 8 days later, and ideally not more than 14 days (see appendix F, “Schedule of Assessments”). Study participants will wear pedometers (Omron Pedometer model HJ-112) for seven consecutive days prior to the baseline treadmill test. Participants will be instructed to wear the pedometer as much as possible for 7 days straight during all waking hours, and a written instruction card should be given to them.

Baseline Visit 2 (Day 0 [if randomized on this day])

Ideally, the second baseline visit will occur at least 8 days after Baseline 1 but as soon after that as possible and in most cases within 2 weeks. However, it is acceptable to delay the second treadmill test up to 60 days to accommodate subject scheduling and minimize the time interval between the second treadmill test and initiation of treatment according to assigned treatment group.

1. Obtain second baseline treadmill test using the Gardner protocol (performed as described in Appendix B). If within 25% of the first treadmill test, the participant is eligible for randomization. Randomization will proceed after eligibility is confirmed and all baseline data is collected and must be done within 24 hours of the completion of the second baseline treadmill test.

   Note: For at least 2 hours prior to undergoing treadmill testing, subjects are required to have fasted and to have not smoked.

2. Query eligible subject on pedometer usage, specifically:
   - Collect pedometer log and review the number of days pedometer was worn, the number of waking hours each day it was worn, and whether the pedometer was worn for consecutive days, for upload into the electronic data collection system.

3. Fasting state (8 hours) blood sample will be drawn and sent to a central core lab for measurement of HDL, LDL, triglycerides, fibrinogen, C-reactive protein (CRP), glucose, creatinine, and HbA_1c. Blood will be stored for possible biochemical or DNA tests in the future. (Refer to Manual of Operations for preparation and shipping instructions).

4. Economic and Quality of Life (EQOL) Assessments: Health utility (EuroQOL/EQ-5D), SF-12, Walking Impairment Questionnaire (WIQ), and the Peripheral Arterial Disease Questionnaire (PAQ), is completed by the participant to assess health utilities/cost-effectiveness, generic QoL, and disease-specific QoL, respectively, and scored according to standard published methods. Questionnaires should be reviewed by coordinators for completeness. The questionnaires are administered by telephone by the EQOL core lab at 6 and 18 months.

   The patient diary, designed to capture outpatient resource utilization, will be given to the patient and will be collected, and new ones distributed, at the quarterly visits. Data is entered into the electronic case-report forms

Note: All EQOL baseline assessments, including the Patient Accounting Form, the Medical Billing Release Form, and the Patient Address Form, will be faxed and originals mailed to the EQOL Core Lab.

5. Coordinator administers the Walking Impairment Questionnaire (WIQ) (also at 6 and 18 months) and enters data into electronic case report form, and performs Independent Exercise Assessment. The Independent Exercise Assessment evaluates if the subject performs independent exercise, whether formal or informal, with the intent to improve fitness when done 2 or more times per week for 20 minutes or more. Refer to Appendix K for assessment and instructions.

6. Cilostazol administration: Participants will start cilostazol if they don't have contraindications or a history of intolerance immediately after eligibility is confirmed. Participants unable to tolerate cilostazol at the 100 mg bid dose per day can be reduced to 50 mg twice daily for 3 weeks, and then increased to 100 mg twice daily. If the increased dose is not tolerated, they will be maintained on 50 mg twice daily. Participants who do not tolerate 50 mg twice daily will discontinue use of the drug. Use of pentoxyfilline is discouraged and study subjects using pentoxyfilline are asked to discontinue this medication. Dispense three month supply and record number of pills dispensed at this visit. Instruct study participants to return quarterly to obtain cilostazol medication.

7. Data collection for concomitant medications (refer to Appendix G for list of specific classes of drugs to be recorded).

8. Randomization: Subjects will be randomized via a Web-based Randomization System to 1 of 4 study groups and stratified based upon cilostazol use and study region.

4.4 INTERVENTION/TREATMENT GROUPS

4.4.1 Optimal Medical Care

1. At baseline, 6 months, and 18 months OMC group participants will receive verbal exercise instructions and receive a brochure with exercise regimen recommendations. Participants allocated to this treatment group will not receive exercise logs.

2. They will be informed that they will receive monthly calls from the study research coordinator (RC); however, calls will not include exercise education. During these calls RCs will ask if participant had any Adverse Events and if so will complete an AE case report form. They will also ask participant if they've had any change in their health status since the last call and if they have been in the hospital for any reason. If yes, RCs will report AEs and any leg revascularization procedures. RCs will review the Independent Exercise Assessments with subjects (Appendix K).

3. Subjects will be scheduled for their 6 month follow-up visit at this time.

4.4.2 Supervised Exercise Testing and Adherence to Physical Activity Intervention

1. Following the baseline assessments, subjects will be scheduled for supervised exercise training visits three times a week for up to 26 weeks (supervised exercise not continue after the 6 month treadmill test).

2. Patients randomized to this group will be trained on the requirements of their individualized exercise regimen at their first session.

3. The initial exercise prescription is based upon the patient's baseline Gardner Treadmill tests that the Research Coordinator provides the Exercise Rehabilitation staff (initial exercise prescription in Appendix E).

4. To ensure continued adherence to physical activity, the patients will receive a telephone-based behavioral intervention by a trained health educator to promote continued walking exercise throughout the remainder of the study (from month 5 through month 18).

4.4.3 Revascularization Intervention

1. Subjects will be scheduled for a revascularization procedure no more than 2 weeks post randomization.

2. For those with significant aortic or iliac artery lesions "direct" or "primary" stent placement will be done —attempts at balloon angioplasty are not allowed in the

aortoiliac segment and pre-dilation with an angioplasty balloon to facilitate stent placement should not be done unless stents cannot be delivered to the treatment site without predilatation, or unless in the operator's judgement incomplete stent expansion of a self-expanding stent may occur that could impact successful post-stent dilatation.

3. Femoropopliteal atherosclerotic lesions must be at least 50% diameter stenosis and AHA type I (focal <3 cm long, concentric, not calcified) and must be on a symptomatic side to qualify for intervention in this study. These femoropopliteal lesions must be treated with balloon angioplasty as the preferred stand-alone revascularization strategy. Selective stenting will only be allowed for unsatisfactory angioplasty results, defined as >30% residual stenosis by visual estimate or evidence of potentially flow-limiting dissection (NHLBI dissection ≥ grade C). The aortoiliac stenting procedure will be conducted in accordance with the Instructions for Use specific to each device contained in the Manual of Operations. Stents permitted for use include only the following stents:

Boston Scientific:	Express Biliary LD
Cordis:	Genesis on Opta Balloon, Genesis on Slalom Balloon, SMART stent
Guidant:	Omnilink Biliary, Absolute Biliary, Herculink Plus

4. This study is designed as a study of patients with claudication and aortoiliac arterial insufficiency. As such, the goal will be to revascularize most symptomatic aortoiliac lesions. It is recognized that many patients will also have femoropopliteal arterial insufficiency. Although this is not a study of femoropopliteal interventions, this protocol will not preclude accepted, standard of care interventions on those patients in the stent groups found to have femoropopliteal lesions that are generally accepted as amenable to endovascular interventions (see below, subsection 4.4.3.1, "Procedures for Aortoiliac and Femoropopliteal Revascularization").

5. At baseline, 6 months, and 18 months ST group participants will receive verbal exercise instructions and receive a brochure with exercise regimen recommendations. Participants allocated to this treatment group will not receive exercise logs. They will be advised that they should allow time to recovery after iliac stent procedure and receive approval from their doctor who performed the stent procedure prior to beginning exercise.

4.4.3.1 Procedures for Aortoiliac and Femoropopliteal Revascularization

Prior to the start of any catheterization procedure, subjects must have had a recent (within 90 days) serum creatinine less than 2.0 mg/dL. Arteriography is performed in the anterioposterior view using iodinated contrast from the level of the renal arteries to the aortic bifurcation, the pelvic arteries, and the ipsilateral (symptomatic) leg(s) artery(s) to the level of the ankles. Any aortoiliac stenosis of 50%

or greater by visual estimate will be assessed by transcatheter pressure measurements, using simultaneous measurements of arterial pressures above and below the stenosis. Systolic and mean pressure gradients will be recorded, and waveforms obtained. A pressure gradient of >5 mm Hg mean by simultaneous pressure measurements will be considered significant and an indication for stent placement. If the arteriogram and pressure measurements do not reveal significant disease consistent with these parameters, no stent should be placed and angioplasty will not be performed. Total occlusions will not require pressure measurements prior to revascularization. Femoropopliteal stenosis will be evaluated by arteriography only, and 50% diameter stenosis by caliper measurement will be considered hemodynamically significant.

Patients with total aortoiliac obstruction will not undergo attempted revascularization due to the technical difficulties and potential for increased complications with this presentation. Therefore, if the aorta is occluded from the renals through to the aortic bifurcation, with or without iliac artery disease, revascularization should not be attempted. This is expected to be rare. Patients who are found to have total aortic occlusion will remain in their assigned treatment group. All other focal aortic lesions, occlusions or stenoses, and total iliac (common and external iliac artery) occlusions or stenoses must undergo attempts to be treated.

It is the intent of this protocol that those assigned to the stent groups not be denied angioplasty for suitable lesions in the femoropopliteal segment. If atherosclerotic lesions at least 50% by diameter on visual estimate are noted in the femoropopliteal segment on a symptomatic side, and are amenable to balloon angioplasty (AHA category 1 lesions[77], defined as focal, concentric, noncalcified stenosis <3 cm in length) in either symptomatic leg, they may be treated using balloon angioplasty with selective stenting reserved for unsuccessful angioplasty as described in section 4.4.3. Femoropopliteal lesions that do not conform to AHA category 1 should not be dilated with balloon angioplasty or stents, nor should lesions in the tibial or peroneal arteries. Since most femoropopliteal PAD is not focal, we anticipate that <5% of stent patients will have angioplasty of the femoropopliteal arteries. More extensive femoropopliteal lesions should not be dilated because they can be technically difficult, can be associated with increased complication rates, and have lower long-term patency. Also, in patients with significant aortoiliac insufficiency, even long-segment occlusion of the femoropopliteal segment is usually well-tolerated after revascularization of the aortoiliac obstruction. Tibial or peroneal artery disease usually is not symptomatically important in patients with claudication and will not be dilated or stented for the same reasons. For these reasons, interventions in the femoropopliteal segment for lesions more extensive than those described in this section, or in any other artery in the leg (profunda femoris, tibial, peroneal, etc.), are prohibited by this protocol.

There are a number of variations in arterial anatomy that might be observed when patients randomized to a stent group undergo arteriography. The CLEVER Study protocol attempts to anticipate these variations and to standardize how each variant should be revascularized. The variations considered by the protocol include those with aortoiliac occlusive disease that is bilateral and symptomatic, bilateral but symptomatic

on only one side, with accompanying symptomatic ipsilateral femoropopliteal disease, and with accompanying contralateral femoropopliteal artery disease, symptomatic or asymptomatic.

4.4.3.1.1. Aortoiliac occlusive disease—bilaterally and symptomatic at baseline

If a study participant in a stent group has sufficient symptoms and findings to be eligible for the study on one side, and is found to have hemodynamically significant disease contralaterally at arteriography (50% diameter stenosis by digital caliper measurement) in the iliac atery(ies) that is also symptomatic but perhaps not meeting eligibility criteria for that leg only, stenting of the contralateral stenose(s) or occlusions should be done as well, either at that time or by staged procedure separated by no more than 30 days.

4.4.3.1.1.1. With femoropopliteal occlusive disease

If symptomatic atherosclerotic lesions at least 50% by diameter on visual estimate are noted in the femoropopliteal segment, and are amenable to balloon angioplasty (AHA category 1 lesions[77], defined as focal, concentric, noncalcified stenosis <3 cm in length) in either symptomatic leg, they may be treated using balloon angioplasty with selective stenting reserved for unsuccessful angioplasty as described in section 4.4.3. Femoropopliteal lesions that do not conform to AHA category 1 should not be dilated with balloon angioplasty or stents, nor should lesions in the tibial or peroneal arteries.

4.4.3.1.2. Aortoiliac occlusive disease—bilateral, with only one side symptomatic at baseline:

With regard to asymptomatic hemodynamically significant aortoiliac lesions on the contralateral side, no stenting should be done on the contralateral, asymptomatic side initially. If the contralateral leg remains asymptomatic during follow-up, no stenting of the contralateral lesion is permitted. For those stented unilaterally with known hemodynamically significant aortoiliac insufficiency on the contralateral side who report contralateral symptoms after successful stenting at any time during the study, contralateral stent placement it should be done within 30 days. For those stented unilaterally without hemodynamically significant aortoiliac insufficiency on the contralateral side during the baseline arteriographic study who report contralateral symptoms after successful stenting at any time during the study, noninvasive testing as described in the eligibility criteria will be required and if they meet eligibility for significant aortoiliac insufficiency on the contralateral side, they should undergo arteriography. If hemodynamically significant aortoiliac insufficiency is confirmed then stent placement should be done within 30 days.

4.4.3.1.2.1 With femoropopliteal occlusive disease

If atherosclerotic lesions at least 50% stenotic by visual estimate are noted in the femoropopliteal segment and are amenable to balloon angioplasty (AHA category 1 lesions[77], defined as focal, concentric, noncalcified stenosis <3 cm in length) in the

symptomatic leg they may be treated using balloon angioplasty with selective stenting reserved for unsuccessful angioplasty as described in section 4.4.3. Femoropopliteal lesions that do not conform to AHA category 1 should not be dilated with angioplasty or stents, nor should lesions in the tibial or peroneal arteries. If the contralateral limb develops claudication symptoms during the follow-up period and will therefore require iliac artery stenting or angioplasty in the femoropopliteal segment, the procedures should be done at the same time, or staged within 30 days.

4.4.3.1.3. Aortoiliac occlusive disease, unilateral at baseline

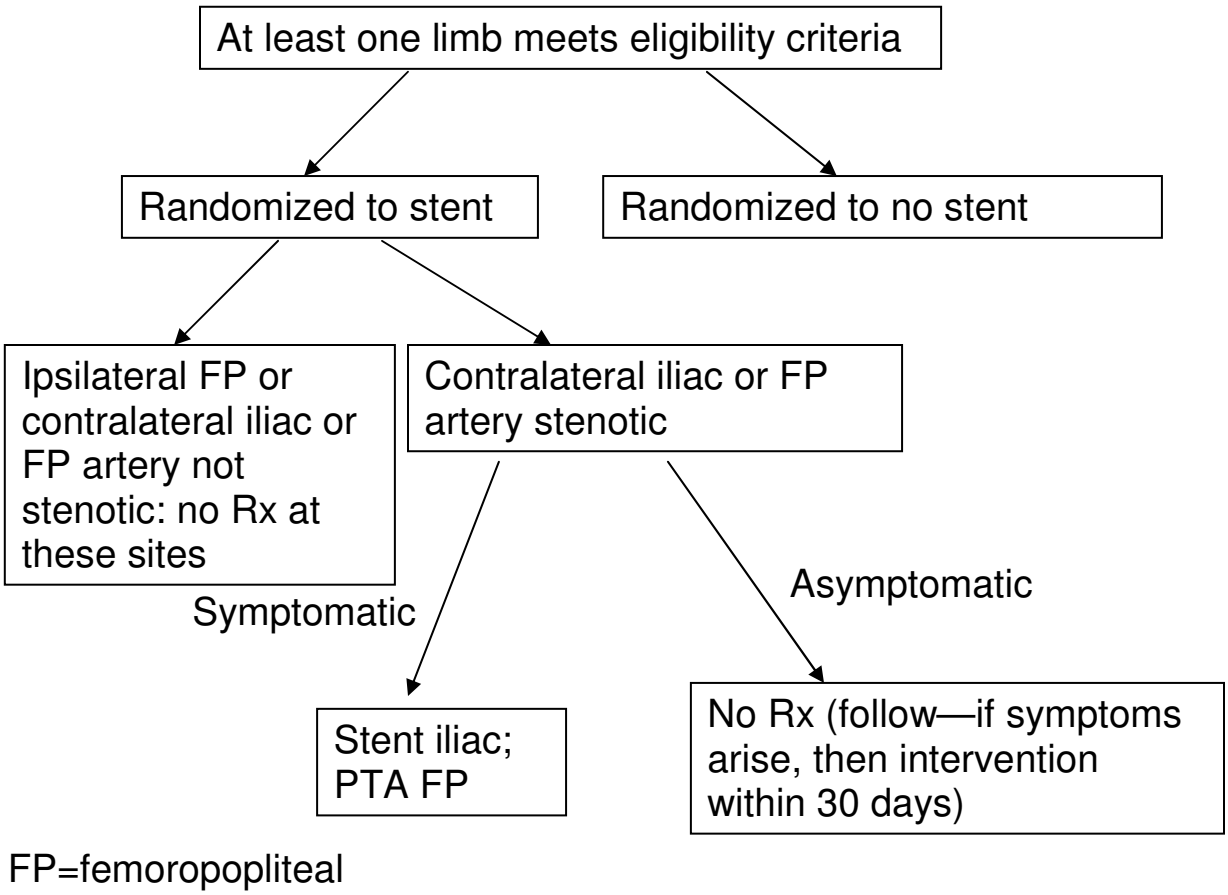
4.4.3.1.3.1. With ipsilateral femoropopliteal artery occlusive disease:

If atherosclerotic lesions with at least 50% diameter stenosis are noted in the femoropopliteal segment and are amenable to balloon angioplasty (AHA category 1 lesions[77], defined as focal, concentric, noncalcified stenosis <3 cm in length), they should be treated using balloon angioplasty with selective stenting reserved for unsuccessful angioplasty as described in section 4.4.3. Femoropopliteal lesions that do not conform to AHA category 1 should not be dilated with angioplasty or stents, nor should lesions in the tibial or peroneal arteries.

4.4.3.1.3.2. With contralateral femoropopliteal occlusive disease, symptomatic or asymptomatic:

For asymptomatic hemodynamically significant femoropopliteal lesions on the contralateral side of a symptomatic iliac artery lesion, no revascularization should be done in the femoropopliteal artery at the time of the study procedure. If the contralateral leg remains asymptomatic during follow-up, no interventional treatment of the contralateral lesion is permitted. For those stented unilaterally with known hemodynamically significant femoropopliteal artery disease on the contralateral side who report contralateral symptoms at any time during the study, if atherosclerotic lesions with at least 50% diameter stenosis are noted in the femoropopliteal segment that are amendable to balloon angioplasty (AHA category 1 lesion[3], defined as focal, concentric, noncalcified stenosis less than 3 cm in length), treatment using balloon angioplasty of the contralateral femoropopliteal artery should be performed within 30 days. For those subjects stented unilaterally WITHOUT hemodynamically significant femoropopliteal artery disease on the contralateral side during the baseline arteriographic study, and who subsequently report contralateral symptoms after successful stenting at any time during the study, diagnostic testing should be done, and if hemodynamically significant ischemia is confirmed, then balloon angioplasty should be done within 30 days if atherosclerotic lesions with at least 50% diameter stenosis are noted in the femoropopliteal segment that are amenable to balloon angioplasty (AHA categry 1 lesions[3], defined as focal, concentric, noncalcified stenosis less than 3 cm in length).

Figure 2: Treatment Algorithm for Participants with Femoropopliteal and/or Contralateral Iliac Stenosis



4.4.3.1.4 Aortoiliac Stent Procedure

Patients with total aortoiliac obstruction should not undergo attempted revascularization. Therefore, if the aorta is occluded from the renals through to the aortic bifurcation, with or without iliac artery disease, revascularization should not be attempted. Patients who are found to have total aortic occlusion will remain in their assigned treatment group. Focal aortic lesions, occlusions or stenoses, and total iliac (common and external iliac artery) occlusions or stenoses should be treated. Participants who have mild or no aortoiliac obstruction by angiography and catheter pressure measurements should not undergo stent placement.

Stent length should be chosen to match the length of the hemodynamically significant lesion, and to cover any plaque that would narrow the contiguous artery more than 20% by diameter compared with its expected diameter. Pelvic arteriography should be performed with a marker catheter in place. No more than two stents should be used for each flow-limiting lesion.

Revascularization will be performed with self-expandable or balloon-expanding stents. Balloon-expanding stents will be indicated for focal ($\leq$3 cm long), ostial, eccentric, or heavily-calcified lesions, whereas self-expanding stents will be used for

lengthy lesions (>3cm) or concentric nonostial stenoses[69]. Stent lengths will be chosen to match the length of hemodynamically-significant plaque, which itself must be ≥50% by diameter. No more than 2 stents can be used per stenotic lesion. When multiple stents are used to treat adjacent arterial lesions or segments, they must be overlapped by at least 5 mm but not more than 15 mm, or they can be placed noncontiguously separated by at least 5 mm. Stents must be dilated to increase the vessel diameter of the diseased segment to approximately 100% of the non-diseased contiguous segment, or of the diameter of the contralateral artery if the entire artery is involved.

Use of adjunctive intraprocedural medications such as heparin, aspirin, or clopidogrel, are utilized at the discretion of the interventionalist. Technical endpoints for the stent procedure are a reduction in the mean trans-stenotic gradient to 5 mm Hg or less with <30% stenosis by angiography. If atherosclerotic lesions are noted on a symptomatic side in the femoropopliteal segment that are amenable to balloon angioplasty (AHA category 1 lesions[77], defined as focal, concentric, noncalcified stenosis <3 cm in length) they should undergo intervention at the same or subsequent procedure. More extensive femoropopliteal lesions should not be dilated because they can be technically difficult, can be associated with increased complication rates, and have lower long-term patency. Also, the in patients with significant aortoiliac insufficiency even long-segment occlusion of the femoropopliteal segment is usually well-tolerated after revascularization of the aortoiliac obstruction. Tibial or peroneal artery disease usually is not symptomatically important in patients with claudication and will not be dilated or stented for the same reasons. Patients with total aortoiliac obstruction not undergo attempted revascularization. Therefore, if the aorta is occluded from the renals through to the aortic bifurcation, with or without iliac artery disease, revascularization should not be attempted. Focal aortic lesions, occlusions or stenoses, and total iliac (common and external iliac artery) occlusions or stenoses should be treated. Patients who are found to have total aortic occlusion will remain in their assigned treatment group.

All interventions must be performed by percutaneous, needle access (Seldinger) methods. Vascular access by surgical exposure of the artery is a protocol violation.

eCRFs will capture arterial segment treated, approximate lesion length, number and type of stent(s), and maximal stent and balloon diameters. Images and pressure tracings from all stent procedures will be submitted to the Revascularization Committee to review adherence to these methods.

Study participants in the stent group who are found to have restenosis during clinical follow-up or during study follow-up should be reintervened upon according to the standard of care, and to prevent thrombotic occlusion of the stent and the attendant risk of acute limb ischemia. These re-interventions will not interrupt the regular scheduled follow-up visits, except that subjects should not undergo treadmill testing until they have recovered from any invasive procedure.

After revascularization is completed, following removal of arterial access, ankle-brachial indexes must be obtained to serve as a baseline for comparison to follow-up measurements.

4.5. FOLLOW-UP VISIT AND SCHEDULE

[Note: All study participants enrolled into the discontinued treatment group "Stent+Supervised Exercise" are to be followed the same as any other participant enrolled in any other treatment group.]

4.5.1 Monthly Contact (all subjects)

All participants in this study will receive monthly telephone contact in order to promote retention in the study. Refer to the Manual of Operations for the phone call script and instructions for recording medication compliance. During that call, the research coordinator will:

1. Keep the patient engaged and enthusiastic about the study to increase subject retention.

2. Ask general medical questions concerning the patient's condition, changes in cilostazol dose, and probe for any adverse events, repeat procedures or repeat hospitalizations experienced by the study subject. Use open-ended questions to elicit adverse events, such as: "How has your health been since the last visit?"

3. Inquire about any progression of symptoms to limb-threatening category (Rutherford II or III). If subjects report symptoms or signs of limb threatening ischemia, the principal investigator should be consulted to perform a physical examination, and if limb-threatening ischemia is present, the participant will be referred for consideration of revascularization and will be scheduled for a study termination data collection visit, including graded treadmill test, if the patient remains ambulatory.

4. Inquire if the patient has entered any supervised exercise program (for patients randomized to OMC or Stent treatment groups).

5. Remind participants about their next visit date, thank them for their continued participation in the study, and answer subject's questions during this call.

4.5.2 Quarterly Contact (all subjects)

Every three (3) months subjects will return to the study site for a brief study visit and re-supply of Cilastozol medication.

During that visit, the research coordinator will:

1. Try to keep the patient engaged and enthusiastic about the study to increase subject retention.

2. Ask general medical questions concerning the patient's condition and probe for any adverse events, repeat procedures or repeat hospitalizations experienced by the study subject. Use open-ended questions to elicit adverse events, such as: "How has your health been since our last call or visit?"

3. Collect patient diaries specifically designed to capture outpatient resource utilization, enter pertinent data to electronic case-report forms, and distribute new diaries for next 3 month interval.

4. Record number of returned cilostazol tablets for compliance.

5. Inquire about any change in cilostazol dose and enter into eCRF if changed since the prior visit

6. Inquire about any progression of symptoms to limb-threatening category (Rutherford II or III). If subjects report symptoms or signs of limb threatening ischemia, the principal investigator should be consulted to perform a physical examination, and if limb-threatening ischemia is present, the participant will be referred for consideration of revascularization and will be scheduled for a study termination data collection visit, including graded treadmill test, if the patient remains ambulatory.

7. Remind participants about their next visit date, thank them for their continued participation in the study, and answer subject's questions during this call.

4.5.3 Additional procedures: Subjects Randomized to Supervised Exercise Training/ Adherence to Physical Activity Activities Group

Months 1 to 6

Subjects randomized to receive exercise supervision will report three times weekly for months 1-6 to receive their supervised exercise intervention, as described in Appendix E. Supervised exercise training sessions end at the 6 month endpoint determination treadmill test.

1. The subject's individual regimen will be developed by the Exercise Rehabilitation staff locally according to the algorithm in the Exercise Training

Manual of Operating Procedures. The coordinator will provide the initial exercise prescription to the Exercise Rehabilitation staff, which is based upon the baseline Gardner Treadmill tests (initial exercise prescription in Appendix E).

2. Record
   a. date of attendance at session
   b. for each exercise bout,
      i. start time of exercise
      ii. finish time
      iii. duration until claudication onset
      iv. duration until "moderate" (level 4) claudication (stop exercise)
      v. duration of rest after exercise
   c. treadmill grade that day
   d. treadmill speed
   e. subject's time spent in travel to and from the exercise center.

3. Complete eCRF within 48 hours for the Exercise Training Committee's weekly review. The Exercise Training Committee will confirm appropriate prescription and communicate with the site research coordinator and/or Exercise Rehabilitation staff to advance the exercise program according to methods outlined in the Exercise Training Appendix E.

4. At month 5, the Health Education Counselor (HEC) from the study will mail a packet of information to begin the transition to the maintenance phase of the program. This packet will contain the Exercise Logs, physical activity tip sheets, and the name, and contact information of their Health Education Counselor (HEC).

5. In Month 5, the HEC will make contact with the participant to introduce him/herself, ask any questions and to set up a convenient day/time for the call the subsequent month.

Month 5 through 18

The goal for the 14-month program (months 5 though 18) is to maintain the amount of walking per the exercise prescription provided at the end of the supervised exercise program. Contact between the Health Educator Counselor (HEC) and the study participant will begin during the fifth month of supervised exercise training.

1. The HEC will call the participant once each month and discuss the process that will occur after the completion of supervised exercise training and the reasons for it (Month 5 and 6 only).
2. Calls with the HEC will be conducted twice monthly for months 7-12.
3. During the final six months (Months 13-18), the calls will tapered to once a month to help patients to recover from any lapses from exercise and resume regular exercise.

The detailed Adherence to Physical Activity Program and Telephone Based Behavioral Change Components are outlined in the Adherence to Physical Activity Protocol (Appendix E).

4.6 ENDPOINT ASSESSMENT VISITS-- MONTH 6 AND MONTH 18 (± 2 WEEKS) AND PRIOR TO CROSS-OVER OR STUDY TERMINATION

7 Days Prior to Visit

Research staff will call subject and remind them about their pending visit..

Day of Visit

Every patient will have repeated measures as performed at the baseline visit and includes:

1. A brief physical exam and history performed with height/weight/waist circumference measured and focused upon limb threatening ischemia.
2. Blood pressure (resting systolic and diastolic).
3. Fasting state (8 hours) blood testing for lipid profile (HDL, LDL, triglycerides), fibrinogen, C-reactive protein, glucose, creatinine, hemoglobin A1c (as outlined in the Manual of Operations).
4. Resting ankle-brachial index
5. Treadmill test (Gardner protocol as described in Appendix B), unless crossover status has been achieved.
6. Adverse events, repeat procedures and repeat hospitalizations.
7. Concomitant medication information (Refer to Appendix J for drugs in specific classes to be recorded.
8. Conduct pill count to assess subject compliance with cilastozol therapy.
9. Health-related quality of life (administered by the Economics and Quality of Life (EQOL) Core Lab)..
10. Medical care resource utilization for cost analysis.
11. Administer Independent Exercise Assessment. It is essential that subjects be asked about any independent exercise, whether formal or informal, performed with the intent to improve fitness and done 2 or more times per week for 20 minutes or more. Refer to Appendix K for assessment and instructions.
12. Administer the Walking Impairment Questionnaire (WIQ).
13. Provide pedometer log and instruct pedometer use over the next 7 days.

After treadmill and other endpoint data are collected, the study participant should be given a pedometer log and instructed to wear the pedometer for the next 7 consecutive days, all waking hours (except showering/bathing/swimming). Data entry in the pedometer log should be reviewed. After that time, they should return and provide the treadmill to the coordinator to record steps and log entries. No further supervised

exercise sessions should occur after the 6-month treadmill test and therefore the pedometer readings should represent community-based walking done by the participant. This should be completed within 2 weeks (14 days) of the 6 month treadmill test.

The physical examination will be focused on an assessment of the grade of limb ischemia in both lower extremities. If limb-threatening ischemia is present in either limb, the patient will be referred for appropriate revascularization. If limb-threatening ischemia is present in the study limb, the patient will be allowed to receive appropriate therapy as described in section 3.7, *Potential for Crossover Between Study Arms.*

Medical care resource usage data will be collected from the patient diaries and entered into the electronic case-report forms at the quarterly and at each of the 6- and 18-month follow-up visits by the research coordinator at the study site.

Ankle-brachial will be performed according to accepted standard techniques.. If the ankle-brachial index is >0.10 less than an immediate post-stent ABI, then further evaluation for restenosis should be done as according to section 3.5.2.

Baseline health utility (EuroQOL/EQ-5D) and health status/quality of life data (SF-12, WIQ, PAQ) will be collected by the research coordinator at the study site. Month 6 and month 18 follow-up utility and quality-of life data will be collected by the Quality of Life and Cost Effectiveness (QoL/CE) Core Lab in order to maximize compliance and ensure uniform assessment. Two weeks prior to each follow-up time point, the patient will be provided with a self-administered survey booklet and a stamped return envelope. Any patient who fails to return the survey by mail will be given the survey by telephone.

5.0 STUDY ENDPOINTS

5.1 EVENT ADJUDICATION

An independent Clinical Events Committee (CEC) will function within the DCC. The CEC is charged by the Study Chair to review and adjudicate all deaths that occur during the study and to adjudicate clinical study endpoints, including major complications, major adverse peripheral vascular events and progression of limb ischemia to limb-threatening status as this occurrence is a reason for sanctioned cross over to stent therapy. Preparation of event summaries by the DCC for review and adjudication by the CEC will be performed under the guidance of the HCRI Chief Medical Officer, Donald Cutlip, MD. The CEC will include a vascular surgeon and a peripheral vascular interventionalist in addition to cardiovascular specialists.

All adverse events will be submitted by the investigators and those determined to be related to study endpoints will be submitted to the Clinical Events Committee for adjudication. These include all major adverse peripheral events (MAPE). Submitted events will be reviewed initially by a nurse specialist to determine that the minimum data required for adjudication are available. The nurse specialist will also write a narrative summary of the event based on the eCRFs and source document data. CEC members will be blinded to study groups whenever possible. Adjudication will be performed at a group face-to-face meeting with adjudication by consensus. Additional data from eCRFs and source documents will also be available for review, but information from these documents will be provided by HCRI staff to avoid inadvertent unblinding of the CEC. It is anticipated that the CEC will meet approximately monthly to review accumulated events. Events will be monitored by the clinical nurse specialist and meetings may be more or less frequent depending on numbers of events and reporting needs. After review of the identified events by the Clinical Reviewer, support documentation for identified events will be obtained from the site and a summary will be written to describe the significant details of the event. These summaries, with appropriate support documentation, will be forwarded to (and used by) the physician members of the CEC to determine the occurrence of study endpoints according to pre-specified protocol definitions. The adjudicated results will be returned to the DCC and added to the DSMB database.

5.2 ASCERTAINMENT OF RESPONSE VARIABLES

Detailed methods for ascertainment of response variables are included in the DCC Manual of Operations for this study and are outlined in general below:

Maximum Walking Duration (MWD): The primary endpoint is the change in maximum walking duration (MWD) between baseline and 6 months between the stent group (ST) and the supervised exercise training (SE) groups. This endpoint, MWD, will be determined by the enrolling center research coordinator in conjunction with Exercise Testing Staff, both of whom having been specifically trained to accurately obtain this data using their own equipment at their site under the direction of Dr. William Hiatt and

the Colorado Prevention Center. Dr. Hiatt's team will travel to each site and train and evaluate their performance using a mock patient trained to commit common errors during administration of the exercise test.

Free-Living Daily Activity Levels: Free-living daily activity levels will be assessed using seven consecutive day pedometer readings at baseline and within 2 weeks of follow-up data collection intervals. Patients will receive a copy of instructions and will review the instructions for use of the pedometer with the research coordinator. Instructions will be to wear the pedometer as much as possible during all waking hours for 7 straight days. Patients will be asked to keep a daily log while wearing the pedometer to document the number of waking hours that the pedometer was worn and number it wasn't worn each day. This information will be recorded and adjustments made for the period of waking hours when the pedometer was worn for secondary analyses of pedometer data.

QoL/CE: Comparison in health utilities and health status questionnaire scores at 6 and 18 months among all treatment groups will be done using standard and validated questionnaires, analyzed according to standard techniques (Appendix C).

Body Mass Index: Training on accepted study method for measurement of height and weight will be done according to instructions provided by the stadiometer manufacturer.

Waist Circumference: Training on CLEVER waist circumference measurement methods, modified from NHANES III methods (Appendix H), will be done and certified. Each site will be required to have one investigator or research coordinator trained, and that person will be able to train subsequent people at the site to obtain this measurement.

Blood pressure: Systolic, diastolic, and pulse blood pressure measurements will be done in accordance with accepted standards published in JNC VII[78]. These will be reviewed prior to enrollment and at investigator meetings, and included in the manual of operations for this study.

Biochemical tests: Measurements of high-density lipoprotein, low-density lipoprotein, triglycerides, fibrinogen, C-reactive protein, and hemoglobin A1c will be standardized by performing them at a central location at the core biochemistry lab at the University of Minnesota, directed by Dr. Michael Steffes. Anonymous samples of blood will also be stored for possible biochemical and/or DNA tests in the future. The core biochemistry lab is accredited by the College of American Pathologists (CAP) and licensed by Health and Human Services under the Clinical Laboratory Improvement Amendments of 1988 (CLIA 88), and will use standard methods of performing these tests.

Major Adverse Peripheral Events: Peri-procedural (24 hour) and procedure-related (30 day) morbidity and mortality will be reported, as will long-term complications and worsening of clinical status by history and physical examination using electronic case report forms. Major adverse peripheral events will track: stent thrombosis, clinically-

apparent distal embolization (loss of palpable or Doppler pulses, blue toe syndrome, livedo reticularis), acute limb ischemia, restenosis, arterial rupture, and acute renal failure.

Restenosis: Monitored long-term by monitoring ankle brachial index. Clinical status will be checked at each of the follow-up visits, including ABI measurements. Any decrease in ABI by >0.10 compared with post-stent ABI should initiate an evaluation for restenosis (see section 1.3.2 and 3.5.2), unless an imaging study indicates patency of the stent without stenoses within or contiguous with the stent ends. If no other lesion can be found to explain the decrease in the ABI, pressure gradients will be performed across the stented arterial segment. Any target site revascularization done will also be reported, as will revascularization or other surgical procedures done to address any complication of intervention.

Rate of Major Complications: Defined as any occurrence of death, myocardial infarction, amputation of the target limb (limb treated in this study), or occurrence of Critical Limb Ischemia or repeat Target Limb Revascularization (TLiR). Data used to determine the occurrence of these events include cardiac enzymes (preferably CK and CK-MB tests for index procedure related assessment), surgical or catheterization laboratory reports, results of duplex ultrasound testing, and death records/certificate or autopsy report (if performed).

6.0 STATISTICAL ANALYSIS PLAN

The proposed randomized trial is designed for the primary aim of contrasting three arms for three pair-wise comparisons at two time intervals (the primary time point is the 6 month time point). The principal comparison will be to assess if the stent treatment is superior to the supervised exercise training arm at 6 months with respect to change in MWD. For sample size purposes, we will power the study to detect an anticipated 30% difference in change in MWD between stent placement and supervised exercise training at 6 months. As will be shown below, the resulting sample size yields adequate power to detect the anticipated difference between stent and optimal medical care, and between supervised exercise training and optimal medical care at 6 months (secondary comparisons of stent plus supervised exercise arm versus stent only arm, exercise only arm, and optimal medical care with respect to change in MWD will also be carried out; given their secondary nature, the study is not specifically powered for these comparisons, though it is anticipated there is more than enough power for at least the comparison of stent plus exercise arm with optimal medical care). These assumptions are based upon three studies of supervised exercise training that utilized the Hiatt protocol[30,52,79] for exercise testing and unpublished data cited previously (also based upon the Hiatt protocol performed pre- and post-stent placement). We are using the more widely-used Gardner protocol for this study and expect that the treatment effect will be similar whether measured on the Gardner or Hiatt treadmill test protocols[101]. The results for supervised exercise training using the Hiatt protocol exercise test, as well as our pilot data for stent patients, follow:

TABLE 5: PUBLISHED DATA FOR SUPERVISED EXERCISE TESTING USING A GRADED (HIATT) TREADMILL TEST, AND PRELIMINARY DATA AFTER STENT PLACEMENT USING THE SAME EXERCISE PROTOCOL.

Reference	"N"	Therapy	Entry MWD	Exit MWD	%Increase
Regensteiner, Meyer, 1997	10	supervised exercise	4.6	10.9	137%
Hiatt, Regensteiner, 1990	10	supervised exercise	6.4	13.9	117%
EXERCISE AVERAGE	**20**	**supervised exercise**	**5.5**	**12.4**	**125%**
Murphy Preliminary data	**26**	**aortoiliac stent**	**3.3**	**8.7**	**164%**

We assumed a mean MWD of 5 minutes at baseline. This is an approximate average of the baseline MWD from the 3 prior studies in the table above, revised downward 10% due to the 11 minute baseline walking ability limit for study exclusion criterion.

6.1 SAMPLE SIZE CALCULATIONS

There are three treatment groups in this study: optimal medical care, supervised exercise, and stent.

For sample size calculations, we assume a standard deviation (s.d.) of the 6-month mean change in MWD scores of 3.8, which was the s.d. for Dr. Regensteiner's series of supervised exercise training patients previously published[52]. This is similar to the standard deviation of the mean change scores of 3.9 in the stent preliminary data presented in the "Preliminary Data" section.

The principal comparison on which sample size estimates are based for this study is ST (stent only) vs. SE (supervised exercise only). A 125% increase (as noted in prior reports) from baseline for mean MWD (baseline MWD assumed to be 5 minutes) in the supervised exercise training group would result in a mean MWD on exit (6 months) of 11.3 minutes. Given the desired and anticipated difference in treatment effect between the two groups of 30% improvement in the stent group (absolute increase of 164%), an MWD of 13.2 minutes on the Gardner protocol on exit for the stent group is needed to meet this threshold.

Using one-way analysis of variance (ANOVA), a sample size of 63 for each of the Stent and Supervised Exercise groups yields 80% power to detect a difference in mean change scores of -1.9 (the difference between supervised exercise group mean change score of 6.3 and stent group mean change score of 8.2) assuming that the common standard deviation is 3.8 (power is calculated using the PASS 2005 software (NCSS, Kaysville, UT). In other words, at a two-sided 0.05 level of significance, under the above assumptions, a sample size of 63 per group yields 80% power to reject H_o: $\mu_{ST} = \mu_{SE}$ in favor of H_a: $\mu_{ST} \neq \mu_{SE}$ where μ_{ST} is the mean change in MWD at 6 months for the stent group and μ_{SE} is the mean change in MWD at 6 months for the supervised exercise therapy group. Rejection of the null hypothesis will signify that the mean walking duration (MWD) between the groups is significantly different. To allow for premature withdrawals by 6 months, the sample will be inflated by 30% to 84 patients randomized into each of the stent only and supervised exercise only groups (further details on anticipated withdrawals are given below).

For the remaining treatment group (optimal medical care), fewer participants will be enrolled. Using half as many patients in the OMC group, or 32 evaluable patients (42 randomized), results in 99+% power for the ST vs OMC comparison, and 98% power for the SE vs OMC comparison (assuming a 60% improvement compared with baseline MWD in the OMC group, which is the upper end of the range expected if none were taking cilostazol at baseline and all were at 6 months, and if the treadmill test were non-graded, so these assumptions are statistically conservative). Thus, there is 97% power to detect a difference between both (a) stent and optimal medical care; and (b) supervised exercise therapy and optimal medical care at a one-sided 0.025 level of significance.

The statistical analysis assessing the superiority of stent will be carried out in a sequential manner as follows:

First, comparisons of (i) stent versus medical care and (ii) exercise versus medical care on mean change in MWD will *each* be carried out at a one-sided 0.025 level of significance (the direction of the alternative hypothesis in each case is: OMC has lower mean increase in MWD than the comparator group) using pairwise analysis of covariance models adjusting for study site, baseline MWD and baseline cilostazol use (yes/no). The comparison of exercise versus medical care is to assess if the sample is the representative of the population. If *both* treatment differences are found to be significant (there is 97% power for this to happen as discussed above), then the analysis will proceed to assessing the significance of the difference between stent versus exercise at a two-sided 0.05 level of significance using pairwise analysis of covariance models adjusting for the same covariates as above. Thus the total study sample size of evaluable patients is 160. In order to evaluate 160 subjects at the end of the study, this sample size at the beginning of this study was increased by 30% to account for:

1. Deaths,
2. Subject cross-over,
3. Subjects lost to follow up,
4. Study subjects in all treatment groups who are false positive by screening criteria for significant aortoiliac PAD, and
5. Patients in the aortoiliac stent group who can not be revascularized with stents

[N.B. In February, 2010, the Data Safety and Monitoring Board reviewed unblended interim data and determined that, based on conditional power, enrollment could be terminated in December, 2010, with a scientific valid result.]

There is a possibility that if the effect of cilostazol use as required in this study, which was not used routinely in patients in whom preliminary data was collected, has an interaction with a treatment group that these estimates may not apply. That is, if the cilostazol effect is greater in stent group participants than supervised exercise training participants the power of the study would increase. If the cilostazol effect is greater in supervised exercise training participants that stent participants, power would decrease. For example, if cilostazol improves the MWD change score in supervised exercise training patients by 5% or 10% without any impact on MWD for stent patients, power would be reduced to 64% and 46%, respectively.

6.2 ANALYSIS POPULATIONS AND ENDPOINT ANALYSES

While an analysis on the evaluable patients will be performed, the primary analysis will be based upon on intention to treat (e.g., all randomized patients).

Approaches to impute missing data and post-cross-over data are discussed below. False positive participants will be analyzed as randomized.

For the secondary endpoints, in our preliminary data set of 35 individuals with claudication we observed physical component scale score of the SF-36 quality of life questionnaire of 35±8 at baseline, increasing to 43±9 at the last follow-up interval, with a standard deviation (SD) of the change score of 9.3. Exercise training has been shown to increase the SF-36 physical component summary scale from 35±7 to 39±9 at 6 months (SD of change score unavailable)[55]. Thus a sample size of 101 in each group would be required to have 80% power to detect a difference in mean change scores of 3.7 (the difference between stent group change score of 7.7 and exercise training group mean change score of 4), assuming that the common standard deviation is 9.3 using a two group t-test with a 0.05 two-sided significance level. With 63 evaluable patients in ST and SE treatment groups, there would be 60% power to detect a difference in mean change scores of the physical component scale between the stent and exercise groups based on these assumptions.

The study is not powered to detect differences between various exploratory endpoints, including: changes in blood pressure (systolic, diastolic, pulse pressure), body mass index, or biochemical tests. Thus we expect that we are potentially underpowered to detect differences in many of these surrogate measures of cardiovascular disease risk between our treatment groups. These measures will be collected because the opportunity to collect these data is presented by this trial and they contribute little to the overall costs of this study. These results may be an interesting aspect of this study from a purely hypothesis-generating perspective. For both the secondary and tertiary exploratory endpoints, if a difference exists in the population, we expect to at least see a trend in results with 63 subjects per group, if not statistical significance.

The DCC will monitor “missingness” assumptions in the protocol, and if the assumptions turn out to not be accurate, we will attempt to adjust the sample size accordingly.

6.3 ANALYSIS OF STUDY AIMS

All statistical analyses will be performed using SAS for Windows (version 8.1 or higher) or other widely accepted statistical or graphical software. Patient data listings and tabular and graphical presentations of results will be provided. All clinically relevant baseline variables will be tabulated and compared between subjects assigned the stent, supervised exercise training or optimal medical care arm of the trial.

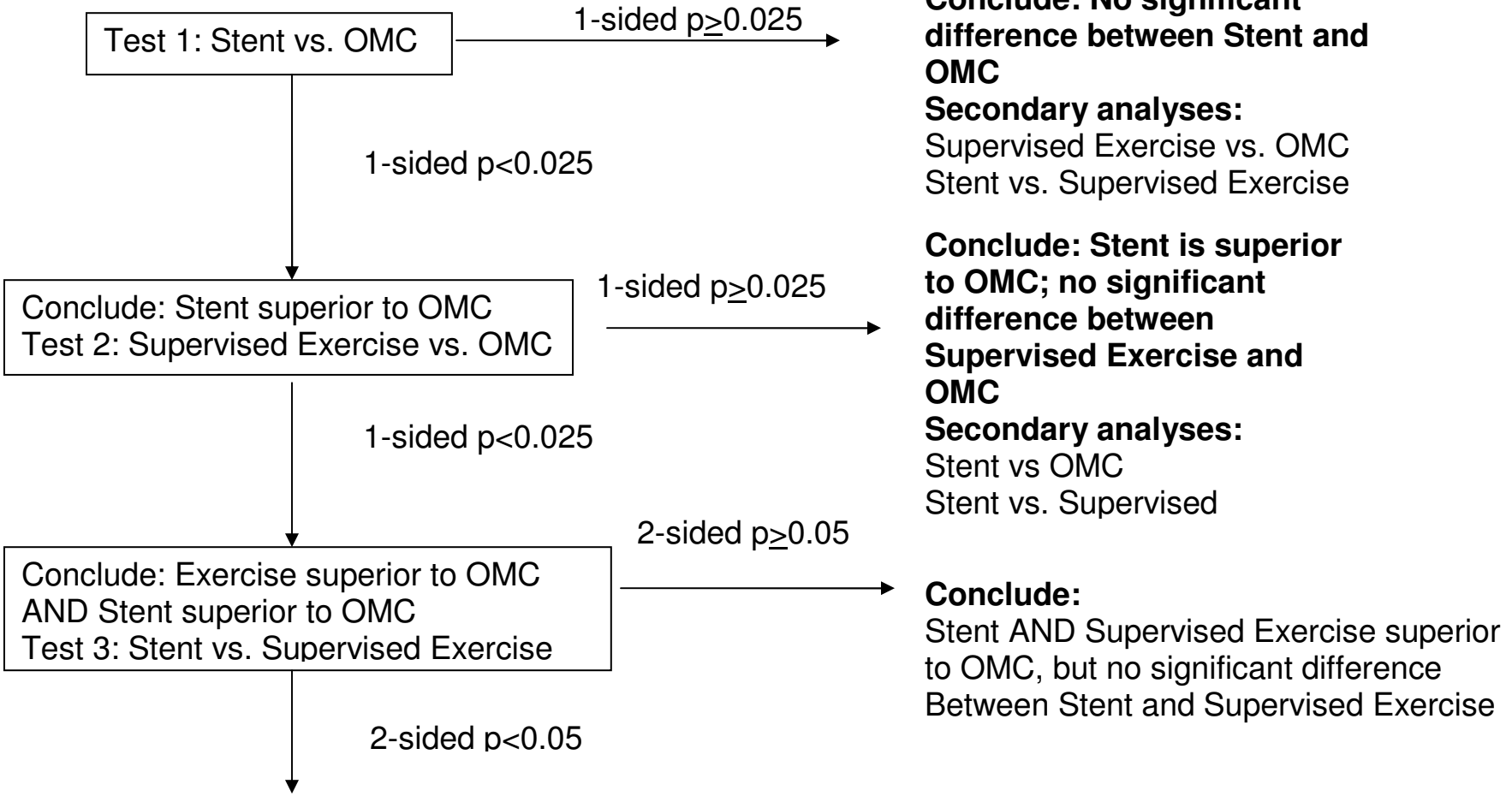
6.3.1 Primary Aim (Aim 1)

To test the primary hypothesis that percutaneous aortoiliac stent improves maximum walking duration (MWD) better than supervised exercise training in patients with claudication due to aortoiliac peripheral arterial disease (PAD) at 6

months. This will be done by comparing treatments on the change in MWD between baseline and 6 months after enrollment, or within 7 days after completion of 6 months of supervised exercise training for those enrolled in that treatment group.

Statistical Analysis: Descriptive statistics (sample size, mean, median, standard deviation, minimum, maximum) of MWD at baseline and at 6-months, and of the change in MWD from baseline to 6-months, will be presented by treatment group. Pairwise treatment contrasts will be used to assess the significance of the difference between (a) stent versus medical care, (b) supervised exercise versus medical care, and (c) supervised exercise versus stent on the change from baseline MWD at 6-months. Each pairwise contrast will be carried out one at a time in the order above, using analysis of covariance, adjusting for baseline MWD, baseline cilostazol use (yes/no), and study region. As discussed above, a one-sided 0.025 level of significance will be used for each of comparisons (a) and (b); if *both* (a) and (b) comparisons are significant, analysis will proceed to comparison (c) at the two-sided 0.05 level, the primary comparison of interest. The following flowchart outlines the order and significance levels to be used for each pairwise test, and the conclusions that can be made from each test. Following the algorithm in this flowchart, the overall significance level for the study (the chance of at least one false positive finding) is controlled at the two-sided 0.05 level.

Figure 3: Sequential Hypothesis Testing Algorithm



Conclude: 1. Stent AND Supervised Exercise are superior to OMC
2. Stent is superior to Supervised Exercise OR Supervised Exercise is superior to Stent

The sequential analysis of the primary endpoint is further explained in the following tables:

Scenario 1: All comparisons significant

Test	Finding	Interpretation
Stent vs. OMC	1 sided p<0.025	Stent is considered superior to OMC; Supervised exercise is considered superior to OMC. Stent considered significantly different from supervised exercise. All results considered primary study findings.
Supervised Exercise vs OMC	1 sided p<0.025	
Stent vs. Supervised Exercise	2 sided p<0.05	

Scenario 2: First comparison (Stent vs. OMC) and second comparison (Supervised Exercise vs. OMC) are significant; Stent vs. Supervised Exercise is not significant

Test	Finding	Interpretation
Stent vs. OMC	1 sided p<0.025	Stent is considered superior to OMC; Supervised exercise is considered to be superior to OMC. Stent not considered significantly different from supervised exercise. All results considered primary study findings.
Supervised Exercise vs OMC	1 sided p<0.025	
Stent vs. Supervised Exercise	2 sided p>0.05 *(NS)*	

Scenario 3: First comparison (Stent vs. OMC) is significant, but the second (Supervised Exercise vs. OMC) is not

Test	Finding	Interpretation
Stent vs. OMC	1 sided p<0.025	Similar to scenario 2, all the alpha is assigned to all three comparisons, so if any (or both) of the first two comparisons are negative, the third comparison (ST vs SE) is presented as a secondary finding *without* adjustments for multiple comparisons
Supervised Exercise vs OMC	1 sided p>0.025 *(NS)*	
Stent vs. Supervised Exercise	2 sided p<0.05	

Scenario 4: First comparison (Stent vs. OMC) is not significant

Test	Finding	Interpretation
Stent vs. OMC	1 sided p>0.025 *(NS)*	Stent is not considered superior to OMC. This is considered the primary study finding. Primary pariwise analysis stops due to sequential testing approach. The comparisons of Supervised Exercise vs. OMC, and Stent vs. Supervised Exercise are carried out as secondary analyses.
Supervised Exercise vs OMC	Not carried out as a primary analysis, due to sequential design	
Stent vs. Supervised Exercise	Not carried out as a primary analysis, due to sequential design	

This sequential approach keeps the overall significance level (probability of at least one false positive finding) at a two-sided 0.05 level across the three comparisons. Assessments of treatment-by-baseline MWD, treatment-by-baseline cilostazol use and treatment-by-region interactions will be made at the 0.10 level of significance. For each interaction assessment, one interaction ANCOVA model will be used, with only the three main treatment groups (ST, SE, OMC) of interest in the interaction model. Any significant interaction deemed to be qualitative in nature (i.e., treatment effect differs in direction across regions and/or baseline values) will be further inspected by subgroup analysis and plots to assess the cause of the interaction. Prior to conducting ANCOVA, the distribution of change in MWD will be inspected and tested for departure from normality. If the assumption of normality is violated, non-parametric regression on ranks of MWD will be performed instead of analysis of covariance.

Patterns of MWD "missingness" will be reviewed. The analyses will assess whether or not Month 6 MWD are missing completely at random (MCAR). Missing data are MCAR if the missingness is unrelated to treatment group, MWD prior to dropout, and post-dropout unobserved MWD. If the coefficients for observed MWD and for the interactions containing observed MWD are not significant, the data are probably MCAR. Otherwise, the missing data are either missing at random (MAR) or missing not at random (MNAR). Missing MWD data are MAR if they depend only on MWD observed prior to dropout and not on any unobserved MWD that would have been collected after dropout. Missing MWD data are MNAR if they depend on unobserved MWD data. Various analyses will be performed assessing treatment difference in the presence of missing values, and include:

1. Analysis on all randomized patients (primary analysis); patients are analyzed as randomized (intent-to-treat approach). Patients with missing data due to death will have MWD imputed as zero. For data missing due to other causes multiple imputation will be used matching on the covariates of gender, age, comorbid conditions, body mass index (BMI), waist circumference, blood pressure (systolic, diastolic, and pulse pressure), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, fibrinogen, C-reactive protein, baseline MWD and hemoglobin A1c from patients in the same treatment group. Cross-over subjects from supervised exercise training or optimal medical care to stent will be analyzed as randomized using the observation obtained after the cross-over and closest to the scheduled visit. Stent patients not false positive for PAD and who cross-over to supervised exercise training (expected to occur minimally) will be analyzed as randomized and will have post-cross-over data multiply imputed from non-cross-over stent patients in a similar manner as discussed above for missing data. If for these patients, imputed data yields, on average, higher MWD post-cross-over than last observation (prior to cross-over) carried forward (LOCF), imputation will instead occur using LOCF. False positive screenings will be analyzed as randomized. ANCOVA or non-parametric regression on ranks will be used depending on the normality of the data.

2. Complete case analysis (all randomized patients excluding dropouts and deaths) will be performed. Cross-over and false positives subjects will be analyzed as discussed in the previous paragraph (and will be analyzed as randomized).

3. Analysis of evaluable patients excludes dropouts, deaths, cross-overs, and false positives. Complete case analysis of participants with 6-month MWD and is presented for completeness only. It is unlikely the results generated here represent the true treatment effect.

Interim Analysis: After approximately 50% of the patients have enrolled and completed 6-month follow-up, interim pairwise contrasts will be performed

(ST vs. OMC, SE vs. OMC, and ST vs. SE) using the pairwise ANCOVA or non-parametric regression methodology discussed above and will be reviewed by only the independent Data Safety Monitoring Board and not by anyone involved in the design, conduct, data management or final statistical analysis of CLEVER. The two-sided O'Brien-Fleming significance levels to be used will be 0.00306 at the interim analysis and 0.049 at the final analysis for the comparison of stent versus exercise; one-sided O'Brien –Fleming significance levels for the comparison of stent and exercise versus medical care will be set to 0.00153 and 0.0245 at the interim and final analysis respectively (overall power still remains at 80% with 63 subjects per group in the presence of this interim analysis). The DSMB may recommend stopping the study early if (a) the interim sequential testing yields a two-sided p-values below 0.00306 for the comparison of stent with exercise; *and* (b) the comparison of each of stent and exercise versus medical care yields a one-sided p-value below 0.00153 at the interim analysis. If the DSMB decides to continue the study, the conditional power for detecting a significant difference between stent and exercise by the end of the study will be calculated, based on the results of the interim point estimate of the treatment difference. This conditional power will be calculated under the assumption the true population treatment difference is the same as the point estimate of the treatment difference seen in this interim analysis. If this conditional power is below 80%, the DSMB may recommend increasing the sample size in order to increase the conditional power to 80%, using the approach discussed in Denne[102] that keeps the overall two-sided significance level at 0.05 in the presence of any sample size increase.

6.3.2. Secondary Aims

Aim 2: Pair-wise comparisons of change in MWD between stent vs. optimal medical care and between supervised exercise training vs. optimal medical care at 6 months.

Statistical Analysis: Though this is a secondary aim, these comparisons will be performed in a pairwise manner, one comparison at a time, prior to assessment of the primary aim (and using the same ANCOVA or nonparametric regression methodology as that used for the primary aim) in order to (a) ensure the sample is representative of the population by showing supervised exercise training yields more improvement in MWD than does medical care; and (b) evaluate the absolute efficacy of stent prior to assessing its relative efficacy versus supervised exercise training. Each pairwise comparison will be performed at a one-sided 0.025 level of significance, and only if both are significant will analysis on the primary aim continue, at a two-sided 0.05 level of significance.

Aim 3: To evaluate the mid-term durability of any treatment effect by performing pair-wise comparisons of change in MWD from baseline to 18 months between the treatment groups.

Statistical Analysis: Analyses as discussed above for 6 month MWD and change from baseline to 6 month MWD will be repeated (with the exception of interim analysis and sequential approach to assessing significance) on:

a. 18 month MWD,
b. change from baseline to 18 month MWD, and
c. change in MWD from 6-months to 18-months.

In addition, if the assumption of normality is not violated, longitudinal generalized estimating equation (GEE) ANCOVA with appropriate pairwise contrasts will be used to assess treatment difference over time in a pairwise manner (one GEE model per pairwise comparison and endpoint). The primary focus is on the comparison between stent and supervised exercise training, though the significance of the other comparisons will be assessed (each pairwise treatment comparison will be assessed using the 0.05 level of significance). The model will contain effects for treatment, time, baseline MWD, baseline cilostazol use and region. The outcome will be change from baseline in MWD. There will be multiple observations per patient (one for each post-baseline MWD measurement time point). The autoregressive correlation structure will be assumed for the multiple observations within subject. Analysis will also be performed using the compound symmetry assumption to assess the effect the correlation assumption has on the results. A comparison of the GEE model-based and empirical (robust) estimates will be carried out. In the longitudinal analysis, interaction of treatment effect (focusing on ST, SE and OMC groups) with time will be assessed to determine if any treatment effect seen is consistent across time. Longitudinal analysis will be supplemented with plots of MWD versus time for each treatment group. Missing data, cross-overs, and false positives will be handled as in Aim 1. However, an "available data" analysis will also be conducted and will include cross-overs and false-positives.

Aim 4: To evaluate free-living daily activity levels and determine if there is a treatment effect on this endpoint for any treatment group, comparing baseline values with those obtained at both follow up intervals (6 and 18 months) for each treatment group. This will be done by obtaining seven day electronic step activity at baseline, 6 months, and 18 months.

Statistical Analysis: With the exception of the sequential testing approach and the formal interim analysis, pairwise treatment group comparisons will be carried out on 6-month change scores using ANCOVA or non-parametric regression on ranks (one model per pairwise comparison), as discussed for MWD in Aims 1 through 3; analysis will be carried out on 18-month change from baseline data as discussed for MWD in Aim 4. Each comparison will be performed at the 0.05 level of significance. Participants will be required to wear the pedometer for most of 5 days, including at least one weekend day, during the 7 day interval or their data will not be included in the primary analysis of this

endpoint. If at least 5 days are included, including one weekend day, missing data will be imputed from their other performance.

Aim 5: Quality of Life (QoL): To examine treatment effects on patient-perceived physical health-related quality of life at 6 and 18 months, and specifically to see if improvement in QoL is greater after aortoiliac stent than supervised exercise training or optimal medical care.

Statistical Analysis: Analyses will be performed on individual item responses and on scale scores created from summing QOL item responses within various domains. The approach for analyzing each QOL item and scale will be similar to the approach used for the MWD discussed in Aims 1-3 above (with the exception of a formal interim analysis and the sequential testing).

The QoL end points will be the physical and mental component summary scores from the SF-12, the WIQ, and the PAQ summary score. Each of these summary scales will be scored using previously published methods.[4,6,25] As with the analysis of the primary end point, pairwise analysis of covariance (ANCOVA) or non-parametric regression on ranks will be used to assess the significance of the difference between (a) supervised exercise versus medical care, (b) stent versus medical care, and (c) stent versus exercise on the change from baseline to 6-months for each of the 4 summary scales. In these models, adjustments will be made for baseline MWD and region.

Exploratory comparisons will also be made comparing the stenting plus supervised exercise arm to the stenting alone and supervised exercise alone arms. These will be performed in analogous fashion to the others.

Change from baseline to 18 months will be evaluated in a secondary analysis to assess the durability of QoL changes associated with the different interventions.

Aim 6: Cost-Effectiveness (CE): To examine inpatient and outpatients costs associated with the three treatment strategies, and to put these costs in context of cost-benefit by calculating incremental cost-effectiveness ratios and cost effectiveness acceptability curves using health utility change in the denominator.

The unit of effectiveness for the cost-effectiveness study will be quality-adjusted life years, calculated according to standard methods[103]. Population-based health state utilities will be assessed directly for the CLEVER trial population using the Euro-QOL/EQ-5D[80], and will be incorporated directly into the analysis by multiplying each patient's utility by his or her survival duration during the assessment period. For example, the utility for months 0-6 will be the mean of the baseline and 6 month utility values, and for the 18 month analysis, the utility for months 6 through 18 will be the mean of the 6-month and 18 month values.

Medical care cost and resource utilization data will be collected for each study patient from the point of study intake through the 18-month follow-up visit. To facilitate analysis from a variety of potential perspectives, overall costs associated with peripheral artery disease will be calculated for three categories:

a. Direct medical costs: the cost of any inpatient care, outpatient care (including outpatient procedures, diagnostic testing, exercise training, and prescriptions), and emergency room visits.
b. Custodial and chronic care costs: the cost of nursing home care, rehabilitation services (inpatient or outpatient), visiting nurses, home health aides, and other non-physician health professionals.
c. Indirect costs: productivity costs associated with time away from work (lost wages) for other family members.

As recently recommended by the National Panel on Cost-Effectiveness in Health and Medicine, costs of lost work or other earnings on the part of the patient will be tabulated as well, but not included in the calculation of medical care costs for the primary cost-effectiveness analysis[81].

The primary economic endpoint will be total medical care costs at 6 months. A secondary economic endpoint will be total medical care costs at 18 months. These will be tabulated and reported for each of the three study groups. Cost and quality adjusted life-expectancy data will then be combined to assess cost-effectiveness, as described below.

Analysis: The approach for analyzing cost will be similar to the approach used for the MWD discussed in Aims 1-3 above (with the exception of a formal interim analysis). Between-group comparisons will be performed by calculating the mean costs for each of the 3 treatment groups and deriving an associated confidence interval for the cost difference (relative to the least costly group) using bootstrap resampling[82]. In addition, bootstrapping will be used to estimate the probability that each one of the three arms is least costly. Multiple linear regression analysis, with log (cost) as the dependent variable, will be used to adjust for baseline imbalances in the estimation of the effect of each of the treatment strategies on cost, and to identify factors significantly associated with increased costs.

A cost-effectiveness analysis will be performed if there are important differences between any of the 3 treatment groups with respect to quality-adjusted life years (QALYs) at 6-months. Because the interventions being considered in this trial are anticipated to impact quality of life but not mortality, the impact on the QALY endpoint will also reflect these predominant quality of life differences. The decision regarding the presence/absence of any important clinical differences between groups will not be made solely on statistical grounds, owing to the possibility that the trial is underpowered to detect a significant effect

of the magnitude observed. Differences between groups may be considered clinically relevant for a cost-effectiveness analysis to be carried out for the trial, even if they do not reach statistical significance.

Assuming that differences in QALYs are found between groups, the general approach will be to rank the therapies in terms of effectiveness (lowest to highest) and compare costs. Any options that are dominated (another less expensive, more effective option exists) are eliminated from further analysis. Cost effectiveness ratios are then calculated for each option, compared to the next less effective option. The number of CE ratios calculated will depend on how many of the treatment options appear to differ from each other in terms of effectiveness, and whether the rank order of effectiveness matches the rank order of costs. However, regardless of the other results, we will calculate and report CE ratios for both stenting and structured exercise compared with optimal medical therapy, since both appear to be reasonable clinical options, and knowing the incremental value of each independently compared to control group therapy will be of interest.

If 2 or more study arms are clinically equivalent in terms of QALYs but differ in costs, a CE ratio is not calculated - rather the less expensive option is reported as cost-saving relative to the other(s).

If the outcomes of the trial indicate the need for a formal cost-effectiveness analysis, the primary cost effectiveness estimate will be measured based on cost and utility outcomes assessed at 6 months. A secondary cost-effectiveness analysis will be based on costs and QALYs measured at 18 months, and in addition, long-term cost-effectiveness analyses will be carried out based on extrapolations of QALY differences over the patient's lifetime and life expectancy estimates from the literature, under varying assumptions with respect to the persistence or diminishment of the observed in-trial benefit over time.

Bootstrap analysis will be used to assess the precision of the cost-effectiveness ratios[83-85], and the results of the analysis will be presented graphically in the cost-effectiveness plane, including percentages of the distribution falling in the dominant (clinical benefit at lower costs) and dominated (higher costs but no clinical benefit) quadrants for important 2-way comparisons. We will additionally use bootstrap simulation-derived estimates of variability in the cost-effectiveness ratios and express this in terms of the probability that each group is "cost-effective" at a given cost-effectiveness threshold using the method of net health benefit and cost-effectiveness acceptability curves (as originally described by Stinett and Weinstein). This will graphically show the desirability of each of the 3 clinical options over a range of cost-effectiveness thresholds.

6.3.3. Tertiary Aims:

Aim 7: To evaluate the impact on classical and novel cardiovascular disease risk factors. Exercise is known to be a "systemic" therapy, while stenting

addresses a localized treatment. Thus, as an exploratory investigation, the impact of the three therapeutic strategies on change in known biochemical and physiologic cardiovascular disease from at baseline to, 6 months, and 18 months will be performed. These exploratory analyses include the following variables as risk factors:

- body mass index (BMI),
- waist circumference,
- blood pressure (systolic, diastolic, and pulse pressure),
- high-density lipoprotein (HDL),
- low-density lipoprotein (LDL),
- triglycerides,
- fibrinogen,
- C-reactive protein, and
- hemoglobin A1c

In addition, age, gender, weight, lipid profile, diabetes, and smoking status will be used to calculate Framingham CHD Risk Scores at baseline and at follow-up.

Statistical Analysis: Each risk factor and the Framingham Risk Score will be analyzed separately at a 0.05 level of significance given the exploratory nature of this aim. Longitudinal generalized estimating equation ANCOVA models will be used to assess pairwise treatment difference (one model per pairwise comparison) across time with respect to change in risk factor, adjusting for the baseline risk factor. The primary focus is on the comparison between stent and supervised exercise training, though the significance of the other treatment group comparisons will be assessed (each comparison will be assessed using the 0.05 level of significance).

The model will contain effects for treatment, time, baseline risk factor and region. The outcome will be change in the risk factor from baseline. There will be multiple observations per patient (one for each post-baseline risk factor measurement time point). The autoregressive correlation structure will be assumed for the multiple observations within subject. A comparison of the GEE model-based and empirical (robust) estimates will be carried out. Treatment-by-time interaction will be used to assess if any treatment effect seen is consistent across time. Longitudinal analysis will be supplemented with plots of MWD versus time for each treatment group. No imputation will be performed for missing data. Analysis will be performed on patients with data through 18 months, followed by analysis on all available data.

Aim 8: Also as an exploratory analysis, we will evaluate baseline criteria associated with increased improvement in MWD, improvement in free-living daily activities, and quality-of-life. It is possible, or even likely, that some patients are more suitable for one or the other treatment. The contribution of specific baseline demographic variables will be analyzed and include:

- Age (treated as a continuous variable),
- Gender (male versus female)
- Coexistent cardiovascular disease risk factors such as continued cigarette use (yes vs. no); high blood pressure (yes vs. no, where a subject with systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 and/or who currently taking antihypertensive medication will be considered as having high blood pressure); systolic blood pressure (baseline value at rest as a continuous variable), high LDL cholesterol (yes vs. no; three definitions of high LDL cholesterol will be assessed, each in separate regression models: (a) LDL ≥ 100, (b) LDL ≥ 130, (c) LDL ≥ 160); LDL as a continuous variable,
- Use of statin medications (yes vs. no),
- Physiological variables (baseline values): treadmill performance as a continuous variable; treadmill performance as a categorical variable formed by various METS levels (maximum baseline workload of 3, 3.6, or 4.1 METS), ABI as a continuous variable; heart rate (baseline at rest, as a continous variable); pulse pressure as a continuous variable
- Use of cilostazol at baseline
- Aortoiliac disease (unilateral versus bilateral, determined by abnormal thigh-brachial index <1.1 as a categorical variable)
- Bilateral vs unilateral disease (determined by abnormal ankle-brachial index <0.9 as a categorical variable)
- Infrainguinal disease (yes/no) (various thresholds of pressure differences between the high-thigh and ankle pressures will be examined, including 20, 30, and 40 mm Hg systolic pressure differences as categorical variables)

Hypotheses will be generated about which patients benefit most from each treatment and conversely which ones benefit least from them.

Statistical Analysis: Linear regression will be used to relate the above-mentioned baseline characteristics to MWD. Specifically:

1. With treatment group forced in the model, stepwise linear regression will be performed using a significance level of entry and stay of 0.10 to assess which of the covariates, after adjusting for treatment group, are significantly related to change from baseline to Month 6 MWD and the direction of the effect. The stepwise linear regression will be repeated where treatment group is not forced in the model but is included as a candidate for entry with all the other covariates.
2. Treatment group-by-covariate interaction on change in MWD at 6 months will be assessed for each above-mentioned covariate. These interactions will be assessed one at a time using a 0.05 level of significance. This analysis will help assess if certain baseline traits indicate a patient is more suitable for one treatment than another. For example, a significant treatment-by-gender interaction may indicate that one treatment may yield better MWD on males than another treatment.

3. Stepwise and interaction analyses will be supplemented with plots (e.g., MWD versus treatment for each gender) and descriptive statistics to help support relationships found, to help assess the cause of significant interactions, and to support conclusions of no significant interaction.
4. Supplemental stepwise regression analyses relating covariates to MWD within each treatment group will be performed, with the caveat that sample sizes may not allow for statistical significance of any trends seen.

No imputation for missing data will be made. The above analyses will be repeated on QOL scores.

After the above stepwise regressions are completed, treatment group comparisons will be performed on baseline variables that enter and remain in any of the above stepwise models, In the unlikely event the three primary treatments (stent, supercised exercise, and OMC) are imbalanced with respect to the distribution of at least one of these variables, treatment group comparisons on change in MWD in Aims 1 through 4 will be repeated, adjusting for these imbalances.

Aim 9: To track major adverse peripheral events (MAPEs) associated with aortoiliac stenting and femoropopliteal intervention. Periprocedural (24 hour) and procedure-related (30-day) morbidity and mortality will be reported, as will long-term complications and worsening of clinical status by history and physical examination. MAPEs that will be tracked include stent thrombosis, clinically-apparent distal embolization (loss of palpable or Doppler pulses, blue toe syndrome, livedo reticularis), acute limb ischemia, arterial rupture, and acute renal failure. Restenosis will be monitored long-term by monitoring ankle-brachial indexes.

Aim 10: Analyze the rate of major complication for all treatment groups defined as any occurrence of death, amputation of the target limb (limb treated in this study), occurrence of Critical Limb Ischemia or repeat Target Limb Revascularization (TLiR), or myocardial infarction.

Statistical Analysis (Aims 9 and 10): The 24-hour, 30-day and long term (6 and 18 month) incidence rates (“rate” is defined as the percentage of patients with the event) of each of the following outcomes will be presented by treatment group, with pairwise treatment comparisons being carried out on the rate of each outcome using the Chi-square test or Fisher’s exact test at a two-sided 0.05 level of significance: mortality, MAPE, each component of MAPE, Major Complications, each component of the Major Complication endpoint, and TLiR.

7.0 ADVERSE EVENTS /SERIOUS ADVERSE EVENTS

7.1 ADVERSE AND SERIOUS ADVERSE EVENT DEFINITIONS

Adverse Events (AE): An AE is any untoward medical occurrence observed in a patient that occurs in association with the use of an administered investigational intervention, whether considered intervention related or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the investigational intervention, whether or not considered related to the investigational intervention. Pre-existing conditions, which worsen during a study, are to be considered adverse events.

Serious Adverse Events (SAE): A SAE is any adverse drug or investigational device experience (occurring at any dose) that results in any of the following outcomes: death, a life-threatening adverse experience, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse when required study medication or investigational device experience when, upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition above. (CFR & ICH Guidelines)

In this study, patients should be encouraged to report AEs spontaneously or in response to general, non-directed questioning (e.g., “How has your health been since the last visit?”). Any time during the study, the patient may volunteer information that resembles an AE. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE Form of the eCRF.

7.2 DOCUMENTATION

Adverse events must be listed on the appropriate eCRF. All AEs will be characterized by the following criteria:

- Intensity or Severity
- Expectedness
- Relatedness
- Outcome
- Treatment or Action Taken

Non-serious adverse events will be reported only for the first 6 months of the subject’s study participation, until the primary endpoint is determined. Thereafter, only serious adverse events (for example, those that result in hospitalization, permanent disability, death or threat of death) will be reported to the DCC.

7.3 INTENSITY OR SEVERITY

The following categories of the intensity of an adverse event are to be used:

- **Mild**: Awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and with no sequelae;
- **Moderate**: Interferes with the patient's usual activity, but the patient is still able to function;
- **Severe**: Events that interrupt a patient's usual daily activity and generally require a systemic drug therapy or other treatment.

7.4 EXPECTEDNESS

All AEs will be evaluated as to its expected occurrence or whether it was unexpected to occur.

- **Expected:** An adverse event is expected when the specificity and severity of the event is consistent with the applicable product information (i.e., Investigator's Brochure or risk information described in the device specific Instructions for Use);
- **Unexpected:** An adverse event is unexpected when the specificity or severity of an adverse event is not consistent with the applicable product information (i.e., Investigator's Brochure or risk information described in the device specific Instructions for Use). Unexpected as defined above refers to an adverse event that has not been observed before.

7.5 RELATEDNESS

The Principal Investigator (PI) will evaluate if the AE or SAE is related to the Study Medication or Study Devices. Relatedness is defined in the following manner:

- **Not related:** The PI has determined that the complication is not related to the study device or medication
- **Unlikely:** The current state of knowledge indicates that a relationship to the use of Study Medication or Devices is unlikely;
- **Possibly or Probably:** The PI has determined that the event has a reasonable relationship to the use of the Study Medication or Devices;
- **Definite:** The PI has determined that the complication is related to the study device or medication

7.6 OUTCOME

The clinical outcome of the AE or SAE will be characterized as follows:

- **Death:** The SAE form must be completed for this outcome;
- **Recovered:** The patient returned to baseline status;
- **Not Yet Recovered:** Patient did not recover and symptoms continue.
- **Recovered with Sequelae:** The patient has recovered but with clinical sequelae from the event

7.7 TREATMENT OR ACTION TAKEN

AEs and SAEs will result in:

- **Intervention:** Surgery or procedure;
- **Other Treatment:** Medication dose reduction/interruption or discontinuation, or medication initiated for event;
- **None:** No action is taken.

7.8 EXPEDITED REPORTING OF SERIOUS ADVERSE EVENTS

The procedure for reporting any Serious Adverse Event is as follows:

- Report any serious adverse events to the DCC within 24 hours of knowledge of event via eCRF.
- Report any serious adverse event to the local IRB according to the investigational site's IRB procedures.
- Complete appropriate eCRF Event Form for any complication and/or serious adverse events.
- Submit physician/nurse notes or summaries regarding the event to the DCC.
- Report of a patient death must be accompanied by a completed Study Exit Form, a brief statement of the pertinent details, the death records/certificate or autopsy report (if performed).
- Provide completed, signed copies of the Study Exit Form and attachments to the DCC.

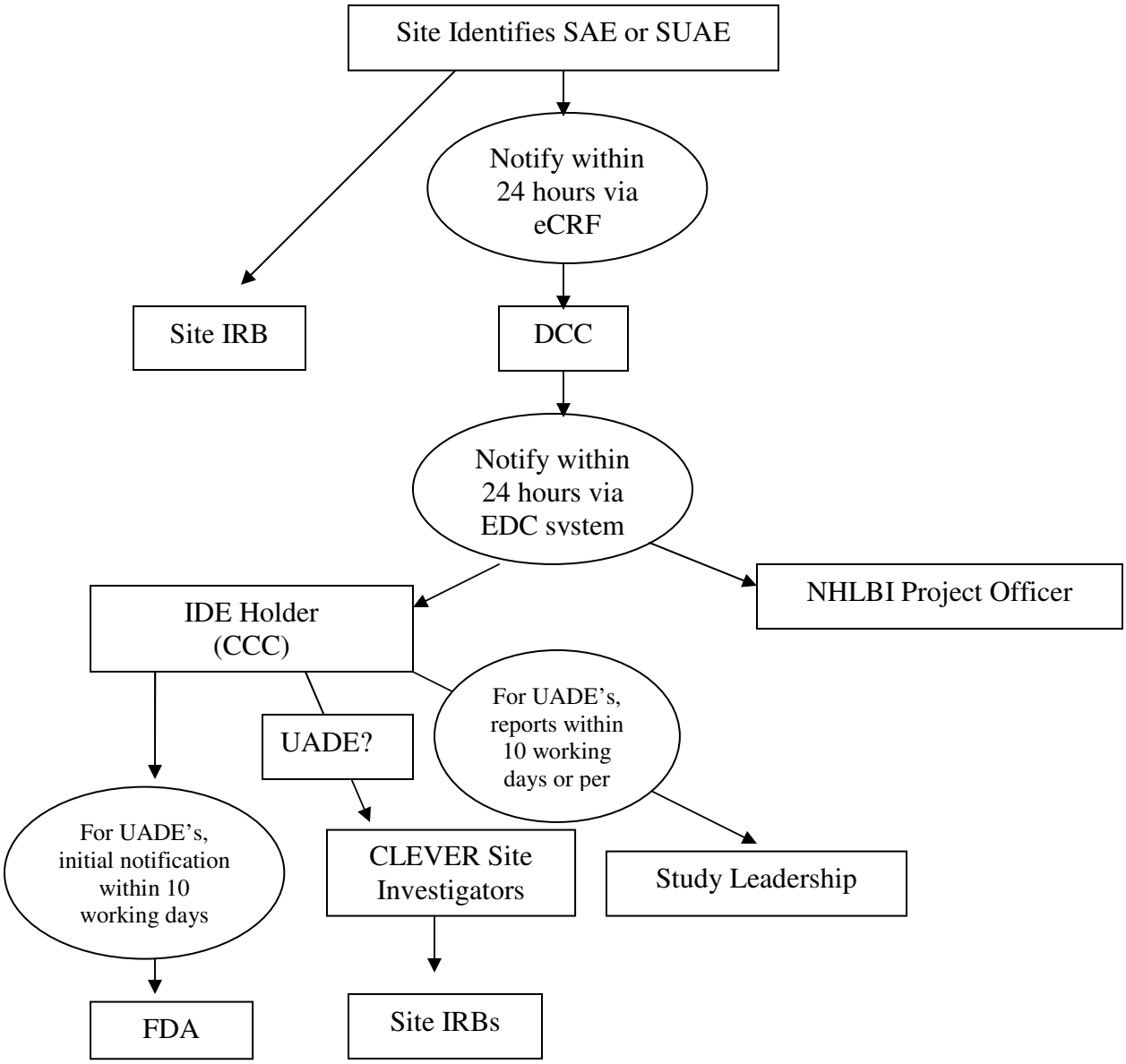
Clear pathways have been developed for the reporting and analysis of serious adverse events (see diagrams below). In this regard, the sites are responsible for SAE identification. SAEs are reported by the site to the local IRB and to the DCC within 24 hours of becoming aware of the event. The DCC will forward SAE reports within 24 hours of receipt during a working day to the IDE Holder (Dr. Timothy Murphy), and the NIH. The SAE report will also be forwarded to the CEC, if appropriate.

The IDE Holder will forward the site reported all unexpected adverse device effects (UADE's) to the FDA, device manufacturer, and sites within 10 working days of its receipt. The site will be responsible to forward the report to its IRB. Utilizing this

strategy allows identification of serious or systematic hazards in a timely fashion, facilitating corrective action and appropriate reporting to regulatory agencies.

Additionally, a clear plan has been developed for monitoring treatment efficacy throughout the conduct of the study utilizing structured interim analyses, with pre-specified efficacy boundaries.

FIGURE 2: SERIOUS ADVERSE EVENT OR SERIOUS UNANTICIPATED ADVERSE EVENT REPORTING.



7.9 REPORTING OF STUDY ENDPOINT ADVERSE EVENTS

Whenever an event is suspected or identified, a Source Document Tracking Checklist should be completed for each suspected event and sent to the DCC as soon as possible along with the required supporting source documentation. The source documentation required for each reported event is listed on the checklist.

8.0 ADMINISTRATIVE RESPONSIBILITIES

8.1 INSTITUTIONAL REVIEW BOARD (IRB) INFORMATION

This protocol and the informed consent document must be reviewed and approved by the appropriate IRB before enrollment of patients can begin. Changes or additions to the study protocol or informed consent document at the enrolling center must be approved in writing by the Clinical Coordinating Center and the enrolling center's local IRB.

8.2 PATIENT INFORMED CONSENT

Informed consent is mandatory and must be obtained from all patients prior to their participation in this trial. Informed consent must be obtained in accordance with the FDA regulation 21CFR, Part 50.

The sample Patient Informed Consent Forms are found in Appendix I. A copy of the approved Patient Informed Consent Forms for each screening phase of the CLEVER Trial along with a copy of each patient's signed and dated consent forms must be maintained by each investigator in a designated clinical trial administrative file. A signed copy of the consent forms must be given to each patient.

8.3 CONFIDENTIALITY

All information and data sent to the CCC, DCC, Non-invasive Testing Committee, Biochemistry Core Lab, Economics-Quality of Life Core Laboratory, Exercise Training Committee, Revascularization Committee, and Risk Factor Reduction Committee concerning patients or their participation in this trial will be considered confidential. Only authorized DCC or other core lab personnel, FDA, NIH and study sponsor personnel will have access to these confidential files. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this trial. All data used in the analysis and reporting of this evaluation will have no identifiable reference to the patient.

8.4 RECORDS AND REPORTS

8.4.1. Records

Records to be maintained by the investigator include:

- Signed Confidentiality Agreement
- Study Protocol
- Protocol Amendments
- Signed clinical trial agreement and/or Investigator's Agreement
- FDA Form 1572
- IRB approval letter
- IRB approved Informed Consent document
- IRB Continuing Review Approval Letters
- IRB Membership List
- IRB Correspondence
- Sponsor Correspondence
- CVs/licenses for all investigators and research coordinators
- Site Personnel Signature List
- Delegation of Responsibility Form
- Financial Disclosure/Conflict of Interest Forms
- Patient Screening & Enrollment Log
- Telephone Logs
- Site Visit/Monitor Log
- Lab certification and lab test normal ranges
- Device and Drug Accountability Logs
- NIH Training Certifications for Responsible Conduct of Research
- Angiography/Revascularization, Exercise Testing, Noninvasive Testing, Waist Circumference Certificates

The following records must be maintained for each patient enrolled in the trial:

- Signed Patient Informed Consent Form
- All completed eCRFs
- Supporting source documentation for values or responses in eCRFs
- Supporting documentation of any complications and/or adverse events

It is recommended that the investigator retain copies of procedure reports, procedure nursing notes and the results of any interventional procedures that occur post-trial procedure. The DCC reserves the right to secure data clarification and additional medical documentation on patients enrolled in this trial.

8.4.2 Reports

Investigators are required to prepare and submit to the local IRB, DCC, CCC, and Core Labs/Committees complete, accurate and timely forms and reports on this investigation when necessary according to the Table 6.

TABLE 6: RESPONSIBILITIES FOR PREPARING AND SUBMITTING FORMS AND REPORTS.

Type of Report	Prepared by Investigator For	Time of Notification
Electronic Case Report Forms	DCC	Within 14 days of contact
Electronic Case Report Forms and Diagnostic Tests/Samples	Non-Invasive Vascular Committee Biochemistry Core Lab EQOL Core Lab Exercise Training Committee Revascularization Committee Risk Factor Reduction Committee	Within 14 days of contact/test
Patient death during the trial	DCC, IRB	Within 24 hours of knowledge of event
Unanticipated complications, Serious AEs	DCC, IRB	If serious or life threatening within 24 hours of knowledge of event
Patient withdrawal	DCC, IRB	Within 5 working days
Withdrawal of IRB approval	CCC, DCC	Within 5 working days
Deviations from the investigational plan	IRB, DCC	Within 5 working days
Informed consent not obtained from randomized patient	IRB, CCC	Within 5 working days
Other information upon the request of the IRB, or DCC	As appropriate	As requested

Records and reports will remain on file for a minimum of two (2) years after the completion/termination of the investigational trial. They may only be discarded upon notification by the CCC. To avoid error, the principal investigator should contact CCC before the destruction of any records and reports pertaining to the trial to ensure they no longer need to be retained. In addition, the CCC should be contacted if the principal investigator plans to leave the investigational site. The CCC and DCC will report any changes in their key personnel to NHLBI, respectively.

9.0 STUDY DATA REPORTING AND PROCESSING

9.1 DATA MONITORING AND QUALITY CONTROL

9.1.1 Electronic Data capture (EDC) and Electronic Case Report Forms (eCRFs)

Electronic CRFs (eCRFs) will be used to collect patient data during the trial. Sample forms are provided in the Manual of Operations. Data will be collected via an Electronic Data Capture (EDC) system. Study coordinators at each clinical site will perform primary data collection based upon source-documented hospital chart reviews and enter the data through a secured EDC portal. eCRFs will be completed and submitted to the DCC via EDC in an expedited fashion. Patient data from the clinical sites should be completed within pre-specified time limits, usually on or within 2 weeks of each patient's study visit.

InForm, a fully relational EDC database, ensures proper tracking of eCRFs between the individual clinical sites and the DCC. Deficiencies identified by the system may be communicated within the EDC system or by regularly scheduled teleconferences between the study site coordinators, the DCC, and the CCC.

To avoid personal identification of patients, all patient forms will be coded with a composite study identifier. This entire patient identifier will be used for all patient-related study materials, including information shared with the committees and core labs. The DCC has no means of identifying individual subjects by their initials provided in this composite study identifier. Only study site research personnel will have the means to identify an individual study subject at their location with the composite study identifier.

9.1.2 Data Reporting

The investigator, or an individual designated by him/her, is responsible for recording all data from the trial via the EDC system supplied by the DCC. The investigator is required to electronically sign the CRF on the appropriate pages/screens to verify that he/she has reviewed the recorded data.
Completed eCRFs will be reviewed at the investigational site by authorized study personnel at regular intervals throughout the trial. To this end, the investigator must permit inspection of the trial files and patient eCRFs by such representatives and/or responsible government agencies.

9.1.3 Data Review

All eCRFs will be reviewed at the DCC and missing or unclear data will be requested as necessary throughout the trial. The DCC will request further documentation such as physician office and/or hospital inpatient or procedure notes when complications, major adverse events, or malfunctions are observed and reported.

Development of the primary database for the trial will be performed by the DCC. The DCC will also be responsible for auditing the database and confirming the overall integrity of the data.

9.2 STUDY DATA COLLECTION

9.2.1 Data Quality Control

Deficiencies identified by the InFORM EDC system and any other specific clinical site monitoring will be communicated within the EDC system or by regularly scheduled teleconference between the study site coordinators, the DCC the CCC and the study Sponsor (NHLBI), as indicated.

9.3 SITE SELECTION AND MONITORING

The Site Selection Committee will review prospective sites to evaluate facilities, investigators, and patients. First, investigators will be asked questions about volume and experience of interventionalists with aortoiliac interventions, experience of the research staff, and availability of qualified medical exercise rehabilitation programs. Curriculum vitae will be reviewed. After passing that review, the site will be visited by clinical coordinating center representatives, who will tour the facility including clinical points of care for where all major study work will be done (angiography labs, exercise testing and training centers, and vascular noninvasive testing centers). The sites will also be visited by members of the exercise training committee, and by the Colorado Prevention Center for endpoint determination training. Any issues or problems that arise during any of these visits will be brought to the clinical coordinating center for resolution.

The CCC will be responsible for site monitoring. Most site monitoring will be done centrally based on data or source documents submitted by the sites. Central monitoring will consist of reviewing data submitted for completeness and for compliance with pre-specified edit checks in the database, review of exercise training baseline prescription and subsequent attendance and performance by the Exercise Training Committee (who will review reports for each participant in receiving exercise training at least monthly), review of submitted source documents including angiograms from stent procedures for those in the stent group(s), and all qualifying imaging or vascular noninvasive tests that determine eligibility (which are routinely submitted to the CCC).

Source document review at the site will not be done routinely, but will be done on an *ad hoc* basis when necessary by representatives of the CCC, as indicated by protocol compliance or data quality issues detected at the DCC or CCC. For each of these *ad hoc* site visits, the monitor or CCC representative will compile and file an observation report that will be provided to the prinicipal investigator. These site visits will ensure that the following items are in compliance with regulations and as stated per protocol:

- the facilities being used by the investigator are acceptable for the purposes of the study
- screening is done regularly and consistent with the study protocol
- study participant enrollment is adequate
- informed consent for study participation is properly obtained and documented (in accordance with 21 CFR Parts 50 and 56)
- accurate data reporting and current records are being maintained

- adequate accounting of shipments/dispensing of study medication and devices
- the study protocol and investigational plan were followed
- changes to the protocol were approved by the IRB and/or reported to the sponsor and the IRB

Additionally, a review of subject records and source documents will be done by comparing a representative number of those subject records to determine:

- there are no omissions in the reports of specific data elements
- study endpoints are obtained and reported accurately
- missing visits or examinations are noted
- subjects failing to complete the study and the reason for each failure are noted in the reports.

An investigator's meeting will occur in order to orient the prospective investigators and staff to the investigational interventions, the study protocol, applicable regulations and requirements, and expectations of the study, including the numbers and time frame for patient selection, consenting and enrollment, and required clinical data and record keeping, etc.

No study site may receive shipment of the study drug until the following documents are received by the CCC:

- Written IRB approval for conduct of the study
- IRB-approved informed consent document
- Signed Investigator's Letter of Agreement
- Signed Clinical Trial Agreement
- Investigator's and Co-investigators' current curriculum vitae
- Core Lab/Committee Certifications

Clinical Coordinating Center staff will maintain personal contact with the investigator and staff throughout the study by phone, fax, mail, e-mail, EDC queries and on-site visits. At the close of the study at an investigational site, the clinical monitor may make a final on-site visit if needed. The purpose of this visit is to collect all outstanding study data documents and resolve any outstanding queries, ensure that the investigator's files are accurate and complete, review record retention requirements with the investigator, make a final accounting of all study supplies shipped to the investigator, provide for appropriate disposition of any remaining supplies, or to ensure that all applicable requirements are met for the study.

9.3.1 Communication

In the initial phases of the study, weekly or biweekly group teleconference calls including the DCC, CCC, and clinical sites may be conducted to resolve any problems concerning the protocol and data collection.

9.3.2 Recruitment Tracking

A recruitment status report generated by the DCC will identify variations in recruitment frequency among sites. The frequency of these reports varies based on speed of enrollment and/or study timeline. For a well-balanced study, a normal distribution in recruitment is expected; however, outliers will be routinely investigated for study compliance.

9.4 CONFIDENTIALITY AND PROTECTION OF STUDY FILES

Passwords will be issued to appropriate study site personnel and HCRI personnel to ensure confidentiality and protection of the data by allowing variable levels of access to the electronic computer system. For example, only the study site coordinator, monitor or Data Manager will have access based upon their pre-specified roles within the EDC system to enter, source verify or manage data. Other personnel may view the data in a read-only format, as pre-specified by study leadership in the data specifications for roles of study personnel determined at the outset of the clinical study.

10.0 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 ROLES OF STUDY LEADERSHIP, THE IDE SPONSOR AND NIH

The National Institutes of Health will oversee and assist the CLEVER Study Leadership for the overall conduct of the study. The Study Leadership will work with NIH and the FDA IDE holder to ensure applicable guidelines and regulations for conducting clinical trials are met. This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), the applicable regulatory requirements of the US Food and Drug Administration (FDA), ICH Guidelines and state and local legal and ethical requirements. The following documents contain the policies and procedures designed to ensure adherence to Good Clinical Practice:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996

2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations)

3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subject, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the Protocol Signature Page, to adhere to the instructions and procedures described in the protocol and thereby adheres to the principles of Good Clinical Practice.

10.2 GENERAL DUTIES (21 CFR 812. 40 AND 312.32))

General duties of the CCC consist of providing the protocol and study documents to the principal investigator for submission to the IRB, obtaining documentation of IRB approval prior to shipping the study drug, selecting investigators, ensuring proper clinical site monitoring and ensuring patient informed consent is properly obtained.

The DCC is responsible for providing the IDE Sponsor with quality data that satisfies federal regulations and informing them of unanticipated adverse events, serious adverse events, and deviations from the protocol. The DCC will prepare written progress reports and a final report.

10.3 SUPPLEMENTAL APPLICATIONS (21 CFR 812. 35 AND 312.30))

As appropriate, the CCC will submit changes in the Investigational Plan to the investigators to obtain Institutional Review Board approval of any such changes.

10.4 MAINTAINING RECORDS (21 CFR 812. 140)

The DCC will maintain copies of correspondence, data, serious adverse events and other records related to the clinical trial. The CCC will maintain records related to the signed Investigator Agreements and all regulatory documents.

10.5 SUBMITTING REPORTS (21 CFR 812. 150 (B) AND EN 540, 5.4.12 AND 5.6.15)

The IDE Holder will submit the required regulatory reports identified in this section of the regulation. This includes reporting of unanticipated adverse device effects, serious adverse events, withdraw of IRB approval, current investigators list, annual progress reports, recall information, final reports and protocol violations, and any other reporting requirements imposed by the reviewing IRB.

The DCC will notify the IDE Sponsor within 24 hours of any unanticipated adverse device effects, serious adverse events, withdrawal of IRB approval or protocol violations. The DCC will also prepare an annual progress report and a final report for the IDE Holder.

10.5 SITE RECORD RETENTION POLICY

All core laboratories and clinical sites will maintain study records for two years after the FDA is notified that research under the Investigational Device Exemption (IDE) has been terminated by the IDE Sponsor.

11.0 BENEFITS AND RISKS

11.1 BENEFITS

There are several potential benefits of study participation to the study subject. They will receive study drug without charge that has been shown to improve symptoms, but costs ~$50-100/month. Subjects may be allocated to a treatment group that would result in their undergoing supervised exercise training for six months, and then having a "personal coach", (i.e., heath education counselor) assigned to help foster continued exercise for a further 12 months. Exercise has clear cardiovascular, as well as psychosocial, benefits. Finally, there is reimbursement for time and travel in the amount of $250 for all study participants, plus up to an additional $1,170 for those who are enrolled in the supervised exercise training group.

11.2 RISKS

Human Subjects Involvement and Characteristics

This study will randomize 130-150 patients with intermittent claudication and aortoiliac PAD. The inclusion and exclusion criteria are described in section 3.3. Vulnerable populations, specifically prisoners, institutionalized individuals and fetuses will not be targeted for recruitment. Pregnant patients are excluded because angiographic studies are required that would increase radiation exposure to a fetus. All key staff members at the clinical centers will undergo education on the protection of human participants in research (http://cme.nci.nih.gov). We anticipate average patient age around 65 years. We started recruitment in February 2007 and recruitment will end in December 2010.

Sources of Materials

Research data obtained from study participants includes health information obtained through medical history and physical examination, response to health-status questionnaires, noninvasive vascular test results, and blood specimens obtained for biochemical analysis. All of the data obtained for this study will be obtained prospectively, as is necessary given the hypothesis to be tested.

Copies of study data source documents will be retained by the sites on all subjects that sign informed consent, irrespective of randomized status. The data utilized in this study are described above and consist of information from patient interview and examination, medical records, or study-specified measures and interventions. At enrollment, all study subjects will be asked to sign a medical release so that records of hospitalizations or office visits that occur outside those specified within the protocol can be reviewed and captured.

Potential Risks

Risks are present for participants for all treatment groups. However, it should be noted that most of the risks of study participation are not materially different than those

entailed by an individual who undergoes one of the study treatments outside of the context of this study. The one exception is that the risks for study participants randomized to supervised exercise training would not generally be incurred by patients with intermittent claudication due to the lack of access to this service because of the lack of reimbursement for exercise training for claudication. However, the risks of exercise training in this population are exceedingly low (see below).

For all study subjects, cardiovascular events can rarely accompany exercise testing[72,86]. For those allocated to stent placement, there is the risk of diagnostic arteriography and stent placement. For those allocated to exercise training, there is the potential risk of exercise precipitating injury or a myocardial infarction. However, all treatment groups represent standard therapy for study subjects' complaints, and the additional risks specific to the study are minimal. The only risks that can be considered attributable to participation in the study are those associated with transportation to and from the medical facility for follow-up data collection, or perhaps related to the 2 follow-up exercise treadmill tests. These are felt to be minimal.

The incidence of death among participants in cardiac rehabilitation programs is about 1/750,000 patient-hours of participation, the incidence of cardiac arrest is 1/117,000 patient-hours and the incidence of non-fatal myocardial infarction is 1/220,000 patient-hours[87]. Other complications that can be seen with exercise testing are: bradyarrhythmias, sinus, atrioventricular junctional, ventricular, atrioventricular block, asystole; sudden death (ventricular tachycardia /fibrillation); myocardial infarction, heart failure, hypotension and shock, musculoskeletal trauma, severe fatigue sometimes persisting for days, dizziness, fainting, body aches, delayed feelings of illness.

The risks of random assignment to the invasive treatment arm are considered. That is, in a given patient, the act of randomization might subject them to a treatment that would not have been undertaken if they were not in the study. In such a case, the following risks (Table 7) are possible:

TABLE 7: POTENTIAL ADVERSE EVENTS IN STENT GROUP

Adverse Event	Severity	Expected Incidence
Bleeding from access site	Low-High	1%
Blood vessel injury/rupture	High	1%
Pseudoanuerysm	Moderate	< 1%
Permanent renal failure	High	<< 1%
Transient Renal Failure	Low	< 5%
Need for Surgery	Moderate-High	<1%
Death	High	<0.1%
Amputation	High	<0.5%
Artery thrombosis/occlusion	Moderate	<2%
Allergic reaction	Low-Serious	<1%
Distal embolization	Moderate	<3%
Fever	Low	<0.1%
Hypotension	Low	<1%
Hypertension	Moderate	<1%
Infection	High	<0.5%
X-ray exposure	Very low	100%
Cardiac event associated with exercise test	Very low	<<<1%
Cardiac event associated with exercise training	Very low	<<<1%

12.0 STUDY COMMITTEES AND ORGANIZATION

12.1 ORGANIZATION

An organizational chart follows. The study will be directed by the NHLBI and will have an independent Data Safety and Monitoring Committee set up by NHLBI. The study administration will consist of a steering committee chaired by Dr. Alan Hirsch that will include NHLBI staff, and all key personnel, and will report to the DSMB.

A smaller working group, the Operations Committee, comprised of key CCC and DCC personnel plus NHLBI staff will serve as the group concerned with day to day issues of the study. There will be several subcommittees to handle specific tasks.

Dr. Timothy Murphy is the study principal investigator and director of the clinical coordinating center. Dr. Alan Hirsch, the study chair, works with the CCC. The data coordinating center is the Harvard Clinical Research Institute and the DCC director is Dr. Donald Cutlip.

The following Committees will operate at the direction of each Committee Chair:

1. Site Selection, Dr. Timothy Murphy; Rhode Island Hospital
2. Exercise Training, Dr. Judy Regensteiner; University of Colorado
3. Adherence to Physical Activity; Dr. Beth Lewis, University of Minnesota
4. Quality of Life and Cost Effectiveness (QoL/CE), Dr. David Cohen, Dr. Matthew Reynolds; Beth Israel-Deaconess Medical Center
5. Revascularization Committee, Dr. Timothy Murphy
6. Noninvasive Vascular Testing, Dr. Michael Jaff; Massachusetts General Hospital
7. Publications/Ancillary Studies, Dr. Timothy Murphy
8. Risk Factor Reduction, Dr. Emile Mohler, University of Pennsylvania
9. Clinical Events Committee, Dr. Donald Cutlip, Harvard Clinical Research Institute
10. Data Safety Monitoring Board, Dr. Thomas Pearson, for NHLBI, NIH
11. Biochemistry Core Lab, Dr. Michael Steffes, University of Minnesota

12.2 ENROLLING CENTERS

Enrolling Centers will be recruited by a four step process. The first step is an application that collects information about the site, personnel, and patients. Included in these data is information about the experience and qualifications of the interventionalist, and also about the availability of a qualified medical exercise rehabilitation center. The second step is obtaining anonymous reports from the 5 most recent aortoiliac stent procedures done in their department. The third step is to send anonymous examples of

aortoiliac angiogram images to prospective investigators and ask if they would be willing to 1. revascularize the patient if randomized to one of the stent groups, and 2. randomize them to a nonrevascularization treatment group. The fourth step will be to set up a conference call with prospective site investigators and research coordinators and probe the issues of access to patients, recruitment, and equipoise.

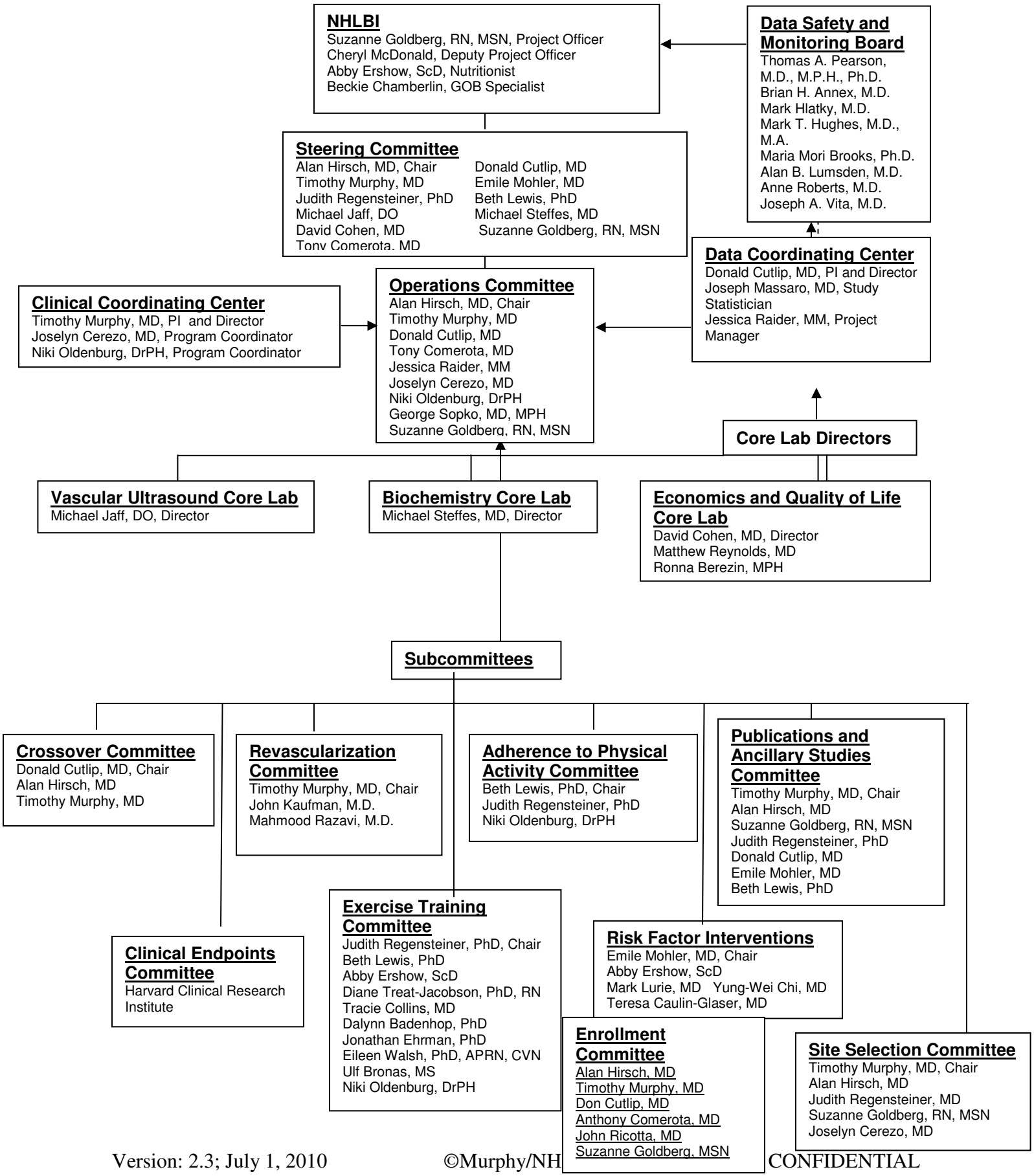
12.3 DATA SAFETY MONITORING BOARD

It is the policy of the NHLBI to establish Data and Safety Monitoring Boards (DSMB) for Institute-sponsored clinical trials (intervention studies) when an independent group is needed to evaluate the data on an ongoing basis to ensure participant safety and/or study integrity. Its members will regularly monitor the data from the study, review and assess the performance of its operations, and make recommendations, as appropriate, to the Institute with respect to the:

- benefits/risks ratio of procedures and the burden under which the participants are placed;
- completeness, quality, and analysis of measurements that are made;
- performance of individual centers (including possible recommendations on actions to be taken regarding any center that performs unsatisfactorily);
- interim results of the study for evidence of efficacy or adverse effects;
- possible early termination of the study because of early attainment of study objectives, safety concerns--if applicable, or inadequate performance;
- possible modifications in the study protocol.

The CLEVER DSMB will meet twice yearly or more frequently if DSMB members determine that more frequent meetirngs are required. DSMB members will carry out their review and roles in accordance with “Responsibilities of the DSMB appointed by the NHLBI” (http://www.nhlbi.nih.gov/funding/policies/dsmb_inst.htm). The DSMB will review and approve all CLEVER-related ancillary studies before initiation of any ancillary study.

CLEVER ORGANIZATIONAL CHART



13.0 PROTOCOL ADHERENCE

The Operations Committee will determine and address protocol violations. If a protocol violation is detected or suspected, investigators will be asked to provide an explanation of the protocol violation. Protocol violations will be categorized as major (eligibility or primary/secondary endpoint determination compromised or indefinite) or minor (data able to be used for baseline or determination of endpoints), and recorded and tracked for each site. For each protocol violation identified, the committee will determine whether the violation is minor or major. For minor violations, a letter or email will be sent to the site investigator and research assistant notifying them of the violation, asking them to explain the violation. If from this communication it is evident that the protocol is misunderstood, then the investigator and research assistant will be spoken to directly to clarify the protocol.

All major protocol violations will generate a letter from the study chair to site investigators, research coordinators, informing the site of the violation, its nature compromising the objectives of the study, and a request for a written explanation. The project director will then communicate verbally with the site investigator and research assistant in order to confirm that a process is in place to ensure that protocol violations do not occur again. If a major protocol violation occurs twice with any site without justification, they will be dropped as an enrollment center.

Procedural angiograms and hemodynamic data will be submitted to the CCC for quality assurance and protocol adherence review. The angiographic and interventional technique will then undergo quality assurance by confirming adequate performance of the following: documentation of arterial supply to the symptomatic lower extremity from the level of the renal arteries to the ankles; visual estimate of aortic and iliac stenoses, measurement of simultaneous pressure gradients across stenosis >50% in the aorta or iliac arteries on the symptomatic side unless occlusion is present (occlusions do not require pressure measurements to document hemodynamic significance); consistency of the pressure waveforms with numbers recorded, including similar diastolic pressures in most cases; $\geq$90% technical success revascularizing all aortic and iliac lesions with stents, including arterial occlusions; $\leq$10% complications that require therapy; adequate location of stents; documentation of hemodynamic results (pressure gradients). Anonymized reports of interventional procedures for study participants may also be requested for review. Investigators will identify on these reports whether complications were observed. Angiograms pre- and post-intervention will be examined by the Clinical Coordinating Center and forwarded to the Revascularization Committee for review if complications are observed but not reported on the CRF submitted by the enrolling investigator. Similar procedures will be followed for arteriograms or interventions done due to failure of stent therapy, suspected restenosis, or recurrent symptoms during the follow-up period. A quality assurance check on the date of the follow-up procedure will be done to determine if it was performed on the patient identified and if it was indeed a follow-up study.

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APPENDIX A: CLAUDICATION ASSESSMENT AND BLOOD AND PULSE PRESSURE PROCEDURES

Contents:

SAN DIEGO CLAUDICATION QUESTIONNAIRE (INTERVIEWER ADMINISTERED VERSION)—TEST VERSION

			Right	Left
1)	Do you get pain or discomfort in either leg or either buttock on walking? (If no, stop)	NO	1	1
		YES.....	2	2
2)	Does this pain ever begin when you are standing still or sitting?	NO	1	1
		YES.....	2	2
3)	In what part of the leg or buttock do you feel it?			
	a) Pain includes calf/calves	NO	1	1
		YES.....	2	2
	b) Pain includes thigh/thighs	NO	1	1
		YES.....	2	2
	c) Pain includes buttock/buttocks	NO	1	1
		YES.....	2	2
4)	Do you get it when you walk uphill or hurry?	NO	1	1
		YES.....	2	2
		Never walks uphill/hurries..	3	
5)	Do you get it when you walk at an ordinary pace on the level?	NO	1	1
		YES.....	2	2
6)	Does the pain ever disappear while you are walking?	NO	1	1
		YES.....	2	2
7)	What do you do if you get it when you are walking?	Stop or slow down	1	1
		Continue on	2	2
8)	What happens to it if you stand still? (if unchanged, stop)	Lessened or relieved	1	
		Unchanged.....	2	2
9)	How soon?	10 minutes or less	1	1
		More than 10 minutes..	2	2

SAN DIEGO CLAUDICATION QUESTIONNAIRE (INTERVIEWER ADMINISTERED VERSION)—ELIGIBILITY VERSION (SCORED)

***To be eligible for the study, responses must correspond to those noted after the questions and must be consistent for the leg that is symptomatic and is used for eligibility. If one leg meets eligibility and the other does not the patient is eligible. If both legs meet eligibility the patient is eligible.**

		Right	Left
1) Do you get pain or discomfort in either leg or either buttock on walking?	No……....	1	1
	Yes…….		
(If no, stop) *{Response must be "yes"}*		**2**	**2**
2) Does this pain ever begin when you are standing still or sitting? *{Response must be "no"}*	No……..	**1**	**1**
	Yes……..		
		2	2
3) In what part of the leg or buttock do you feel it?[a] *{Response to a, b, or c must be "yes"}*			
a) Pain includes calf/calves	No…….	1	1
	Yes…….	2	2
b) Pain includes thigh/thighs			
	No…….	1	1
	Yes…….	2	2
c) Pain includes buttock/buttocks	No…….	1	1
	Yes……..	2	2
4) Do you get it when you walk uphill or hurry? *{Response must be "Yes" or "Never walks uphill/hurries"}*			
	No…….	1	1
	Yes …….....	**2**	**2**
	Never walks uphill/ hurries.....	**3**	**3**
5) Do you get it when you walk at an ordinary pace on the level? *{Either response is acceptable}*			
	No…….	**1**	**1**
	Yes…….	**2**	**2**
6) Does the pain ever disappear while you are walking?[b] *{Either response is acceptable}*			
	No…….	**1**	**1**
	Yes…….	**2**	**2**
7) What do you do if you get it when you are walking?[c] *{Response must be "Stop or slow down"}*	Stop or slow down…….	**1**	**1**
	Continue on…….	2	2
8) What happens to it if you stand still?			
(if unchanged, stop) *{Response must be "Lessened or relieved"}*	Lessened or relieved.....	**1**	**1**
	Unchanged.....….	2	2
9) How soon? *{Response must be "10 minutes or less"}*			
	10 minutes or less…….	**1**	**1**
	More than 10 minutes……	2	2

BLOOD PRESSURE MEASUREMENTS

Equipment
1. Automated blood pressure cuff

Procedure
Establish that the patient has not eaten, ingested caffeine (from coffee, tea or soda), participated in heavy physical activity, smoked and/or used alcohol 30 minutes prior to the recording of the blood pressure.

- People should be seated quietly for at least 5 minutes in a chair (rather than on an exam table), with feet on the floor, and arm supported at heart level.
- An appropriate-sized cuff (cuff bladder encircling at least 80 percent of the arm) should be used to ensure accuracy.
- At least two measurements should be made. Blood pressure should be taken in both arms twice if possible and the higher of the two values recorded as the patient's blood pressure.

Pulse Pressure Measurements

Ankle-Brachial Index (ABI) Measurements

To perform a Resting ABI:

- A resting ABI measurement must be taken after the patient has rested for at least 10 minutes in a supine position *and* before the treadmill test. All ABI measurements must be made using a 5-10 MHz Doppler probe. Flat head Doppler and pencil type Dopplers are both acceptable.
- An appropriately sized cuff (bladder width 1.2 times the diameter of the limb) should be used for each limb that is being assessed
- Resting ABI pressures are obtained in a horseshoe shape starting with the right arm, moving to the right leg, followed by the left leg and left arm.
- Using a generous amount of gel, adjust the probe until the strongest (loudest) pulse sound is heard.
- The Doppler probe and hand should be stabilized. It is recommended that the technician obtaining the pressures be in a sitting position.
- Watch the Doppler probe while inflating the cuff, not the sphygmomanometer. This will ensure that the probe is not inadvertently moved, thereby losing the pulse.
- Inflate the cuff two pumps above the last audible arterial Doppler signal (about 20 mmHg).
- Turn attention to the sphygomomanometer and deflate the cuff slowly (about 2 mmHg per second). Record the reading of the first sound you hear that you are confident is a pulse sound.
- Wait at least 20 seconds, with the cuff completely deflated. Repeat the steps needed to obtain a second pressure at each vessel. Use the average of the two measurements to define a single pressure for each vessel. If individual pressures for a vessel are $\geq$10 mmHg different from each other, repeat the process until the difference between the pair of systolic pressures is <10 mmHg.

To Calculate the Resting ABI:

Calculate the resting ABI for the right lower extremity by dividing the higher of the two average right ankle readings (the average right DP or the average right PT readings) by the higher of the two average brachial readings (either the left average brachial or the right average brachial). To calculate the resting ABI for the left lower extremity, repeat this calculation using the higher left average DP or PT reading and the higher of the left or right brachial reading. The formulas are as follows:

Right Side: _____ / _____ = _____
Highest RIGHT average Ankle Pressure / Highest overall average Brachial Pressure*

Left Side: _____ / _____ = _____
Highest LEFT average Ankle Pressure / Highest overall average Brachial Pressure*

* The number used as the average brachial pressure, i.e., the higher brachial pressure, must be used as the denominator for both the left side and the right side calculations.

To Perform a Post-Exercise ABI:

During the RESTING ABI, mark the following vessels with a marker:

- Arm vessel with the highest systolic pressure at rest
- For the symptomatic leg, or both if both are symptomatic, mark the ankle vessel with the highest systolic pressure at rest

IMMEDIATELY AFTER COMPLETION OF THE TREADMILL TEST, AS SOON AS REASONABLY POSSIBLE, OBTAIN THE PRESSURES FOR THE POST-EXERCISE ABI FOR THE MOST SYMPTOMATIC SIDE (OR BOTH SIDES IF BOTH ARE EQUALLY SYMPTOMATIC) USING EITHER THE PT OR DP PRESSURE, WHICHEVER WAS HIGHER ON THE RESTING ABI. For CLEVER eligibility, the ankle pressure measured at either the dorsalis pedis or posterior tibial artery, whichever is highest, MUST decrease by at least 25 mm Hg on this "immediate" post-exercise measurement (or for those with incompressible arteries, the immediate post-exercise examination must reveal absent Doppler signals) (see inclusion criteria, number 5).

Obtain only ONE pressure at the arm and ankle vessels, identified above (one arm vessel pressure, one left ankle pressure and one right ankle pressure).

To Calculate the Post-Exercise ABI:

1. Calculate the ABI in the Right Leg:

Right Leg Ankle Pressure	÷	Selected Arm Pressure	=	___.___ ___ Post-Exercise Right Leg ABI

2. Calculate the Post-exercise ABI for the Left Leg:

Left Leg Ankle Pressure	÷	Selected Arm Pressure	=	___.___ ___ Post-Exercise Left Leg ABI

Thigh-Brachial Index Procedure

Equipment:

Acoustic gel
"Narrow" blood pressure cuffs (12 cm)
Continuous Wave (CW) 5-10MHz Doppler probe

Procedure:

1. The test should be performed with the patient's pants or dress removed, only underwear and a hospital gown should be worn.

2. Have patient rest for 10 minutes in the supine position. Apply an appropriately sized blood pressure cuff on the upper arm with the lower edge of the cuff 1 inch above the antecubital fossa.

3. Wrap both thighs with blood pressure cuff appropriately sized. The "narrow" cuff (12 cm wide) is used for this test as it is better able to discriminate inflow/outflow disease than the "thigh" cuff. Place the cuff as high on the thigh as the patient will tolerate.

4. Apply acoustic gel to the antecubital area

5. Place Doppler probe at the antecubital area at an angle of less than 60 degrees to the skin surface. Move the probe until the loudest arterial signal is detected.

6. Inflate the cuff until the arterial signal disappears. Then continue to inflate another 20 mmHg above the last audible signal.

7. Slowly deflate the cuff at a slow rate until the first arterial sound is heard. Record this arm systolic pressure on the worksheet.

8. Repeat steps 1 through 5 for the left arm. The highest brachial pressure is recorded and used to calculate the thigh brachial index.

Apply the blood pressure cuff to the ankle on the same side of the body:

9. If ankle-brachial indexes have been calculated, it is known which of the pedal arteries (dorsal pedis or posterior tibial) yields the higher pressure—use that artery for measuring thigh-brachial indexes.

10. Apply acoustic gel to the area over that artery

11. Place Doppler probe at the ankle at an angle of less than 60^{o} to the skin surface. Move the probe around until the loudest arterial signal is detected. Then slowly inflate the cuff until the signal disappears. Once the signal is absent continue to inflate the cuff for another 20 mmHg.

12. Deflate the cuff slowly until the first arterial sound is heard. This is the systolic pressure. The foot may move slightly while inflating the cuff to check your findings secure probe placement and repeat. Record this systolic pressure on the worksheet

13. Repeat the procedure on the opposite extremity.

14. Repeat the procedure on the contralateral limb.

Documentation of Results:

Thigh Brachial Index Calculation

High Thigh Pressure
Highest Brachial Pressure = Thigh-BI

APPENDIX B: GARDNER TREADMILL TEST PROCEDURES

Perform 2 baseline treadmill tests at 2 mph using a graded treadmill test (per Gardner protocol described below) with ECG monitoring to assess eligibility. Participants should be instructed to fast for at least 2 hours prior to the treadmill test except for clear liquids and should refrain from smoking for at least 2 hours prior to the treadmill test. For each of these tests report:

1. maximum walking duration,
2. initial claudication duration; which is used for the initial exercise prescription;
3. treadmill grade when exercise terminated (or peak METS, which is required for study eligibility);
4. maximum heart rate;
5. post-exercise blood pressure; and
6. stability of the ECG during exercise (absence of ST-segment changes and arrhythmias to document safety).

TERMS

Maximum Walking Duration (MWD) is defined as the maximum time in minutes and seconds walked by a patient on a treadmill under standardized conditions. The patient should continue the test until walking can no longer be tolerated because of claudication symptoms. It is critical that the patient **not** stop walking when they normally would do so. The patient should be asked to continue to walk until they feel they must stop due to claudication symptoms.

Initial Claudication Duration (ICD) is defined as the time in minutes and seconds walked by a patient on a treadmill under standardized conditions before the onset of claudication symptoms, regardless of whether this is manifested or characterized as muscle pain, ache, cramp, numbness or fatigue. This does not include joint pain or other pain not associated with claudication.

TREADMILL SET UP

The treadmill must be programmed with the attached Gardner protocol.

The treadmill's function must be assessed by an appropriate technician using appropriate methodology to check the accuracy of the speed and gradient. The treadmill speed and gradient must be within manufacturer specifications and assessed prior to commencement of the study. For purposes of this study, a calibration should be performed annually during the study.

The treadmill room should be free of distractions that might interfere with the treadmill test. These distractions include, but are not limited to, televisions, other staff present that are not involved in the treadmill testing, other procedures being performed on other patients and general background noise. Ideally, there should be a gurney or exam table next to the treadmill to accommodate pre-exercise and post-exercise ABI testing. The treadmill should be situated such that the staff is able to assist the patient if they have difficulty while walking on the treadmill.

TREADMILL FAMILIARIZATION

A short familiarization session on the treadmill must precede the official treadmill test at the Screening Visit. The treadmill familiarization should begin at a slow treadmill speed of 1.0 mph and 0% grade. Familiarization should also include distinct walking bouts at 1.5 mph and 2.0 mph. Each bout of walking should only last between 10 to 15 seconds, but may be repeated as

necessary. The treadmill belt should be stopped between each bout of walking so the patient can get comfortable transitioning from straddling the belt to walking on the belt.

1. Prior to the patient performing the treadmill test, they should be advised to immediately notify the staff performing the treadmill test if they experience any physical difficulty such as chest pain/discomfort, shortness of breath (SOB), or lightheadedness. If this occurs, the treadmill should be stopped immediately and appropriate medical intervention should be administered.
2. Have the patient straddle the treadmill belt and step on it once it is fully up to speed at 1.0, 1.5 and 2.0 mph for a minimum of 3 separate bouts of walking. Additional bouts of walking may be repeated as necessary.
3. During familiarization the patient should be instructed to walk on a treadmill in as normal a manner as possible. Make sure they are using a normal stride and not doing a shortened stutter step or shuffle step. They should be instructed to walk with their back straight and looking forward instead of looking down at the belt as this may make them dizzy.
4. Ensure the patient walks on the treadmill with their hands resting lightly on the rail, for balance only. Discourage the patient from using the rail for support.
5. This treadmill familiarization should be repeated as often as necessary during the course of the trial.

PRE-EXERCISE VITAL SIGNS AND ABIS

In order to determine participant eligibility, in addition to treadmill test data, vital sign and ABI changes after exercise are required (see inclusion criterion 5, “Ankle pressure reduced by at least 25 mm Hg after exercise compared to resting pressure”, and exclusion criterion 21, “Post-exercise systolic blood pressure within the first five minutes after eligibility treadmill test lower than pre-exercise systolic blood pressure”. Therefore, it is imperative that blood pressure and ankle-brachial index for the symptomatic limb(s) be obtained immediately prior to and following the treadmill test. The blood pressure will be obtained routinely with the patient supine immediately following the test as it is part of the ABIs. Because this is a supine blood pressure, the blood pressure pre-exercise must also be obtained with the patient supine. This may be done at the end of the supine rest period after participant familiarization with the treadmill, but prior to the actual treadmill test.

BEFORE THE TREADMILL TEST

The treadmill controller timer should be used to measure MWD and ICD. In some cases a stopwatch or other suitable timing device may be used. Time should be recorded in _min _sec format.

Continuous ECG testing is required during treadmill testing. If the PI or designee observes a clinically significant abnormality in the ECG, assess whether the patient is appropriate to continue in the study. A 12-lead printout should be done to document the ICD and the MWD and submit to the DCC. Patients are ineligible if ST-segment depression >1mm in any lead or sustained (>30 seconds) arrhythmia other than tachycardia or occasional premature atrial or ventricular contractions occur during exercise testing. If these occur during 6 month or 18 month tests investigators should refer patients for medical evaluation and consider modifying study-related exercise/activity instructions.

It is strongly recommended that the treadmill test be performed at a consistent time of day and consistent time interval after the last meal for each patient. If patients will be fasting for visits with a blood draw, a small snack is recommended to be given to the patient before the treadmill testing and after blood samples have been obtained, but this too should be consistent from visit to visit.

1. The patient must rest for 10 - 20 minutes prior to the test. If the room in which the patient is resting is not in the immediate vicinity of the treadmill station, then the patient must be brought to the treadmill station in a wheelchair.
2. Patients should refrain from consuming any alcoholic beverage prior to the test (i.e., on the day of the test). Smoking is not permitted within 2 hours of the test.
3. The room should be maintained at a comfortable temperature.
4. The patient must wear a pair of comfortable low-heeled walking shoes, preferably tennis shoes. Hospital booties are not considered acceptable and bare feet are never acceptable.
5. The patient must not wear a watch and must be positioned where he/she cannot see a clock or timer during the test. Cover the treadmill timer if necessary.
6. Carefully explain MWD to the patient prior to the treadmill test (i.e. "We want you to walk as far as you possibly can").
7. Explain the Claudication Symptom Rating Scale to the patient prior to treadmill testing. Ensure this scale is posted directly in front of the treadmill where the patient can easily refer to it. (Claudication Symptom Rating Scale: 1=no pain, 2=onset of pain, 3=mild pain, 4=moderate pain, and 5=severe pain)
8. Stress to the patient that they must let the staff know the moment they begin to experience claudication symptoms during the treadmill test. This corresponds to "2 -Onset" of the Claudication Symptom Rating Scale.
9. Assess what words the patient uses to describe their claudication symptoms. Be certain to use these same words when questioning the patient about their claudication symptoms during the treadmill.
10. Instruct the patient to let you know if they experience shortness of breath, chest pain or dizziness during the treadmill.
11. At the screening visit, patients who are forced to discontinue walking for reasons other than ischemic leg pain (e.g., angina pectoris, dyspnea, dizziness, etc.) must be excluded from the study.

STARTING THE TREADMILL TEST

1. When starting the actual treadmill test, ensure the treadmill belt is moving at 2.0 mph before the patient steps on and before starting the Gardner protocol.
2. Be sure to start the Gardner protocol and timer for both the MWD and ICD when the patient's second heel makes contact with the treadmill belt.
3. Ask the patient to rate their claudication symptoms, using the Claudication Symptom Rating Scale, frequently throughout the treadmill test. Remind the patient to inform you the moment their symptoms start, number 2 – "Onset" on the scale.
4. Give the same feedback/encouragement to each patient.

5. Document the ICD when the patient first begins to experience claudication symptoms.
6. Note the time when level 4, “moderate” claudication, begins.
7. Ensure that the patient is walking with a comfortable gait.
8. Ensure the patient is using the bar on the treadmill for balance only.

ENDING THE TREADMILL TEST

1. Remember that “severe” claudication (“5” on the Claudication Rating Scale) does not mean that the patient should stop walking. Many patients can continue walking even though their symptoms are severe
2. Encourage the patient to continue walking until they can no longer tolerate walking due to claudication symptoms.
3. When the patient states that they must stop and MWD is achieved, stop the treadmill belt and the timer at the same time. Do not “cool down” the exercise, stop the treadmill as quickly as can safely be done.
4. As quickly as is safe, transfer the patient to a chair or exam table to rest after the treadmill testing is completed.
5. Once the patient stops walking, transfer them as quickly as reasonably possible to a stretcher, attach blood pressure cuffs, and obtain systolic blood pressure (use either the dorsalis pedis or posterior tibial artery, whichever gave the HIGHER reading at rest) for the MOST symptomatic extremity(ies) [use both if symptoms are roughly equal bilaterally], IMMEDIATELY (as soon as possible after exercise is stopped) and then every two minutes for up to 10 minutes. The first set of pressures should be obtained “immediately” after completion of the treadmill test, so it is important to have the stretcher or bed nearby and set up for the participant ahead of time. For some participants, the “immediate” ankle pressure on the most symptomatic side will be nondetectable due to absence of Doppler signals—this result should be entered as “zero” (“0”). It may be helpful to mark the location of the Doppler signal pre-exercise to increase confidence post-exercise that the location is correct if Doppler signals are not detected. Usually, if this occurs, Doppler signals will return in a couple of minutes, and usually a systolic blood pressure can be obtained at either the 2 or 4 minute interval. The highest resting brachial pressure should also be measured and recorded at the same intervals post-exercise.
6. Verify the reason that the patient stopped the treadmill test and document both the reason stopped and the MWD.

If the patient experiences shortness of breath, chest pain, dizziness, significant ECG changes or any other significant sign or symptom that makes the site staff concerned for the patient’s safety, **STOP** the treadmill test **IMMEDIATELY** and take appropriate medical intervention.

Note: follow your institutional procedure for monitoring patients during treadmill exercise testing.

Gardner Treadmill Protocol

Stage	Speed (mph)	Elevation (% grade)	Duration (min)
Rest/Recovery*	2.0	0	--
1	2.0	0	2 minutes
2	2.0	2	2 minutes
3	2.0	4	2 minutes
4	2.0	6	2 minutes
5	2.0	8	2 minutes
6	2.0	10	2 minutes
7	2.0	12	2 minutes
8	2.0	14	2 minutes
9	2.0	16	2 minutes
10	2.0	18	2 minutes
11	2.0	18	At least 20 minutes

** On some treadmills this stage may be called Sitting, Supine and/or Standing. Other treadmills may not have this stage. The purpose of this stage is to get the belt up to 2.0 mph prior to the patient stepping on the belt. The patient should not straddle the belt for longer than necessary.*

APPENDIX C: QUALITY OF LIFE AND COST EFFECTIVENESS PROTOCOL

This appendix will describe in detail the background, data collection, and analytic methods for the secondary end points of quality of life and cost-effectiveness in the CLEVER study.

Quality of Life (Aim 5).

To examine treatment effects on patient-perceived physical health-related quality of life at 6 and 18 months, and specifically to see if improvement in QoL is greater after aortoiliac stent than supervised exercise training or optimal medical care.

Background

It has been shown previously that aortoiliac disease impairs health-related quality of life[1], and that the interventions under study in this protocol improve symptoms, functional capacity, and quality of life[2-4]. It is unknown, however, how well aortoiliac stenting and exercise therapy improve these end points relative to each other. Neither aortoiliac stenting nor a structured exercise intervention, compared with optimal medical care, is expected to impact on all-cause mortality in a study of this size and duration. For these reasons, distinct and comprehensive QoL measures are planned as a major secondary endpoint for this study.

QoL Methods

Choice of Instruments

For the current investigation, we will be using the SF-12[6] as the main generic QoL instrument. The SF-12 is derived from the larger Medical Outcomes Study Short-Form 36 (SF-36), a 36 item questionnaire that assesses eight dimensions of general health: physical function, social function, mental health, general health perception, pain, vitality, role limitations due to physical problems, and role limitations due to mental health problems, as well as 2 summary scales (physical and mental component scales)[7]. The SF-36 has undergone extensive consistency, reliability, and validity testing and has been used to assess quality of life outcomes in more than 250 clinical trials[8-10]. The physical and mental component summary scores for the SF-12 have been shown to correlate well with those obtained from the longer, more time consuming SF-36.[6] Calculation of the physical and mental component scores in this study population will allow for comparison of this study group to other groups with PAD in whom the SF-36 or SF-12 has been used, as well as to patients with other health conditions.

Disease specific QoL data collected in this study will include the Walking Impairment Questionnaire (WIQ), as well as the Peripheral Arterial Questionnaire (PAQ). The WIQ was developed and validated specifically for patients with claudication to assess treatment effects on claudication-limited walking ability[11]. Questionnaire scores have been shown to correlate well with graded treadmill results. The WIQ has been used previously to evaluate changes in community-based walking ability in response to exercise training and surgical interventions[2,3].

Although the WIQ has proven useful in clinical studies of patient with PAD, it is primarily focused on the domain of physical functioning. The PAQ was recently developed in an effort to capture a broader array of PAD related QoL domains.[4] In a population of patients undergoing percutaneous peripheral arterial revascularization procedures, the PAQ exhibited excellent reliability and validity, and its summary score showed greater sensitivity to change following revascularization than any score on the WIQ or SF-36.

Data Collection

Baseline quality of life data, using the instruments described above, will be obtained from each patient by written, self-administered questionnaire at the time of study intake, prior to randomization. A trained research assistant at each site will review the questionnaires for completeness and will attempt to ask any incomplete or poorly understood questions. Measurement of baseline QOL for each patient is critical to the study design as this will allow for the use of change scores as the principal secondary end point (i.e., the difference between the measure at follow-up and at baseline), thus adjusting for any minor imbalances in baseline health between the treatment groups and increasing statistical power.

Follow-up quality of life will be assessed in a similar manner by mailed questionnaires at 6 and 18 months after randomization in all study patients, except the WIQ will be administered in person by the site research coordinator during the 6 and 18 month follow-up visits and data entered into the EDC system. Two weeks prior to each follow-up time point, each patient will be mailed a self-administered survey booklet and a stamped return envelope. Any patient who fails to return the survey by mail will be given the survey by telephone, administered by a trained research assistant from the HCRI core laboratory. In our experience, central coordination of the follow-up quality of life assessments is important in order to maximize compliance and ensure uniform assessment.

QOL Data Analysis

The approach for analyzing each QOL item and scale will be similar to the approach used for the MWD discussed in Aims 1-3 in the main application (with the exception of a formal interim analysis).

All multi-item scales (composite scores) will be counted as missing if more that 50 percent of the items are blank. When the respondent answers at least 50 percent of the items in a scale, the completed items will be averaged to obtain values for the incomplete items. For single-item measures, if a response is missing, the score is set to missing. Because the mortality rate in the study population is not expected to be high, missing data due to patient death will be treated as missing in the QoL analysis, rather than imputing missing scores for patients who have expired.

The primary QoL end points will be the physical and mental component summary scores from the SF-12, the WIQ, and the PAQ summary score. Each of these summary scales will be scored using previously published methods.[4,6,25] As with the analysis of the primary end point, pairwise analysis of covariance (ANCOVA) models will be used to assess the significance of the difference between (a) supervised exercise versus medical care, (b) stent versus medical care, and (c) stent versus exercise on the change from baseline to 6-months for each of the 4 summary scales. In these ANCOVA models, adjustments will be made for baseline MWD and region.

Exploratory comparisons will also be made comparing the stenting plus supervised exercise arm to the stenting alone and supervised exercise alone arms. These will be performed in analogous fashion to the others. Change from baseline to 18 months will also be evaluated in secondary analyses to assess the durability of QoL changes associated with the different interventions.

Cost and Cost-Effectiveness (Aim 6)

To examine inpatient and outpatients costs associated with the three treatment strategies, and to put these costs in context of cost-benefit by calculating incremental cost-effectiveness ratios and cost effectiveness acceptability curves using health utility change in the denominator.

Background

The economic evaluation of health care interventions assumes particular importance when the disease under consideration is either highly prevalent or very costly. Peripheral arterial disease is known to be a prevalent condition in the population, with an age-related, and therefore increasing incidence[5]. The costs of treating this condition are largely unknown, but recent CMS data suggest a steeply rising increase in use of peripheral arterial stent procedures – projected to approach 100,000 procedures next year (files available at http://cms.hhs.gov/physicians/pfs/default.asp) – implying that related health care costs are substantial. Both aortoiliac stenting and a structured exercise intervention are expected to yield clinical benefits to patients, with some increase in aggregate health care costs. Whether one intervention or the other represents a superior value from a health care economic perspective will be studied in this protocol by collecting detailed health care economic data and performing a cost-effectiveness analysis.

Cost-Effectiveness Methods

Derivation of Utility Weights

The U.S. Panel on Cost-Effectiveness in Health in Medicine has recommended quality-adjusted life years (QALYs) as the preferred unit of effectiveness in cost-effectiveness analysis[12]. Calculation of QALYs requires the use of utility weights for different study populations or health states. The utility weights to be used in CLEVER will be derived from the EuroQoL/EQ-5D[13]. The EuroQol is a multi-attribute health status classification questionnaire with an empirically-derived preference based scoring system based on analysis of time trade-off utilities for selected health states among 2997 randomly-selected members of the adult population of England, Scotland, and Wales[14]. The EuroQol may be administered by either a 5-item written questionnaire or telephone interview. EuroQol data will therefore be collected at baseline, 6, and 18 months in conjunction with the QoL data collection described above.

Economic Data Collection

For the calculation of health care costs, the following specific data will be collected for each randomized patient:

1. Itemized hospital charges and summary bills (UB-92 forms) for any index hospitalizations or hospital-based revascularization procedures, and treatment for peripheral vascular disease or its complications. UB-92 forms and itemized hospital bills will be collected directly by a trained research assistant at the DCC/EQOL core lab, working in concert with the director of patient accounts at each participating hospital. Prior to enrollment in the study, patients will be asked to provide permission to obtain such billing records, and all related data will be kept in a secure, confidential database. Of note, data for other hospitalizations will not be collected as we do not expect that revascularization or exercise training will result in meaningful differences in medical care costs unrelated to peripheral vascular disease over the 18 month follow-up period. Given the relatively modest sample size for the study, it is therefore more likely that any differences in unrelated costs will reflect random variation and not a consistent treatment effect.

2. Catheterization laboratory resource utilization for the index PTA/stent procedure as well as for any subsequent peripheral vascular interventions during the follow-up period. Data collected will include total procedure duration; number of angioplasty balloons, stents, guide wires, and guiding catheters used; adjunctive medications used and the amount and type of radiographic contrast required. These data will provide a direct measure of resource utilization for the PTA procedures and thus allow for accurate measurement of the cost of these procedures using standard, “bottom-up” accounting methods[15].

3. Measures of global resource utilization for any index and follow-up hospitalizations associated with peripheral vascular disease. These measures will include length of stay, number of ICU days, principal diagnosis (ICD-9 codes), principal procedure (CPT) codes, and DRG.

4. Outpatient medical resource utilization is expected to account for an important component of costs in this patient population, particularly for study patients who do not undergo iliac stenting procedures. To facilitate accurate data collection, we will ask study participants to keep a diary of all health care interactions related to PAD during the follow-up period, including physician office visits, emergency room visits, and out-patient diagnostic testing. In addition, we will obtain patient (or proxy) self report estimates of the number of visits by allied health professionals including visiting nurses, home health aides, occupational therapists, and physical therapists during the follow-up period, again, aided by the use of the same specially designed diaries. Local study investigators will be asked to review these diaries on a quarterly basis and to record out-patient resource utilization on standard case report forms which will be transmitted to the EQOL core laboratory.

5. Number and duration of admissions to rehabilitation hospitals, nursing homes, and other chronic care facilities.

6. Productivity costs attributable to the patient’s peripheral vascular disease will be estimated from self-reported employment classification, work days missed and work effectiveness. At baseline, the patient will be asked about his/her years of formal education (none; 1-8 years; 9-12 years; trade/technical school; college/university), current employment status (working full time; working part time; not working/not disabled; homemaker/house-wife; never worked; retired; not working/disabled) and employment classification (professional; business; clerical; skilled labor; general labor;

self-employed; home-maker; farmer; police/military; receiving disability/Social Security; other). Patients will also be asked to rate their effectiveness on the job (0% to 100%) in light of their disease status, for the time they did work. At each follow-up the patient will be asked their current employment status and, if currently working full or part-time, the number of days of work and hours per week missed since the last follow-up due to a) home disease management and b) outpatient office visits and testing. Patient-reported work effectiveness (0% to 100%) will also be assessed at each follow-up visit.

7. The Supervised Exercise Training group will incur unique costs resulting directly from their planned intervention. These will include the costs related to the structured exercise protocol during months 0-6 (patient and staff time costs, as well as a portion of overhead costs for the exercise centers) as well as the adherence to physical activity intervention (printed materials and time/staff costs for 1-2 monthly phone calls) during months 7-18.

Cost Calculations

Catheterization laboratory or interventional radiology costs for index hospitalization procedures (stenting arm) will be calculated for each patient using standard "bottom-up" cost accounting methods[1688]. For major disposable items (including angioplasty balloons, stents, guidewires and guiding catheters), costs will be based on a survey of hospital administrators regarding the acquisition costs for the item during the last 12 months of the study period. Drug costs (e.g., heparin, clopidogrel) will be calculated based on the unit cost of each vial and the total number of vials opened for each patient. Consistent with previous studies, we will assume that any unused portions of opened vials will be discarded[17]. By using updated cost data for the final calculations and analysis, we will assure that our cost estimates are accurate at the time of publication. The cost of other disposables, depreciation and overhead for catheterization laboratory maintenance, and non-physician personnel will be estimated based on the average cost per procedure at Boston's Beth Israel Deaconess Medical Center during the same time frame and adjusted for measured procedure duration.

For those index hospitalizations for which UB-92s and associated itemized bills are collected, non-procedural costs will be calculated using "top-down" methods based on each hospital's Medicare Cost Report. Hospital room and nursing costs will be based on the average per diem cost for the specific care unit (e.g. ICU, general medical unit) multiplied by the length of stay on the particular unit. Ancillary costs will be determined by multiplying itemized hospital charges by the direct cost-to-charge ratio for the specific cost center that provided the service. Previous studies by our group and others have shown this method to correlate well with data from detailed cost-accounting systems, particularly for the purposes of group comparisons[17-19]. [89,90]Although the use of both resource-based accounting techniques (for catheterization lab costs) and "top down" techniques (for ancillary and nursing services) is labor-intensive, in the absence of a uniform cost-accounting system across all enrolling hospitals, it is the best method currently available for measuring costs in the context of a multicenter clinical trial[20].

For index hospitalizations with no available UB92's or itemized bills, ancillary hospital costs will be estimated from resource utilization based on unit costs derived from the hospitalizations with available billing data. For each hospital admission, unit costs for key resources (length of stay, ICU days, number of angiograms, percutaneous interventions, blood transfusions, other diagnostic studies) will be derived from a regression model developed using the billing-derived cost data, with supplementation from CMS data and selected cost data from the Beth Israel Deaconess Medical Center cost accounting system as needed.

For all follow-up hospitalizations, DRGs will be assigned using a pre-defined algorithm, and Medicare reimbursements will be applied. Physician fees for hospital days, procedures, tests and office visits will be estimated based on the Resource-Based Relative Value Scale[23]. Costs associated with outpatient care will be assigned using the Medicare fee schedule. Medication costs will be based on wholesale prices as listed in the Drug Topics Red Book[24].

Programmatic costs of the exercise therapy intervention will be estimated based on average national wages according to the number of nursing/research assistant hours per session and the number of sessions, and associated training and ongoing monitoring of nurses/research assistants. For the estimation of indirect (productivity) costs associated with peripheral artery disease and it's management, average annual wages will be obtained separately for men and women for different age categories (from the U.S. Bureau of Labor Statistics and Bureau of the Census: http://www.bls.census.gov/cps/ads/adsmain.htm) from which the costs associated with lost productivity will be estimated, based on changes in employment status and effectiveness, and workdays missed.

Cost Effectiveness Analysis

The unit of effectiveness for the cost-effectiveness study will be quality-adjusted life years, calculated according to standard methods[12]. Population-based health state utilities will be assessed directly for the CLEVER trial population using the Euro-QOL/EQ-5D[28], and will be incorporated directly into the analysis by multiplying each patient's utility by his or her survival duration during the assessment period. For example, the utility for months 0-6 will be the mean of the baseline and 6 month utility values, and for the 18 month analysis, the utility for months 6 through 18 will be the mean of the 6-month and 18 month values.

Medical care cost and resource utilization data will be collected for each study patient from the point of study intake through the 18-month follow-up visit. To facilitate analysis from a variety of potential perspectives, overall costs associated with peripheral artery disease will be calculated for three categories:

a. Direct medical costs: the cost of any inpatient care, outpatient care (including outpatient procedures, diagnostic testing, exercise training, and prescriptions), and emergency room visits.
b. Custodial and chronic care costs: the cost of nursing home care, rehabilitation services (inpatient or outpatient), visiting nurses, home health aides, and other non-physician health professionals.
c. Indirect costs: productivity costs associated with time away from work (lost wages) for other family members.

As recently recommended by the National Panel on Cost-Effectiveness in Health and Medicine, costs of lost work or other earnings on the part of the patient will be tabulated as well, but not included in the calculation of medical care costs for the primary cost-effectiveness analysis[12].

The primary economic endpoint will be total medical care costs at 6 months. A secondary economic endpoint will be total medical care costs at 18 months. These will be tabulated and reported for each of the three study groups.

Cost and quality adjusted life-expectancy data will then be combined to assess cost-effectiveness, as described below.

Analysis: The approach for analyzing cost will be similar to the approach used for the MWD discussed in Aims 1-3 above (with the exception of a formal interim analysis). Between-group comparisons will be performed by calculating the mean costs for each of the 3 treatment groups and deriving an associated confidence interval for the cost difference (relative to the least costly group) using bootstrap resampling[26]. In addition, bootstrapping will be used to estimate the probability that each one of the three arms is least costly. Multiple linear regression analysis, with log (cost) as the dependent variable, will be used to adjust for baseline imbalances in the estimation of the effect of each of the treatment strategies on cost, and to identify factors significantly associated with increased costs.

A cost-effectiveness analysis will be performed if there are important differences between any of the 3 treatment groups with respect to quality-adjusted life years (QALYs) at 6-months. Because the interventions being considered in this trial are anticipated to impact quality of life but not mortality, the impact on the QALY endpoint will also reflect these predominant quality of life differences. The decision regarding the presence/absence of any important clinical differences between groups will not be made solely on statistical grounds, owing to the possibility that the trial is underpowered to detect a significant effect of the magnitude observed. Differences between groups may be considered clinically relevant for a cost-effectiveness analysis to be carried out for the trial, even if they do not reach statistical significance.

Assuming that differences in QALYs are found between groups, the general approach will be to rank the therapies in terms of effectiveness (lowest to highest) and compare costs. Any options that are dominated (another less expensive, more effective option exists) are eliminated from further analysis. Cost effectiveness ratios are then calculated for each option, compared to the next less effective option. The number of CE ratios calculated will depend on how many of the treatment options appear to differ from each other in terms of effectiveness, and whether the rank order of effectiveness matches the rank order of costs. However, regardless of the other results, we will calculate and report CE ratios for both stenting and structured exercise compared with optimal medical therapy, since both appear to be reasonable clinical options, and knowing the incremental value of each independently compared to control group therapy will be of interest.

If 2 or more study arms are clinically equivalent in terms of QALYs but differ in costs, a CE ratio is not calculated - rather the less expensive option is reported as cost-saving relative to the other(s).

If the outcomes of the trial indicate the need for a formal cost-effectiveness analysis, the primary cost effectiveness estimate will be measured based on cost and utility outcomes assessed at 6 months. A secondary cost-effectiveness analysis will be based on costs and QALYs measured at 18 months, and in addition, long-term cost-effectiveness analyses will be carried out based on extrapolations of QALY differences over the patient's lifetime and life expectancy estimates from the literature, under varying assumptions with respect to the persistence or diminishment of the observed in-trial benefit over time.

Bootstrap analysis will be used to assess the precision of the cost-effectiveness ratios[26,2984,85], and the results of the analysis will be presented graphically in the cost-effectiveness plane, including percentages of the distribution falling in the dominant (clinical benefit at lower costs) and dominated (higher costs but no clinical benefit) quadrants for important 2-way comparisons. We will additionally use bootstrap simulation-derived estimates of variability in the cost-effectiveness ratios and express this in terms of the probability that each group is "cost-effective" at a given cost-effectiveness threshold using the method of net health benefit and cost-effectiveness acceptability curves[30-32]. This will graphically show the desirability of each of the 3 clinical options over a range of cost-effectiveness thresholds.

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APPENDIX D: DEFINITIONS

Acute Limb Ischemia:
A clinical condition in the leg caused by sudden decrease in arterial perfusion characterized by pain, pallor, pulselessness, paresthesias, and paralysis.

Acute Renal failure
Worsening renal function resulting in one of the following:

1. A new requirement for dialysis, or
2. Increase of serum creatinine to > an absolute value of 220 µmol/L (2.5 mg/dl) and two times the baseline creatinine level, but does not require dialysis.

Angioplasty, Percutaneous Transluminal (PTA)
Altering the structure of a vessel, either by a surgical procedure or by dilating the vessel using a balloon inside the lumen.

Amputation (Target Limb)
Surgical removal of tissue anywhere from the toe to hip in the ipsilateral limb of the target site. Amputations will be subclassified as follows:

a) Above knee amputation-amputation of limb with resection point above the knee.
b) Below knee amputation-amputation of limb with resection point below the knee.
c) Transmetatarsal amputation-amputation of limb with resection point in the metatarsal bones of the foot.
d) Toe amputation-amputation of toe(s).

Ankle-brachial Index
A ratio of the highest ankle systolic blood pressure in one leg, usually measured with a 10 cm cuff at the ankle and using a continuous wave Doppler to detect return of blood flow in the anterior tibial and posterior tibial arteries, to the highest of either arm systolic blood pressure.

Atherosclerosis
A form of arteriosclerosis characterized by a variable combination of changes in the intima of arteries, consisting of the focal accumulation lipids, complex carbohydrates, blood and blood products, fibrous tissue and calcium deposits, and associated with changes in the media of the arteries.

Claudication
A pain, cramps, fatigue, or equivalent in leg muscles occurring during walking that results from inadequate blood supply, usually due to atherosclerotic arterial obstruction.

Closure, Abrupt

The deterioration of the target site or appearance of a new lesion that severely compromises flow and requires rescue by a non-assigned treatment strategy. Abrupt closure requires proven association with the target site and does not indicate “no reflow” (due to microvascular flow limitation), or distal embolization in which the artery is patent but has reduced flow. Abrupt closure also does not indicate transient closure with reduced flow in which the index treatment application reversed the closure.

Closure, Subacute
Abrupt closure that occurs after the index procedure is completed and the patient has left the catheterization laboratory; and before the 30-day follow-up endpoint.

Complication, Major
Defined as the occurrence of any of the following:

1. Death
2. Myocardial infarction
3. Amputation of the limb(s) treated in this procedure
4. Occurrence of critical limb ischemia
5. Repeat Target Limb Revascularization (TLiR) involving the target limb treated during this study.

Complication, Major Bleeding
A procedure-related event which requires a transfusion of blood or blood products.

Complication, Vascular Access
The need for transfusion or vascular repair of the access site due to pseudoaneurysm of the superficial femoral artery or arteriovenous fistula formation**.**

Critical Limb Ischemia
A clinical condition caused by chronically decreased perfusion of a leg that results in rest pain, ischemic tissue loss, or gangrene.

Death
All causes of mortality will be recorded.

De Novo Lesion
A lesion in a native vessel that has not been previously treated.

Distal Embolization
A new abrupt cut-off or filling defect distal to the treated lesion.

Emergent Surgery
Vascular surgery performed on an urgent or emergent basis for severe vessel dissection or closure, or treatment failure resulting in new ischemia.

Flow Limiting Dissection

A flow limiting dissection is a dissection that either results in (a) limb ischemia, or (b) would preclude safe delivery of the stent device.

Hematoma
A swelling or collection of blood at the access site > 5 cm.

Initial Claudication Duration
The total time that an individual can walk on an exercise treadmill test until experiencing symptoms of intermittent claudication. Defined as the time in minutes and seconds walked by a patient on a treadmill under standardized conditions before the onset of claudication symptoms, regardless of whether this is manifested or characterized as muscle pain, ache, cramp, numbness or fatigue. This does not include joint pain or other pain not associated with claudication.

Major Adverse Peripheral Event (MAPE)
Defined as stent thrombosis, clinically-apparent distal embolization (loss of palpable or Doppler pulses, blue toe syndrome, livedo reticularis), acute limb ischemia, arterial rupture, restenosis and acute renal failure.

Maximum Walking Duration
Defined as the maximum time in minutes and seconds walked by a patient on a treadmill under standardized conditions. The patient should continue the test until walking can no longer be tolerated because of claudication symptoms. It is critical that the patient **not** stop walking when they normally would do so. The patient should be asked to continue to walk until they feel they must stop due to claudication symptoms.

Myocardial Infarction
The diagnosis of MI will be made on the basis of clinical information available from hospitalization (discharge summaries, laboratory data, ECG) and will require an appropriate clinical history consistent with acute MI.

QMI is defined as symptomatic or asymptomatic (discovered during routine follow-up). A symptomatic QMI is confirmed if the patient is admitted to hospital, has abnormal cardiac enzymes as defined below and develops a new 2-grade Q wave worsening. New permanent LBBB will be confirmed as a QMI when enzymes are abnormal. An asymptomatic QMI is confirmed when ECG QMI criteria are detected during a routine follow-up visit and there is no intervening event from the prior scheduled visit that would explain the finding.

Non-QMI is defined by the ACC/ESC MI consensus document. A non-QMI is confirmed if the patient is admitted with an abnormal cardiac enzyme profile (typical rise and fall) defined below and has either:

(1) new ST-T wave changes or
(2) chest pain or clinical history consistent with MI or

(3) a coronary revascularization procedure in the preceding 48 hrs with a subsequent increase in cardiac enzymes that meet criteria.

Criteria for Abnormal Cardiac Enzymes

1. The enzyme profile must exhibit a typical rise and fall and result from an ischemic event.
2. For CK-MB or CK, the elevation must be > 2ULN for the local laboratory. CK-MB result takes precedence over total CK result.
3. For cTn, the elevation must be > 2ULN using local laboratory criteria established as diagnostic of MI. cTn takes precedence over CK-MB (i.e. when CK-MB is abnormal but cTn is normal, the enzyme profile will be considered normal)
4. When CK-MB is collected after a coronary revascularization procedure, the threshold for abnormality is increased to >3ULN for PCI procedures and >10ULN for CABG procedures. cTn post-procedure will not be used to diagnose post-procedure MI because of the lack of reliable long-term data at the current time, except in the situation where there are no available CK MB data, in which case cTn will be used to establish a diagnosis.
5. Isolated cardiac enzyme rise alone does not qualify as an MI event.

Notes: By requiring the cardiac enzymes to have a higher threshold (2ULN), the sensitivity to detect MI events is diminished to enhance specificity. If we lower it to just the ULN, we enhance sensitivity at the expense of specificity.

Restenosis

Restenosis will be monitored long-term by monitoring the ankle brachial index. Any decrease in ABI by >0.10 compared with post-stent ABI indicates restenosis, unless an imaging study indicates patency of the stent without stenoses within or contiguous with the stent ends. If no other lesion can be found to explain the decrease in the ABI pressure gradients will be performed across the stented arterial segment.

Restenotic Lesion

A lesion in the vessel segment that has undergone a prior percutaneous treatment.

Systolic Acceleration Time:

A feature of a pulse Doppler waveform obtained in a blood vessel characterized as the time required from the beginning of systole to the peak antegrade velocity within the segment.

Target Site Revascularization (TSR)

Any repeat percutaneous intervention or bypass surgery performed on the target lesion.

Target Limb Revascularization (TLiR)

Repeat percutaneous intervention or bypass surgery of the target limb but not the target lesion.

Thigh-brachial Index

The ratio of the highest thigh systolic blood pressure in one leg, done an appropriately sized (air bladder width 1.2 times the diameter of the limb) blood pressure cuff as high on the thigh as tolerable, using a continuous wave Doppler as the pulse detector in the anterior tibial artery or posterior tibial artery, to the highest arm systolic blood pressure on either side.

APPENDIX E: SUPERVISED EXERCISE TRAINING/ ADHERENCE TO PHYSICAL ACTIVITY

A. Supervised Exercise Training Regimen Protocol

B. Adherence to Physical Activity

A. SUPERVISED EXERCISE TRAINING

1. Optimal Medical Care (OMC): Home Exercise

Study participants will be advised at baseline to exercise by walking a regimen similar to the supervised exercise group: at least three times a week, goal of five times, for an hour each. Walking should continue while they experience mild or moderate claudication pain, and then to stop and rest before the pain becomes severe (grade 5) or limits their ability to walk with a normal gait. Participants should not stop as soon as they experience claudication pain but should walk with it as tolerated until before they would describe discomfort as severe; that is, they should stop when pain is mild or moderate (grade 3 or 4 on the claudication scale). Participants should rest between bouts of walking until claudication pain resolves, usually within a few minutes, and then start walking again, repeating the entire process for roughly 50 minutes. Patients should be told to increase their walking time as often as possible. Verbal and written instructions on the benefits of exercise with information on exercise regimens will be provided at baseline, 6 months, and 18 months. Home exercise patients will receive monthly phone calls from local research coordinators asking open-ended questions about their health. They will receive exercise recommendations only at baseline and 6 months.

2. Supervised Exercise Training (SE)

a. Exercise Locations

The exercise protocol for the supervised program is based on published optimal programs for improving claudication pain distances in patients with PAD using intermittent treadmill walking (see below). Supervised exercise will be performed 3 times per week, for 26 weeks. In addition, patients will be encouraged to exercise two additional times a week on their own. An exercise physiologist, exercise nurse, or other exercise staff will supervise the training, and a physician will be in the building for indirect supervision and emergencies. Most sites will use existing cardiac rehabilitation centers for exercise training, but some may use dedicated peripheral vascular rehabilitation centers. Cardiac rehabilitation centers will have to be willing to follow centrally prescribed training and should be accredited, for example by the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR).

For enrolling centers who want to provide exercise training at more than one location, up to three exercise training centers are allowed at each enrolling center, one designated the Core CLEVER Research Site and the others the Satellite CLEVER Exercise Rehabilitation Training Centers. Satellite training centers must be approved by the Exercise Training Committee and allowed if the site investigators can ensure that:

- Exercise **testing** (i.e., study endpoint visits) must be done at the “Core” site for all participants, even those who perform exercise training at the satellite site
- There must be an adequate enrolled CLEVER Study population or anticipated patient density to warrant the effort to train and maintain the satellite site(s)
- Ideally, the satellite will be identified prior to the initial site visit by the exercise training committee and the satellite staff will attend the exercise training

committee visit at the Core site. All satellite sites will be required to undergo the standard CLEVER exercise rehabilitation site training prior to randomization of any study participant intended for exercise training at that site

- If a satellite training center is requested after the Exercise Training Committee visit, the PI is responsible to see that the satellite staff are trained, usually by the staff at the Core training center
- The principal investigator remains equally responsible for delivery of exercise therapy at the satellite site as at the Core site

b. **Initial Exercise Prescription**

Exercise prescriptions will be created according to guidelines of the American College of Sports Medicine for patients with peripheral arterial disease [72]. The exercise prescription consists of a treadmill speed and grade. All participants will begin supervised exercise training at 2 mph. The initial treadmill grade is that grade where claudication pain was first noted on the baseline treadmill test with the longer exercise performance.

The goal of the initial training session is for the patient to spend at least 10-15 minutes on the treadmill, exclusive of the warm-up and cool-down periods.

Participants will walk on a constant grade throughout each session. Grade and/or speed may be increased between sessions by site exercise staff working as described in section “e”, Advancing Exercise Prescription”, below, in conjunction with the Exercise Training Committee. The goal is to increase the exercise prescription when patients are able to walk without stopping at least 8-10 minutes on a grade (see below).

c. **Claudication Symptom Rating Scale**

The claudication pain scale is integral to monitoring improvement in exercise performance and advancing exercise prescriptions. At the initial supervised exercise training session, participants will be taught to grade their claudication pain using a five point Claudication Symptom Rating Scale where 1=no pain, 2=onset of pain, 3=mild pain, 4=moderate pain, and 5=severe pain. Patients will then meet with Exercise Rehabilitation Personnel. During this meeting, they will receive an exercise prescription. Patients in the supervised exercise training (SE) program will have their prescription applied to the supervised program while Optimal Medical Care (OMC) patients will be given the prescription to implement at home. Supervised exercise training participants will receive an exercise diary at this time for them to use during the course of the study.

Claudication Symptom Rating Scale grades are subjective. Patients should learn to use the pain scale to help guage their walking bouts during each exercise training session (see section “d”, “Supervised Exercise Sessions”).

d. **Supervised Exercise Sessions**

Supervised exercise sessions will be held three times a week for one hour each over a six-month period. Each session of exercise training will involve a warm up and cool down of five minutes each. The warm up period is designed to increase the heart rate

slowly and to promote flexibility, and will be done by simple stretching exercises designed to stretch the muscles of ambulation using recommendations of the Aerobics and Fitness Association of America (AFAA) for stretching for an elderly population based on a widely-used program obtained from Visual Health Information (Tacoma, WA) as well as by walking on the treadmill at 2 mph with no grade. The cool down period is designed to return the heart rate to baseline values and will be done by by walking on the treadmill at 2 mph with no grade and by stretching. During the remainder of the hour, it is anticipated that up to 50 minutes can be used for walking exercise, exclusive of warm up and cool down.

Most exercise will be done without telemetry monitoring. If a study participant eligible at baseline develops coronary symptoms, or other significant medical problems, during follow-up, s/he must be referred for evaluation and exercise postponed until it is assured that a contraindication for study eligibility has not developed. If a study contraindication develops, the patient will be withdrawn from the study and data analyzed as according to the Statistical Analysis Plan (section 6.0).

Supervised exercise training will occur three times a week. Treadmill walking should continue while they experience mild or moderate claudication pain, and then to stop and rest before the pain becomes severe (grade 5) or limits their ability to walk with a normal gait. Participants should not stop as soon as they experience claudication pain but should walk with it as tolerated until they describe discomfort as severe; that is, they should stop when pain is mild or moderate (grade 3 or 4 on the claudication scale). Participants should rest between bouts of walking until claudication pain resolves, usually within a few minutes, and then start walking again, repeating the entire process for roughly 50 minutes. After that time, cool down activities should be done, and then the session is ended. The research coordinator will record attendance and the start time of exercise, the finish time, the number and duration of each walking episode, the duration of each episode of rest, and the treadmill grade and speed that day.

Data collected at each exercise session to be forwarded to the DCC and from there to the Exercise Training Committee including participant ID and date, duration of session, duration of each treadmill walking bout and resting period, and grade and speed on treadmill.

e. **Advancing Exercise "Prescription"**

Exercise needs to be advanced as performance improves to get the most out of supervised exercise training. Exercise "prescription" should be adjusted locally by exercise staff and research coordinators when patients are able to walk for at least 8-10 minutes on a given work load.

If a participant can walk at a given exercise grade for at least 8 minutes before severe claudication is experienced (grade 5) (i.e., while experiencing only mild-to-moderate pain (grades 3-4)) the grade should be increased for the next session by 2% up to a maximum of 10%. Once they reach 10% grade and they are able to walk 8 minutes without mild-moderate claudication pain, increase the speed by 0.2 mph increments

instead of the grade, up to 3 mph. Then increase the grade by 2% increments up to 15%. If patients get to this level, begin to advance speed in 0.2 mph increments as tolerance progresses.

It is important to note that target heart rates can not be used for exercise prescription routinely in CLEVER because CLEVER participants are limited by their extremity pain and may not achieve such target heart rates by walking. However, some participants, such as those undergoing stent + supervised exercise, may experience rapid increases in their exercise prescription (for example, walking more than 8 minutes with only mild-to moderate claudication on 3 or more exercise training sessions, despite increases in exercise prescription each time). For participants with minimal residual limitation due to claudication symptoms who experience rapid increases in exercise tolerance, a Rating of Perceived Exertion Scale should be used, and exercise prescription only advanced until they describe their effort as, “hard exertion” (not “very hard”). Similarly, some patients may not complain of claudication even with walking more than 8 minutes. If this happens, it is suggested that after walking 15 minutes they be offered the option of sitting and resting for up to 5 minutes. If chest pain or other symptoms are reported that could potentially indicate cardiac disease, patients must be referred to their primary care doctor or sent to an emergency room if necessary.

The Exercise Training Committee will receive reports every two weeks from the DCC which will be structured to identify participants walking for bouts at least 8 minutes long whose prescriptions are not advanced. In that way the ET committee can monitor exercise programs administered locally by exercise staff. If prescriptions are not appropriate or not advanced according to this schedule, the site PI and RC will be contacted to educate and to ensure improvement in exercise prescriptions for specific study participants.

f. **Exercise Session Supervision and Monitoring**

Sessions will be led by the exercise physiologists and the nurse coordinators with indirect supervision of an attending physician in the building and available for emergencies. All exercise training is ultimately under the supervision and the responsibility of the site Principal Investigators. The exercise physiologist or nurse will assure that exercise training is performed properly and that the intensity is adequate based on a prescription from the Exercise Training Committee that will be received every two weeks.

Study sites and their participating exercise training staff will also be required to undergo training for the supervised exercise intervention prior to site activation and enrollment of study subjects. Training will occur at the investigator’s meeting prior to study initiation and at all sites prior to study initiation. Completion of this training will be required prior to certification of each site for enrollment in CLEVER. Additionally, sites will provide data from all supervised exercise visits for all supervised exercise group participants throughout the study so that the Exercise Training Committee can review progress and increase the exercise prescription appropriately so that improvement in MWD is optimized. Discrete data from the sites for these participants will include date of

exercise, number of episodes of exercise and their duration, time of onset of claudication and time each bout was stopped, duration of rest, treadmill grade and speed, duration of exercise session. Missing data or incorrect implementation of the exercise regimen will be apparent on weekly review by the Exercise Training Committee, and sites who are not implementing the exercise training protocol correctly will be told to stop enrollment.

g. Data To Be Collected

Case report forms (CRFs) will be developed to record total exercise time as well as length of each bout of walking exercise for each exercise session, and the walking episode times when symptoms began and when walking was stopped for symptoms. Reasons for unscheduled absences should also be recorded. These CRFs should be sent to the DCC weekly. Reimbursement for exercise sessions will be based on receipt of these case report forms.

h. Rationale for 26 Weeks of Exercise Training

Studies have specifically addressed the issue of optimal length of time of exercise training for improving symptoms and walking time in PAD subjects. Ninety percent of the benefit of exercise conditioning occurs by 3 months, with an additional 10 % improvement by 6 months.[15]

i. Attendance

The hospital-based, supervised exercise program will consist of 78 sessions over 26 weeks. Patients will be encouraged to come three times/week. To remove personal expense as a barrier to compliance, subjects are given a stipend to cover parking, local transportation, laundry, and other expenses. Subjects who fail to attend 70% of the exercise sessions at the time of final analysis will be considered non-compliant with the exercise training program. A 30% inflation rate is factored into the sample size calculations to account for non-compliant patients, drop outs, and false positive screening. Patients in the SE group who miss 1 session (i.e., an unscheduled absence) will be called by rehab personnel to discuss reasons for non-adherence. Patients in the OMC group will be called every two weeks to reinforce exercise habits and to collect information about exercise logs.

j. Exercise Behavioral Issues: Compliance

Compliance is a key part of the exercise components of the study. Participants will be encouraged by local research coordinators to attend as many supervised exercise sessions as possible, and will receive financial reimbursement for their travel and time if they achieve 80% attendance. Participants are allowed "make up" sessions if exercise sessions are missed if they can be accommodated by the rehabilitation center. These should be scheduled as tolerated by exercise staff. Patients in SE groups also will receive points for returning their logs. If they return 80% of their logs, they will be able to pick from among incentive items (e.g., t-shirts, water bottles).

Exercise training is expected to be associated with approximately 73% compliance [46], with approximately 68% of patients attending at least 70% of the scheduled exercise

sessions[46] (this was out of 19/28 exercisers). It will be our goal to have study subjects comply with 70% of possible sessions[46]. We will foster attendance at exercise sessions by providing continued feedback to participants about any advances or gains made in their exercise performance, by continuing to emphasize the positive health, including psychological and emotional, benefits of continued exercise, and by noting that results of exercise are superior when supervision is done[45]. Patients will be informed of the value of exercise training according to going Medicare rates, and will be made aware that the study is paying for their attendance at up to 100% of scheduled sessions. Patient satisfaction will be assessed monthly by research coordinators and reported to the clinical coordinating center. If patient dissatisfaction is detected, especially if a study participant or study site is having attendance problems, issues that are detected by this process as barriers to continued exercise participation will be discussed between the CCC and the study site. If any patients attend less than 67% of prescribed supervised exercise sessions, the study site will be advised of this and an intervention initiated to improve compliance by the patient. If a patient has one unscheduled absence, the study site will contact him/her to inquire as to the reason for the missed session and problem solve through any barriers he/she might have. If patients miss more than 3 sessions in a row without notifying the investigators, the study site coordinator will be contacted by the Exercise Training Committee to find out why and encourage their return. Each exercise center will maintain attendance for each supervised exercise study participant and report this to the DCC once a month. These data will be reviewed by the APA committee. They will be asked to identify impediments to attendance for the given patient and they will be asked to take remedial measures to improve attendance. If more than 40% of study subjects at any site fail to meet this threshold, the site will be asked to stop recruitment for all arms of the study.

CLEVER STUDY SUPERVISED EXERCISE REGIMEN--SUMMARY

1. Initial Exercise Session

Treadmill Speed = 2 mph

Treadmill Grade = Grade when claudication pain was first noted on the baseline treadmill test with the higher maximum walking duration (MWD).

Review claudication symptom grading scale (1=no pain, 2=onset of pain, 3=mild pain, 4=moderate pain, and 5=severe pain)

Instructions—warm up for 5 minutes; then start walking session at the appropriate grade and walk until pain is experienced but is not yet severe or restricting of normal gait (before severe claudication (grade 5) is reached), stop and sit down and rest until pain is completely gone, then begin walking again.

Session duration—50 minutes total of treadmill walking and rest (not counting warm up and cool down).

Cool down—walking and stretching exercises.

The research coordinator will provide the patient's initial exercise prescription to the exercise rehabilitation staff before the patient's first exercise session, using the Exercise Rehabilitation Entry Form provided to the coordinators.

2. Subsequent Exercise Regimen

If a participant can walk at starting exercise grade for at least 8 minutes without severe (grade 5) claudication pain, the grade should be increased for the next session by 2%, up to a maximum of 10%. Once they reach the 10% grade and they are able to walk 8 minutes without mild-moderate claudication pain, increase the speed by 0.2 mph increments instead of the grade up to 3 mph. Then increase the grade by 2% increments up to 15%. If patients get to this level, begin to advance speed in 0.2 mph increments as tolerance progresses.

Either the research coordinator or Exercise Rehabilitation staff will record the walking and resting time periods for each session on the Exercise Rehabilitation Data Collection Tool provided to the coordinators and Exercise Rehabilitation staff. This data must be entered into the eCRF within 24 hours.

CLEVER STUDY EXERCISE REHABILITATION DATA SHEET

For all baseline data, use the treadmill test that had the higher Maximum Walking Duration (MWD)

Baseline SPEED when claudication pain first noticed:

Baseline GRADE when claudication pain first noticed:

Baseline DURATION (TIME) when moderate (level 4) claudication pain first noticed*:

***First Exercise Workload: SPEED should be 2 mph, and GRADE should be set the same as when claudication pain started on the better of the two baseline treadmill tests**

Date								
For each date, please record the following:								
Treadmill SPEED								
Treadmill GRADE								
Walk until moderate (level 4) claudication is experienced. Please record the DURATION of each bout of walking, and the DURATION of rest between each bout:								
Start	WALKING (min/sec)							
	REST (min/sec)							
2nd Walking Episode	WALKING (min/sec)							
	REST (min/sec)							
3rd Walking Episode	WALKING (min/sec)							
	REST (min/sec)							
4th Walking Episode	WALKING (min/sec)							
	REST (min/sec)							
5th Walking Episode	WALKING (min/sec)							
	REST (min/sec)							
6th Walking Episode	WALKING (min/sec)							
	REST (min/sec)							
7th Walking Episode	WALKING (min/sec)							
	REST (min/sec)							
8th Walking Episode	WALKING (min/sec)							
	REST (min/sec)							
9th Walking Episode	WALKING (min/sec)							
	REST (min/sec)							
10th Walking Episode	WALKING (min/sec)							
	REST (min/sec)							
****If the "Start", or first walking, exceeds 8 minutes, please increase treadmill grade 2% for the next session***								
Time required for travel to and from the exercise rehabilitation center:								
Reason for unexpected absences:								

B. ADHERENCE TO PHYSICAL ACTIVITY (EXERCISE MAINTENANCE)

Physical activity counseling has been evaluated the primary care settings in several studies, including three short-term studies[91-93] and two long-term multiple risk factor studies[94,95]. Although intensive physician based interventions have been shown to significantly increase activity at one year[95], these efforts are expensive and not widely available. Given the pressures among primary care doctors to see increasingly more patients, it is unlikely that this strategy can be implemented on a wide scale.

Due to the costs of direct physician or other health care worker involvement, there is an increasing interest in developing interventions to promote physical activity that did not involve face-to-face contact with health professionals[96]. Therefore, some automated or semi-automated behavioral modification techniques would need to be enforced through education and the patient's initiative at some point in time. In a recent study, Castro and colleagues[97] compared two maintenance approaches among adults (50 to 65 years old) who had previously participated in a home-based exercise intervention. The home-based intervention consisted primarily of telephone counseling, written materials and exercise monitoring. Half the sample were instructed to exercise at 73-88% of maximum heart rate (three 60-min. sessions per week) and the other half at 60-73% of maximum heart rate (five 30 min. sessions per week). In Year 2, the subjects were randomized to receive either continued monthly telephone and mail contact or predominantly mail contact. The results showed that among those who exercised at lower intensity (more similar to the moderate-intensity exercise prescribed for patients with peripheral vascular disease), exercise levels were maintained throughout Year 2 (2-3 sessions per week) regardless of the type of maintenance contact[97]. The investigators speculated that the lack of added benefit of telephone counseling could have been due to the subjects' previous year-long exposure to telephone-based counseling. We do not expect that this problem will occur among patients who have participated in a 6 month on-site supervised exercise program. We have opted to perform a maintenance program for 12 months following exercise rehabilitation using very low cost and labor-nonintensive methods such as two-way mail communications between 6 and 18 months, written educational materials, regular telephone consultations and feedback score cards for daily activity logs. Participants will be encouraged to wear their pedometers each day and record steps walked each day in their activity logs. We will not provide supervised exercise rehabilitation maintenance after the initial six months as part of this study in the supervised exercise intervention group, but will focus on physical activity counseling during this period for this treatment group. We do not expect that exercise maintenance activities will need to be started during the period of supervised exercise as the one-to-one attention provided and frequency of these sessions is in itself motivational. We do have a plan to encourage attendance at these sessions as outlined below.

During the maintenance phase of the program, we will offer an intervention that was delivered over the telephone to promote exercise among older, primary care patients by Dr. Pinto[98]. In that experience, after receiving brief advice to exercise from their primary care physician, half the patient sample received exercise counseling on the telephone.

Exercise activities included moderate- intensity exercise such as brisk walking, swimming or use of home exercise equipment. Staff used the telephone calls to monitor exercise participation, identify relevant health problems, problem solve any barriers to exercise, and reinforce and encourage patients to exercise. Over 6 months, the frequency of telephone contacts were gradually tapered from weekly to bi-weekly and then to monthly calls. At both 3 and 6-month assessments, the extended telephone counseling group reported higher levels of exercise than the comparison group. Objective monitoring of exercise using electronic activity monitors (pedometers) supported the self-reported data. Researchers have also used a similar telephone-based intervention successfully to promote exercise adoption among breast cancer survivors[99].

Since research has found that telephone-based interventions are effective in helping older adults to exercise[98], we will offer this intervention to patients who have completed a 6-month on-site supervised exercise program to maintain their exercise for the remainder of the study (from months 6 through 18). We will also provide educational and behavioral change materials to this study group. The specifics of both behavioral interventions are outlined below:

Telephone-based maintenance counseling
Contact between the Health Educator (HE) and the study participant will begin during the fifth month of supervised exercise. During the fifth and sixth months, the HE will call the participant one time each month and discuss the process that will occur after the completion of supervised exercise and the reasons for it. The goal for the 14-month program will be to maintain the amount of walking per the exercise prescription provided at the end of the supervised exercise program. Calls with the HE will be conducted twice monthly for months 7-12. During the final six months (months 13-18), the calls will tapered to once a month to help patients to recover from any lapses from exercise and resume regular exercise. The Health Educator (HE), supervised by Dr. Beth Lewis, will be trained to provide brief (approximately 12-15 minutes.) exercise education using a patient-centered model that has five steps: (1) ASSESS current stage of motivational readiness for exercise, confidence in maintaining exercise, perceived barriers and benefits to exercise, (2) ADVISE about the benefits of regular exercise for secondary prevention of cardiovascular disease, provide personalized messages based on medical history and risk, (3) AGREE with the patient on a specific plan for maintaining exercise (4) ASSIST the patient to maintain exercise by matching the counseling to his/her motivational readiness and (5) ARRANGE follow-up. The 5 A's strategies were developed from a physician-delivered counseling strategy at the Smoking, Tobacco and Cancer Program, NCI[100] and have been recommended as an effective approach for integrating health behavioral counseling within medical settings by the U.S. Preventive Services Task Force[101]. Researchers have used these methods in trials of exercise promotion in the primary care setting[98,102,103], and they have been recommended as an effective approach for integrating health behavioral counseling within medical settings by the U.S. Preventive Services Task Force[101].

At about halfway through month 4 of the supervised portion, the on-site staff will begin to introduce and discuss, with patient, the transition to the phone calls, including the pedometer, exercise logs, tip sheets, and phone counselor's name. The participant will receive a packet of information developed by the Adherence to Physical Activity Committee which will include the exercise logs, tip sheets, stamped envelopes, and phone counselor contact information. During month 5 and month 6, the HE will contact each participant in the supervised exercise group to continue the dialogue, foster the relationship, set up a regularly scheduled call time, ask the participant if he/she has any questions, and discuss what will be expected when supervised exercise stops, including exercise as described for the optimal medical care (OMC) group. Exercise will be recommended at least 3 times a week with a goal of 5 times, lasting at least 30 minutes and up to one hour each time. Participants will be asked to exercise by walking to the point of pain, keep walking until 60% maximum pain, stop and rest until pain resolves, then start again up to the time 30 or 60 minute time limit. In addition to the instructions for exercise that the investigators will provide to the study participant at the 6 month data collection visit, the HE will contact each patient and encourage continued exercise. The HE will begin the primary behaviorally-based counseling starting in month 7. The HE will contact each patient by telephone bi-weekly over months 7-12, and monthly over months 13-18 (total of 20 calls), and calls will be monitored as described in the section below. Each call will take about 10 minutes. The purpose of these contacts is to build on the supportive relationship established during the on-site supervised exercise program, assess motivational readiness, perceived barriers/benefits of exercise, monitor exercise behavior, identify any health concerns, assist the patient to identify relevant barriers to maintaining exercise and help him/her to problem solve to overcome such barriers (e.g., time constraints, perceived barriers such as, "I would worsen any existing health problem if I exercise regularly," and "Exercising regularly could lead to injury." The HE will remind patients about the benefits of regular walking in reducing cardiovascular disease risk, help maintain/improve health, and maintain independence. Another role of the HE is to provide feedback, and reinforce and encourage the patient's attempts to stay active. The counseling will be tailored to address each patient's motivational readiness to change. At the end of the supervised exercise program, we expect that a majority of the participants who have stayed with the program will be exercising (Preparation or Action stages of motivational readiness); however it is possible that after the supervised program ends, some patients may slip back to Contemplation (not currently exercising but intending to exercise) or even to Precontemplation (not currently exercising and not intending to begin). These participants will be given messages and feedback to increase their awareness of the benefits of walking for their symptoms. Those who are exercising below the prescribed levels will receive more specific information on how to increase exercise in a safe and appropriate manner (e.g., to reduce risk of cardiac symptoms). Those who are exercising at prescribed levels will be guided on finding ways to make exercise enjoyable, anticipate slips from an exercise routine and ways to recover from slips so as to maintain regular exercise. They will be encouraged to prepare for potential lapses in their exercise regimen and learn ways of recovering from such lapses (or relapses) and resuming exercise. They may also experience boredom with exercise and hence, perceived enjoyment of exercise will be assessed and when necessary, the study staff

will help patients to identify and explore other forms of exercise that they may enjoy. The patient's health status and risk will be fed back to him/her to enhance motivation to change. Additionally, they will be guided in developing self-management techniques necessary for exercise adherence.

The Health Educator will also be trained to respond to and address health concerns relevant to this patient population. If participants report physical symptoms such as chest pain, or difficulty breathing, they will be referred to their cardiologist or primary physician. With the patient's permission, the Health educator will inform the cardiologist about any significant new symptom experienced by the participant.

The HE will document the delivery of telephone calls (the number of calls, their duration, the main issues discussed, the exercise plan discussed on the call, etc.), as has been done in previous trials. This will be documented in the database kept by Dr. Lewis and the research team at the University of Minnesota. The telephone counseling protocol used by other researchers for primary-care patients and breast cancer patients will be adapted for the trial. In an exercise intervention for primary care patients[98] 86% of the scheduled exercise phone contacts (mean duration=14.7 minutes) were delivered over the 6 month program, and preliminary results show higher moderate-intensity exercise in the group that received the telephone counseling at 6 months. In an exercise trial for breast cancer patients, 94% of scheduled telephone calls[99] were delivered and found that the Intervention group reported significantly greater moderate-intensity exercise at 3 months. This experience and those of other researchers[104,105] show that exercise maintenance can be enhanced through the use of periodic telephone contact to address patients' concerns and to review exercise logs.

Educational/Behavioral Change Components

To complement the support offered via telephone calls, SE participants will be provided printed materials that will include: (1) exercise tip sheets, (2) logs to record exercise, and (3) a pedometer. (1) Exercise tip sheets: These will be adapted from those used in the exercise intervention for primary care patients: 92% of the group reported that the tip sheets were useful in helping them to become active, 75% read all 14 tip sheets and all reported that the tip sheets were easy to read[98]. The tip sheets will be modified to provide guidance on cardiovascular health benefits of exercise, pros and cons of regular exercise and tips on maintaining exercise. The content will be based on behavioral and social-cognitive concepts relevant to exercise maintenance (e.g., getting natural social support systems to sustain exercise[106,107]). Participants in the Supervised exercise/lifestyle intervention arm will receive an exercise tip sheet once a month (months 6-12). These materials, along with the counseling, identifying barriers to regular exercise and overcoming these barriers, will work towards increasing the subject's self-efficacy for exercise, that may enhance readiness to stay active and maintain exercise participation[108]. (2) Exercise logs: Patients will be asked to monitor frequency, duration, and intensity of exercise (and side-effects, if any). These logs will be used for problem solving during the telephone contacts. In our previous study with older, primary care patients, those assigned to the Extended Advice were expected to log their weekly/monthly exercise that was discussed at a subsequent telephone call with study

staff. Research by Dr. Pinto found that a majority of the participants were able to report their weekly exercise participation[98]. Exercise logs will be mailed to the Health Educator after each call in a provided self-addressed envelope. Exercise logs will be reviewed during all biweekly and monthly calls with Health Educator during months 7-12 to help encourage continued exercise. Log information will be entered into a database maintained at HealthPartners Research Foundation. Descriptive data summaries and exploratory analyses on intervention delivery will be conducted by the Adherence to Physical Activity Committee. Patients will also be given a pedometer (Omron Pedometer model HJ-112) to keep at the end of the supervised exercise program. They will be encouraged to wear the pedometer during their planned walking sessions and record the steps on their logs. The pedometer will provide more immediate feedback to participants on their progress. The readings will also be reviewed during the telephone calls thereby providing more opportunities for the Health educator to provide reinforcement and encouragement.

Quality control of the HE telephone calls will be done. During the study, all "maintenance" telephone contacts with participants will be audio-tape recorded, and a random sample (10%) of the calls will be audited on an ongoing basis by the Adherence to Physical Activity Committee (i.e., adherence to tailoring of exercise education to the participant's motivational readiness). Corrective feedback and coaching will be provided as needed.

Process evaluation is important for understanding the successes and failures of health and social programs. The process indicators will monitor whether the maintenance intervention is delivered as designed. The HE will be trained to complete detailed logs on telephone counseling (e.g., assessment of exercise, overcoming barriers to exercise participation), tipsheets and exercise logs delivered to each participant during the maintenance phase.

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APPENDIX F: SCHEDULE OF ASSESSMENTS

Interval	Baseline Visit 1 (Day -8)	Baseline Visit 2 (Day 0**)	3 times weekly to Wk 26	Biweekly Months 7-12	Monthly Month 13-18	Quarterly	Month 6, 18 and pre-Crossover Visit
Window of assessment	**NA (many of these may be in the record or done prior to the visit)**	**Usually +/- 14 days; absolutely ±60 days**	**NA**	**±1 Week**	**±1 Week**	**±2 weeks**	**±2 weeks**
Visit Type	*Clinic*	*Clinic*	*Clinic*	*Phone*	*Phone*	*Clinic*	*Clinic*
Review Screen Criteria[1]	X						
Informed Consent[2]	X						
History and brief Physical Exam for BP/height/ weight/waist circumference and limb threatening ischemia.	X						X
San Diego Claudication Questionnaire	X						
ABI/Thigh BI	X						X
Duplex Ultrasound / CFA Systolic Acceleration Time	X						
Biochemistry Samples		X					X
Gardner Treadmill Test	X	X					X
7 Day Electronic Step Monitoring[3]		X					X[4]
Treatment Assignment[4] OMC Stent Supervised Exercise / Adherence		 X[5] X[5] X[5]	 X	 X	 X X[6] X[7]		
Health Cost Data Collection[5]				X			X
Quality of Life Questionnaires		X					X
Independent Exercise Assessment[8]		X					X
Adverse events		X			X[6,7]	X	X
Concurrent Medications		X				X	X

Cilostazol Dispensed/Pill Count		X				X	X

[1] HIPPA waiver and consent required for all subjects referred to CLEVER study site.
[2] Informed consent required prior to all invasive testing and for subjects referred to study site for study screening.
[3] Pedometer is issued to subject after 1st baseline treadmill test; provide usage instructions to subject; 7 days prior to Month 6 & 18 visit reminder call to subject is made to subject for pedometer use compliance.
[4] Randomization occurs after 2nd baseline treadmill test is performed and investigator reviews subject's final eligibility based upon test result being within 25% of first treadmill test result.
OMC: Subject is provided brochure on usual care instructions;
Stent: Revascularization procedure is scheduled to occur within 14 days post-randomization;
Supervised Exercise/ Adherence: Initiate exercise visits within 14 days post-randomization;

[5] This information is collected directly by the EQOL core lab; the only obligation is to collect the patient diaries quarterly and upload any adverse events, hospitalizations, or other medical resource utilization in the eCRF
[6] Subjects randomized to stent procedure are assessed ***at clinic*** at day 30; all subjects are assessed for adverse events at each contact.
[7] In months 5 and 6, the Health Educator will call subject monthly to discuss transition to adherence to physical activity phase of study.
[**] Day of randomization is considered "day zero", in many that will be the same day as baseline 2 treadmill test (see section 3.5.2).

APPENDIX G: CONCURRENT MEDICATION LISTING

Trade	*Generic*	*Drug Class*
Accupril	Quinapril	ACE Inhibitor
Aciphex	Rabeprazole Sodium	Proton Pump Inhibitor
Activase, t-PA	Alteplase	Thromobytic
Actos	Pioglitazone	Diabetic Medication
Advicor	Lovastatin and niacin	Lipid Lowering Agent
Aggrastat	Tirofiban	Antiplatelet
Aggrenox	Dipridamole/ASA	Antiplatelet
Agrylin	Anagrelide	Antiplatelet
Altace	Ramipril	ACE Inhibitor
Amaryl	Glimepiride	Diabetic Medication
Amicar	Aminocaproic acid	Hematological agent
amlodipine (Norvasc), felodipine, nifedipine (procardia, adalat), isradipine, nisoldipine (Sular) cardene	Dihydropyridines	Calcium Channel Blocker
Ansaid	Flurbiprofen	NSAID
Arthrotec	Diclofenac/ Misoprostol	NSAID
Aspirin	Acetylsalicylic acid	NSAID
Atacand	Candesartan	Angiotensin II Inhibitor

Trade	***Generic***	***Drug Class***
Avandia	Rosiglitazone	Diabetic Medication
Avapro	Irbesartan	Angiotensin II Inhibitor
Axid	Nizatidine	H2 Blocker
Betapace	Sotalol	Betat Blocker (ß1,ß2)
Blocadren	Timolol	Beta Blocker (ß1,ß2)
Brevibloc	Esmolol	Beta Blocker (ß1)
Caduet	Amlodipine and Atorvasttatin	Combination Anti-hypertensive
Calan, verelan, covera, isoptin, dilacor XR	Verapamil	Calcium Channel Blocker
Calcium channel blocker and hydrochlorothiazide	Calcium channel blocker and Hydrochlorothiazide	Combination Anti-hypertensive
Capoten	Captopril	ACE Inhibitor
Cardizem, tiazac, cartia	Diltiazem	Calcium Channel Blocker
Celebrex	Celecoxib	NSAID
Clinoril	Sulindac	NSAID
Coreg	Carvedilol	Beta Blocker (ß1,ß2, alpha)
Corgard	Nadolol	Beta Blocker (ß1,ß2)
Cozaar	Losartan	Angiotensin II Inhibitor
Crestor	Rosuvastatin	Lipid Lowering Agent (HMG COA Reductase Inhibitor)

Trade	*Generic*	*Drug Class*
Daypro	Oxaprozin	NSAID
Diovan	Valsartan	Angiotensin II Inhibitor
Disalcid	Salsalate	NSAID
Dolobid	Diflunisal	NSAID
Epogen	Erythropoietin	Hematological agent
Feldene	Piroxicam	NSAID
G-CSF, Neupogen	Filgrastim	Hematological agent
Ginko Biloba	Ginko Biloba	Over the counter medication
Glucagon	Glucagon	Diabetic Medication
Glucophage	Metformin	Diabetic Medication
Glucotrol	Glipizide	Diabetic Medication
Glycet	Miglitol	Diabetic Medication
Heparin	Heparin	Anticoagulant
Inderal	Propranolol	Beta Blocker (ß1,ß2)
Inderide	HCTZ and propranolol	Combination Anti-hypertensive
Indomethacin	Indomethacin	NSAID

Trade	***Generic***	***Drug Class***
Integrilin	Eptifabatide	Antiplatelet
Ismo, Monoket	Isosorbide mononitrate	Nitrates
Isordil	Isosorbide dinitrate	Nitrates
Kerlone	Betaxolol	Beta Blocker (ß1)
Lescol	Fluvastatin	Lipid Lowering Agent (HMG COA Reductase Inhibitor)
Lexxel	Enalapril and Felodipine	Combination Anti-hypertensive
Lipitor ®	Atorvastatin	Lipid Loweirng Agent (HMG COA Reductase Inhibitor)
Lodine	Etodolac	NSAID
Lopid	Gemfibrozil	Lipid Lowering Agent (Triglyceride)
Lopressor	Metoprolol	Beta Blocker (ß1)
Lotensin	Benazepril	ACE Inhibitor
Lotrel	Amlodipine and Benazepril	Combination Anti-hypertensive
Lovenox	Enoxaparin	Anticoagulant
Mavik	Trandolapril	ACE Inhibitor
Mevacor	Lovastatin	Lipid Loweirng Agent (HMG COA Reductase Inhibitor)
Micardis	Telmisartin	Angiotensin II Inhibitor

Trade	*Generic*	*Drug Class*
Micronase, Diabeta	Glyburide	Diabetic Medication
Monopril	Fosinopril	ACE Inhibitor
Motrin	Ibuprofen	NSAID
Naprosyn	Naproxen	NSAID
Neumega	Oprelvekin	Hematological agent
Niaspan, Niacin etc.	Niacin	Lipid Lowering Agent
Nitrobid	Nitrobid	Nitrates
Nitroglycerin ointment:	Nitroglycerin ointment:	Nitrates
Nitroglycerin transdermal	Nitroglycerin transdermal	Nitrates
Normiflo	Ardeparin	Anticoagulant
Normodyne	Labetalol	Beta Blocker (ß1,ß2, alpha)
Omacor, OTC, etc. Variable Dose	Fish Oil	Lipid Lowering Agent
Orgaran **Removed from the market**	Danaparoid	Anticoagulant
Orudis	Ketoprofen	NSAID
Pepcid	Famotidine	H2 Blocker
Persantine	Dipyridamole	Antiplatelet

Trade	***Generic***	***Drug Class***
Plavix	Clopidogrel	Antiplatelet
Pletal	Cilostazol	Hematological agent
Prandin	Repaglinide	Diabetic Medication
Pravachol	Pravastatin	Lipid Loweirng Agent (HMG COA Reductase Inhibitor)
Precose	Acarbose	Diabetic Medication
Prevacid	Lansoprazole	Proton Pump Inhibitor
Prilosec	Omeprazole	Proton Pump Inhibitor
Prinivil	Lisinopril	ACE Inhibitor
Refludan	Lepirudin	Anticoagulant
Relafen	Nabumetone	NSAID
Reopro	Abciximab	Antiplatelet
Retevase	Reteplase	Thromobytic
streptokinase	streptokinase	Thromobytic
Tagamet	Cimetidine	H2 Blocker
Tarka	Trandolapril and Verapamil	Combination Anti-hypertensive
Ternomin	Atenolol	Beta Blocker (ß1)

Trade	***Generic***	***Drug Class***
Teveten	Eprosartan mesylate	Angiotensin II Inhibitor
Ticlid	Ticlopidine	Antiplatelet
Toradol	Ketorolac	NSAID
Trental	Pentoxifylline	Hematological agent
Tricor	Fenofibrate	Lipid Lowering Agent (Triglyceride)
Univasc	Moexipril	ACE Inhibitor
Urokinase	Urokinase	Thromobytic
Vasotec	Enalapril	ACE Inhibitor
Visken	Pindolol	Beta Blocker (ß1,ß2, ISA)
Voltaren, Cataflam	Diclofenac	NSAID
Vytorin	Ezetimibe/ simvastatin	Lipid Lowering Agent
Warfarin	Warfarin	Anticoagulant
Zantac	Ranitidine	H2 Blocker
Zebeta	Bisoprolol	Beta Blocker (ß1)
Zetia	Ezetamibe	Lipid Lowering Agent
Zocor	Simvastatin	Lipid Loweirng Agent (HMG COA Reductase Inhibitor)

APPENDIX H WAIST CIRCUFERENCE MEASUREMENT PROTOCOL

Instructions for Measuring Waist Circumference, According to NHANES III Protocol

Instruct the participant to remove any extra layers of clothing or belts (only non-binding undergarments can be worn). Ask the patient to remove girdles, binding pantyhose, and all outer clothing. Instruct him/her to stand with weight distributed evenly on both feet, abdomen relaxed, arms at sides and feet together.

To define the level at which waist circumference is measured, a bony landmark is first located and marked. The subject stands and the examiner, positioned at the right of the subject, palpates the upper hip bone to locate the right iliac crest. Just above the uppermost lateral border of the right iliac crest, a horizontal mark is drawn, then crossed with a vertical mark on the midaxillary line. The measuring tape is placed in a horizontal plane around the abdomen at the level of this marked point on the right side of the trunk. The plane of the tape is parallel to the floor and the tape is snug, but does not compress the skin. The measurement is made at a normal minimal respiration.

Measurements should be taken twice until two consecutive measurements are within 1 cm of each other. Record the each of the two measurements, rounding to the nearest half centimeter

REF: U.S. Department of Health and Human Services, PHS. NHANES III Anthropometric Procedures Video. U.S. Government Printing Office Stock Number 017-022-01335-5. Washington, D.C.: U.S. GPO, Public Health Service; 1996. (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=obesity.box.236)

APPENDIX I: INFORMED CONSENT TEMPLATE

****

Affiliate	☒<Blank> Hospital	☐<Blank> Hospital
	☐<Blank> Hospital	☐<Blank> Hospital

Agreement to Participate in a Research Study

_____ _____
Committee # Name of Study Volunteer

Claudication: Exercise Vs. Endoluminal Revascularization (CLEVER)

You are asked to take part in a research study. All research studies carried out at <blank hospital/institutions> are covered by rules of the Federal government as well as rules of the State and <blank hospital/institution>. Under these rules, the researcher will first explain the study, and then he or she will ask you to participate. You will be asked to sign this agreement. By signing this consent document, you agree that the study risks, benefits and procedures have been explained to you, that your questions have been answered, and that you agree to volunteer in this study.

The principal investigator for this study at <institution> is <blank>. His/her telephone number is <blank>. The lead research coordinator for this study at <blank> is <blank>, and her telephone number is <blank>. If you have a medical problem during nonworking hours, please contact your doctor, go to the emergency room, or call 911.

This study is sponsored primarily by the National Institutes of Health National Heart, Lung, and Blood Institute. Support for this study was also received by Otsuka Pharmaceuticals, Boston Scientific, Cordis/Johnson&Johnson, and Guidant Corporation.

The researcher will explain the purpose of the study. He or she will explain how the study will be carried out and what you will be expected to do. The researcher will also explain the possible risks and possible benefits of being in the study. You should ask the researcher any questions you have about any of these things before you decide whether you wish to take part in the study. This process is called informed consent.

This form also explains the research study. Please read the form and talk to the researcher about any questions you may have. Notify your physician or research

coordinator if you are pregnant, planning on becoming pregnant, or lactating. If so, you are not eligible for this study. Then, if you decide to be in the study, please sign and date this form in front of the person who explained the study to you. You will be given a copy of this form to keep.

1. Nature and Purpose of the Study

You have been diagnosed as having blockages in your arteries due to a medical problem called "peripheral arterial disease". These blockages are causing symptoms such as pain or cramping in your leg muscles when you walk, called "claudication". The most effective treatment for claudication is unknown. Treatment options may include vascular surgery (replacing a portion of your artery), stent placement (a metal tube placed through the catheter into your artery), exercise therapy, or medications. At the current time, it is not clear which of these treatments is most beneficial and safe. The purpose of this study is to evaluate the use of stents compared to supervised exercise therapy (exercise rehabilitation), and to also compare each of these treatments to optimal medical care. Optimal medical care for most people with claudication includes encouragement to stop smoking, use of home-based unsupervised exercise, and use of claudication medications. If you agree to join the study, the total commitment to this study is 18 months. During that time, data will be collected at 3 intervals: baseline, 6 months, and 18 months. The baseline data collection requires 2 visits separated by at least 7 days.

Approximately 130-150 participants will be enrolled in the research study.

The following description of the study and study procedures is provided so that you can clearly understand the information about this study before agreeing to participate and signing your name on the final page. Your doctor will also explain all treatment procedures to you.

2. Explanation of Procedures

To determine your eligibility for this study, you will be asked to have screening tests. You will undergo a brief history and physical exam, and your local investigator may review some of your imaging tests. You will undergo measurement of the blood pressure in your arms and legs. To obtain blood pressure in the legs, blood pressure cuffs will be applied and inflated on your upper thighs and at your ankles. If these values are abnormal, you may have an ultrasound exam (an exam using sound waves to form images of the body that involves placing a gel on your legs, and a sensing device (a wand or "probe") across the skin to examine the blood vessels). Depending on the results of all of these evaluations, you may then undergo a specialized exercise treadmill test. The screening tests should take about 2 hours to complete.

If the results of the screening tests show that you are eligible to participate in this study, you will be given a pedometer to wear for 7 consecutive days during your waking hours. You will be asked to return in 1-2 weeks to complete brief questionnaires about your walking ability and about your quality of life. During this visit, the following procedures

will be done. You will undergo a 2nd exercise treadmill test and repeat ankle-brachial pressure measurements (blood pressure cuffs applied and inflated on your legs and arms). A blood sample of approximately 3 teaspoons will be taken. Your height, weight, and waist circumference will be measured.

After completing the questionnaire and the treadmill tests you will be randomly assigned (like the toss of a coin) to one of three treatment groups: placement of a stent in a leg artery(ies), supervised exercise therapy in a rehabilitation program, or optimal medical care (defined as encouragement to stop smoking and walk regularly). All study participants will receive study medication, cilostazol (Pletal, Otsuka Pharmaceuticals), known to improve symptoms of claudication without charge throughout the study if tolerated.

All procedures and treatments being evaluated in this study are considered accepted standard of care therapy that are routinely provided by doctors in the U.S. and elsewhere for people with claudication. The purpose of this study is to compare commonly provided treatments for intermittent claudication to determine which is the most effective. Some of the stents used in this study are investigational devices when used in iliac arteries (i.e. they are biliary stents indicated for use in the liver instead of in blood vessels such as the iliac artery). However, it is very common for doctors in the United States to use biliary stents to treat blockages in blood vessels, including iliac arteries. The devices to be used in this study have been approved by the FDA and therefore available for vascular use by physicians since between April 12, 2001 and June 1, 2004.

A sample of the blood taken during the study may be frozen to allow for potential future research. Any such research using these samples will be approved by an Institutional Review Board, like the one that has approved this study. When such research is done, the investigators using these samples will not receive any information that would identify you (like your name, medical record number, or social security number). You can change your mind about the use of these samples at any time. The results of this testing will not be told to you and will not be placed into your medical record, unless you request that at the end of this form. If you do so, your results will be transmitted back to your local researchers and they will match your results to your identity and contact you with the results. Your samples will only be used for research and will not be sold.

This study also contains a health economics review (analysis of costs) that will be done to compare medical care costs for the three treatment strategies being tested in this study. As part of this study, you will be asked to sign a Medical Billing Release Form. This form will be used by the Economic and Quality of Life Assessments Group of the Harvard Clinical Research Institute (HCRI) to collect hospital bills from the patient accounting department at any hospital to which you are admitted, from the time of your enrollment in CLEVER through the study follow-up period. Subject diaries will also be a part of the economic study. You will be asked to keep this diary and enter health care interactions that you may have during follow up period. All health economic information

will be kept strictly confidential and be used solely to assess the medical expenses that occur as a direct result of participating in the CLEVER trial.

Also, as part of this study, your research coordinator will have you, or a person you permit (your proxy) complete a questionnaire called a Quality of Life Survey during your enrollment in the study. Part of this survey will also be completed with your research coordinator at the 6 and 18 month follow-up visits. You will be asked to sign a Patient Address Form as part of this study. This form will be used by the Economic and Quality of Life Assessments Group, at the Harvard Clinical Research Institute (HCRI), to contact you or your proxy via mail or telephone to answer questions regarding your overall health status. You will answer questions about your general health, and symptoms that you may or may not have (i.e. leg pain, shortness of breath, ability to walk, etc). All of your responses to the questions will remain completely confidential and you may choose not to answer any question. The time points of contact will be at 6 months and 18 months.

2.1 Procedures for those randomized to optimal medical care:
If you are randomized to "optimal medical care" group, you will receive the care that many of those with intermittent claudication receive: advice and referral if needed for smoking cessation, verbal recommendations to exercise by walking as much as possible (at least three times a week) and free supplies of the drug cilostazol. You will be contacted monthly, by a member of the study, to identify any health concerns you may have.

2.2 Procedures for those randomized to stenting:
If you are randomized to stent placement, you will receive care similar to that described in the optimal medical care section above, plus you will undergo a diagnostic test known as an arteriogram, which is an x-ray of your blood vessels of your abdomen and leg arteries (iliac, femoral and/or popliteal) that uses a dye (also called "contrast") to see your blood vessels. The arteriogram is done by placing a catheter (tube) into the artery in your groin and passing it through the arteries in your pelvis and abdomen, to the artery to be examined. The "contrast" is administered via this catheter to permit the physicians to see your arteries on x-rays.

If you agree to have a stent(s) placed, the stent(s) will be placed via a small tube or catheter into an artery in your abdomen (aorta) or pelvis (iliac artery). The stent(s) will support the walls of the artery and allow the blood to pass freely through the artery. A balloon may be used to enlarge the opening within the stent after it is placed in the artery. This angioplasty (balloon inflation) and stent procedure will be done in a radiological suite to permit x-ray guidance for the placement of the catheters and the stent(s).

After the stent(s) is (are) in place, x-ray pictures will be taken to decide if the artery is open and if the stent needs to be enlarged with a balloon. Once the stent is in place and the artery is open, all the catheters (tubes) will be removed and pressure will be applied to your groin area. Your x-ray images from your arteriogram, or other vascular tests,

will be sent to the clinical coordinating center for this study at Rhode Island Hospital. All of these tests will be maintained strictly confidential in the clinical coordinating center and identifiable information will not be sent from the clinical coordinating center to any data center, site, or other person outside of the clinical coordinating center.

At any time after treatment, you may be asked to have a repeat arteriogram, if your symptoms or test results worsen and your doctor and feels that it is necessary to re-evaluate your artery(ies) or the stent. Repeat angioplasty or stent placement, in your artery (ies), may be done again to treat your artery(ies).

Bypass surgery for a blockage in your artery(ies) is not a study treatment but may be needed clinically if your peripheral arterial disease severely worsens, and your symptoms progress beyond claudication and result in foot pain at rest, skin ulceration, or gangrene. If your doctor decides that you require bypass surgery of your leg artery(ies), your research doctor or nurse should be told immediately, so that you may have some repeat tests done before the surgery is performed. This possibility is described below in section 2.5.

You will be contacted monthly, by a member of the study, to identify any health concerns you may have and to inquire about changes in your health status.

2.3 Procedures for those randomized to supervised exercise/exercise maintenance:

If you are randomized to the supervised exercise/adherence to physical activity group, you will receive a free supply of the drug cilostazol and you will be asked to attend free supervised exercise therapy classes for one hour three times a week for 26 weeks. Usually, these sessions will be conducted at rehabilitation centers used for cardiac or pulmonary rehabilitation. Facilities will be staffed by nurses, doctors, and often exercise specialists. At exercise classes, you will exercise on a treadmill in the presence of an instructor. In addition to being monitored by this staff, a central study committee also will monitor your progress and increase your exercise regimen based upon the results of each exercise session. At month 5, you will be assigned a health educator, who will contact you by telephone once a month in months 5 and 6, then every 2 weeks during months 7-12, and then once a month in months 13-18. The purpose of this health educator is to help motivate you to maintain a healthy, physically active lifestyle. Each call will take about 10 minutes. You will also receive educational and motivational materials by mail, and will be asked to complete a specially designed exercise log book to review on the telephone with your health educator.

2.4 Follow-up Procedures for all treatment groups:

Cilostazol medication will be provided throughout the study without charge. You will receive a telephone call every month during the study to review any health changes and to see if you have any questions about your participation. If you experience any new symptoms during this study, you should tell your research doctor or nurse. If at any time the symptoms are severe you can go to the emergency room, or call 911.

You are asked to return every 3 months to receive a new supply of cilostazol. During your 6 and 18 month follow-up visits you will also have a repeat exercise treadmill test, and have repeat ankle-brachial pressures on your legs performed. Brief demographic and medical information will be gathered, and blood work will be repeated. You will also be asked to complete one additional questionnaire in person with your research coordinator. During these visits you will also be asked about hospital admissions or hospital treatments, your use of other medical resources for example at your doctor's office, and will answer health-related questionnaires similar to your screening visit.

The total length of your participation in this study is 18 months. After you have completed all follow-up visits, you will be reimbursed $250.00 for your time and travel. If you are in the supervised exercise group, you will receive up to an additional $15 per exercise training session for time, travel, and expenses (up to $1,170 total).

Finally, if you have any questions during this study, you can contact your research coordinator or principal investigator at the telephone numbers listed at the beginning of this form. Should you have any questions concerning this project you may call <Principal Investigator> at <phone number>.

2.5. Procedures for Subjects with Disease that Worsens to Critical Limb Ischemia

During this study, it is possible that your peripheral arterial disease may worsen and you will have more frequent or more severe symptoms. ***If you agree to participate in this study, you are specifically asked to not undergo vascular bypass surgery or other artery procedure (angioplasty, stent placement) outside of this study during the study period unless your symptoms progress beyond claudication to symptoms such as pain in the foot at rest, skin ulceration, or gangrene. If these symptoms arise, you are asked to contact your local investigator to discuss necessary treatment.*** The need to open blocked arteries when these conditions are present is usually not an emergency. If such conditions are detected, you will be informed that your disease has worsened and will be offered recommendations for additional treatment, including revascularization either by surgery or catheter-based means, like stent placement. You will be asked to have a study visit to provide data prior to having this additional recommended treatment. All study data collected at baseline, including treadmill testing, will be collected if possible.

3. Discomforts and Risks

The discomfort and risks associated with screening procedures and study participation are: the time lost in undergoing a brief physical examination, performing multiple treadmill tests, undergoing Doppler ultrasound testing, blood sampling, leg blood pressures, having an invasive procedure with exposure to contrast dye in order to balloon and stent a blockage in the artery(ies) of the leg, increasing regular exercise activity and answering health questionnaires and quality of life questionnaires. Specific risks and discomforts for the more invasive and challenging tests performed in this study are described below in further detail:

Treadmill Test

Lightheadedness, dizziness, shortness of breath and chest pain can be associated with the treadmill test and you will be monitored closely to try and avoid any of these problems. In addition, very rare (3-4 out of 10,000) patients may have a heart attack or die during the treadmill test.

Segmental Leg Pressures and Doppler pressures
You may experience pressure in your legs (from the blood pressure cuffs) as the pressure evaluations are being performed similar to when blood pressure is obtained from the arm. You may feel mild pressure as the ultrasound wand is passed over your abdomen.

Supervised exercise
For those assigned to perform exercise training, there is the potential risk of exercise precipitating a heart attack. The incidence of death among participants in cardiac rehabilitation programs is about 1/750,000 hours patient hours of participation, the incidence of cardiac arrest is 1/117,000 patient hours and the incidence of non-fatal myocardial infarction is 1/220,000 patient hours. Other potential complications that can be seen with exercise training are: heart rhythm problems, which could be life-threatening or fatal, heart attacks, heart failure, low blood pressure and shock, musculoskeletal trauma, severe fatigue sometimes persisting for days, dizziness, fainting, body aches, or delayed feelings of illness.

Stent Placement
For those assigned to stent placement, there are risks related to both the diagnostic arteriogram and stent placement (including balloon angioplasty). The procedure to place the stents in the artery have the same potential risks of complications as those encountered during routine arteriography (injection of contrast or “dye” into the artery and taking x-rays). These risks include but are not limited to: blood clots on the wall of the blood vessel, a blood clot traveling in the vessel that needs treatment with medication or surgery, a tear in the wall of the vessel, an infection at the site where the catheter is placed or at the site where the stent is placed, clotting of the artery after stent placement and/or failure of the stent to open the artery, spasm (tightening), pain, bleeding at the site where the catheter is placed which sometimes causes a small collection of blood around the blood vessel, a weakness in the wall of the blood vessel, an abnormal rhythm of the heart beat, heart failure, damage to the heart muscle tissue, stroke, limb loss, and death. A reaction to the x-ray dye is rare, but it may cause brief or permanent damage to your kidneys, cause heart and lung problems or rarely death. If serious bleeding or other complications occur, an emergency operation may be required to control the problem. You may also experience burning as numbing medicine is injected at the site where the tube will be placed into the artery in your groin; and possible pressure as the stent(s) is(are) being placed.

On long-term follow-up, if you receive a stent there is a chance that the artery could become narrowed again. It is estimated that fewer than one in 5 will have this complication. If it occurs, it may be treated by your doctors by catheter-based procedures like the one you had initially to place the stent.

The approximate rate that study procedure adverse events may occur is summarized below:

Adverse Event	Severity	Expected rate of event occurrence
Bleeding from access site	Low to High	1%
Blood vessel injury or rupture	High	1%
Pseudoaneurysm	Moderate	<1%
Permanent renal failure	High	<<1%
Transient renal failure	Low	<5%
Need for surgery	Moderate to High	<1%
Death	High	<0.1%
Amputation	High	<0.5%
Artery thrombosis/occlusion	Moderate	<2%
Allergic reaction	Low to Serious	<1%
Distal embolization	Moderate	<3%
Fever	Low	<0.1%
Hypotension (low blood pressure)	Low	<1%
Hypertension (high blood pressure)	Moderate	<1%
Infection	High	<0.5%
X-ray exposure	Very Low	100%
Cardiac event related to exercise test	Very Low	<<<1%
Cardiac event related to exercise training	Very Low	<<<1%

The greatest risk associated with the storage of these blood samples for genetic testing is a possible loss of confidential information that you may not want disclosed. However, this risk has been minimized by storing your samples so that they will be identified only by code, so that they remain private and confidential. Investigators utilizing the stored samples will not have access to the code that links them to any study participant. Most narrowings can be treated with one stent; according to this protocol your doctor should use no more than two stents per narrowing, but your doctor will make the final determination based on what is needed for you.

Risks to Pregnant Women

This research represents a significant risk to unborn children. Namely, complications of the procedure could result in early termination of pregnancy, and radiation exposure to fetuses or children has been associated with increased risk of childhood cancer. Therefore, all women of childbearing age will be screened for pregnancy. This screening is standard procedure for all women of childbearing age prior to undergoing an angiogram. This screening may include a blood or urine pregnancy test. If you think that you may be pregnant or plan to become pregnant you should not participate in this study. If you become pregnant during this study, immediately contact your research physician.

4. Benefits

There are few if any benefits to undergoing the screening procedures and not enrolling in the study. You may gather some information about the status of blood flow to your extremities, blood pressure, or learn other health information. If your ability to walk, exercise and/or improve activity levels long-term is improved due to involvement in this study, you may experience improved quality of life. Although it is possible that you will benefit from this project, it is also possible that no such improvements will occur.

The potential benefit of the use of the stored samples is to identify new information about claudication and peripheral arterial disease that may improve the care of patients in the future.

5. Alternative Therapies

The alternatives available to you include surgery to bypass a portion of your diseased artery(ies). This surgery is major surgery and is usually not advised as an initial treatment for individuals with only claudication symptoms (leg pain while walking). If you agree to participate in this study, you are specifically asked to not undergo vascular surgical bypass or other artery procedure during the study period unless your symptoms progress beyond claudication to very severe symptoms that threaten your leg and then require opening of the blood vessel (see section 2.5 above).

6. Costs and Payments

You will be billed in the standard fashion for routine medical care for which you are scheduled and either you or your insurance provider will be responsible for this payment. Neither you, nor your third-party insurance provider will be billed for any research procedures that are not part of your routine medical care.

7. Payment for Research-Related Injuries

<Institution> and the study sponsor(s), the National Heart, Lung, and Blood Institute (NHLBI), have made no provision for monetary compensation to you in the event of physical injury resulting from this study. Should physical injury occur, treatment is available, but treatment <may not be> provided free of charge. <Insert Institution policy>

8. Confidentiality

All of your records from this study will be treated as private health care records. The records will be protected according to the rules of <blank hospital/institution>. The <blank hospital/institution> privacy practices and policies are based on the rules about protection of private health care information contained in <State> law and in the Federal Health Insurance Portability and Accountability Act of 1996 and its regulations ("HIPAA"). The privacy practices of <blank hospital/institution> and of the people who provide services at or with <blank hospital/institution> are explained in more detail in the <blank hospital/institution> Joint Privacy Notice (the "Privacy Notice') which will be given to you.

As required by HIPAA, you will be given a separate Research Authorization Form that will tell you the people and organizations that may use, receive and share information learned about you during the Study. Signing the Authorization Form means you give permission for your health care information to be used and shared for study purposes.

You should also know that there are times when the law might require or permit <blank hospital/institution> to release your health information without your permission. The Privacy Notice explains when this might happen. To give you some examples, state law often requires health care workers to report abuse or neglect of children to the Department of Children, Youth and Families (DCYF). State law often also requires health care workers to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

9. Refusal/Withdrawal

You decide whether or not you want to be in the study. Participation is voluntary. If you decide now to participate, you can change your mind later and quit the study.

If you decide not to participate, or if you quit the study, it will not affect the health care services that you normally receive. If the researcher or your doctor feels it is in your best interest, they may choose to take you out of the study at any time before you complete the study.

As soon as it becomes available, the researcher will give you new information about the study that may or may not affect your decision to stay in the research study

In addition, the sponsor may choose to end the study at any time, for reasons unrelated to health care.

10. Rights and Complaints

If you have any complaints about your taking part in this study, or would like more facts about the rules for research studies, or the rights of people who take part in research studies, you may contact <blank>, in the <blank hospital/institution> Office of Research Administration, at <blank>.

CONSENT AND SIGNATURES

I HAVE READ THE ABOVE DESCRIPTION OF THIS STUDY. ALL OF MY QUESTIONS HAVE BEEN SATISFACTORILY ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.

_____ _____
Signature of study volunteer/authorized representative* Date/Time (24 hour clock)

I was present during the consent process and signing of this agreement above by the study volunteer or authorized representative.

_____ _____
Signature of witness (required if consent is given orally or at the request of the IRB) Date/Time (24 hour clock)

Blood samples will be stored for future potential studies. These studies will be approved by institutional review boards. Potential future research includes the possibility of genetic or DNA studies. The purpose of this part of the consent is to give you information so that you can decide whether you want to allow these tests in the future. The specific testing to be performed on the blood samples has not been established at this time. Techniques have been developed which allow evaluation of the inherited factors called genes, as well as of the genetic make-up of your cells, called DNA. By studying material obtained from your blood sample, researchers might identify the gene(s) that carry the trait(s) for peripheral artery disease. Participation in this genetic research study is entirely voluntary. If you agree to participate, blood samples used for biochemical analysis will be saved and stored for possible future genetic testing. These samples will be stored indefinitely or until the genetic material (DNA) used for testing is no longer useful.

Please answer the following three questions by circling the response at the right:

1.	Samples of my blood may be stored for future testing?	**Yes**	**No**
2.	Samples of my DNA may be stored for future **genetic** testing?	**Yes**	**No**
3.	I wish to be contacted about information pertaining to my Health if genetic information is obtained and if my study doctor believes it would alter my care.	**Yes**	**No**

I ASSURE THAT I HAVE FULLY EXPLAINED TO THE ABOVE STUDY VOLUNTEER/AUTHORIZED REPRESENTATIVE, THE NATURE AND PURPOSE, PROCEDURES AND THE POSSIBLE RISK AND POTENTIAL BENEFITS OF THIS RESEARCH STUDY.

_____ _____

Signature of researcher or designate Date

Consent form copy: ☐ study volunteer ☐ medical record ☐ researcher ☐ other(specify)
*If signed by agent other than study volunteer, please explain below.

APPENDIX J: RISK FACTOR REDUCTION METHODS

I. PAD Risk Factor Treatment Goals

The following are recommended to reduce cardiovascular events and progression of disease in patients with PAD:

Smoking: Subjects who use tobacco products should be urged to quit and offered assistance with medication such as bupropion and transcutaneous nicotine patch.

Smoking cessation is most effective when a three-prong approach is used, consisting of psychological counseling, transdermal, intranasal, or inhaled tapered nicotine administration, and buprion, and oral antidepressant whose effectiveness in promoting smoking cessation is poorly understood but appears to be distinct from its antidepressant effect.

Psychological counseling is best done in a supervised smoking cessation program, if such a program is available locally. To get information on local smoking cessation programs, contact your local chapter of the American Lung Association (www.lungusa.org). If there are no programs locally, have patients get someone else involved in their efforts for moral support. This is particularly helpful if the other person also wants to quit smoking. Patients who smoke heavily should be encouraged to decrease their cigarette use, switch to low tar and nicotine cigarettes, or supplement their smoking with nicotine chewing gum prior to quitting altogether.

Transdermal nicotine patches reduce cravings for cigarettes in patients who have stopped smoking, and are available over the counter. They should be worn during waking hours, and deliver a steady dose of nicotine transdermally throughout the day. The starting dose is usually 21 mg of nicotine per day, but may be reduced for light smokers, those with small body habitus, or those with cardiac disease. Nicotine patches taper the administered dose over 6 to 8 weeks. During this period, and subsequently, nicotine chewing gum can be used to supplement the patch when cravings are acute. Nicotine may cause tachycardia or arrhythmias in some patients with a history of cardiac disease, and these patients should be monitored during initiation of therapy to ensure proper dose and lack of side effects.

Buproprion should be started 3 days prior to quitting smoking, and is given in divided doses of up to 300 mg per day orally for 7 weeks. Buproprion at the 300 mg per day dose may cause seizures in 1 out of 1,000 patients; this side effect is dose-dependent. Using buproprion in conjunction with transdermal nicotine and psychological counseling, over 50% of patients will be cigarette-free up to 10 weeks.

Cholesterol: The low density lipoprotein (LDL) goal, according to NCEP III guidelines is <100 mg/dL. Investigators are urged to follow all NCEP III guidelines for treating dyslipidemia.

FROM ATP_III (http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.htm)
Therapeutic Lifestyle Changes in Low-Density Lipoprotein-Lowering Therapy

The Adult Treatment Panel III recommends a multifaceted lifestyle approach to reduce risk for coronary heart disease. This approach is designated therapeutic lifestyle changes (therapeutic lifestyle changes). Its essential features are:

- Reduced intakes of saturated fats (<7% of total calories) and cholesterol (<200 mg per day) (see Table 5, below, for overall composition of the therapeutic lifestyle changes diet).
- Therapeutic options for enhancing low-density lipoprotein lowering such as plant stanols/sterols (2 g/day) and increased viscous (soluble) fiber (10 to 25 g/day)
- Weight reduction
- Increased physical activity

Table 5. Nutrient Composition of the Therapeutics Lifestyle Changes Diet

Saturated Fat*	Recommended Intake: Less than 7% of total calories
Polyunsaturated Fat	Recommended Intake: Up to 10% of total calories
Monounsaturated Fat	Recommended Intake: Up to 20% of total calories
Total Fat	Recommended Intake: 25% to 35% of total calories
Carbohydrate#	Recommended Intake: 50% to 60% of total calories
Fiber	Recommended Intake: 20 to 30 g/day
Protein	Recommended Intake: Approximately 15% of total calories
Cholesterol	Recommended Intake: Less than 200 mg/day
Total Calories (Energy)$	Recommended Intake: Balance energy intake and Expenditure to maintain desirable body weight/prevent weight gain

* Trans fatty acids are another low-density lipoprotein-raising fat that should be kept at a low intake.

Carbohydrate should be derived predominantly from foods rich in complex carbohydrates including grains, especially whole grains, fruits, and vegetables.

$ Daily energy expenditure should include at least moderate physical activity (contributing approximately 200 Kcal per day).

II. Drug therapy

- Consider drug simultaneously with TLC for CHD and CHD equivalents
- Consider adding drug to TLC after 3 months for other risk categories.

Drugs Affecting Lipoprotein Metabolism

Drug Class	Agents and Daily Doses	Lipid/Lipoprotein Effects	Side Effects	Contraindications
HMG CoA reductase inhibitors (statins)	Lovastatin (20-80 mg), Pravastatin (20-40 mg), Simvastatin (20-80 mg), Fluvastatin (20-80 mg), Atorvastatin (10-80 mg), Cerivastatin (0.4-0.8 mg)	LDL-C ↓18-55% HDL-C ↑5-15% TG ↓ 7-30%	Myopathy Increased liver enzymes	Absolute: • Active or chronic liver disease Relative: • Concomitant use of certain drugs*
Bile acid Sequestrants	Cholestyramine (4-16 g) Colestipol (5-20 g) Colesevelam (2.6-3.8 g)	LDL-C ↓15-30% HDL-C ↑3-5% TG No change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	Absolute: • dysbeta-lipoproteinemia • TG >400 mg/dL Relative: • TG >200 mg/dL
Nicotinic acid	Immediate release (crystalline) nicotinic acid (1.5-3 gm), extended release nicotinic acid (Niaspan ®) (1-2 g), sustained release nicotinic acid (1-2 g)	LDL-C ↓5-25% HDL-C ↑15-35% TG ↓20-50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Absolute: • Chronic liver disease • Severe gout Relative: • Diabetes • Hyperuricemia • Peptic ulcer disease
Fibric acids	Gemfibrozil (600 mg BID) Fenofibrate (200 mg)	LDL-C ↓5-20% (may be increased in patients with high TG)	Dyspepsia Gallstones Myopathy	Absolute: • Severe renal disease • Severe hepatic

	Clofibrate (1000 mg BID)	HDL-C ↑10-20% TG ↓20-50%		disease

* Cyclosporine, macrolide antibiotics, various anti-fungal agents, and cytochrome P-450 inhibitors (fibrates and niacin should be used with appropriate caution).

Hypertension: The systolic blood pressure goal, according to JNC-7 guidelines, is <140 mmHg and < 135 mmHg for those with diabetes mellitus.

From JNC VII
(http://www.guidelines.gov/summary/summary.aspx?doc_id=4771&nbr=003450&string=hypertension#s31)

- **Lifestyle Modifications**: Adoption of healthy lifestyles by all persons is critical for the prevention of high BP and is an indispensable part of the management of those with hypertension. Major lifestyle modifications shown to lower BP include weight reduction in those individuals who are overweight or obese, adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan which is rich in potassium and calcium, dietary sodium reduction, physical activity, and moderation of alcohol consumption. See Table below.

  Table. Lifestyle Modifications to Manage Hypertension*@

  - Weight reduction: Maintain normal body weight (BMI, 18.5–24.9 kg/m^2)

    Approximate SBP Reduction, Range: 5–20 mmHg/10 kg weight loss

  - Adopt DASH eating plan: Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat.

    Approximate SBP Reduction, Range: 8–14 mmHg

  - Dietary sodium reduction: Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride)

    Approximate SBP Reduction, Range: 2–8 mmHg

  - Physical activity: Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week).

    Approximate SBP Reduction, Range: 4–9 mmHg

  - Moderation of alcohol: Limit consumption to no more than 2 drinks (1 oz or 30 mL ethanol [e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey]) per day in most men and to no more than 1 drink per day in women and lighter weight persons.

    Approximate SBP Reduction, Range: 2–4 mmHg

  * For overall cardiovascular risk reduction, stop smoking.

[@]The effects of implementing these modifications are dose and time dependent, and could be greater for some individuals.

- **Pharmacologic Treatment**: There are excellent clinical outcome trial data proving that lowering BP with several classes of drugs, including angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers (BBs), calcium channel blockers (CCBs), and thiazide-type diuretics, will all reduce the complications of hypertension. Tables 10 and 11 in the original guideline document provide a list of commonly used antihypertensive agents and their usual dose range and frequency of administration.

  Thiazide-type diuretics should be used as initial therapy for most patients with hypertension, either alone or in combination with one of the other classes (ACEIs, ARBs, BBs, CCBs) demonstrated to be beneficial in randomized controlled outcome trials. The list of compelling indications requiring the use of other antihypertensive drugs as initial therapy is provided in Table 12 in the original guideline document. If a drug is not tolerated or is contraindicated, then one of the other classes proven to reduce cardiovascular events should be used instead.

- **Achieving Blood Pressure Control in Individual Patients**: Most patients who are hypertensive will require two or more antihypertensive medications to achieve their BP goals. Addition of a second drug from a different class should be initiated when use of a single drug in adequate doses fails to achieve the BP goal. When BP is more than 20/10 mmHg above goal, consideration should be given to initiating therapy with two drugs, either as separate prescriptions or in fixed-dose combinations. (See Figure 16 in the original guideline document.) The initiation of drug therapy with more than one agent may increase the likelihood of achieving the BP goal in a more timely fashion, but particular caution is advised in those at risk for orthostatic hypotension, such as patients with diabetes, autonomic dysfunction, and some older persons. Use of generic drugs or combination drugs should be considered to reduce prescription costs.

- **Diabetes Mellitus:** The hemoglobin A1C goal, according to ADA guidelines, should be <6%.

APPENDIX K: INDEPENDENT EXERCISE ASSESSMENT

1. Have you participated in any formal or non-formal exercise programs, either on your own or with a group over the past 2 weeks?

   Definition: Refers to exercise with the intent to improve fitness or health that is done 2 or more times per week for 20 or more minutes and that has been done for at least 2 consecutive weeks?

2. During the past week (even if it was not a typical week for you), how much total time (for the entire 2 weeks) did you spend on each of the following? Circle one number for each question:

How much time during the past week:					
0=None	1=Less than 30 minutes/week		2=30-60 minutes/week		
3=1-3 hours/week	4=More than 3 hours/week				

a.	Stretching or strengthening exercises (range of motion, weights, etc.):	0	1	2	3	4
b.	Walk for exercise:	0	1	2	3	4
c.	Swimming or aquatic exercise:	0	1	2	3	4
d.	Bicycling (including stationary exercise bikes):	0	1	2	3	4
e.	Other aerobic exercise equipment: (Stairmaster, rowing, skiing machine, etc.)	0	1	2	3	4
f.	Other aerobic exercise:	0	1	2	3	4
	(specify:_____)					