

# BEST-CLI Trial

**Randomized, Multicenter, Controlled Trial to Compare Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb Ischemia**

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## **Protocol Signature Page**

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in accordance with the design and specific provisions outlined herein; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the devices and the conduct of the study.

I will use the informed consent form template approved by the NHLBI and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board or Ethics Committee (IRB/EC) responsible for this study.

I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) as defined in Section 7 of this protocol.

I further agree that the NHLBI, FDA, and New England Research Institutes has access to any source documents from which case report form information may have been generated.

I also agree to collect and handle all clinical specimens, if applicable, in accordance with the protocol.

The below signed confirm herewith to have read and understood this trial protocol and/or amendment and appendices; furthermore, to accomplish this study in accordance to the protocol and Good Clinical Practice guidelines, as well as local and federal regulations; and to accept respective revisions conducted by authorized personnel of NHLBI and by regulatory authorities.

PRINTED OR TYPED NAME(S)

SIGNATURE

DATE

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Principal Investigator – Vascular Medicine

**Protocol Synopsis**

|                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Protocol Title            | Randomized, Multicenter, Controlled Trial to Compare <u>B</u> est <u>E</u> ndovascular versus Best <u>S</u> urgical <u>T</u> herapy in Patients with Critical Limb Ischemia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Abbreviated Title         | BEST-CLI Trial                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Funding Sponsor           | National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Investigational Product   | Any commercially available device used in open vascular or endovascular surgery, excluding cryoplasty                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Intended Use              | Adults with infrainguinal arterial occlusive disease and critical limb ischemia (CLI).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Objective                 | To evaluate the effectiveness of best endovascular (EVT) compared to best surgical (OPEN) revascularization in patients with CLI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Study Population          | Men and women age 18 years or older with infrainguinal peripheral arterial occlusive disease (PAOD) and CLI eligible to undergo both endovascular therapy and surgical bypass with either single-segment great saphenous vein (SSGSV; Cohort #1) or alternative conduit (Cohort #2).                                                                                                                                                                                                                                                                                                                                                                                               |
| Study Design              | Two prospective, multicenter, randomized, open label (two-arm), superiority trials, one in Cohort 1 and one in Cohort 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Study Centers             | Subjects will be recruited from 160+ multidisciplinary vascular centers and practices in the US, Canada and additional countries.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Primary Endpoint          | MALE (Major Adverse Limb Event)-free survival                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Duration of Participation | All subjects are evaluated at baseline, time of procedure, 30 days, 3 months, 6 months, and every 6 months thereafter, until the end of the trial. There will also be an end-of-study telephone contact. Depending on the assumptions made, minimum study participation will be between 8 and 36 months, while maximum study participation will be between 64 and 96 months.                                                                                                                                                                                                                                                                                                       |
| Sample Size and Power     | A range of assumptions were considered. Cohort #1 (SSGSV), N= in the range of 1076-1620: based on aggregate event rates as of the November 1, 2017 data freeze and a hazard ratio of 1.25, there will be between 82.8% and 96.2% power to detect a difference between treatment groups for the primary endpoint assuming a Type I error rate of 0.05.<br>Cohort #2 (Alternative Conduit), N= in the range of 287-480: based on aggregate event rates as of the November 1, 2017 data freeze and a hazard ratio of 0.70, there will be between 70.4% and 91.5% power to detect a difference between treatment groups for the primary endpoint, assuming a Type I error rate of 0.05 |
| Secondary Endpoints       | <p>Secondary efficacy endpoints are:</p> <ul style="list-style-type: none"> <li>• <b>Clinical:</b> Re-intervention and amputation-free survival (RAFS); Freedom from MALE-POD (MALE or death within 30 days of index procedure); Amputation-free survival; Freedom from POD; Freedom from myocardial infarction (MI); Freedom from stroke; Freedom from re-interventions (major and minor) in index leg; Number of re-interventions (major and minor) per limb salvaged;</li> </ul>                                                                                                                                                                                                |

|                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                    | <p>Freedom from hemodynamic failure; Freedom from clinical failure; Freedom from CLI; Freedom from all-cause mortality.</p> <ul style="list-style-type: none"> <li>• <b>Functional:</b> Quality of life (QoL) and functional assessments using the VascuQoL and EuroQoL EQ-5D. The SF-12, Numerical Rating Scale (NRS) for pain, and (at selected sites) the six-minute walk test will supplement the main QOL measurements. <b>Costs and cost-effectiveness:</b> Treatment-associated costs (in- and out-patient) and incremental cost-effectiveness measured in dollars per quality-adjusted life years.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Safety Endpoints                                   | <ul style="list-style-type: none"> <li>• Serious Adverse Events from randomization through 30 days post-procedure</li> <li>• Serious Adverse Events from randomization throughout time on study</li> <li>• MACE from randomization through 30 days post-procedure (Major Adverse Cardiovascular Events) - a composite of all cause death, MI and stroke</li> <li>• MACE from randomization throughout remaining time on study</li> <li>• Non-serious adverse events from randomization through 30 days post-procedure</li> <li>• Perioperative complications</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Major Eligibility Criteria (see Section 4 for all) | <p>Major Inclusion Criteria:</p> <ol style="list-style-type: none"> <li>1) Male or female, age 18 years or older.</li> <li>2) Infrainguinal PAOD (occlusive disease of the arteries below the inguinal ligament).</li> <li>3) CLI, defined as arterial insufficiency with gangrene, non-healing ischemic ulcer, or rest pain consistent with Rutherford categories 4-6.</li> <li>4) Candidate for both open and endovascular infrainguinal revascularization as judged by the treating investigators (see Manual of Operations (MOO) for guidelines on decision-making).</li> <li>5) Adequate aortoiliac inflow (see protocol Section 4.1 for definition)</li> <li>6) Adequate popliteal, tibial or pedal revascularization target defined as an infrainguinal arterial segment distal to the area of stenosis/occlusion which can support a distal anastomosis of a surgical bypass.</li> <li>7) Willingness to comply with protocol, attend follow-up appointments, complete all study assessments, and provide written informed consent.</li> </ol> <p>Major Exclusion Criteria:</p> <ol style="list-style-type: none"> <li>1) Presence of a popliteal aneurysm (&gt;2 cm) in the index limb.</li> <li>2) Life expectancy of less than 2 years due to reasons other than PAOD.</li> <li>3) Excessive risk for surgical bypass (as determined by the operating surgeon and the CLI Team)</li> <li>4) Planned above ankle amputation on ipsilateral limb within 4 weeks of index procedure.</li> <li>5) Active vasculitis, Buerger's disease, or acute limb-threatening ischemia.</li> <li>6) Any prior index limb infrainguinal stenting or stent grafting associated with significant restenosis within 1 cm of the stent or</li> </ol> |

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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|  | <p>stent-graft, unless the occlusion/restenosis site is outside the intended treatment zone (i.e., a tibial vessel that is not currently intended to be revascularized as a part of the treatment for CLI).</p> <p>7) Any of the following procedures performed on the index limb within 3 months prior to enrollment:</p> <ul style="list-style-type: none"><li>a. Infrainguinal balloon angioplasty, atherectomy, stent, or stentgraft;</li><li>b. Infrainguinal bypass with either venous or prosthetic conduit</li></ul> <p>8) Open surgical inflow procedure (aortofemoral, axillofemoral, iliofemoral, thoracofemoral or femorofemoral bypass) within 6 weeks prior to enrollment</p> <p>9) Current chemotherapy or radiation therapy.</p> <p>10) Absolute contraindication to iodinated contrast due to prior near-fatal anaphylactoid reaction (laryngospasm, bronchospasm, cardiorespiratory collapse, or equivalent) which would preclude patient participation in angiographic procedures.</p> <p>11) Pregnancy or lactation.</p> <p>12) Administration of an investigational drug for PAOD within 30 days of randomization.</p> <p>13) Participation in a clinical trial (except observational studies) within the previous 30 days.</p> <p>14) Prior enrollment or randomization into BEST-CLI.</p> |
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**List of Abbreviations**

|          |                                                                                                                                             |
|----------|---------------------------------------------------------------------------------------------------------------------------------------------|
| ABI      | Ankle-brachial index                                                                                                                        |
| ACCF     | American College of Cardiology Foundation                                                                                                   |
| AE       | Adverse Event                                                                                                                               |
| AFS      | Amputation-free survival                                                                                                                    |
| AHA      | American Heart Association                                                                                                                  |
| BASIL    | Bypass versus Angioplasty in Severe Ischemia of the Leg                                                                                     |
| BEST-CLI | Randomized, Multicenter, Controlled Trial to Compare Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb Ischemia |
| BMC      | Boston Medical Center                                                                                                                       |
| BWH      | Brigham and Women's Hospital                                                                                                                |
| CCC      | Clinical Coordinating Center                                                                                                                |
| C-E      | Cost-effectiveness                                                                                                                          |
| CFR      | Code of Federal Regulations                                                                                                                 |
| CLI      | Critical Limb Ischemia                                                                                                                      |
| CRF      | Case Report Form                                                                                                                            |
| CTA      | Computed Tomography Angiography                                                                                                             |
| CTMS     | Clinical Trial Management System                                                                                                            |
| DCC      | Data Coordinating Center                                                                                                                    |
| DSMB     | Data and Safety Monitoring Board                                                                                                            |
| DW       | Doppler Waveform                                                                                                                            |
| EC       | Executive Committee                                                                                                                         |
| EDC      | Electronic Data Capture                                                                                                                     |
| eGFR     | Estimated glomerular filtration rate                                                                                                        |
| EVT      | Endovascular Therapy                                                                                                                        |
| FDA      | Food and Drug Administration                                                                                                                |
| GCP      | Good Clinical Practice                                                                                                                      |
| HUI      | Health Utility Index                                                                                                                        |
| ICF      | Informed Consent Form                                                                                                                       |
| ICH      | International Conference on Harmonization                                                                                                   |
| IDE      | Investigational Device Exemption                                                                                                            |
| IRB/EC   | Institutional Review Board/ Ethics Committee                                                                                                |
| ITT      | Intention-to-treat                                                                                                                          |
| LOS      | Length of stay                                                                                                                              |
| MACE     | Major Adverse Cardiovascular Event                                                                                                          |
| MALE     | Major Adverse Limb Event                                                                                                                    |
| MDRD     | Modification of Diet in Renal Disease                                                                                                       |
| MedDRA   | Medical Dictionary for Drug Regulatory Activities                                                                                           |
| MGH      | Massachusetts General Hospital                                                                                                              |
| MOO      | Manual of Operations                                                                                                                        |
| MRA      | Magnetic Resonance Angiography                                                                                                              |
| NERI     | New England Research Institutes, Inc.                                                                                                       |
| NHLBI    | National Heart, Lung and Blood Institute                                                                                                    |
| NIH      | National Institutes of Health                                                                                                               |
| OHRP     | Office for Human Research Protection                                                                                                        |
| OMT      | Optimal Medical Therapy                                                                                                                     |

|         |                                                                                    |
|---------|------------------------------------------------------------------------------------|
| OPEN    | Open surgical revascularization                                                    |
| OPG     | Objective Performance Goals                                                        |
| PAD     | Peripheral Artery Disease                                                          |
| PAOD    | Peripheral Arterial Occlusive Disease                                              |
| PI      | Principal Investigator                                                             |
| POD     | Perioperative death                                                                |
| PTA     | Percutaneous transluminal angioplasty                                              |
| PSV     | Peak Systolic Velocity                                                             |
| QA      | Quality Assurance                                                                  |
| QC      | Quality Control                                                                    |
| QOL     | Quality of Life                                                                    |
| RAFS    | Re-intervention and Amputation-Free Survival                                       |
| SAE     | Serious Adverse Event                                                              |
| SC      | Steering Committee                                                                 |
| SOP     | Standard operating procedure                                                       |
| SSGSV   | Single-Segment Great Saphenous Vein                                                |
| SVS     | Society of Vascular Surgery                                                        |
| TASC    | TransAtlantic Inter-Society Consensus                                              |
| TBI     | Toe-brachial index                                                                 |
| UADE    | Unanticipated Adverse Device Event                                                 |
| UKNIHRT | United Kingdom National Institute of Health Research Technology Assessment Program |
| UP      | Unanticipated Problem                                                              |
| US      | United States                                                                      |

## **1. BACKGROUND INFORMATION**

### **1.1 Description of Investigational Product**

This trial will operate under a non-commercial, proof-of-principle Investigational Device Exemption (IDE) with the Food and Drug Administration (FDA). If a subject is randomized to endovascular therapy (EVT), the exact modality or modalities of treatment rendered with regard to commercially available endovascular devices and strategies will be left to the discretion of the treating physician, within the parameters defined by the BEST-CLI Manual of Operations (MOO) and accepted standard of care.

The list of approved revascularization procedures can be found in the MOO. As new devices become commercially available, they must be formally evaluated and approved by the Evolving Technology Committee and the Executive Committee, prior to use in the BEST-CLI Trial. The use of cryoplasty balloons is prohibited in the BEST-CLI Trial.

### **1.2 Background Information**

#### **1.2.1 Public Health Impact**

Atherosclerosis is widespread in Western society and constitutes the leading overall cause of morbidity and mortality in the United States (US). Epidemiological studies indicate that peripheral artery disease (PAD) has a prevalence of 3-10% in the general population. This rate increases to 15-20% in persons over 70 years of age, and PAD is particularly common in individuals who smoke or have diabetes [1, 2]. A subset of patients with PAD have critical limb ischemia (CLI) marked by intractable foot, ankle, or leg pain at rest and/or the presence of ischemic ulcerations or necrotic tissue. CLI is associated with significant disability, morbidity and mortality. In the absence of successful revascularization, up to 40% of patients will require limb amputation; the annual mortality rates exceed 20% [1]. The incidence of CLI in the US ranges from 500-1,000 per million per year. However, given the aging of the American population, the global increase in metabolic syndrome, and the ongoing impact of diabetes, smoking and dietary indiscretion, the prevalence of both PAD and CLI is predicted to further escalate [1]. Management of CLI is associated with substantial health-care and societal costs [3, 4] and these are expected to grow, given current demographic, disease and economic trends [1].

#### **1.2.2 Current Therapy**

Given the absence of effective medical therapy, CLI is typically treated with revascularization to improve limb perfusion distal to the zone of arterial stenosis or occlusion. Open surgical bypass has historically been the gold standard therapy for patients with infrainguinal occlusive disease, and is associated with excellent limb salvage rates and clinical durability [5]. Outcomes of surgical bypass are significantly affected by the quality of the conduit utilized [6, 7], the severity of ischemia at presentation [8], and the extent of infrainguinal arterial obstruction [8].

Over the last two decades, the widespread adoption of endovascular techniques has led to a sharp increase in their application to patients with CLI [9] [10, 11]. There are numerous reports of excellent limb salvage rates [12, 13]. In comparison to surgical bypass, endovascular therapy is associated with decreased peri-procedural morbidity and mortality. However, questions over durability, cost, and appropriate case selection have not been answered [14].

At present, a diverse group of practitioners, among them interventional cardiologists, vascular medicine specialists, interventional radiologists and vascular surgeons, provide treatment for CLI

[11]. The decision to recommend surgical or endovascular revascularization varies significantly among providers and is based on a range of factors, including disease pattern, availability of autogenous conduit, physician training and experience, surgical and endovascular skill sets, access to an appropriate procedural environment, and perhaps most importantly, disparate treatment biases [14-17]. There is general agreement that some patients considered poor candidates for surgery are well served by endovascular revascularization [18, 19]. What is presently not known is which therapy is more suitably offered to patients who are candidates for both open and endovascular treatment. This uncertainty regarding optimal treatment algorithms also has economic implications, potentially leading to increase in health care expenditures. [14].

The absence of consensus underlying the current therapeutic approach to CLI directly stems from the paucity of unbiased high quality data upon which to base treatment decisions. Although there is an abundant literature dedicated to the management of CLI, most published studies are flawed due to retrospective design, lack of controls, sponsor and operator bias, inclusion of claudicants, and short or incomplete follow-up [20, 21]. There are few prospective randomized trials that compare endovascular techniques with surgical revascularization for PAD; the European Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial is the only such randomized controlled trial in patients with CLI [22, 23].

### **1.3 Summary of Findings from Relevant Clinical Trials**

#### **1.3.1 The BASIL Trial**

Only one relevant randomized trial of CLI has been conducted – the BASIL trial [22, 23]. The BASIL trial, sponsored by the United Kingdom National Institute of Health Research Technology Assessment Program (UKNIHRT), was commissioned in 1996 to compare the efficacy of balloon percutaneous transluminal angioplasty-first (PTA) versus bypass surgery-first (Bypass) treatment strategies in patients with severe limb ischemia. The trial enrolled 452 patients over a 5-year period. Bypass was associated with significantly lower immediate failure (3% vs 20%), higher 30-day morbidity (57% vs 41%), and lower 12 month re-intervention (18% vs 26%) rates than PTA. Thirty-day mortality was similar between the 2 groups (5% for Bypass and 3% for PTA). There was no difference in the primary endpoint of amputation-free survival (AFS) by intention-to-treat assignment between the two arms (57% for Bypass and 52% for PTA at 3 years). Post-hoc analysis, however, revealed that after 2 years, Bypass was associated with improved clinical outcomes. These findings led UKNIHRT to fund an extension of follow-up for the BASIL trial. While there was no significant difference in AFS for the overall follow-up period, patients surviving more than 2 years who underwent Bypass demonstrated significantly improved overall survival and a trend toward improved AFS. [24]. Critique of BASIL included the fact that endovascular treatments were limited to balloon alone; use of stents or debulking techniques was not allowed.

#### **1.3.2 Society of Vascular Surgery Objective Performance Guidelines Working Group**

In light of the rapid emergence and adoption of endovascular techniques in the management of CLI and the difficulties involved in accurate interpretation of efficacy of catheter-based devices, the SVS sponsored a working group to review the best available literature and propose a set of OPG (Objective Performance Goals) to form guidelines for both the evaluation of novel endovascular technology and the design of clinical trials comparing treatment strategies in patients with CLI [8]. After reviewing all controlled randomized trials of surgical, endovascular, biologic, and pharmacologic treatment of CLI from 1990 to 2007, selected data from the BASIL [22], Prevent III [25] and Circulase [26, 27] trials were compiled into a common database, comprised of 838 patients with infrainguinal PAD and CLI revascularized with autogenous vein.

Traditional efficacy and safety outcome variables, including death, amputation, AFS, and MACE (Major Adverse Cardiovascular Event) were characterized. A consensus was reached that there was a general need for novel endpoints that more accurately describe both limb-related morbidity and procedural re-intervention rates. To that end, MALE (Major Adverse Limb Event) defined as above-ankle amputation of the index limb or major re-intervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis), MALE + POD (perioperative death) and hemodynamic endpoints were devised. A series of safety and efficacy OPGs were created for the various outcome variables and risk-stratified guidelines were outlined for defined subgroups based on clinical, anatomical, and conduit criteria. By integrating the best available efficacy and safety data for open surgical revascularization in patients with CLI, a previously unavailable rigorous framework for comparison of open surgical revascularization as a standard against other treatment modalities now exists. The recommendations of the working group with regard to endpoint selection and overall trial design have been endorsed by both the SVS [8] and the FDA [28] and serve as an important foundation for the BEST-CLI trial [18].

#### **1.4 Summary of the Known and Potential Risks and Benefits to Human Subjects**

The two treatment arms, endovascular therapy and open vascular surgery, under investigation in the BEST-CLI trial, both represent a currently accepted standard of care and as such, neither is considered experimental therapy [18, 19]. The associated risks of the care rendered to any patient in this trial would therefore represent the known risks inherent to the two treatment modalities. These risks will be reviewed in detail with each patient in the process of obtaining full informed consent.

The potential limb-related risks of surgical revascularization include: graft and wound infection; bleeding complications; distal embolization; leg swelling; nerve injury; lymphatic complications; compartment syndrome; graft thrombosis; graft stenosis; need for minor or major graft re-intervention; failure of clinical improvement despite a functioning graft; worsening or recrudescence of symptoms and amputation. Systemic complications associated with surgical revascularization include myocardial infarction; stroke; pulmonary complications such as atelectasis, pneumonia, pulmonary embolism or ventilator dependence; renal failure; contrast- and non-contrast-related allergic reactions; deep venous thrombosis; ileus; heparin-induced thrombocytopenia; sepsis; and death.

Specific risks associated with endovascular revascularization include contrast-induced acute renal failure; contrast-related allergic reactions; vascular access-related hematoma, pseudoaneurysm, arteriovenous fistula, arterial dissection, or thrombosis; lymphatic complications; infection or nerve injury; intervention-related arterial stenosis, thrombosis, dissection, embolism (including atheroembolism) or rupture; nerve injury; compartment syndrome; renal dysfunction; acute or subacute worsening of limb perfusion, with possible need for urgent thrombolysis or urgent or emergent surgical revascularization; treated segment restenosis; need for minor or major re-intervention; failure of clinical improvement despite technical procedural success; worsening or recrudescence of symptoms; and amputation. Systemic complications associated with endovascular revascularization include myocardial infarction; stroke; pulmonary complications such as atelectasis, pneumonia, pulmonary embolism or ventilator dependence; renal failure; non-contrast related allergic reactions; deep venous thrombosis; ileus; heparin induced thrombocytopenia; sepsis and death.

Risks associated with drawing blood include discomfort and/or bruising at the puncture site. Rarely, infection, excess bleeding, clotting or fainting may occur.

If the study results show which type of treatment is better at treating patients with CLI, vascular specialists may be able to make more informed choices in the future about which procedures to offer their patients.

All study costs not related to standard clinical care and performed solely for the purpose of research will be paid for by the sponsor. Given the anticipated benefits to subjects and others with CLI, the risks to subjects are reasonable. The types and magnitudes of these risks for BEST-CLI subjects are within the same range as risks related to similar standard of care procedures performed outside of the trial.

### **1.5 Instructions for Use**

Best surgical and best endovascular therapy will be performed according to established standards of care and guidelines. Investigators utilizing commercially available endovascular stents, stent-grafts, or other devices should follow the Instructions for Use provided for each specific device. Any observed device malfunction or complication will be collected on appropriate adverse event forms.

### **1.6 Trial Conduct**

The trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP) guidelines and applicable federal regulatory requirements [Title 21 Code of Federal Regulations Parts 50, 54, 56, 812 and 45CFR46]. Before enrollment begins, this trial will be registered on ClinicalTrials.gov.

### **1.7 Description and Importance of the Population to be Studied**

Up to 2100 subjects aged 18 years or older with CLI undergoing infrainguinal revascularization with either single-segment great saphenous vein (SSGSV) or an alternative conduit and stratified by clinical and anatomic presentation, will be recruited from 160+ multidisciplinary vascular centers and practices in the US and Canada and possibly additional countries.

The target population is defined as patients with CLI, which is defined as arterial insufficiency with gangrene, a non-healing ischemic ulcer, or rest pain, corroborated by at least one of the following hemodynamic criteria:

- a. For ischemic rest pain without tissue loss (Rutherford category 4): Ankle systolic pressure  $\leq$  50 mm Hg, toe pressure of  $\leq$  30 mm Hg, transcutaneous PO<sub>2</sub> of < 30 mm Hg, or flat-line transtarsal pulse volume recording.
- b. For tissue loss (Rutherford category 5,6): Ankle systolic pressure  $\leq$  70 mm Hg, toe pressure of  $\leq$  50 mm Hg, transcutaneous PO<sub>2</sub> of < 30 mm Hg, or flat-line transtarsal pulse volume recording. In certain patients with significant tissue loss these criteria may not be available or reliably measurable, thus the definition of CLI in such patients is up to the discretion of the site CLI team.

Because acute vasculitis and Buerger's disease are unique disease processes that are typically managed differently and are associated with worse outcomes, patients with these clinical entities are excluded. For the same reason, patients with acute limb ischemia are also excluded. BEST-CLI focuses on subjects who are candidates for both open surgery and endovascular therapy as determined by the treating investigator(s) and fall into the area of treatment equipoise. To that

end, BEST-CLI will exclude individuals who, based on clinical parameters, are considered to be at excessive risk for open vascular surgery, as determined by the operating surgeon [29]. From an anatomic standpoint, subjects without a patent outflow target vessel will be excluded, as treatment options in this population are usually limited to medical management, amputation or experimental therapies.

## **2. TRIAL OBJECTIVES AND PURPOSE**

The BEST-CLI Trial is a multicenter randomized trial of best endovascular (EVT) or best open surgical (OPEN) revascularization in patients with CLI and infrainguinal peripheral arterial occlusive disease (PAOD) who are candidates for both open and endovascular treatment. The trial has a superiority design and has the following specific aims:

**Primary Aim:** To compare the primary endpoint event rate of Major Adverse Limb Event (MALE)-free survival in subjects with CLI randomized to best endovascular (EVT) revascularization to the rate in those randomized to best open surgery (OPEN). Best revascularization, whether EVT or OPEN, is defined as the technique deemed most appropriate for the subject by the operator(s), with respect to the index limb.

Treatment comparisons (EVT vs. OPEN) will be made in two cohorts (See Section 3.1): 1) patients with an available SSGSV (total N= up to 1620); and 2) patients without a SSGSV (in whom an alternative conduit is to be used if randomized to OPEN) (total N up to 480).

### **Secondary Aims:**

- 1) To compare other clinical event rates (see secondary endpoints in Section 3.2) of subjects with CLI randomized to best EVT or best OPEN revascularization.
- 2) To compare functional status and quality of life after 2 years of follow-up in subjects with CLI randomized to best EVT or best OPEN revascularization.
- 3) To compare costs of 2 years of follow-up associated with treatment of subjects with CLI randomized to best EVT or best OPEN revascularization. Cost-effectiveness (C-E) will be compared between the 2 treatment groups.

## **3. TRIAL DESIGN**

### **3.1 Trial Cohorts**

The trial will be comprised of two subject cohorts, in which the two primary treatment comparisons will be made separately.

**Cohort #1 (N= up to 1620):** Subjects with an available SSGSV.

**Cohort #2 (N= up to 480):** Subjects without available SSGSV (i.e., alternative conduit to be used if randomized to OPEN; alternative conduit may include arm vein, short saphenous vein, composite vein, cryopreserved vein, and prosthetic conduit).

Although the question of whether OPEN or EVT procedures are preferable is important for both cohorts, it is anticipated that the preferable approach may differ between the two cohorts. Therefore, no pooling of data between cohorts is planned.

### 3.2 Primary Endpoints and Secondary Endpoints

The primary efficacy endpoint is: MALE (Major Adverse Limb Event)-free survival. MALE is defined as above ankle amputation of the index limb or major re-intervention (e.g. new bypass graft, jump/interposition graft revision, or thrombectomy/ thrombolysis; see Section 6.1).

Secondary efficacy endpoints are:

- **Clinical:** Re-intervention and amputation-free survival (RAFS); Freedom from MALE-POD, i.e., a composite (earliest occurring) of MALE and perioperative death (POD, defined as death within 30 days of index procedure); Amputation-free survival; Freedom from POD; Freedom from myocardial infarction (MI); Freedom from stroke; Freedom from re-interventions (major and minor) in index leg; Number of re-interventions (major and minor) per limb salvaged; Freedom from hemodynamic failure; Freedom from clinical failure; Freedom from CLI; Freedom from all-cause mortality.
- **Functional:** Quality of life (QoL) and functional assessments using the VascuQoL and EuroQoL EQ-5D. The SF-12, Numerical Rating Scale (NRS) for pain, and at selected sites, the six-minute walk test will be performed to supplement the main QOL measurements.
- **Costs and cost-effectiveness:** Treatment-associated costs (in- and out-patient) and incremental cost-effectiveness measured in dollars per quality-adjusted life years.

MALE captures all major repeat vascular procedures on the index limb, including the creation of a new bypass graft, the use of thrombectomy or thrombolysis, and major surgical graft revisions such as a jump grafts and interposition grafts. Limb-related morbidity and procedure-related re-interventions are of particular importance in the evaluation of endovascular procedures that have significant associated costs and unproven long-term durability. Two key secondary endpoints of the BEST-CLI trial are MALE-POD and RAFS. MALE-POD is an important measure of limb-based treatment efficacy that includes peri-operative treatment-related mortality but excludes longer term mortality that is less likely related to the specific revascularization strategy under investigation. RAFS encompasses survival free of above-ankle amputation along with the total burden of re-interventions, both major and minor.

For patients with bilateral disease, limb-specific outcomes and limb-specific components of composite outcomes will be based only on the limb specified as the “index limb” at the time of randomization. For example, major adverse limb events for the primary outcome of MALE-free survival will be adverse limb events related only to the index limb.

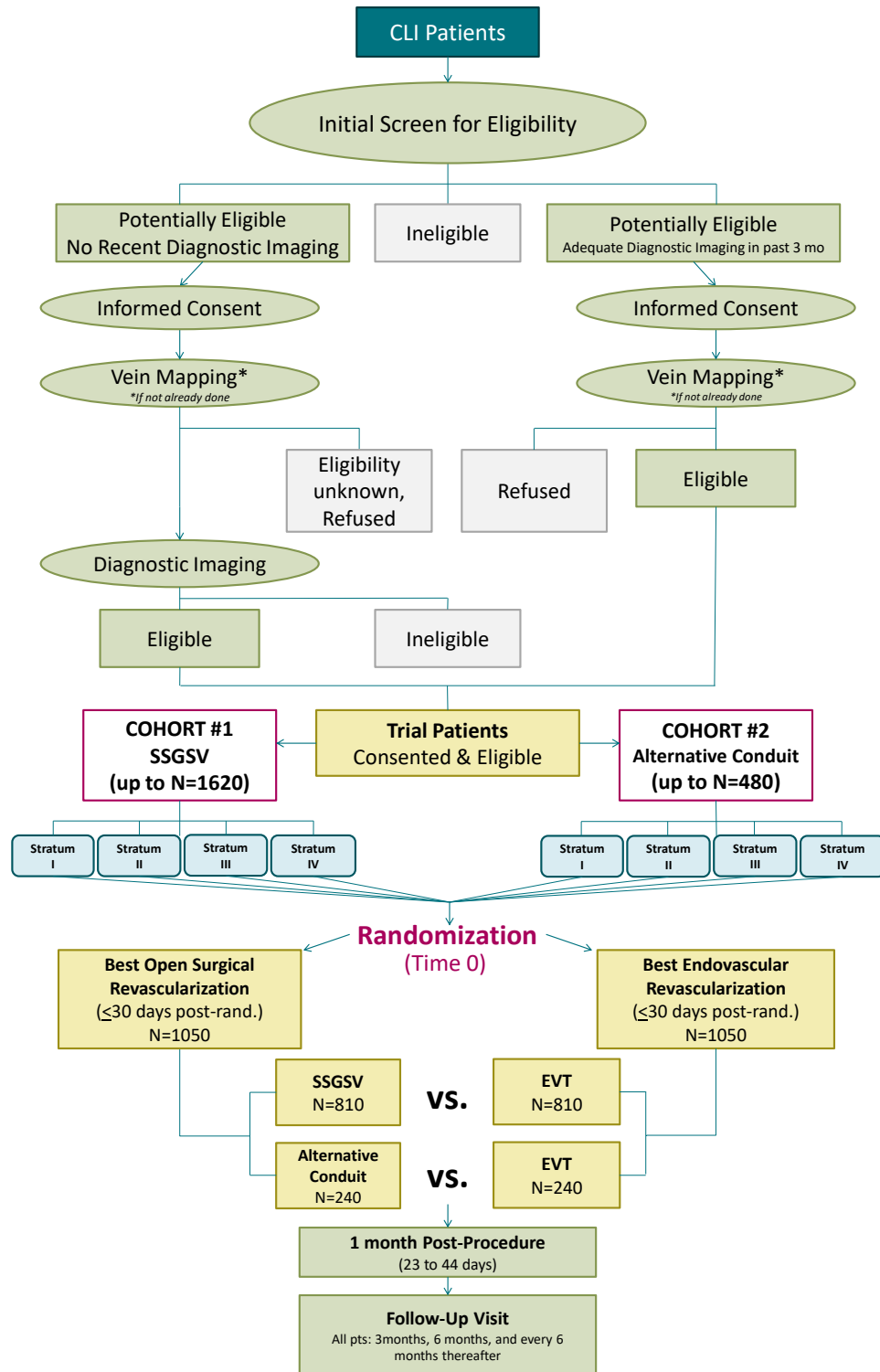
Safety endpoints are:

- Serious Adverse Events from randomization through 30 days post-procedure
- Serious Adverse Events from randomization throughout remaining time on study
- MACE from randomization through 30 days post-procedure (Major Adverse Cardiovascular Events) - a composite of all cause death, MI and stroke
- MACE from randomization throughout remaining time on study
- Non-serious adverse events from randomization through 30 days post-procedure
- Perioperative complications (see definition in Section 7.1)

Note that Serious Adverse Events are collected from the time of informed consent throughout the subject's remaining time on study. However, Serious Adverse Events (including components of MACE) which have their onset before a consented subject is randomized will not be considered in the safety endpoint comparisons of the treatment groups. These early events will nevertheless be reported to the DSMB.

### 3.3 Trial Design

Figure 1 Patient flow through trial and flow by cohort



The BEST-CLI Trial is a prospective, randomized, open label (two-arm), multicenter, superiority trial comparing the effectiveness of best endovascular (EVT) to best surgical (OPEN) revascularization in up to 2,100 subjects with infrainguinal peripheral arterial occlusive disease and CLI. Treatment comparisons (EVT vs. OPEN) will be made separately in the two cohorts (See Section 3.1) on an intention-to-treat (ITT) basis. Randomization to the two treatments will occur within cohort and within each of 4 strata (see Section 3.4.2) defined by anatomic presentation and clinical classification (Rutherford category).

Section 8.2 presents detailed information on trial duration and statistical power for a range of assumptions.

### 3.4 Measures to Minimize/Avoid Bias

#### 3.4.1 Randomization

Subjects will be assigned in the order they are enrolled into the study, to receive the allocated treatment according to a computer-generated randomization plan. A subject's membership in Cohort #1 or Cohort #2 (see Section 3.1) will first be determined. Within each cohort, subjects will be randomized in a 1:1 ratio to one of the 2 treatment arms, within each of the 4 strata as defined in Section 3.4.2. That is, within Cohort #1 and Cohort #2, patients will be randomly assigned to EVT or OPEN within clinical stratum (defined by Rutherford category and presence vs. absence of significant infrapopliteal occlusive disease). Permuted randomized blocks will define the allocation sequence in each stratum. If a patient has bilateral disease (CLI involving both limbs), one limb meeting all study eligibility criteria must be designated as the index limb for the BEST-CLI study. The cohort and stratum for randomization will be based on the index limb.

#### 3.4.2 Stratification

Within each cohort (#1 and #2), subjects will be randomized within four strata defined by two dichotomous factors based on (a) the clinical classification (Rutherford) [30] and (b) anatomical classification as in **Figure 2**.

Figure 2. Design Strata (Within Each Cohort)

|                                        |                                                                                        | Factor A:<br>CLINICAL CLASSIFICATION          |                                                                       |
|----------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------------------------------|
|                                        |                                                                                        | Ischemic Rest Pain<br>(Rutherford Category 4) | Tissue Loss with or<br>without Rest Pain<br>(Rutherford Category 5,6) |
| Factor B:<br>ANATOMICAL CLASSIFICATION | Infrainguinal PAD<br><b>without</b> significant<br>infrapopliteal<br>occlusive disease | I                                             | II                                                                    |
|                                        | Infrainguinal PAD<br><b>with</b> significant<br>infrapopliteal<br>occlusive disease    | III                                           | IV                                                                    |

Definitions:

**FACTOR A: CLINICAL CLASSIFICATION**

a) Ischemic rest pain alone (Rutherford category 4) defined as ankle systolic pressure  $\leq$  50 mm Hg, toe pressure of  $\leq$  30 mm Hg, transcutaneous PO<sub>2</sub> of  $<$  30 mm Hg, or flat-line transtarsal pulse volume recording.

b) Tissue loss with or without ischemic rest pain (Rutherford category 5, 6) defined as ankle systolic pressure  $\leq$  70 mm Hg, toe pressure of  $\leq$  50 mm Hg, transcutaneous PO<sub>2</sub> of  $<$  30 mm Hg, or flat-line transtarsal pulse volume recording.

**FACTOR B: ANATOMICAL CLASSIFICATION**

a) Presence of significant femoropopliteal occlusive disease, but with preservation of at least one infrapopliteal runoff vessel extending to the ankle without hemodynamically significant stenosis.

b) Presence of significant infrapopliteal disease, defined by hemodynamically significant occlusive disease in all tibial runoff vessels. Significant femoropopliteal occlusive disease may or may not be present.

The clinical stratification FACTOR A, clinical presentation, is a variable that has a significant impact on the clinical course, therapeutic approach to, and outcomes of subjects with CLI. Subjects with CLI and isolated ischemic rest pain (Rutherford category 4) have lower limb loss rates than those who present with tissue loss (Rutherford category 5, 6). Indeed, tissue loss was one of the most potent predictors of poor outcome in the SVS OPG analysis. Because of these distinctions, we aim to stratify subjects in both cohorts according to clinical presentation (ischemic rest pain alone vs. tissue loss with or without ischemic rest pain) prior to randomization in order to ensure balance with respect to this factor.

The anatomical stratification FACTOR B is a second variable with important implications for treatment management and outcomes. For EVT, there is evidence that technical and clinical success is correlated with target vessel quality and lesion location and length. In the surgical literature, differences in outcomes have long been noted between bypasses performed to popliteal and tibial targets. To optimize our ability to detect treatment-related differences in the study population, subjects will also be stratified by anatomical presentation (presence or absence of significant infrapopliteal arterial occlusive disease). Determination of anatomical status will be made by the treating vascular specialist using well established classification schema and standard radiographic landmarks. Of note, all preoperative, intraoperative and postoperative angiographic studies will be archived to allow for potential later evaluation and adjudication.

**3.4.3 Masking**

The independent CEC will be masked to treatment assignment for adjudication. The emphasis is on objective and central measurement. Because this is an open label trial, the primary and key secondary endpoints include definitive, documentable components: all-cause mortality, amputation of limb above the ankle, or re-intervention (see Section 6.1 for definitions).

Cost data will be abstracted from the medical record and cannot be masked. QOL and functional questionnaires will be completed by subjects with assistance from site staff as needed and will also not be masked.

### 3.4.4 Conflict of Interest (COI)

A conflict of interest policy will be enforced throughout the duration of the trial. All investigators will be required to disclose all conflicts related to trial participation. These will be adjudicated by a COI committee, as defined by the MOO.

## 3.5 Subject Participation

**Table 1** summarizes the proposed measurements and the visit schedule for their acquisition. The 30-Month visit, the visits every 12 months thereafter, and the end-of-study contact, are planned as telephone visits. All other visits are planned as in-person visits, because some types of data can only be obtained in person. However, if an in-person visit does not occur, the site will collect as many of the data elements as possible through other means such as telephone contact or medical record review.

**Table 1: Schedule of Measurements**

|                                                                                                                               | Base                 | Procedure<br>(w/i 30d of rand.) | Post-Proc <sup>1</sup> | Months Post Randomization <sup>2</sup> |   |    |    |    |                                       |                          |                  |
|-------------------------------------------------------------------------------------------------------------------------------|----------------------|---------------------------------|------------------------|----------------------------------------|---|----|----|----|---------------------------------------|--------------------------|------------------|
|                                                                                                                               |                      |                                 | 30 Days                | 3                                      | 6 | 12 | 18 | 24 | 30, 42,<br>54, 66,<br>78 <sup>3</sup> | 36, 48,<br>60, 72,<br>84 | EOS <sup>3</sup> |
| Informed consent                                                                                                              | X                    |                                 |                        |                                        |   |    |    |    |                                       |                          |                  |
| Catheter-based angiogram (preferred); or CTA, MRA, or arterial Duplex if considered adequate by site CLI team                 | X                    |                                 |                        |                                        |   |    |    |    |                                       |                          |                  |
| Medical history                                                                                                               | X                    |                                 |                        |                                        |   |    |    |    |                                       |                          |                  |
| Physical examination                                                                                                          | X                    |                                 | X                      | X                                      | X | X  | X  | X  |                                       | X                        |                  |
| Focused peripheral vascular history                                                                                           | X                    |                                 | X                      | X                                      | X | X  | X  | X  |                                       | X                        |                  |
| Duplex vein mapping                                                                                                           | X                    |                                 |                        |                                        |   |    |    |    |                                       |                          |                  |
| Medications                                                                                                                   | X                    |                                 | X                      | X                                      | X | X  | X  | X  | X                                     | X                        | X                |
| In-person clinical evaluation                                                                                                 | X                    |                                 | X                      | X                                      | X | X  | X  | X  |                                       | X                        |                  |
| Telephone clinical evaluation                                                                                                 |                      |                                 |                        |                                        |   |    |    |    | X                                     |                          | X                |
| Assessment of CLI symptoms                                                                                                    | X                    |                                 | X                      | X                                      | X | X  | X  | X  | X                                     | X                        | X                |
| Pain scale (NRS)                                                                                                              | X                    |                                 | X                      | X                                      | X | X  | X  | X  |                                       |                          |                  |
| Hemodynamic assessment (ankle & toe pressures; DW or transtarsal pulse volume recording if ankle or toe pressures inaccurate) | X                    |                                 | X                      | X                                      | X | X  | X  | X  |                                       | X                        |                  |
| Renal function                                                                                                                | X                    | X                               | X                      |                                        |   | X  |    | X  |                                       |                          |                  |
| Quality of Life (VascuQoL, SF-12, EQ-5D) <sup>4</sup>                                                                         | X                    |                                 | X                      | X                                      |   | X  |    | X  |                                       | X                        |                  |
| Health resources utilization                                                                                                  |                      | X                               | X                      | X                                      | X | X  |    | X  |                                       | X                        |                  |
| Six-minute Walk Test <sup>5</sup>                                                                                             | X                    |                                 |                        |                                        | X |    |    |    |                                       |                          |                  |
| Vital Status                                                                                                                  |                      | X                               | X                      | X                                      | X | X  |    | X  |                                       | X                        | X                |
| Arterial duplex <sup>6</sup>                                                                                                  |                      |                                 | X                      | X                                      | X | X  | X  | X  |                                       | X                        |                  |
| Revascularization of non-index limb <sup>7</sup>                                                                              |                      | x                               | X                      | X                                      | X | X  | X  | X  | x                                     | x                        | X                |
| Blood draw, if in ancillary study <sup>8</sup>                                                                                |                      |                                 |                        |                                        |   |    |    |    |                                       |                          |                  |
| AE/SAEs                                                                                                                       | -----continuous----- |                                 |                        |                                        |   |    |    |    |                                       |                          |                  |

1. 30 days post-procedure, or 30 days post-randomization if index procedure was not performed.
2. Minimum follow-up for each subject may be as low as 8 months or as high as 36 months, and maximum follow-up may be as low as 64 months or as high as 84 months. Each subject is followed through as many semi-annual visits that occur within the total study duration.
3. Month 30, 42, 54, 66, and 78 visits, and the end of study visit, will generally be conducted via telephone interview (although in-person visits will be allowed).
4. Quality of life questionnaires may be administered with use of an interpreter and/or via phone
5. Six-minute Walk Test will be performed at a subset of the clinical sites for which the test is standard of care.
6. Arterial duplex of the index limb is not mandatory for sites that do not perform it as standard of care; measure will be collected at sites that perform as standard of care at indicated time points, on all randomized subjects, for potential ancillary study use.
7. Collected at each visit, reported only at end-of-study visit
8. Blood draws for potential ancillary studies if separate funding obtained.

**Table 2: Target Visit Windows**

| Visit                   | Target Window  |
|-------------------------|----------------|
| 1 Month (-7d, +14d)     | 23-44 days     |
| 3 Months ( $\pm 30$ d)  | 60-120 days    |
| 6 Months ( $\pm 30$ d)  | 152-212 days   |
| 12 Months ( $\pm 30$ d) | 335-395 days   |
| 18 Months ( $\pm 45$ d) | 502-592 days   |
| 24 Months ( $\pm 60$ d) | 670-790 days   |
| 30 Months ( $\pm 60$ d) | 852-972 days   |
| 36 Months ( $\pm 60$ d) | 1035-1155 days |
| 42 Months ( $\pm 60$ d) | 1218-1338 days |
| 48 Months ( $\pm 60$ d) | 1401-1521 days |
| 54 Months ( $\pm 60$ d) | 1583-1703 days |
| 60 Months ( $\pm 60$ d) | 1765-1885 days |
| 66 Months ( $\pm 60$ d) | 1948-2068 days |
| 72 Months ( $\pm 60$ d) | 2130-2250 days |
| 78 Months ( $\pm 60$ d) | 2313-2433 days |
| 84 Months ( $\pm 60$ d) | 2495-2615 days |

**Baseline Assessment**

- Sign informed consent form, which contains language explaining that when angiography is performed post-consent, participation in the trial is contingent on full confirmation of trial eligibility.
- Perform pre-procedure imaging to ensure the eligibility criteria are met. Catheter-based angiography is strongly encouraged, although computed tomography (CTA), magnetic resonance angiography (MRA), or arterial Duplex is acceptable if considered adequate by the site CLI team. If a subject has had imaging which provides adequate diagnostic information within the past 3 months, this prior imaging may be used.
- Perform pre-randomization vein mapping to ensure eligibility criteria are met and to classify subject into Cohort #1 or Cohort #2.
- Review past medical history, risk factors for atherosclerosis, peripheral vascular history, and current medications.
- Perform physical examination, including full body examination, and documentation of the following: blood pressure, heart rate, weight, height, and bilateral femoral, popliteal, dorsalis pedis, and posterior tibial pulses. If tissue loss is present, the lesion and its location(s) will be described. CLI symptoms will be assessed.
- Evaluate hemodynamic status by measuring ankle pressures and/or toe pressures. If one or both of ankle pressures and toe pressures are unobtainable or unreliable, then tibial Doppler Waveforms (DW), transtarsal pulse volume recordings (PVR), or transcutaneous PO<sub>2</sub> must be obtained.
- Perform six-minute walk test. This measure will be performed at a subset of clinical sites (for whom this test is standard of care) and will be limited to patients for whom rest pain, wounds, or foot surgery (recent or anticipated) do not preclude weight-bearing.
- Collect blood for locally-conducted renal function test (creatinine).
- Collect demographics.

- Have subject complete quality of life questionnaires and a pain scale (the NRS, ranging from 0 to 10).
- Randomize subject via the internet using DCC assignments. A treatment code corresponding to either endovascular (EVT) or open surgical (OPEN) revascularization will be generated.

#### Follow-Up Study Visits

Health status and adverse event monitoring will be evaluated at all scheduled visits throughout the study. Subjects will remain in the trial and complete follow-up visits even if the primary trial endpoint is met.

Subjects will be scheduled for visits at 30 days after the procedure (or at 30 days after randomization if the procedure was not done), at 3 months, at 6 months and every 6 months thereafter until the end of the study. The month 30 visit and the visits every 12 months thereafter will generally be conducted via telephone interview (although in-person visits will be allowed). At each of these visits except months 30, 42, 54, 66, and 78, the following will be obtained:

- Current signs/symptoms.
- Current medications.
- Body weight, heart rate, and blood pressure.
- Pain scale (NRS) – at visits up to 2 years only.
- Femoral, popliteal, dorsalis pedis and posterior tibial pulse exam
- If tissue loss, location and description of lesion.
- Hemodynamic assessment by ankle pressures and/or toe pressures. If one or both of ankle pressures and toe pressures are unobtainable or unreliable, then tibial Doppler Waveforms (DW) transtarsal pulse volume recordings (PVR), or transcutaneous PO2 must be obtained.
- Revascularization of non-index limb (collected at each visit, but reported only at the end-of-study visit)

In addition, the following information will be collected at selected study visits or at selected sites:

- Blood will be collected for locally-conducted renal function test (creatinine) at time of the procedure and at Day 30, Month 12 and 24.
- Subjects will be asked to complete quality of life questionnaires at Day 30, Months 3, 12, and every 12 months thereafter.
- Subjects will be asked to provide health care utilization information at time of the procedures, and at Day 30, Months 3, 6, 12, and every 12 months thereafter.
- Six-minute walk test will be performed at selected clinical sites (for whom this test is standard of care) at Month 6.
- Arterial duplex studies of the index limb will be collected. This measure is not mandatory for sites that do not routinely perform arterial duplex. However, at sites which perform it routinely, arterial duplex will be tracked at indicated time points on all randomized subjects.

Vital and hospitalization status will be monitored through subject contacts and by interview as well as through medical record review at the clinic site. If a death occurs, a death Case Report Form (CRF) will be required, indicating the date, time and official cause of death as well as a description of events leading up to the death.

There will also be an end-of-study phone contact to collect information on subject symptoms, medication use, smoking status, and information on the contralateral, non-index limb. It is

expected that subjects will be asked about medication use, smoking status, and information on the contralateral, non-index limb at every visit, but it will only be recorded at the end-of-study visit.

### **3.6 Investigational Product Accountability**

It is the responsibility of the Principal Investigator at each Clinical Site to ensure the appropriate use and disposition of any commercially available endovascular stent or other device for each subject including angioplasty balloons, covered or uncovered stents, atherectomy devices, laser catheters, re-entry devices or embolic protection devices.

## **4. SELECTION AND WITHDRAWAL OF SUBJECTS**

### **4.1 Subject Inclusion and Exclusion Criteria**

Inclusion criteria (all must be met for eligibility)

- 1) Male or female, age 18 years or older.
- 2) Infrainguinal PAOD (occlusive disease of the arteries below the inguinal ligament).
- 3) CLI, defined as arterial insufficiency with gangrene, non-healing ischemic ulcer, or rest pain consistent with Rutherford categories 4-6.
- 4) Candidate for both endovascular and open infrainguinal revascularization as judged by the treating investigators (see MOO for guidelines on decision-making).
- 5) Adequate aortoiliac inflow, either already present at baseline or to be established prior to or at the time of the index revascularization.\*
- 6) Adequate popliteal, tibial or pedal revascularization target defined as an infrainguinal arterial segment distal to the area of stenosis/occlusion which can support a distal anastomosis of a surgical bypass.
- 7) Willingness to comply with protocol, attend follow-up appointments, complete all study assessments, and provide written informed consent.

Exclusion criteria (none can be met for eligibility)

- 1) Presence of a popliteal aneurysm (>2 cm) in the index limb.
- 2) Life expectancy of less than 2 years due to reasons other than PAOD.
- 3) Excessive risk for surgical bypass (as determined by the operating surgeon and the CLI Team).
- 4) Planned above-ankle amputation on ipsilateral limb within 4 weeks of index procedure.
- 5) Active vasculitis, Buerger's disease, or acute limb-threatening ischemia.
- 6) Any prior index limb infrainguinal stenting or stent grafting associated with significant restenosis within 1 cm of the stent or stent-graft, unless the occlusion/restenosis site is outside the intended treatment zone (i.e., a tibial vessel that is not currently intended to be revascularized as a part of the treatment for CLI).
- 7) Any of the following procedures performed on the index limb within 3 months prior to enrollment:
  - a. Infrainguinal balloon angioplasty, atherectomy, stent, or stentgraft;
  - b. Infrainguinal bypass with either venous or prosthetic conduit
- 8) Open surgical inflow procedure (aortofemoral, axillofemoral, iliofemoral, thoracofemoral or femorofemoral bypass) within 6 weeks prior to enrollment
- 9) Current chemotherapy or radiation therapy.
- 10) Absolute contraindication to iodinated contrast due to prior near-fatal anaphylactoid reaction (laryngospasm, bronchospasm, cardiorespiratory collapse, or equivalent) which would preclude patient participation in angiographic procedures.

- 11) Pregnancy or lactation.
- 12) Administration of an investigational drug for PAOD within 30 days of randomization.
- 13) Participation in a clinical trial (except observational studies) within the previous 30 days.
- 14) Prior enrollment or randomization into BEST-CLI.

\*Definition of adequate aortoiliac inflow

A patient will have adequate aortoiliac flow when the following criteria are met:

- 1) Patients must have adequate inflow to the common femoral artery, as defined by presence of at least one of the following:
  - normal ipsilateral femoral pulse.
  - biphasic or triphasic Doppler waveform in the ipsilateral common femoral artery.
  - normal radiographic appearance of ipsilateral iliac artery.
  - if radiographic evidence of ipsilateral common and external iliac artery occlusive disease, all lesions are of <50% severity.
  - if radiographic evidence of ipsilateral common and external iliac artery occlusive disease, there is  $\leq 10$  mmHg aortic to femoral mean pressure gradient
- 2) In the setting of Rutherford category 4 ischemia (ischemic rest pain), patients with the following clinical scenarios are eligible:
  - a. patients with <70% stenosis of the aorta or ipsilateral iliac arteries (endovascular treatment of stenoses of <70% will be allowed and left to the discretion of the treating investigator).
  - b. patients with  $\geq 70\%$  iliac or aortic stenosis or occlusion who have undergone successful endovascular revascularization and still have persistent symptoms of ischemic rest pain and continue to meet the hemodynamic definition of CLI on repeat assessment.
- 3) Patients with Rutherford category 5 or 6 ischemia (tissue loss) are eligible if they have iliac or aortic stenosis or occlusion and undergo endovascular revascularization prior to or at the same time as the index infrainguinal revascularization.
- 4) Patients cannot undergo contemporaneous open surgical inflow procedures (aorto-femoral, axillo-femoral, ilio-femoral, thoracofemoral, femorofemoral bypass).

Criteria for treating the common femoral or deep femoral artery

- 1) In the setting of Rutherford category 4 ischemia (ischemic rest pain), patients with the following clinical scenarios are eligible:
  - a. patients with < 70% stenosis of the ipsilateral (index limb) common femoral artery (Surgical endarterectomy or endovascular treatment of stenoses of <70% will be allowed and left to the discretion of the treating investigator).
  - b. patients with  $\geq 70\%$  stenosis of the ipsilateral (index limb) common femoral artery who have persistent symptoms of ischemic rest pain and continue to meet the hemodynamic definition of CLI (secondary to additional more distal arterial occlusive disease) on repeat assessment following successful open surgical endarterectomy or endovascular revascularization of the common femoral artery.
    - Surgical endarterectomy of the profunda femoral artery and/or superficial femoral artery origin at the time of the common femoral artery endarterectomy is acceptable and will be left to the discretion of the treating investigator.
    - It is necessary to repeat assessment of both symptoms and hemodynamic status following revascularization (open or endovascular) of the common femoral artery in the setting of rest pain to ensure persistence of CLI and

continued eligibility.

- 2) Patients with Rutherford category 5 or 6 ischemia (tissue loss), who have an occlusion or any degree or stenosis of the common femoral artery are eligible and can undergo either open surgical endarterectomy or endovascular revascularization of the common femoral artery. This revascularization can be done prior to or at the same time as the index limb revascularization, irrespective of whether the randomized treatment of the more distal arterial occlusive disease is endovascular or open surgical bypass.
  - Surgical endarterectomy of the profunda femoral artery and/or superficial femoral artery origin at the time of the common femoral artery endarterectomy is acceptable and left to the discretion of the treating investigator.

#### Criteria for inclusion of previously stented vessels

Patients with prior superficial femoral artery or popliteal artery stent or stentgraft are eligible for randomization in BEST-CLI if both of the following criteria have been fulfilled:

- The stent or stentgraft (including 1cm proximal and distal to the stent or stentgraft) is patent, defined as having  $\leq 30\%$  stenosis based on visual assessment on a catheter-based contrast angiogram
- The stent or stentgraft has been in place  $\geq 3$  months

Patients with prior tibial stenting are eligible for randomization under the following circumstances:

- If the pre-existing stent is located within a tibial vessel that is intended to be revascularized as part of the index BEST-CLI procedure, all of the following criteria are fulfilled:
  - The stent is patent, defined as having  $\leq 30\%$  stenosis based on visual assessment of a catheter-based contrast angiogram
  - The previously stented site, including 1cm proximal and distal to the stent, is not within the target lesion intended for treatment
  - The stent has been in place  $\geq 3$  months
- The pre-existing stent is *not* located within the tibial vessel that is intended to be revascularized as part of the BEST-CLI procedure

#### Criteria for bilateral disease

Patients with bilateral lower extremity CLI are eligible for enrollment. However, for such patients, only one limb meeting all eligibility criteria will be designated as the index limb for the BEST-CLI study.

#### Staging of procedures

Staged procedures will be allowed under certain limited circumstances, as described in the MOO.

#### Hybrid procedures

Planned combinations of endovascular iliac revascularization and open infrainguinal bypass are allowed if the inclusion and exclusion criteria are otherwise met. Open or endovascular common femoral artery revascularization is also allowed in conjunction with the randomized open or endovascular infrainguinal treatment assignment. Combined open and endovascular infrainguinal procedures are not allowed distal to the common femoral artery.

## **4.2 Subject Withdrawal Criteria**

Subjects may be withdrawn from the study for the following reasons:

- Subject declines further study participation.

- In the investigator's judgment, it is in the subject's best interest.

All protocol-specified visits and follow-up procedures should be performed for every subject enrolled in the trial, even if the primary trial endpoint is met. If the subject refuses to continue with the study visits, every attempt should be made to continue contact by telephone, written communication, or record review to determine if outcome events have occurred, unless the subject specifically refuses such follow-up. The reason for withdrawal will be documented for all subjects withdrawn from the study. If the withdrawing subject is unwilling to have his/her medical records reviewed until the end of the trial period (to document vital status and cause of death), he/she should submit a written refusal.

A Master Patient Log of all subjects who provided informed consent will be maintained at the investigational site irrespective of whether they have been treated or not and irrespective of their randomization or treatment status.

## **5. TREATMENTS TO BE ADMINISTERED**

### **5.1 Product Administration**

Subjects randomized to BEST-CLI endovascular therapy will receive treatment according to established standard of care for all commercially available endovascular devices. Interventionalists and surgeons will be certified for participation in the trial according to criteria) specified by the Surgical and Interventional Management Committee and outlined in the MOO. Records of investigator certification will be kept on file by the DCC.

### **5.2 Medications/Treatments Permitted and Not Permitted during the Trial**

No medications are specifically excluded from the trial. Guidelines for medical therapy and risk management have been developed by the Optimal Medical Therapy (OMT) Committee and will be provided in the trial MOO. Investigators should follow standard of care guidelines, as well as adhere to contraindications, warnings, and precautions published in the instructions for use of each commercially available endovascular device.

### **5.3 Treatment Violations**

Some subjects assigned to one study treatment (EVT or OPEN) may receive the other one instead. The details of such events will be carefully recorded, including the reason for the treatment violation, which could occur through either subject or physician preference.

This type of treatment violation is defined as:

- Completion of open surgery when randomized to endovascular procedure, or completion of endovascular procedure when randomized to open surgery, *without prior initiation* of the randomly assigned procedure.

In some instances, the assigned treatment may be initiated, but the subject receives the other treatment following that initiation. In such cases, the administration of the opposite procedure indicates a failure of the assigned procedure, and is defined as treatment failure rather than treatment violation.

In order to differentiate between “treatment violation” and “treatment failure”, it is important to identify whether the assigned treatment has been initiated or not. Accordingly, when a patient undergoes the non-assigned treatment after randomization, defining the precise moment of initiation of the assigned treatment is critically important. Detailed definitions for initiation of an open surgical procedure and initiation of an endovascular procedure are provided in the MOO.

Two scenarios are useful to help define when an assigned procedure is initiated. This definition is dependent, in part, on the circumstances under which randomization occurs:

Scenario #1 - Randomization occurs in a non-procedural setting, and is based on acceptable diagnostic imaging study performed prior to the index procedure. In such instances, the procedure **initiation will be defined as occurring at the moment of induction of anesthesia or administration of conscious sedation in the treatment area.**

Scenario #2 – Randomization occurs in a procedural setting, at time of diagnostic angiography, with the patient on the table. In such instances, if the patient is randomized to endovascular therapy, then procedure **initiation will be defined by the introduction of the interventional guidewire to attempt to cross the target (infra-inguinal) lesion.** If the patient is randomized to surgery and if surgery takes place concomitantly, then **initiation will be defined as occurring at the time of the surgical incision.** If surgery is not immediate, then **initiation will be defined as occurring at the moment of induction of anesthesia before surgery.**

In all cases, the subject will remain in his or her assigned treatment group for intention-to-treat analyses.

#### **5.4 No Study Treatment**

All randomized subjects must undergo their assigned treatment within 30 days following randomization. If neither endovascular revascularization nor open surgical revascularization is attempted within this time period, data will be collected on the reasons why neither procedure was attempted. Such subjects, unless deceased, will remain in the trial. The data of such subjects will be analyzed according to the conditions specified in Section 8.1.1.

### **6. ASSESSMENT OF EFFICACY**

#### **6.1 Specification of the Efficacy Parameters**

All-cause mortality will be as reported to occur any time after randomization. Perioperative death is the subset occurring within 30 days after the index procedure.

Amputation above the ankle in the index (treated) leg, as reported in surgical notes.

Major Re-interventions are defined as new bypass graft, jump/interposition graft revision, surgical thrombectomy with or without surgical patch angioplasty and thrombectomy of an occluded graft or arterial segment using pharmacologic or mechanical thrombolysis. These major re-interventions are components of the primary endpoint.

Minor Re-interventions are defined as surgical patch angioplasty (without graft thrombectomy), balloon angioplasty, atherectomy, laser treatment and/or stenting or stent/grafting via either an open surgical exposure (i.e. a “hybrid” approach) or percutaneous approach.

All re-interventions (hospitalizations) will be recorded, with length of stay (LOS) discharge diagnoses and (coded) procedures performed for the cost-effectiveness analysis.

Freedom from MI and Freedom from Stroke – suspected MI and stroke will be adjudicated by the CEC (See Section 8.8). Definitions of what will be deemed an MI and Stroke for BEST-CLI are detailed in the MOO.

Hemodynamic failure is defined as occurrence of one or more of the following events:

- above ankle amputation of the index limb
- any re-intervention to maintain vascular patency in the index limb
- failure to increase Ankle Brachial Index (ABI) by at least 0.15 post-procedure as compared to baseline value (for patients with non-compressible vessels, failure to increase the toe-brachial index (TBI) by 0.10)
- decrease in ABI by 0.15 (or TBI drop of 0.10) or greater as compared to post-procedure value
- Duplex ultrasound demonstrating occlusion of the graft or treated native vessel
- Duplex ultrasound demonstrating critical graft stenosis (Peak Systolic Velocity (PSV) >300 cm/sec and velocity ratio > 3.0)
- Angiogram demonstrating occlusion of any graft or treated vessel, or greater than 50% stenosis in the presence of recurrent clinical symptoms

Clinical failure is defined as death, MALE, non-healing of index limb wound (either the original wound or the surgical wound from a minor index limb amputation to treat tissue loss), worsening of Rutherford category, recurrence of index limb wound, or recurrence of ischemic rest pain that resolved completely after initial revascularization.

Freedom from CLI will be assessed at each of the protocol-specified in-person follow-up visits. Freedom from CLI at a particular visit is defined as survival to that time point without index limb major amputation, AND without wound or ischemic rest pain at the time of the visit.

Functional Status will be assessed using the 4-week recall SF-12, which is widely used in cardiovascular trials and is available in Spanish and French. [31].

Quality of Life will be assessed with two questionnaires – VascuQoL [32] and EQ-5D [33]. These are standard, validated instruments, available in Spanish and Canadian French as well as in English, for this trial. The VascuQoL is a disease-specific questionnaire that makes it possible to detect subtle changes in disease severity, and will be used as the main CLI-specific quality of life outcome. The well-standardized EQ-5D comprehensively gauges global health-related QoL and utilities, and will be the primary measure for cost-utility analysis. Other instruments, including Numerical Rating Scale (NRS) for pain and (at selected sites) the six-minute walk test, are complementary secondary instruments that will supplement the main QoL measurements. It is clear that CLI is associated with severely impaired QoL, and any comparative assessment of CLI treatment options would be incomplete without measuring their impact on this important parameter. The EQ-5D and 4-week recall SF-12 are complementary assessment tools that comprehensively gauge global health related QoL/function and utilities for cost-effectiveness analysis, while the VascuQoL is a more disease-specific questionnaire that better allows one to detect subtle changes in disease severity.

Cost Effectiveness - Because endovascular and open revascularization may be associated with different rates of treatment success and safety as well as cost, cost-effectiveness will serve as a

vitality important secondary endpoint that will allow for an evaluation of net clinical benefit based on both quantity and quality of life and the economic value of any observed differences in these outcomes. This analysis will rely on prospectively collected information to characterize the resources consumed during each subject's initial revascularization hospitalization and all related subsequent inpatient and outpatient contacts with the medical system (including rehospitalizations, outpatient physician visits, outpatient tests and procedures, emergency department visits, and medication use). To perform cost-utility analyses, measurements of QOL and functional status will be mapped to utilities.

### Resource Utilization

- Revascularization Hospitalization Abstraction Pilot – The Division of Pharmacoepidemiology and Pharmacoeconomics of the Brigham and Women's Hospital will work with DCC staff to identify and review hospital records of at least 20 subjects who would have been eligible for the trial. These records will be drawn from at least 3 hospitals participating in the trial with varying standards of care for CLI, with appropriate Institutional Review Board (IRB) approval. At least one will be a non-academic hospital. From this review, more detailed diagnostic groups will be developed than those DRGs currently used by Medicare for reimbursement, (which are not able to adequately distinguish procedures likely to be used in each treatment group). The resulting CRF for record abstraction will then be tested on another 20 records from the same hospitals.
- The final, tested CRF will then be used by each site in the trial to abstract the index revascularization hospitalization as well as all subsequent re-hospitalizations during 2 years of follow-up post-randomization. Any revascularization occurring at a hospital other than the participating site during the 2-year follow-up will be abstracted by the DCC using a HIPAA-compliant process.
- The CRF for resource utilization will include:
  - Length of hospital stay
  - Number of days in ICU, general ward, etc.
  - Specific vascular procedure performed and any complications
  - Other diagnostic tests and interventions performed (including use of stents and other devices)
- Out-Patient Rehabilitation, (and Long-Term Care Facility) Services Utilization – Standard questionnaires (CRFs) in use at the DCC and BWH Division of Pharmacoepidemiology and Pharmacoeconomics will be modified for this trial.
- Costs will be separately determined and applied to the resource components to provide an analytic data set.

## **7. ASSESSMENT OF SAFETY**

### **7.1 Specification of Safety Parameters**

All safety endpoints will be captured according to Adverse Event reporting rules and will include:

- Serious Adverse Events (SAEs) from randomization through 30 days post-procedure
- SAEs from randomization throughout time on study
- MACE (Major Adverse Cardiovascular Events) - a composite of death, MI and stroke – from randomization through 30 days post-procedure
- MACE from randomization throughout time on study
- Non-serious adverse events from randomization through 30 days post-procedure
- Perioperative complications

Note that Serious Adverse Events are collected from the time of informed consent throughout the subject's remaining time on study. However, Serious Adverse Events (including components of MACE) which have their onset before a consented subject is randomized will not be considered in the safety endpoint comparisons of the treatment groups, although these early events will be reported to the DSMB.

Surgical complications are defined as:

- hematoma or local bleeding complications
- pseudoaneurysm
- arterial dissection
- distal embolization
- acute or subacute graft thrombosis
- graft or wound infection
- nerve injury
- lymphatic complications
- compartment syndrome

Endovascular complications are defined as:

- Hematoma or local bleeding complications
- pseudoaneurysm
- arteriovenous fistula (hemodynamically significant)
- arterial dissection
- distal embolization
- acute or subacute arterial thrombosis
- access site or related infection
- nerve injury
- lymphatic complications
- compartment syndrome

Systemic complications associated with surgical or endovascular revascularization include:

- contrast- and non-contrast-related allergic reactions
- contrast-induced acute renal failure
- renal failure unrelated to contrast
- deep venous thrombosis
- systemic bleeding complications
- heparin-induced thrombocytopenia
- pulmonary complications such as pneumonia, pulmonary embolism, or ventilator dependence
- myocardial infarction
- stroke
- sepsis
- death

Of note, safety reporting of adverse events is driven by the occurrence of a sentinel event and those events will be classified and reported according to body system and by treatment arm in at

least semi-annual safety monitoring reports (or more often as required by regulatory bodies). Events such as death and amputation are outcomes of adverse events, and will be examined by treatment arm to assess efficacy (not safety) at the pre-specified interim look times and at the end of the trial.

## **7.2 Recording and Reporting Adverse Events**

The EDC system at the DCC maintains a safety database which allows for AE/SAE coding using the most recent version of MedDRA (Medical Dictionary for Drug Regulatory Activities).

### **7.2.1 Adverse Event (AE)**

An AE is defined as any unfavorable medical occurrence experienced by a subject during participation in the trial. An adverse event may be a disease, a set of related symptoms or signs, or single symptom or sign (including an abnormal laboratory finding). Note: an AE is not a procedure (e.g. PTA), action (e.g. hospitalization), or outcome (e.g. death). AEs are divided into two categories (1) non-serious AEs and (2) serious AEs (SAEs).

### **7.2.2 Serious Adverse Event (SAE)**

A SAE is defined by regulation as any adverse event (as defined above) that results in one or more of the following:

- death;
- is life threatening (at the time of the event);
- requires initial hospitalization or prolongation of existing in-patient hospitalization (initial hospitalization for study surgery will not be considered an adverse event or serious adverse event);
- persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is an important medical event defined as a new event likely to affect the safety of the subjects in the trial (such as an unexpected outcome of an adverse reaction, or major safety finding from a newly completed animal study).

Life-threatening means that the subject was, in the view of the investigator, at immediate risk of death from the event as it occurred. It does not mean that the event, had it occurred in a more severe form, might have caused death.

### **7.2.3 Unanticipated Adverse Device Event (UADE)**

An Unanticipated Adverse Device Event (UADE) is defined as a serious adverse event (as defined above) that is either possibly, probably, or definitely related to the endovascular device in which the nature or severity of the event is not consistent with information in the Instructions for Use.

### **7.2.4 Unanticipated Problem (UP)**

An Unanticipated Problem (UP) is any incident, experience, or outcome involving risk to subjects that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

### Reporting Requirements

All observed AEs and their suspected causal relationship to the study procedure and/or endovascular device will be reported as described in the following sections. Non-serious AEs will be reported only during the period from randomization through 30 days after the index revascularization procedure, or through 30 days post-randomization if no revascularization procedure has taken place during that time. SAEs will be reported from the time a subject signs consent, to the end of subject participation.

For all AEs, the Investigator must obtain information adequate both to determine the outcome of the AE and to assess whether it meets criteria for classification as an SAE requiring immediate notification to the Sponsor (the National Heart, Lung, and Blood Institute).

All SAEs, as defined above, must be reported by the Investigator to the DCC and (if applicable), they must also be reported to the Site's IRB/EC, in accordance with applicable national regulations and guidelines set forth by the Site's IRB/EC. Specifically, all fatal or life-threatening SAEs must be reported to the DCC on the AE/SAE CRF within 24 hours of the Investigator's awareness of the event. All other SAEs must be reported to the DCC within 48 hours on the AE/SAE CRF.

### Causality Assessment

For all AEs, the Investigator will make an initial determination of the causality of the AE. The Investigator will also submit sufficient information to the DCC to review and assess causality for AEs. Causality assessment is the determination of whether a reasonable possibility exists that the study device or procedure caused or contributed to an AE. If the determination of causality is unknown because the reviewer does not know whether or not the study device or procedure caused the AE, then the AE will be handled as "related to study device or procedure" for reporting purposes. If the final determination of causality is "unknown but not related to study device or procedure", this information should be clearly documented on trial records.

The determination of causality made by the Investigator will be recorded and will be used as a guideline to determine which AEs require expedited review by the CEC.

In addition, if the Investigator determines an SAE is associated with the study device or procedure, the Investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements.

## **7.3 Follow-up of Subjects after Adverse Events**

All reportable adverse events [i.e. non-serious AEs within first 30-days post-procedure (or 30 day post-randomization if the procedure has not taken place) and all SAEs] should be followed until resolution, return to normal or baseline values, stabilization, death, subject withdrawal or until they are judged by the investigator to no longer be clinically significant, whichever occurs first. Supplemental measurements and/or evaluations may be necessary to fully investigate the nature and/or causality of a reportable adverse event. This may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. CRF pages should be updated with any new or additional information as appropriate.

## 8. STATISTICS

### 8.1 Statistical Analysis Plan

#### 8.1.1 Analysis of the Primary Endpoint

The primary analysis of the primary endpoint will be according to the intention-to-treat (ITT) principle. All randomized subjects will be included in ITT analyses, even if they do not undergo either an open or an endovascular procedure. Any subject who undergoes a treatment other than the treatment they were randomized to, or undergoes no index procedure, will remain in their assigned treatment group for ITT analyses.

Evaluation of the primary endpoint will be two cohort-specific comparisons of the distributions of freedom from MALE/Death by treatment arm, where the distributions are based on all available follow-up at trial end. In each cohort, the null hypothesis ( $H_0$ ) is that there is no difference in time from randomization to MALE/Death by treatment arm. In each cohort, the primary comparison of the two treatment groups will be made using the likelihood ratio test from a stratified Cox model, in which the underlying hazard function is allowed to differ by randomization stratum, but the hazard ratio comparing EVT to OPEN is assumed to be common for all strata within a cohort. These cohort-specific Cox models for the primary analysis of the primary endpoint will also be adjusted for end-stage renal disease (present or absent at baseline); whether or not the subject had had a prior revascularization procedure on the index leg before entering the BEST study; diabetes (present or absent at baseline); and smoking status at baseline (never a smoker, prior smoker who ceased smoking more than one year ago, prior smoker who ceased smoking between one year ago and two weeks ago, or current smoker, i.e. any smoking within the prior two weeks).

Of note, based on consensus of experts in the field at a BEST-CLI trial planning summit in August 2011, a test of interaction of treatment effect by cohort is not of clinical relevance for this trial, as patients with SSGSV and others are distinctly different patient populations. Each cohort (#1 and #2) will be analyzed separately, with a false positive rate of 0.05 for each test of the primary endpoint hypothesis.

The secondary analytic approach of the primary endpoint will utilize the likelihood ratio test from a Cox regression model, stratified by randomization stratum and adjusting for end stage renal disease, prior revascularization of the index leg, diabetes, and smoking status, but also including adjustment for any additional baseline subject factors (covariates) that are known to be associated with the outcome, either in the current literature or in the observed data. The results of this secondary analysis will be compared to the results of the primary analysis that does not include adjustment for these additional covariates, to assess whether the magnitude or statistical significance of the treatment group comparison is substantially altered after adjusting for other important baseline characteristics.

An additional exploratory approach will be a non-ITT model, similar to the primary analysis, but excluding any subjects who do not initially undergo the therapy to which they were assigned and instead undergo the opposite intervention or no intervention. However, such an analysis may introduce bias with regard to comparability of the two groups. A time-dependent treatment indicator for the non-ITT analysis is unlikely to be needed, as treatment violations in this clinical setting almost always occur immediately.

### Pre-Specified Subgroup Analyses

Several exploratory subgroup analyses are planned, based on characteristics known at the time of randomization. These pre-specified subgroup analyses are listed below. Within each cohort, a test for the interaction of the treatment group assignment variable by the subject subgroup factor will be conducted to assess whether there may be a differential treatment effect depending on the value of the baseline characteristic [34]:

- Isolated femoral disease vs. tibial disease
- Rutherford category 4 (ischemic rest pain only) vs. category 5 and 6 (tissue loss)
- Gender
- Race (White vs. Black vs. Asian vs. All others)
- Ethnicity (Hispanic vs. non-Hispanic)
- Race/ethnicity (Hispanic vs. Black non-Hispanic vs. All others)
- Age < 80 years vs. ≥ 80 years
- Presence vs. absence of diabetes
- Presence vs. absence of WIF1 Grade 3 wound on index limb
- Presence vs. absence of renal dysfunction
- Absence of renal dysfunction vs. non-dialysis-dependent renal dysfunction vs. dialysis-dependent renal dysfunction

If the p-value for the test of interaction between treatment group and a subgroup variable is < 0.05, it will be considered as evidence that the effect of randomized treatment group may differ between patients depending on which category of that subgroup they belong to. For the primary trial endpoint, the test of interaction will be conducted using the likelihood ratio test from a Cox proportional hazards regression, stratified by randomization stratum and adjusted for presence or absence of end-stage renal disease at baseline; whether or not the subject had a revascularization procedure on the index leg prior to randomization in BEST, diabetes at baseline, and smoking status at baseline. (The subgroup analyses for subgroups based on renal status will not include the adjustment for presence or absence of end-stage renal disease at baseline.)

### **8.1.2 Analysis of Secondary Outcomes**

The primary analytic approach of the secondary trial endpoints will also be according to ITT and conducted separately within each cohort. The primary analysis of each time-to-event secondary endpoint, such as amputation-free survival or MALE-POD, will be analyzed using the likelihood ratio test from a Cox model stratified by randomization stratum. In addition to the stratification, the model for each secondary outcome will also be adjusted for a pre-specified list of covariates expected to be related to that outcome.

Mixed model linear regression will be utilized to examine treatment effect for continuous endpoints such as quality of life (VasculQoL, EQ-5D, SF-12 questionnaires) [31-33], both longitudinally and with contrasts of treatment differences at specific time points. A Wilcoxon rank sum test will be used to compare six-minute walk times from the six-month visit for the two groups.

### Cost Effectiveness Analysis

The cost-effectiveness analysis will be executed at the Division of Pharmacoepidemiology and Pharmacoeconomics in close collaboration with DCC to obtain clinical/hospitalization data. The primary analysis will use measures of costs and outcomes assessed during the trial period itself (i.e. the in-trial analysis) to estimate differences in the cost-effectiveness (measured in incremental dollars per incremental quality-adjusted life year) between the two treatment strategies. Supplementary evaluations will be performed for all patients for whom data are

available through the end of the trial. Because the actual long-term clinical consequences (and the cost-effectiveness of each study arm) will be incompletely captured by the within-trial analysis, we will also develop a Markov state-transition model to estimate the cost-effectiveness of each treatment arm over a lifetime horizon. This model will simulate longer-term follow-up of the trial participants as they move through a series of health states that represent the occurrence of specific clinical events. We will perform our modeling based on intention-to-treat principles from a societal perspective. The simulation will be programmed in TreeAge Pro Suite 2011 (TreeAge Inc, Williamstown, Massachusetts).

Costs will be estimated by multiplying the magnitude of resources each patient consumes by unit prices obtained from nationally and regionally representative data sources. These unit costs will be estimated from the Premier Perspective Comparative database, currently in use at the Division of Pharmacoepidemiology and Pharmacoeconomics. This database, a repository of hospital administrative data that includes approximately one-sixth of all hospitalizations in the United States. Premier data are audited, verified, and validated and are provided to hospitals for the purpose of tabulation and benchmarking against the performance of other institutions. This source contains a record of daily charges for all medications, procedures, and diagnostic tests during each patient's hospitalization, as well as patient and hospital characteristics, discharge diagnoses, and discharge status (including death). Premier data have been extensively used to evaluate population-based medication use and health outcomes. This source is also used by the Food and Drug Administration (FDA), as well as the Centers for Medicare and Medicaid Services Hospital Quality Incentive Demonstration to link hospital reimbursement to the quality of care and outcomes for selected procedures or conditions.

We will validate our estimates of hospitalization costs with actual hospital charge data from selected hospitals participating in the trial; appropriate cost-to-charge ratios will be applied. Relevant physician service costs (e.g. for surgeons and anesthesiologists) will be estimated from DRG-specific ratios of physician to hospitalization costs and validated using the Medicare Physician Fee Schedule.

We will aggregate the cost of all resources consumed during the index hospitalization to calculate summary estimates for each patient. To this, we will add resources consumed during follow-up – in addition to re-hospitalization - including the use of rehabilitation facilities, other institutional care, outpatient physician visits, outpatient tests and procedures, emergency department visits, and medication use. Costs for disease-related rehabilitation stays, home health care and long-term care will be obtained from published sources. Costs for informal care will be estimated by multiplying the average hourly wage of a home health aide, as a proxy for the monetary value of an hour of informal care giving, by the number of hours of informal care use reported by patients. The value of patient-time required for outpatient procedures and testing will be estimated based on the average hourly wage of age-matched US workers using the standard approach recommended by the US panel on cost-effectiveness [36].

The prospectively collected functional status and quality of life measures will be used to generate time-weighted utility estimates. These utility measures will be applied to trial outcomes to calculate quality-adjusted life year estimates. In the primary cost-utility analysis, we will report incremental cost-effectiveness ratios as cost per additional quality-adjusted life year, where QOL is measured using the well-validated EQ-5D scale. Other types of incremental cost effectiveness ratios will be estimated secondarily to supplement the primary outcomes. For example, QOL measurements using the standard SF-12 questionnaire will be also mapped onto SF-6D utilities to provide an alternative scale for measuring quality-adjusted life years and the incremental cost-effectiveness

ratio. In addition, cost-effectiveness ratios specific to CLI-related clinical outcomes will be reported as incremental cost per unit increase in the VascuQoL scale.

In our trial-based Markov model, patients will move among a set of predefined states of health, reflecting the procedure performed, any resulting complications, post-procedural symptoms, and death. In specific, the following health states will be considered: 1) no claudication without major morbidity; 2) no claudication with major morbidity; 3) persistent claudication without major morbidity; 4) persistent claudication with major morbidity; 5) CLI without major morbidity; 6) CLI with major morbidity; 7) post-amputation without major morbidity; 8) post-amputation with major morbidity; and 9) dead. Data from the BEST-CLI trial will inform short-term transition probabilities and costs and will be used to calibrate our model. Longer term data, such as event rates and mortality rates beyond the trial period, will be generated from published sources. These data will define transition probabilities between health states over time, the trajectory of complications after treatment, and the costs and utilities associated with specific health states and paths.

We will model major morbidity (e.g., major cardiopulmonary, renal, or cerebrovascular complications), which will have a lifelong impact on HRQoL and costs, and death as complications of each revascularization strategy and amputation. We will assume that patients with successful revascularization experience no claudication but could still suffer from major morbidity as a complication of their procedure. Patients who experience no claudication following successful revascularization may experience disease re-progression to persistent claudication or CLI over time. We will assume that patients who fail revascularization and are left with persistent claudication will only undergo further revascularization if they subsequently progress to CLI. We will limit the maximum number of interventions per limb to three. If the maximum number of interventions is reached and the patient has CLI then the affected limb will assume to be amputated. Patients who undergo amputation will remain in the post-amputation state, unless they die from other causes. The incidence of procedure-related morbidity and mortality will be directly obtained from the BEST-CLI trial. A disease-specific, excess all-cause mortality rate will be incorporated in the model and determined using the declining exponential approximation of life expectancy (DEALE) equation. Death resulting from other causes will be possible at any time and in any health state. All patients will make transitions between the health states every 3 months until they die or reach 100 years of age.

Our primary outcomes measures will be QALY and lifetime costs (both discounted at an annual discount rate of 3%). If a more effective strategy is also more expensive, an ICER will be calculated by dividing the additional cost of the strategy by its additional effectiveness. We will conduct comprehensive deterministic sensitivity analysis on all model parameters and explore ICERs for various cohorts of patients, defined as age, preexisting risk, and comorbidity. Uncertainty in cost-effectiveness will be represented using cost-effectiveness acceptability curves, showing the probability of each revascularization strategy being the most cost effective for a range of values that one might be willing to pay for an additional QALY.

## **8.2 Number of Subjects to be Enrolled and Statistical Power**

Aggregate event rates observed in the study to date are higher than the aggregate event rates assumed in the power calculations in the original protocol and the August 10, 2015 protocol amendment. With other assumptions held constant, higher event rates increase statistical power.

Therefore, for each cohort, power calculations for the primary outcome have been made for all combinations of the following 3 factors:

- 3 sets of 2.95-year event rates
  - The event rates powered for in the original protocol. The open surgery event rate of 53.0% for Cohort 1 is derived from the Objective Performance Goal meta-analysis of 3 randomized trials [8]. Event rate extrapolation to 2.95 years assumed, based on related CLI data, that the year 2 event rate was half of year 1 and year 3 was 43% of year 2. The BASIL trial data were used to estimate the OPEN event rate for Cohort 2.
  - The event rates powered for in the August 10, 2015 version of the protocol.
  - The event rates based on the aggregate event rates as of the October 31, 2017 data freeze. These were calculated as the event rates in each treatment arm that would average to the aggregate event rate, and result in a hazard ratio of 1.25 in Cohort 1 and 0.70 in Cohort 2.
- 2 enrollment scenarios
  - Scenario A, a very conservative scenario enrolling 1363 subjects by August 31, 2018 (1076 in Cohort 1 and 287 in Cohort 2)
  - Scenario B, an ideal scenario enrolling 2100 subjects by December 31, 2019 (1620 in Cohort 1 and 480 in Cohort 2).
- 4 total study durations
  - 64 months (except for Enrollment Scenario B which has an enrollment period of 64 months)
  - 72 months
  - 76 months
  - 84 months

All power calculations make the following additional assumptions

- Two-sided tests
- Up to 10% of subjects assigned to open surgery actually receive endovascular treatment first (except for the event rates based on the observed aggregate event rates which already include actual crossover rates)
- Up to 2% of subjects assigned to endovascular treatment actually receive open surgery first (except for the event rates based on the observed aggregate event rates which already include actual crossover rates)
- Treatment violations are assumed to be immediate
- Loss to follow-up rate of 5% over 2.95 years
- 2% sample size inflation to account for interim looks

Tables 2a-c shows the power calculations for Cohort 1. Tables 3a-c shows the power calculations for Cohort 2. The power for each cohort that will actually be obtained by the study is very likely to fall within the range of calculated powers shown in these tables.

Based on aggregate event rates observed in the BEST-CLI trial as of the October 31, 2017 data freeze, even the most conservative enrollment scenario with the minimum total study duration has 82.8% power to detect a hazard ratio of 1.25 for endovascular intervention versus open surgery. Power is lower in Cohort 2 because of the relative rarity of these patients. However, the inclusion of these patients in the comparative effectiveness paradigm is considered to be of greater importance to the successful execution of a CLI trial, and the information it may provide to clinicians and patients, than omission of this cohort for separate study at a later time.

Table 2a. Power calculations for Cohort 1 using event rates powered for in the original protocol

| <b>Event Rates 53.0% Open Surgery, 61.1% Endovascular Treatment, Hazard Ratio 1.25</b> |                                |                                   |              |
|----------------------------------------------------------------------------------------|--------------------------------|-----------------------------------|--------------|
| <b>Enrollment Scenario</b>                                                             | <b>Study Duration (Months)</b> | <b>Minimum Follow-Up (Months)</b> | <b>Power</b> |
| A                                                                                      | 64                             | 16                                | 68.2%        |
| A                                                                                      | 72                             | 24                                | 72.9%        |
| A                                                                                      | 76                             | 28                                | 74.7%        |
| A                                                                                      | 84                             | 36                                | 77.6%        |
| B                                                                                      | 72                             | 8                                 | 82.1%        |
| B                                                                                      | 76                             | 12                                | 84.6%        |
| B                                                                                      | 84                             | 20                                | 88.2%        |

Table 2b. Power calculations for Cohort 1 using event rates powered for the August 10, 2015 version of the protocol

| <b>Event Rates 53.0% Open Surgery, 61.3% Endovascular Treatment, Hazard Ratio 1.26</b> |                                |                                   |              |
|----------------------------------------------------------------------------------------|--------------------------------|-----------------------------------|--------------|
| <b>Enrollment Scenario</b>                                                             | <b>Study Duration (Months)</b> | <b>Minimum Follow-Up (Months)</b> | <b>Power</b> |
| A                                                                                      | 64                             | 16                                | 70.6%        |
| A                                                                                      | 72                             | 24                                | 75.1%        |
| A                                                                                      | 76                             | 28                                | 76.9%        |
| A                                                                                      | 84                             | 36                                | 79.7%        |
| B                                                                                      | 72                             | 8                                 | 84.0%        |
| B                                                                                      | 76                             | 12                                | 86.4%        |
| B                                                                                      | 84                             | 20                                | 89.8%        |

Table 2c. Power calculations for Cohort 1 using event rates based on the aggregate event rates as of the October 31, 2017 data freeze

| <b>Event Rates 59.3% Open Surgery, 67.5% Endovascular Treatment, Hazard Ratio 1.25</b> |                                |                                   |              |
|----------------------------------------------------------------------------------------|--------------------------------|-----------------------------------|--------------|
| <b>Enrollment Scenario</b>                                                             | <b>Study Duration (Months)</b> | <b>Minimum Follow-Up (Months)</b> | <b>Power</b> |
| A                                                                                      | 64                             | 16                                | 82.8%        |
| A                                                                                      | 72                             | 24                                | 86.3%        |
| A                                                                                      | 76                             | 28                                | 87.5%        |
| A                                                                                      | 84                             | 36                                | 89.4%        |
| B                                                                                      | 72                             | 8                                 | 93.0%        |
| B                                                                                      | 76                             | 12                                | 94.4%        |
| B                                                                                      | 84                             | 20                                | 96.2%        |

Table 3a. Power calculations for Cohort 2 using event rates powered for in the original protocol

| <b>Event Rates 74.0% Open Surgery, 61.1% Endovascular Treatment, Hazard Ratio 0.70</b> |                                |                                   |              |
|----------------------------------------------------------------------------------------|--------------------------------|-----------------------------------|--------------|
| <b>Enrollment Scenario</b>                                                             | <b>Study Duration (Months)</b> | <b>Minimum Follow-Up (Months)</b> | <b>Power</b> |
| A                                                                                      | 64                             | 16                                | 57.3%        |
| A                                                                                      | 72                             | 24                                | 61.3%        |
| A                                                                                      | 76                             | 28                                | 62.8%        |
| A                                                                                      | 84                             | 36                                | 65.3%        |
| B                                                                                      | 72                             | 8                                 | 75.0%        |
| B                                                                                      | 76                             | 12                                | 77.9%        |
| B                                                                                      | 84                             | 20                                | 82.0%        |

Table 3b. Power calculations for Cohort 2 using event rates powered for the August 10, 2015 version of the protocol

| <b>Event Rates 74.0% Open Surgery, 60.7% Endovascular Treatment, Hazard Ratio 0.69</b> |                                |                                   |              |
|----------------------------------------------------------------------------------------|--------------------------------|-----------------------------------|--------------|
| <b>Enrollment Scenario</b>                                                             | <b>Study Duration (Months)</b> | <b>Minimum Follow-Up (Months)</b> | <b>Power</b> |
| A                                                                                      | 64                             | 16                                | 59.4%        |
| A                                                                                      | 72                             | 24                                | 63.5%        |
| A                                                                                      | 76                             | 28                                | 65.0%        |
| A                                                                                      | 84                             | 36                                | 67.5%        |
| B                                                                                      | 72                             | 8                                 | 77.1%        |
| B                                                                                      | 76                             | 12                                | 79.9%        |
| B                                                                                      | 84                             | 20                                | 83.9%        |

Table 3c. Power calculations for Cohort 2 using event rates based on the aggregate event rates as of the October 31, 2017 data freeze

| <b>Event Rates 76.5% Open Surgery, 63.7% Endovascular Treatment, Hazard Ratio 0.70</b> |                                |                                   |              |
|----------------------------------------------------------------------------------------|--------------------------------|-----------------------------------|--------------|
| <b>Enrollment Scenario</b>                                                             | <b>Study Duration (Months)</b> | <b>Minimum Follow-Up (Months)</b> | <b>Power</b> |
| A                                                                                      | 64                             | 16                                | 70.4%        |
| A                                                                                      | 72                             | 24                                | 74.1%        |
| A                                                                                      | 76                             | 28                                | 75.5%        |
| A                                                                                      | 84                             | 36                                | 77.6%        |
| B                                                                                      | 72                             | 8                                 | 86.6%        |
| B                                                                                      | 76                             | 12                                | 88.8%        |
| B                                                                                      | 84                             | 20                                | 91.5%        |

### **8.3 Interim Monitoring**

#### Safety

By definition, the efficacy endpoints for this trial include both perioperative and all-cause mortality. Deaths will not be explicitly considered as a SAE, but rather, as the outcome of a SAE precipitated by a change in clinical condition. Such clinical events will be reported in a standardized fashion. In particular, there are aspects of the perioperative period that will be monitored on a periodic basis to assess ongoing safety of the two procedures under study. Safety endpoints include procedural complications at 30 days post-procedure, such as wound infection, bleeding, re-operation for surgical subjects; and access site complications, contrast-induced complications, major and minor embolization for endovascular subjects. Rates of procedure complications in the

first 30 days will be compared by treatment arm using Poisson regression to compare incidence rates, as well with use of a Fisher exact test to compare the proportion of subjects in each treatment arm who experience at least one post-procedural complication. These events will be compared by treatment arm overall as well as within stratum, defined by seriousness of event (serious vs. non-serious).

#### **8.4 Stopping Guidelines for Termination of the Trial**

The study will be monitored by a DSMB as described in Section 9.8.

The DSMB plans to have two interim looks, the first at the June 2018 DSMB meeting and the second at a time to be determined by the DSMB. There will also be a final look after all study follow-up and event adjudication has been completed. An alpha-spending approach approximating an O'Brien-Fleming stopping boundary for the primary treatment comparison is proposed for this trial. The O'Brien-Fleming plan is conservative; most of the Type I error is conserved for the final analysis. Both cohorts will be monitored for early stopping using this guideline. For each cohort, the information fraction at each interim look will be based on the number of subjects who have experienced the primary outcome, compared to the number of subjects expected to have primary outcome events under the assumptions of Enrollment Scenario A, 64 months total study duration, and event rates based on the observed aggregate event rates as of the November 1, 2017 data freeze (692 events in Cohort 1 and 201 events in Cohort 2). The final p-value boundary will be recalculated using the actual information fractions at each interim look, based on the final number of subjects in each cohort with primary outcome events. If two formal interim analyses of the primary efficacy endpoint (MALE-free survival) are conducted at information fractions of 40% and 70%, the nominal p-values for rejection of the null hypothesis are shown in **Table 4** (p=0.0454 at the final analysis). The alpha-spending approach can accommodate changes in the number or timing of the interim looks during the course of the trial.

| <b>Analysis</b>                       | <b>First</b> | <b>Second</b> | <b>Final</b> |
|---------------------------------------|--------------|---------------|--------------|
| <b>Fraction of total information</b>  | 40%          | 70%           | 100%         |
| <b>Nominal p-value to reject null</b> | 0.0008       | 0.0145        | 0.0454       |
| <b>Nominal z-score to reject null</b> | ± 3.36       | ± 2.44        | ± 2.00       |

In addition, premature termination of this trial may occur because of a regulatory authority decision, or withdrawal of study approval by clinical site IRBs. The NHLBI also retains the right to discontinue the trial prior to the inclusion of the intended number of subjects, but intends to exercise these rights only for valid scientific or administrative reasons. The NHLBI will promptly notify the Investigators. As directed by the NHLBI, all trial materials must be collected and all case report forms completed to the greatest extent possible.

#### **8.5 Procedures for Handling Spurious Data**

Consistency checks and range checks will be built into the data management system. This will allow many errors to be identified and corrected at the time of data entry. Queries regarding any problems with data will be sent to site coordinators regularly throughout the course of the trial. Therefore, questionable data are expected to be rare. Any data which are judged by the medical monitors to be definitely incorrect, and which cannot be resolved, will be identified as missing.

All reasonable efforts will be made to limit missing data. If the frequency of missing data is low (e.g. < 5%) the data will be analyzed using a complete-case approach. The study report will

indicate the number of subjects who have missing data on study outcomes. For covariate-adjusted analyses, the number of subjects who have missing data on the covariates will be reported. To assess the sensitivity of study results to missing data if missingness is more frequent, secondary analyses may include estimation of missing values for key variables [35]. Low rates of missing data (<5%) are anticipated, in addition to low (<5%) subject loss to follow-up.

## **8.6 Deviation Reporting Procedures**

Any modifications or deviations from the statistical plan described in this protocol will be documented in a "Revised Statistical Plan" document.

## **8.7 Subjects to be Included in Analyses**

Subjects in whom the randomly-assigned procedure (EVT or OPEN) is attempted, even if not completed, will be considered appropriately treated as intended, irrespective of corrective surgery or future procedures attempted in that subject. A treatment violation is defined as completion of open surgery when randomized to endovascular procedure, or completion of endovascular procedure when randomized to open surgery, without first attempting the randomly assigned procedure (see Section 5.3 for the full definition), or not attempting either procedure within 30 days after randomization. Loss to Follow-up is defined as: the subject being permanently lost-to-follow-up, either because of refusal to continue study follow-up (even by telephone or medical record review), withdrawal of consent or because of a geographic move that is not traceable. This is expected to be a rare occurrence with an estimated rate of 5% based on prior trial experience.

## **8.8 Clinical Events Committee**

The CCC will establish an independent Clinical Events Committee (CEC). The CEC will be comprised of expert physicians with appropriate expertise.

The CEC will be responsible for reviewing and adjudicating events. The MOO outlines the events to be adjudicated, the definitions of events, the required source documents, and the parameters by which the CEC will function.

## **8.9 Data and Safety Monitoring Board**

The NHLBI will establish an independent DSMB in accordance with established policies (see <http://www.nhlbi.nih.gov/research/funding/human-subjects/data-safety-monitoring-policy>). The DSMB will consist of a group of individuals with pertinent expertise in vascular disease and in the design and conduct of clinical trials, such as biostatistics and bioethics. The primary responsibilities of the DSMB will be to advise the NHLBI about the safety of current and future study participants, as well about the continuing validity and scientific merit of the trial.

Early stopping guidelines are specified in the protocol so that the DSMB can stop the study early, in one or both cohorts, if the incidence of the primary outcome in one arm is greater than in the other arm. Formal stopping boundaries are not proposed for other endpoints. However, the DSMB may recommend stopping the study for other reasons, taking into account the efficacy and safety data from this trial and other studies, or concerns about study conduct.

The Data and Safety Monitoring Plan for this trial will follow standard monitoring principles. The DSMB will meet at least twice a year. The DSMB reviews data on adverse events, data quality,

and study recruitment at regular intervals, and makes recommendations about study conduct to the Director, NHLBI.

## **9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

The investigator will make available to authorized monitoring and auditing personnel all source documents for this study. The verifications of CRF data must be made by direct review of source documents. It may be necessary to have access to the complete medical record in some instances.

## **10. QUALITY CONTROL AND QUALITY ASSURANCE**

The CCC and DCC agree to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice (GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical trial.

During the trial, the Sponsor or DCC will conduct periodic monitoring visits to ensure that the protocol and good clinical practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on the case report forms is accurate. The Investigator and the Clinical Site will allow the monitors and appropriate regulatory authorities direct access to source documents to perform this verification.

The Clinical Site may be subject to review and/or inspection by the IRB, the FDA and Health Canada or other regulatory/competent authority, and/or to quality assurance audits performed by NHLBI, the CCC, or the DCC.

It is important that the Investigator(s) and the relevant Clinical Site personnel be available during the monitoring visits and possible audits or inspections, and that sufficient time is devoted to the process.

All sites will be visited at least once during the trial by representatives from the DCC, CCC, Regional leader teams, and/or the NHLBI. For monitoring purposes, "All sites" refers to all sites that enroll three or more subjects in the trial. Sites not meeting this criterion may not have an in-person visit; however a for-cause visit may be warranted. Additional visits will generally be reserved for sites with problems (audits for cause). The monitoring visit consists of reviewing and evaluating three separate components: conformance to IRB/EC and consent form requirements, compliance with trial protocol, and source document data verification. Any site found to be Unacceptable or Acceptable/Needs Follow-up on any monitoring visit is required to submit a written response and/or corrective action plan to the DCC within 21 days of the receipt of the final monitor findings. Sites that fail to meet the standards for acceptable performance will undergo follow-up action, which will be determined by the severity of the discrepancies and may include repeat on-site monitoring, probation, or suspension.

### **Data Management System**

A web-based electronic data capture (EDC) system will be used for entering and maintaining the data for the trial protocol. The EDC system is designed to support reliable and secure data entry for clinical research purposes. The system also provides seamless integration of electronic CRFs; implementation of protocol amendments; and SAS and XML study data exports. The EDC system

enables the Sponsor, NHLBI, and the DCC to directly manage every aspect of the clinical trial through an intuitive interface.

#### Data Management Procedures

Data will be collected and entered into the EDC at each site participating in the trial, and transferred electronically to the Coordinating Center. The DCC will monitor timely entry of data into the study database. Access to all source documentation maintained by the Investigator, including correspondence and source data, will be available for monitoring and audit purposes. The EDC includes a number of standard features designed to ensure consistently high quality data. Each case report form question is associated with a validation range which is executed in real-time during data entry so that errors can be corrected immediately. Validations include both inter- and intra-instrument data checks. In addition to alerting the user to invalid entry of items, edit reports (i.e. queries) are automatically generated at the completion of CRF data entry. The EDC tracks expected, partially completed (edit queries pending), and missing CRFs.

DCC will regularly monitor data for consistency and correctness. If DCC observes inconsistent data or patterns of protocol violations or missing data, site staff will be contacted to address the finding.

#### Confidentiality

Each subject is assigned a unique number to assure confidentiality. Any publication or presentation will refer to subjects by this number and not by name. The medical records department, affiliated with the institution where the subject receives medical care, maintains all original in-patient and out-patient chart documents. Subject research files will be kept in a locked room at each clinical site. For additional information, see Section 12.

#### Data Archive

At all times, appropriate backup copies of the database and related software files will be maintained and the information will be appropriately protected from illegitimate access.

If a response to a particular question falls outside the range of allowable values specified in the validation for that question, the user will be alerted so that the error can be corrected as soon as possible.

In addition to alerting the user to invalid entry of items, edit reports will be automatically generated at the completion of data entry for a form. These edit reports will provide the information necessary to investigate any data entry errors or resolved questions regarding out-of-range or questionable values. Edit reports will list subject I.D. number, instrument name, and a detailed description of why each specific data item was flagged. These edit reports can be printed out and reviewed by a supervisor, and returned to the data collector for resolution.

#### Study Closeout

The DCC will be responsible for notifying the regulatory authorities in the participating countries that the clinical trial has ended according to the laws and regulations of those countries. The objectives of the closeout phase are to:

- Resolve all missing and inconsistent data to the extent possible.
- Evaluate the data as fully as possible to permit assessment of the primary endpoint.
- Fulfill ethical obligations to trial participants.
- Exploit the scientific value of study data as fully as possible.

## **11. ETHICS**

The trial will be conducted in accordance with GCP guidelines, FDA rules and regulations, the rules and regulations of the Institutional Review Board at each participating institution, and applicable state and federal regulatory agency requirements and laws.

Good Clinical Practice requires that the clinical protocol, any protocol amendments, the Informed Consent, all other forms of subject information related to the trial and any other necessary documents be prospectively reviewed by an IRB at each Clinical Site. An informed consent template will be provided to the Clinical Sites by DCC, which will include the basic elements of Informed Consent. DCC will review each site-specific consent form before the Clinical Site submits for IRB approval. Clinical Sites will be responsible for submitting appropriate documents for IRB approvals, including any protocol amendments.

## **12. DATA HANDLING AND RECORD KEEPING**

### **12.1 Confidentiality of Data**

By signing this protocol, the Investigator affirms to the Sponsor that information furnished to the Investigator by the Sponsor will be maintained in confidence and such information will be divulged to the IRB/EC or similar expert committee, affiliated institution, and employees only under an appropriate understanding of confidentiality with such board or committee. Data generated by this clinical trial will be considered confidential by the Investigator, except to the extent that it is included in a publication.

### **12.2 Confidentiality of Patient Records**

By signing the protocol, the Investigator agrees that the IDE Sponsor (or Sponsor representative), IRB/EC, NHLBI, or Regulatory Agency representative may consult and/or copy study documents in order to verify CRF data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying CRF information, the subject will be identified by unique code only and full names and similar identifying information (such as medical record number or social security number) will be masked.

The Clinical Site Investigators will ensure that the identity of subjects will be protected. All study records will be maintained in a secure fashion with access limited to essential study personnel only. All study documents submitted to the Coordinating Center will have identifiers removed and subjects will be identified with a study-specific identification number only. The Clinical Site Investigators will maintain, in a secure location, an enrollment log that includes subject identifying information and links subjects to their study-specific identification number.

### **12.3 Study Documentation and Record Retention**

A Clinical Site Investigator is required to prepare and maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. The Clinical Site Investigators' files will contain the protocol/amendments, IRB communication and associated documentation, samples of all approved Informed Consents, investigational product records, staff curriculum vitae, authorization forms, and other appropriate documents/correspondence. The clinical records for all subjects at the Clinical Site will include source documents and all original signed and dated informed consents. The DCC should be

informed of the storage location of study files. The Clinical Site Investigators must keep these documents on file for at least 39 months after completion of the trial. After that period of time, the documents may be destroyed subject to local regulations.

### **13. PUBLICATION POLICY**

The Publications Committee will review all publications following the guidelines given below. The scientific integrity of the project requires that data from all of the sites be analyzed study wide and reported as such. An individual center is expected to not separately report its data. The development of reports of data from individual sites for the determination of institutional variability is the prerogative of the Executive Committee. Additionally, all presentations and publications are expected to protect the integrity of the major study objectives. With the exception of interim analyses for the DSMB, endpoint data will not be presented prior to the release of the main study results. Recommendations as to the timing of presentation of endpoint data and the meetings at which they are presented will be provided by the Executive Committee.

Each proposal for a manuscript or abstract must be submitted to the Publications Committee for review of its scientific merit and appropriateness for submission. The Publication Committee will decide on whether or not approval for a given project is warranted. The Publications Committee may recommend changes to the authors and will make a final decision about submission. Each manuscript or abstract should also be sent to the sponsor for review prior to submission. All manuscripts for submission must be approved by the Publications Committee.

The primary outcome papers are defined as those that present outcome data for the entire trial cohort. The determination of whether or not a particular analysis represents a primary outcome report will be made by the Publications Committee. Papers and abstracts will have named authors based upon involvement and ending with the phrase "on behalf of the BEST-CLI Trial Investigators." For all manuscripts, there will be an appendix containing the names of all participating site investigators and their organizational affiliation.

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