



BEST-CLI MOO Chapter List_20170718

Chapter	Chapter Name	Version Number	Version Date	Link
1	Project Overview	3.0	23-Jun-17	https://eshare.neriscience.com/PWA/G01283%20-%20BEST%20CLI%20Trial-%20DCC/BEST%20Audit%20Documents/BEST-CLI%20MOO%20Ch%2001%20-%20Project%20Overview.pdf
2	Site Roles and Responsibilities	2.0	23-Jun-17	https://eshare.neriscience.com/PWA/G01283%20-%20BEST%20CLI%20Trial-%20DCC/BEST%20Audit%20Documents/BEST-CLI%20MOO%20Ch%2002%20-%20Site%20Roles%20and%20Responsibilities.pdf
3	Site Investigator Credentialing	4.0	30-Jun-17	https://eshare.neriscience.com/PWA/G01283%20-%20BEST%20CLI%20Trial-%20DCC/BEST%20Audit%20Documents/BEST-CLI%20MOO%20Ch%2003%20-%20Site%20Investigator%20Credentialing.pdf
4	Site Activation	2.0	27-Jun-17	https://eshare.neriscience.com/PWA/G01283%20-%20BEST%20CLI%20Trial-%20DCC/BEST%20Audit%20Documents/BEST-CLI%20MOO%20Ch%2004%20-%20Site%20Activation.pdf
5	Trial Procedures	4.0	28-Jun-17	https://eshare.neriscience.com/PWA/G01283%20-%20BEST%20CLI%20Trial-%20DCC/BEST%20Audit%20Documents/BEST-CLI%20MOO%20Ch%2005%20-%20Trial%20Procedures.pdf
6	Adverse Event Reporting	2.0	28-Jun-17	https://eshare.neriscience.com/PWA/G01283%20-%20BEST%20CLI%20Trial-%20DCC/BEST%20Audit%20Documents/BEST-CLI%20MOO%20Ch%2006%20-%20Adverse%20Event%20Reporting.pdf
7	Data Management and Data Flow	2.0	29-Jun-17	https://eshare.neriscience.com/PWA/G01283%20-%20BEST%20CLI%20Trial-%20DCC/BEST%20Audit%20Documents/BEST-CLI%20MOO%20Ch%2007%20-%20Data%20Management%20and%20Data%20Flow.pdf
8	Quality Assurance and Quality Control	2.0	28-Jun-17	https://eshare.neriscience.com/PWA/G01283%20-%20BEST%20CLI%20Trial-%20DCC/BEST%20Audit%20Documents/BEST-CLI%20MOO%20Ch%2008%20-%20QA%20and%20QC.pdf
9	Optimal Medical Therapy	2.0	28-Jun-17	https://eshare.neriscience.com/PWA/G01283%20-%20BEST%20CLI%20Trial-%20DCC/BEST%20Audit%20Documents/BEST-CLI%20MOO%20Ch%2009%20-%20Optimal%20Medical%20Therapy.pdf
10	Clinical Events Committee Adjudication	2.0	28-Jun-17	https://eshare.neriscience.com/PWA/G01283%20-%20BEST%20CLI%20Trial-%20DCC/BEST%20Audit%20Documents/BEST-CLI%20MOO%20Ch%2010%20-%20Clinical%20Events%20Committee%20Adjudication.pdf

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11	Ancillary Studies Policy and Procedures	1.0	06-Aug-14	https://eshare.neriscience.com/PWA/G01283%20-%20BEST%20CLI%20Trial-%20DCC/BEST%20Audit%20Documents/BEST-CLI%20MOO%20Ch%2011%20-%20Ancillary%20Studies%20Policy%20and%20Procedures.pdf
12	Publication and Presentation Policy and Procedures	1.0	06-Aug-14	https://eshare.neriscience.com/PWA/G01283%20-%20BEST%20CLI%20Trial-%20DCC/BEST%20Audit%20Documents/BEST-CLI%20MOO%20Ch%2012%20-%20Publication%20and%20Presentation%20Policy%20and%20Procedures.pdf

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Chapter 1

PROJECT OVERVIEW

1.0 BEST-CLI OVERVIEW

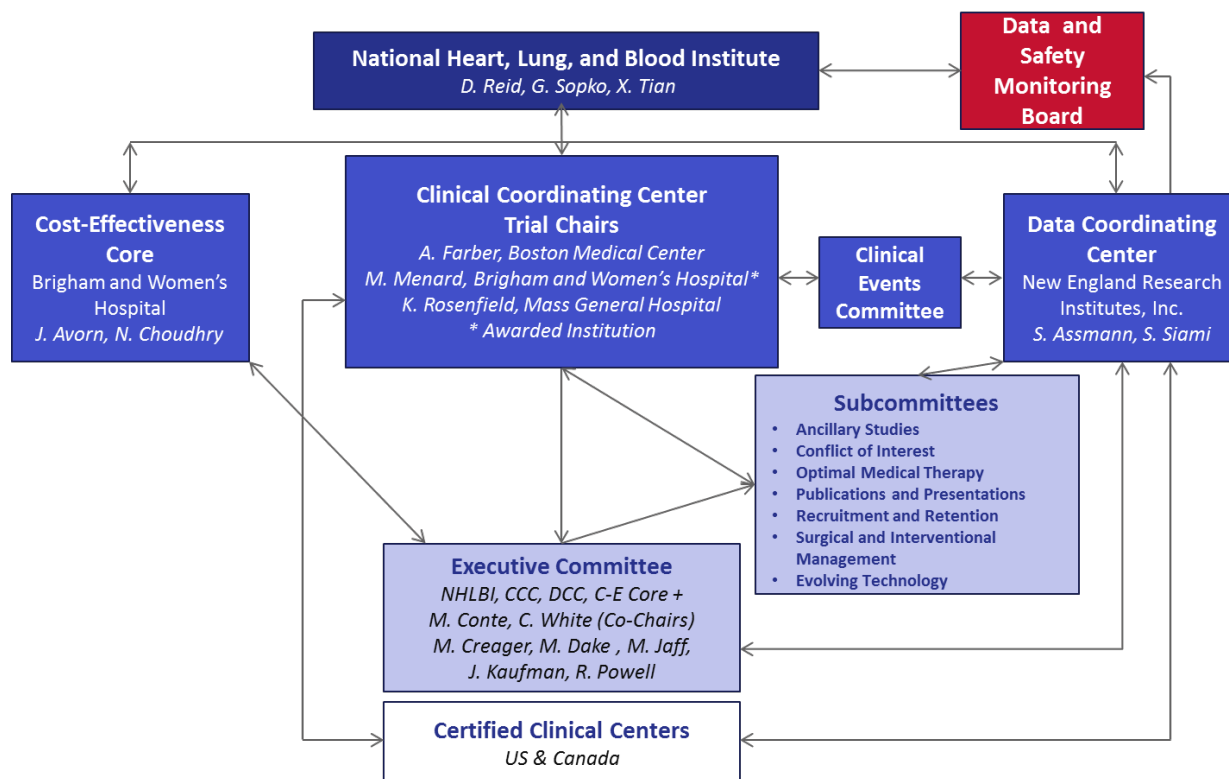
The BEST-CLI Trial is a multi-center, prospective, randomized, clinical trial to evaluate the safety and effectiveness of best endovascular (EVT) versus best open surgery (OPEN) therapy in subjects with critical limb ischemia (CLI). Best revascularization, whether EVT or OPEN, is defined as the technique thought most appropriate for the patient by the operator with respect to the index limb.

This trial requires an Investigational Device Exemption (IDE) with oversight by the Food & Drug Administration (FDA). Therefore, the following regulations are applicable to this trial:

- 21 CFR 812 – Investigational Device Exemption
- 21 CFR 50 – Human Subject Protection
- 21 CFR 56 – Institutional Review Board
- 21 CFR 54 – Financial Disclosure

1.1 STUDY ORGANIZATION

The figure below demonstrates the overall organizational structure for the BEST-CLI trial. Project team staff and contact information are also outlined in the subsections below.



1.1.1 Contact Information

Contact information for the Clinical Coordinating Center (CCC), Data Coordinating Center (DCC) and NHLBI Staff is available on the BEST-CLI SharePoint website located at <https://connect.neriscience.com>.

1.1.2. BEST-CLI Trial Committee and Chair List

Committee	Chair	Institution
Ancillary Studies	Mark Creager	Brigham and Women's Hospital
Conflict of Interest	Christopher White	Ochsner Clinic
Executive	Michael Conte Christopher White	University of California, San Francisco Ochsner Clinic
Evolving Technology	John Kaufman	Oregon Health & Science University Hospital
Operations Committee	Sandi Siami	New England Research Institutes
Optimal Medical Therapy	Michael Jaff	Massachusetts General Hospital
Publications & Presentations	Alik Farber	Boston Medical Center
Site Selection & Management	Alik Farber Kenneth Rosenfield	Boston Medical Center Massachusetts General Hospital
Subject Recruitment & Retention	Matthew Menard	Brigham & Women's Hospital
Surgical & Interventional Management	Richard Powell	Dartmouth-Hitchcock Medical Center

1.2 Study Protocol

The most current version of the protocol is available on the BEST-CLI SharePoint website located at <https://connect.neriscience.com>.

The protocol must be submitted to a certified IRB [i.e. with federal wide assurance (FWA)] for review, and written approval must be obtained and submitted to the DCC prior to enrolling any subjects, or implementing any changes in a protocol amendment, as applicable.

The Investigator or authorized designee will promptly report all changes in research activity and all unanticipated problems involving risks to human subjects to the IRB and to the DCC, which will inform the NHLBI. Any changes to research activities must be approved by the DCC and IRB prior to implementation. Protocol amendments, and any other major changes to research activities, including any changes involving significant risk, require written approval by the IRB, the DSMB and DCC, except when these activities are necessary to eliminate a hazard to the subject.

1.3 Informed Consent Template and HIPAA Authorization

The most current version of the informed consent template is available on the BEST-CLI SharePoint website located at <https://connect.neriscience.com>.

The DCC must approve the drafted site-specific Informed Consent Form (ICF) prior to submitting the document to the IRB. The ICF, HIPAA authorization, and other applicable study-related documents must be submitted to a certified IRB for review. Written IRB approval must be obtained and submitted to the DCC prior to enrolling any subjects. If the IRB requires additional changes, these must be reviewed and approved by the DCC or designee prior to resubmission to the IRB. A copy of the final, IRB-approved ICF and all other IRB approved study documents must be submitted to the DCC.

Each subject must sign and date the most current version of the IRB-approved ICF (and other locally required documents) as well as a HIPAA authorization after the nature of the study has been fully explained and prior to performance of any study-specific activities or procedures which are not standard-of-care.

The Investigator and/or designee must clearly document the process of obtaining informed consent in the subject's medical record. It is the Investigator's responsibility to ensure that the informed consent process is performed in accordance with ICH-GCP and applicable local and federal regulations.

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Chapter 2

SITE ROLES AND RESPONSIBILITIES

2.0 Site Roles and Responsibilities

The Contact Principal Investigator (PI), Specialty Principal Investigators, Co-Investigators (Co-I), and Clinical Research Coordinators (CRC) at each site should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, including but not limited to knowledge of:

- Good Clinical Practice
- 21 CFR 812 Investigational Device Exemptions
- 21 CFR 50 Protection of Human Subjects
- 21 CFR 54 Financial Disclosure by Clinical Investigators
- 21 CFR 56 Institutional Review Boards

In addition, all involved Investigators need to demonstrate a track record, professional interest and expertise in treating subjects with CLI.

The Contact PI, Specialty PIs, Co-Is, and CRCs should conduct the trial in compliance with the DSMB and site IRB/EC approved protocol and informed consent. All protocol deviations and violations must be documented.

2.1 Contact Principal Investigator (PI)

The Contact PI is the primary investigator under 21 CFR 812 and will have overall responsibility for:

- ensuring that a clinical investigation is conducted according to the signed agreement for clinical investigations of medical devices (i.e. the Statement of Investigator), the investigational plan (i.e. the protocol), and applicable regulations (as referenced above).
- protecting the rights, safety, and welfare of subjects under the investigator's care
- controlling devices under investigation (21 CFR 812.100)

The Contact PI bears overall scientific, fiscal and administrative responsibility for conducting the trial at his/her institution in compliance with applicable laws and regulations, meeting the terms and conditions of the clinical trial agreement, and representing the project to the funding agency (NHLBI). He/she is responsible for the completion and, where applicable, PI signatory approval of, all administrative and regulatory documents (including FDA documents). He/she also serves as the primary point of contact for the trial, and is responsible for disseminating key information to and facilitating effective and regular communication between Specialty PIs and Co-Is and project staff at his or her institution (see section 2.4).

The Contact PI will sign the Statement of Investigator form, under 21 CFR 812, which is submitted to the FDA and which states that he/she has overall responsibility for protocol adherence, approval of all IRB submissions, malfunction/SAE notifications, maintenance of accurate source documents and record retention. One Contact PI will be designated from each site and will sign this form at each site, unless the site changes the Contact PI.

The Contact PI should:

- Maintain a list of appropriately qualified persons to whom he/she has delegated significant trial-related duties (please refer to site delegation and signature logs)
- Demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period
- Ensure that all persons assisting with the trial are adequately informed about the protocol, and their trial-related duties and functions

- Participate in the investigator credentialing process that is overseen by the BEST-CLI Trial Surgical and Interventional Management Committee (SIMC). He/she will confirm, in writing, the procedural experience to be reported by all Specialty PIs and Co-Is. As such, the Contact PI will vouch for every Specialty PI and Co-I with regard to their individually reported open surgery and/or endovascular experience (See MOO Chapter 3, section 3.2).

2.2 Specialty Principal Investigators

Given that a variety of specialists treat CLI, a Specialty Principal Investigator (PI) is appointed, at every site, for each specialty that treats CLI and is participating in the trial. These specialties include:

- Interventional Cardiology
- Interventional Radiology
- Vascular Medicine
- Vascular Surgery

The Specialty PI will serve to both represent and oversee the conduct of the Co-Is within their own specialty (see section 2.4).

Other specialists that may participate in the BEST-CLI Trial include podiatrists, internists and wound care physicians. Such specialists may be involved at a given site if they play a significant role in treating CLI, they request to participate in the trial as a co-Investigator and their participation in the trial is felt to be appropriate by the Contact PI and the SIMC.

2.3 Co-Investigators (Co-Is)

It is the express intention and desire of the BEST-CLI Trial leadership, as well as the NHLBI, that all specialists within the fields of interventional cardiology, interventional radiology, vascular medicine and vascular surgery who routinely treat CLI at a given trial site, either by open surgical revascularization or percutaneous endovascular therapy, actively participate in the BEST-CLI Trial. All relevant and interested PIs and Co-Is will be assessed by the SIMC to ensure they possess the necessary qualifications to perform the revascularization procedures under investigation in the trial (see MOO Chapter 3).

Certain Investigators may be granted Co-Investigator status by the SIMC even though they are not granted credentials to perform either open surgical or endovascular revascularization. Inclusive in this group are any vascular medicine, interventional radiology, interventional cardiology and vascular surgery physicians who do not, per the SIMC, possess the requisite qualifications to be granted revascularization privileges, but who remain interested in participating as a Co-Investigators. Also inclusive in this group are any podiatrists, internists and wound care specialists who actively manage CLI patients and who meet the description outlined in Section 2.2. Such Investigators may be granted the authority to obtain informed consent for Trial participation if deemed appropriate by the relevant trial site Contact PI and the SIMC.

2.4 CLI Team Approach

The BEST-CLI Trial is a multidisciplinary trial and to that end has defined a mandate to engage all physicians who treat CLI at any given site to the extent possible. Interdisciplinary collaboration is essential to the success of the trial and will take place within the construct of a CLI Team as described below.

The NHLBI in funding this trial clearly delineated their intention that all stakeholders who manage patients with CLI be engaged and included in the Trial. As such, Investigators who are part of BEST-CLI Trial will be expected to communicate and interact with one another, across and within participating specialties, in such a way as to facilitate enrollment of subjects into the trial. Furthermore, both in the interest of optimizing subject care and to ensure balanced comparison between study cohorts, optimal surgical and endovascular treatment should be provided by those with greatest skill and experience. This implies that, at each site, there are operators who are knowledgeable, broadly trained in the evaluation and management of patients with CLI, highly skilled, experienced, and in the aggregate, capable of performing the therapy to which each subject is randomly assigned. Implicit in this expectation is a demonstrated commitment to the longitudinal care of subjects with CLI pre- and post-revascularization, inclusive of outcome assessment and ongoing surveillance in an effort to optimize long term results.

The CLI Team is defined as a group of individuals at a given site who are treating subjects with CLI within the confines of the BEST-CLI Trial and any associated ancillary study or registry. It consists of Specialty PIs (including the Contact PI), Co-Is, and CRCs. Its mission is to maximize inter-specialty collaboration within each site to ensure successful conduct of the BEST-CLI Trial.

The goals of the CLI Team are:

1. To ensure enrollment of subjects into the Trial, through open communication among participating specialists.
2. To create and support an environment at every Trial site that is conducive to physician collaboration and subject recruitment.
3. To deliver the optimal open surgical or endovascular treatment and to ensure standard of care treatment within the strategy to which each subject is randomized in the Trial.
4. To foster constructive collegiality, information exchange and education amongst Investigators and optimal communication of the Trial aims and mission throughout the local medical community.
5. To ensure that best medical therapy and vascular risk factor management is practiced.

The strategy to fulfill those goals is predicated on the following five processes that will be implemented at each trial site under the guidance of the Clinical Coordinating Center (CCC) of the BEST-CLI Trial.

1. Site-specific BEST-CLI collaborative processes. Collaborative processes will be established at each site. The Contact PI, in conjunction with Specialty PIs, will develop:

- a. An institution-wide plan for screening CLI subjects.
- b. A detailed plan specifying how the Specialty PI and Co-Is, within each specialty, will collaborate with one another
- c. At sites with more than one participating specialty, a detailed plan specifying how the Specialty PIs, Co-Is and research coordinators will collaborate with one another across specialties. This will specifically address the process of referring subjects between specialties following randomization when such a need or opportunity arises.
- d. A plan for distribution of site payments
- e. A list of potential site-specific obstacles to subject recruitment and enrollment

These processes will be developed with a view to establishing an optimal multi-disciplinary collaborative framework, a construct through which to resolve any significant disagreements among the site Specialty PIs and Co-Is, and a positive environment for the conduct and completion of the Trial at each given site. This discussion needs to occur before and at the latest within 1 month of site initiation and its outcome needs to be communicated in writing to the CCC.

2. Communication between Specialty PIs/Co-Is at the time of subject randomization and at re-intervention. Before a subject is randomized in the BEST-CLI Trial, the randomizing PI will be expected to review the clinical details of the case with another Specialty PI or Co-I to reach consensus regarding eligibility. This interaction can occur in person, over the phone, or over a secure internet connection. The purpose of such expanded communication is to ensure that at least 2 physicians, within one specialty or across specialties, have agreed that a particular subject is an appropriate candidate for the Trial and has met all of the inclusion and exclusion criteria as outlined in the BEST-CLI Trial protocol and MOO. This communication will be recorded in the electronic Case Report Form (eCRF). Similarly, if at any point following the index revascularization the treating Investigator considers the subject potentially appropriate for or in need of re-intervention, it is expected that the treating PI review the case with another Specialty PI or Co-I. It is again required that this communication involve at least 2 physicians, within one specialty or across specialties, from within the site CLI Team, and that this communication be recorded in the eCRF.

It is expected that this communication will include a comprehensive discussion and general consensus on:

- the benefit or need for any imaging studies (e.g. arterial duplex, computed tomography angiography (CTA), magnetic resonance angiography (MRA) and/or formal angiography) that will facilitate optimal decision-making and a review of all such studies once performed
- the advantages and disadvantages of all open surgical and endovascular re-intervention options
- the advantages and disadvantages of alternative conservative management and ongoing surveillance

It is recognized that there is substantial variation in decision making with regard to re-interventions, and it is expected that all such decisions are based solely and exclusively on the best interests of the Trial subject.

Re-interventions that will require such CLI Team communication are those involving the infrainguinal arteries or bypass graft of the index limb and include the following: creation of a new surgical bypass graft, open surgical or mechanical thrombectomy, chemical thrombolysis, performance of an open surgical patch angioplasty and/or patch angioplasty, balloon angioplasty, atherectomy or stent/stent-graft placement. This interaction can occur in person, over the phone, or over a secure internet connection. This communication will be recorded in the eCRF.

The Contact PI will appoint a physician on the CLI Team to oversee site education and implementation of best medical therapy and risk factor management as defined by BEST-CLI Optimal Medical Therapy guidelines. This physician may be the Contact PI her/himself, another Specialty PI or a Co-I and should have a demonstrated interest in the medical management of vascular patients.

3. Regular meetings between members of the CLI-Team. Regular meetings of the CLI team will be strongly encouraged. These meetings should occur in addition to the communication expected at randomization and re-intervention. The primary focus of such meetings will be to enhance collaboration through dedicated discussion of the BEST-CLI Trial and its progress. The Contact PI will be responsible for ensuring that such meetings take place, and that they include members of all participating specialties and all involved CRCs. The meeting agenda should include:

- a. a monthly roster of screened and enrolled subjects;
- b. screen failures;
- c. protocol questions;
- d. obstacles to recruitment;
- e. a review of cases to ensure consistency and quality;
- f. a review of major adverse events; and,
- g. an assessment of compliance with best medical therapy guidelines.

4. Struggling site telephone conference calls between Site PIs and Trial Chairs (CCC and DCC PI's) and NHLBI Project Officers. Sites determined to be struggling to meet enrollment targets for a period of 6 months, will be eligible for a teleconference. A BEST-CLI Trial Chair member and NHLBI will hold a telephone conference with site PIs to discuss any and all issues related to the conduct of the Trial. Particular attention will be given to a discussion of site enrollment and the identification of any potential obstacles to target enrollment. The Contact PI, CRC, and at least one Trial Chair should be in attendance during such conference calls. These conference calls will serve to facilitate continuous, open communication between sites and the BEST-CLI Trial leadership.

5. In-person meeting between Trial Chairs and CLI team. The Trial Chairs will travel to various sites to meet with the CLI Team on a periodic basis as deemed necessary. The goal of such meetings will be to comprehensively review all aspects of Trial conduct at the site. It is the expectation that all participating Investigators will be made aware of, and make every effort to attend, BEST-CLI Trial conference calls and/or meetings.

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Chapter 3

SITE INVESTIGATOR CREDENTIALING

3.0 Site Investigator Credentialing

All operators in BEST-CLI, including the Contact PI, Specialty PIs and Co-Is, will be certified for participation in the trial according to the criteria developed by the BEST-CLI Surgical and Interventional Management Committee (SIMC). Investigator certification and credentialing records will be kept on file by the DCC.

3.1 The Surgical and Interventional Management Committee (SIMC)

The SIMC has established specific guidelines that relate to physicians performing open vascular surgery and endovascular intervention. These guidelines will guide the SIMC in credentialing an investigator as a surgeon, interventionalist, or both within the confines of the Trial. They are based on a number of factors including physician training, experience, current volume, and current practice. The SIMC will review qualifying data gathered on physicians who could potentially participate as surgeons and/or interventionalists at a given site. Relevant data may be submitted to the SIMC by individual investigators and/or the Contact PI. The SIMC, upon review of these data, will make recommendations to the Operations Committee (OC) on the inclusion of qualified operators in BEST-CLI.

3.2 Qualification Criteria

Investigators must provide evidence of board certification or specific specialty training, and evidence of sufficient volume of procedures, if so requested by the SIMC. With regard to annual volume of procedures, the SIMC will determine whether additional information, e.g., procedure or operative notes, should be reviewed prior to approval in individual cases.

Investigators will be designated as one of the following:

1. Credentialed to perform open surgical revascularization only
2. Credentialed to perform endovascular revascularization only
3. Credentialed to perform both open surgical **and** endovascular revascularization.
4. Conditionally approved for open surgical, endovascular, or both types of revascularization.
5. Approved to obtain written informed consent but not to perform either open surgical or endovascular revascularization (NON-OPERATOR)

The 5th designation will be afforded to those individuals who have not been credentialed to perform either open vascular surgery or endovascular therapy as part of the BEST-CLI Trial, but who have expertise in the management of patients with CLI, and/or have demonstrated a high level of interest in and knowledge of the BEST-CLI Trial. Such individuals will have been deemed capable of promoting the trial and obtaining informed consent (see Chapter 2, sections 2.2 and 2.3).

3.2.1 Open Surgical Revascularization

The investigator must be a board certified Vascular Surgeon, Cardiothoracic Surgeon or General Surgeon. The investigator must also have performed either

- A minimum of 50 infrainguinal open surgical bypasses over preceding 5 years or
- A minimum of 10 infrainguinal open surgical bypasses over preceding 2 years

Regardless of the categories above, at least 5 of the lower extremity bypasses performed must have involved an artery below the knee joint, and at least 5 must have been performed with a venous conduit.

3.2.2 Endovascular Revascularization

The investigator must have either

- Board certification in Interventional Cardiology, Vascular Surgery, Interventional Radiology, or Vascular Medicine (interventional) or
- Proof of completion of training in endovascular therapy that meets the Society for Vascular Surgery (SVS) endovascular training guidelines. These guidelines require performance of at least 100 endovascular diagnostic procedures of which 75% involve arteries and at least 50% are selective catheterizations; and 80 endovascular therapeutic procedures of which 75% involve arteries. ([Reference: Calligaro KD, Toursarkissian B, Clagett PG, et al. Guidelines for hospital privileges in vascular and endovascular surgery: Recommendations of the Society for Vascular Surgery. J Vasc Surg 2008;47:1-5.](#))

The investigator must also have performed at least 12 infrainguinal endovascular procedures in patients with CLI involving an artery below the knee joint over the preceding 2 years.

3.2.3 Conditional Approval

In an effort to ensure the highest level of quality and safety for patients enrolled in the BEST-CLI trial, the Surgical and Interventional Management Committee (SIMC) has decided to recognize junior investigators who are within -12 months of graduation from their specialty training program, and who otherwise are felt appropriate for participation as BEST-CLI investigators, as "conditionally approved" to provide revascularization services as part of the trial. The SIMC strongly encourages conditionally approved investigators to enroll any eligible critical limb ischemia patients in their practice into the BEST-CLI trial.

Conditionally approved investigators should perform revascularization procedures with a proctor/collaborator who is a fully approved investigator for revascularization procedures in the BEST-CLI trial. The status of conditionally approved investigators will be reviewed after one year to determine if sufficient experience has been gained to warrant a change to full credentialing as an approved investigator. At the appropriate time for reevaluation, a letter will be sent to the Contact PI and/or Specialty PI requesting input about proficiency of the investigator acquired since the time of original SIMC credentialing. The recommendation will be shared with the SIMC Contact who may approve it or first opt to speak directly with the Contact PI to obtain more information. If the SIMC Contact has concerns, he will notify the SIMC Chair. Not hearing concerns, the Chair will approve an upgrade to full approval. The investigator names and decisions will be discussed at the following SIMC meeting. If there are no objections from the group, SIMC will send an updated credentialing letter to the site reflecting the approved change(s) in investigator status.

In the event where a site has only one fully approved investigator to perform both open and endo procedures and the second investigator is conditionally approved, SIMC will review the specific situation on a case-by-case basis to determine whether approval for the site to continue randomizing subjects into the trial can be granted.

3.3 Data Submission and Approval Process

Attestations regarding training and experience can be sent to the SIMC by individual Investigators, Specialty PIs, or Contact PIs.

Petition for exemption will be allowed based on known significant contributions to the field, experience and other relevant factors. The intent of the BEST-CLI Trial and the SIMC is to include all skilled participating Investigators who manage patients with CLI as part of their regular practice and who do so in a competent fashion consistent with current standards of care.

The SIMC will deliberate following a review of all potential Investigators at each BEST-CLI Trial site. The committee will discuss the qualification of potential Investigators with site Contact PIs and Specialty PIs (when appropriate) prior to making eligibility decisions.

The decision to approve potential Investigators for the BEST-CLI Trial will be at the discretion of the SIMC and OC. If there is uncertainty or persistent concern regarding qualifications of individual investigators, additional discussion with the Contact PI or Specialty PIs may be initiated. Additional information including operative reports, procedure notes and/or procedural angiograms may be requested for review.

3.4 Monitoring Process

Ongoing monitoring is important to ensure subject safety and the scientific integrity of the BEST-CLI Trial. As part of the DSMB's semi-annual review of the study, the DSMB receives reports for each site, showing the number and percentage of patients in each combination of cohort and treatment arm who experience the primary study outcome and each of its components (death, above-ankle amputation of the index limb, major re-intervention on the index limb) within 14 days after the index revascularization procedure. If the DSMB indicates a concern about one or more sites, this information will be shared with SIMC. SIMC will assess whether any approved or conditionally approved investigators at that site should have their approval status reconsidered.

3.5 Credentialing Audits

SIMC audits may be undertaken at the discretion of the Committee by a majority vote of members.

SIMC audits may serve one or more purposes, including but not limited to the following:

- To ensure minimum standards with regard to clinical practice, experience, and expertise in the conduct of BEST-CLI Trial procedures and clinical care.
- To confirm attestations regarding clinical, operative, and /or endovascular experience (e.g., to confirm that site investigators fulfill the criteria set forth by the SIMC for approval to enroll and treat patients in BEST-CLI)
- To investigate credentialing in instances where the DSMB, in their independent review of primary outcomes, has identified a possible safety issue at a site. In such an instance, the SIMC would not be reviewing BEST-CLI cases, but rather historical or contemporaneous cases, outside the BEST-CLI trial, provided by investigators to support their credentialed operator roles.

Random Audits

- A minimum of 15% of sites will be audited at random over the course of the trial.
- Sites to be audited will be chosen randomly by computer.
- All credentialed investigators at a site will be reviewed.
- Documents requested will include three reports (operative reports or procedure notes) of CLI cases over the previous 12 months supporting study criteria for each SIMC-credentialed operator role (open surgical and/or endovascular).

Focused Audits

Examples where a focused audit may be triggered include:

- Sites in which there is a possible discrepancy between a site investigator's signed attestation and actual experience based on information obtained by the SIMC from its members, colleagues at the trial site, or colleagues from outside the institution.
- Sites identified by the DSMB with potential safety issues that could relate to credentialing errors.
- Sites identified by the DCC or DSMB with protocol violations that could relate to credentialing errors.

In focused audits, one or more credentialed investigators at a site will be reviewed. Documents requested for focused audits will include reports (10 operative reports and/or 12 procedure notes) of CLI cases over the previous 24 months supporting study criteria for each SIMC-credentialed operator role (open surgical and/or endovascular).

Audits of SIMC members' sites

- All sites of SIMC members will be audited.
- SIMC members will recuse themselves from discussions about their own sites.
- All credentialed investigators at each site will be reviewed.
- Documents requested will include three reports (operative reports or procedure notes) of CLI cases over the previous 12 months supporting study criteria for each SIMC-credentialed operator role (open surgical and/or endovascular).

Case reports on patients enrolled in the BEST-CLI trial should **not** be included in documents submitted for a credentialing audit.

In general, for all audits, a minimum of two SIMC reviewers will be assigned, one vascular surgeon and one endovascular expert, to review the case reports that have been submitted by site investigators. The primary reviewers will report back to the SIMC for a general discussion regarding credentialing of each investigator. All SIMC members will be provided with the case reports for their reference. In the event that materials provided are insufficient to reach a credentialing determination, additional case reports will be requested.

For every type of credentialing audit, an audit report will be provided by the SIMC to all investigators at each site. An audit data spreadsheet will be compiled by SIMC and kept by the DCC as a record. Questions regarding SIMC audits should be directed to Dr. Richard Powell, SIMC Chair through the BEST Trial Mailbox at BEST@neriscience.com.

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Chapter 4

SITE ACTIVATION

4.0 Site Activation

Prior to beginning enrollment, all sites must complete the following steps to become an active site on the BEST-CLI Trial.

4.1 Site and Staff identification

Key staff from each participating site should be identified as soon as possible. **For the purposes of this study, key staff will include at the very least the Contact Principal Investigator (PI) and Clinical Research Coordinator (CRC).** Sites must complete a Site Application to identify the site name and address, Contact PI, Specialty PIs (as applicable) and other study staff members. In the event that there are staffing changes at a site over the course of the study, sites must contact the Data Coordinating Center (DCC) via email to communicate details of the change in staff.

Additionally, it is important for key staff to be aware of, and attend, BEST CLI Trial conference calls and/or meetings. As new staff members join the BEST CLI Trial, they will be added to the DCC distribution lists for announcements and updates. Trained staff members will be expected to train new site staff, with assistance from the DCC.

While the identification of key study staff is critical to study operations, it is also quite important to identify all staff that will be responsible for specific study tasks. These tasks include, but are not limited to:

- Identifying potential subjects and communicating this information to the study team
- Obtaining approval to approach subjects regarding participation in the study
- Obtaining informed consent from subjects
- Determining subject eligibility for participation in study
- Randomization of study subjects
- Performing physical examinations and medical history per protocol
- Collecting study data and entering data into the electronic data capture (EDC) system
- Resolving queries in a timely manner
- Maintaining regulatory binders and source documents
- Adverse event (AE) assessment and reporting AEs as necessary

4.2 Submission of Consent Form

Each site must submit their informed consent form (ICF) to the DCC prior to submitting it to the local IRB and again after IRB approval but before beginning enrollment, per NHLBI regulation.

The current version of the ICF template can be found on the BEST-CLI SharePoint website (<https://connect.neriscience.com>). Once the ICF has been submitted to the DCC, it will be reviewed and returned to the sites with comments and suggestions as appropriate. The site will be notified once the ICF is approved by the DCC so that it may be submitted to the local IRB.

4.3 Site Training

The Contact PI and at least one other research staff member participating in BEST-CLI must attend a webinar-based training session provided by DCC staff; however, we encourage all research staff and investigators to attend training as well. Attendees are expected to train remaining staff members who will participate in the study. Additional training webinars will be schedule as required during the course of the trial

Training will include review of study background, protocol, eligibility criteria, randomization process, study visit schedule, measurements, procedures, and EDC training.

4.4 Required Regulatory Steps and Documents

In order to activate the BEST-CLI Trial at each site the following documents must be completed and submitted to the DCC as appropriate. Once a site has submitted all of the required regulatory documents, IRB approval is obtained, the CTA is executed and the site has been trained, a remote site activation will occur.

4.4.1. Requirements for All Participating Sites

Templates for the following documents can be found on the BEST-CLI SharePoint website: <https://connect.neriscience.com>).

1. Site Application Form

Identifies site address, and contact information for the Contact PI, Specialty PIs, Co-Is, and other site staff. If there have been any changes to contact information, or a staff member has left the Trial, or a new staff member has been added to work on BEST-CLI, sites must contact the Data Coordinating Center (DCC) via email to communicate details of the change in staff.

2. Delegation of Authority Log

Each site must submit a Delegation of Authority Log identifying the responsibilities of each study staff member. If study staff responsibilities change, please complete and submit a revised Delegation of Authority Log to the DCC.

3. FWA Number

Each site must provide the DCC with their Federal Wide Assurance (FWA) number. Please ensure a copy is present on-site for review, as needed.

4. Statement of Investigator Form

Each site must complete and submit a copy of this form to the DCC prior to activation. The form should identify the following:

- Principal Investigator (Contact PI)
- Site Staff (including Specialty PIs, co-investigators (Co-Is), and other staff as applicable) collecting or assessing data

5. Curriculum Vitae

The Contact PI, Specialty PIs, Co-Is, and key study staff must submit copies of their signed and dated CVs to the DCC. BEST-CLI requires resubmission of these documents at least every two years or when a substantial change occurs.

6. Medical Licenses

The Contact PI, Specialty PIs, and Co-Is must submit copies of their current medical licenses to the DCC. BEST-CLI requires that sites submit medical licenses to the DCC as they are renewed.

7. Financial Disclosure Form (Conflict of Interest Form)

Contact PI, Specialty PIs, Co-Is and other key staff conducting BEST CLI must submit Conflict of Interest forms.

BEST CLI requires resubmission of the Financial Disclosure Form (FDF) at least annually, or when a change occurs. The DCC will send an annual email reminder to staff to update their FDF if a change has occurred. BEST-CLI is committed to avoiding any real or

perceived conflicts of interest, such as circumstances that would bias study design, conduct, data analysis or interpretation of the research. All BEST-CLI key personnel have an obligation to disclose potential ethical, legal, financial or other conflicts of interest that reasonable peers or an informed public could construe to conflict or appear to conflict with the investigator's unbiased contributions to the research.

Federal regulations ([42 CFR Part 50, Subpart F](#)) establish financial conflict of interest standards, and provide that a conflict of interest exists when the designated official at the grantee institution "reasonably determines that a significant financial interest could directly and significantly affect the design, conduct, or reporting of the...funded research." A significant financial interest is defined as anything of monetary value including but not limited to salaries or other payments, equity interest, and intellectual property rights. This does not include salaries or other payments from the investigator's institution, or income from public or nonprofit entities for selected services. The threshold for triggering reporting for a publicly-traded entity is the aggregated value of any remuneration and value of equity interest in the previous 12 months that exceeds \$5,000. The threshold for triggering reporting for a non-publicly traded entity is remuneration that exceeds \$5,000 in the previous 12 months and any equity holding regardless of value or remuneration. These limits apply to investigators and their immediate households. Site Contact PI, Specialty PIs and Co-Is will be asked to provide information about significant financial interest annually. The DCC will coordinate the conflict of interest assessment process, and the BEST-CLI Conflict of Interest Committee will review and identify conflicts and develop a plan for addressing them.

8. EDC User Form

List of staff members from each site who will access the EDC system to perform data entry and view study reports.

9. Protocol Signature Page (one per site)

The Contact PI and Specialty PIs of each site must read, sign, and date the protocol signature page for each protocol version (as applicable) and submit it to the DCC.

10. Lab Certification

Each site must submit a copy of their lab certification (CLIA).

11. Normal Lab Reference Ranges

Each site must submit a copy of their normal lab ranges.

12. IRB membership list, approval letter for protocol and approved informed consent

Each site must submit these documents to the DCC once the local IRB has approved the protocol and informed consent form.

As a reminder, per NHLBI guidelines, the DCC must review and approve each site's consent forms before they are submitted to the site's local IRB.

13. Electronic Signature Authorization Form

Each site must complete the Electronic Signature Documentation for BEST CLI.

14. Executed Clinical Trial Agreement (CTA) (i.e. site contract)

Each site must have a fully executed CTA signed by both the site (institution) and the DCC authorized business official indicating agreement with the terms, conditions, and per-subject payment schedule.

15. Surgical and Interventional Management Committee (SIMC) Credentialing

Per MOO, Chapter 3, all operators in BEST-CLI, including the Contact PI, Specialty PIs and Co-Is, will be certified for participation in the trial according to the criteria developed by the BEST-CLI SIMC. For site activation, a site must have a minimum of one investigator fully credentialing to perform open surgical revascularization and another investigator credentialed to perform endovascular revascularization.

16. Activation Email

Each site must receive a formal activation email from the DCC in order to start enrolling subjects at their respective site.

4.5. Regulatory Binder

A Regulatory Binder must be created and maintained throughout the site's participation in BEST CLI. The Regulatory Binder must include the following:

- Confidentiality Agreement (CDA)
 - Protocol and Amendments (all versions)
 - Curricula Vitae (CVs) of key investigators and research team members where appropriate
 - Completed Financial Disclosure Forms (Conflict of Interest forms) for key investigators and research team members where appropriate
 - Completed and signed Statement of Investigator
 - IRB approval documentation for:
 - o Protocol
 - o Protocol amendments (as applicable)
 - o Original informed consent form
 - o Revised informed consent forms (as applicable)
 - o Other written (educational) materials provided to the subjects
 - o Continuation of the study (based on annual or periodic reviews)
 - o Telephone Script (for telephone study visits)
 - o Advertising for study recruitment (as applicable)
 - IRB Correspondence
 - o Notification of new safety information and the IRB's recommendations pertaining to this information
 - o Notification of all Adverse Events and Serious Adverse Events, per IRB requirements
 - o Informed Consent (and Assent Form, if applicable)
 - o Original copies of versions approved by the IRB
 - All Correspondence
 - Monitoring Visit Log
 - Master Subject Log
- NOTE: This is a confidential list of the names of all subjects with their assigned identification number. It is only maintained at the site and allows the investigator or institution to quickly identify study subjects in the event of an emergency
- Electronic Signature Authorization Form
 - Clinical Laboratory Certification through the Clinical Laboratory Improvement Amendments (CLIA)
 - Study Closeout Information, when applicable

The Clinical Trial Agreement must be maintained but kept separate from the Regulatory Binder.

BEST-CLI
Manual of Operations

Chapter 5

TRIAL PROCEDURES

5.0 Trial Procedures

Once a site has been activated, as determined by the DCC, study enrollment can begin. All site study members must be familiar with the procedures outlined in this chapter.

5.1 Subject Recruitment and Recruitment Tools

Subjects will be recruited from existing patients at practice sites and from referrals. Any tools used to recruit study subjects must be approved in advance by both the DCC and the local or central IRB/Ethics Committee. Recruitment tools include, but are not limited to flyers, newspaper advertisements, radio announcements, posters, pamphlets, or letters to potential subjects.

5.2 Obtaining Informed Consent

Before any trial-related procedure is performed, the site investigator or designated study staff will obtain written informed consent from the study subject by means of the informed consent form approved by the local or central IRB/Ethics Committee. The subject must be allowed ample time to read the informed consent document and ask questions before deciding to participate in the study. He or she must be allowed to take the consent form home to review and discuss with family or significant others.

The informed consent process includes individual discussion with the subject about what study participation will involve. The information to be discussed will include all the information provided in the BEST-CLI Trial informed consent form. The discussion process includes informing the study subject both verbally and in writing that:

- if he/she declines to participate in the study, the quality of medical care he/she receives will not be affected
- he/she may withdraw at any time without giving reason and without affecting his/her future care
- without disclosing his/her name, relevant medical and personal data will be disclosed to the sponsor, study coordinating centers, and the DSMB who are obliged to use the anonymous or de-identified information solely for scientific purposes

The consent form must be signed and dated by both the subject and the PI or trained study staff at the same time. The subject must be given a copy of the signed and dated consent form. The original copy of the consent form should be kept in the study file. Once all the subject's questions have been addressed the consent form is signed by all necessary parties, and the screening process can begin.

It is recognized that there are situations in which information needed for certain components of the screening process (e.g. laboratory work, vein mapping or angiography) may be available prior to the time at which informed consent is obtained.

New to protocol version 5.0 is the ability to obtain information from subjects for centralized follow-up (for example, if the subject moves away from the BEST-CLI site, the DCC would be able to track the subject and collect information), longer-term follow-up (for example, if there is a follow-on grant to allow for longer centralized follow-up of subjects enrolled in BEST-CLI), linkage to Medicare claims data to supplement the cost-effectiveness component of the trial, or for those subjects who are insured by Anthem Inc, the ability to centrally access claims to Anthem to determine if endpoints were met and to supplement the cost-effectiveness

component of the trial. Therefore, we are asking sites to re-consent all current and active subjects to the protocol version 5.0 revisions of the informed consent template, as well as to reach out to re-consent those subjects who have indicated they will not come in for visits but who have agreed for vital status follow-up or medical record review, per the study change status form.

5.3 Study Identification Number and Confidentiality

Once a subject provides written consent, a unique study identification number is assigned. The link between subject name and subject ID will be stored only on the **Master Subject Log** at the site where the subject receives his/her care, thereby ensuring that all data transferred from a subject's medical records to a case report form and any process derived from the case report form is handled confidentially. Patient confidentiality will be maintained according to ICH guidelines for GCP, the Health Insurance Portability and Accountability Act (HIPAA) and applicable local and national data protection laws.

5.4 Subject Screening

During the screening process, data will be obtained to determine whether or not the subject is eligible to proceed to randomization. The screening, baseline, randomization, and procedure visits may all occur on the same day if the subject consents and all necessary data are available to assess eligibility. Creatinine, catheter-based contrast angiography (Angiogram), computed tomography angiography (CTA), magnetic resonance angiography (MRA), and arterial duplex results will remain valid for up to 3 months prior to randomization. If there has been a major change in the clinical status of the patient, creatinine should be rechecked. Vein mapping results will remain valid for up to 6 months prior to randomization.

A Screening /Uninterested Log must be maintained to track the subjects who are either not approached due to known ineligibility or who refuse to participate in the trial. No identifying information will be captured on the Screening/Uninterested Log. The Screening/Uninterested Log will be completed on paper and faxed/mailed to the DCC on the first and third Friday of every month. Information regarding subjects who are consented, screened, randomized, participating and/or withdrawn will be captured in the eCOS EDC system.

5.5 Determination of Eligibility and Randomization

Subjects included in this study must meet all the inclusion and none of the exclusion criteria in order to be considered for entry and randomization into the study. If the subject does not meet all the eligibility criteria, their participation in the study will end at that point.

5.5.1 Treatment Decision Making Guidelines

According to the protocol, all subjects must be a candidate for both open and endovascular infrainguinal revascularization as judged by the treating Investigators. The following guidelines should be applied for treatment decision-making:

- The decision as to whether a patient is a candidate for both open and endovascular revascularization will be made by the treating Investigator with input from the CLI team (see MOO Chapter 2) and will be based on multiple available clinical factors. The Investigator will need to be comfortable with either open or endovascular revascularization being performed to treat the potential subject's CLI.
- Patients deemed to be at prohibitively high perioperative risk for infrainguinal bypass surgery (e.g. those with severe un-reconstructable coronary artery disease) or who are not appropriate candidates for infrainguinal bypass surgery for reasons other than high medical risk (e.g. those with severe limb contractures or severe dementia) should be excluded.

5.5.2 Angiography and Other Imaging

A number of imaging techniques are available to assess lower extremity arterial anatomy in patients with CLI. These include catheter-based contrast angiography (Angiogram), CTA, MRA, and lower extremity arterial duplex (Duplex). Some form of imaging (Angiogram, CTA, MRA, or arterial duplex) is required to determine eligibility for randomization of subjects into the BEST-CLI Trial. Given its overall superior resolution and reliability, an **Angiogram** is strongly recommended for this purpose. If a subject has had imaging within the past 3 months that provides the requisite diagnostic information, this prior imaging may be used to determine eligibility for randomization.

- Investigators will 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.

The following strategies to optimize Angiogram imaging are recommended:

1. All contiguous arterial segments from the visceral aorta through to the distal forefoot and toes of the index limb should be sequentially imaged, with sufficient overlap between imaged segments.
2. Oblique views should be utilized to ensure accurate visualization of the iliac bifurcation, the femoral bifurcation, the tibial vessels and the foot vessels as appropriate.
3. Additional views should be used as needed to clarify the degree of stenosis present whenever a single (anteroposterior or oblique) view is insufficient to do so.
4. Appropriate oblique views should be used to fully image any vessel obscured by metallic hardware (e.g. spinal rods, hip or knee prostheses).

When performing an Angiogram, either for initial screening or related to a re-intervention, efforts should be made to minimize contrast exposure whenever appropriate, particularly in subjects with known renal insufficiency. Investigators are encouraged to use the following strategies to minimize the risk of contrast-induced acute renal failure:

1. Judicious intravenous hydration, both prior to and following angiography
2. Utilization of non-ionic, low osmolality contrast
3. Utilization of dilute contrast (e.g. one-half or one-third strength)
4. Utilization of carbon-dioxide angiography
5. Discretion should be used to determine if full visualization of the relevant arterial anatomic segments can be deferred in the interest of reducing contrast exposure (e.g. it may be acceptable to defer angiographic imaging of the entire aorto-iliac inflow in a patient with renal insufficiency, a normal femoral pulse in the index leg, and/or a prior CTA or MRA demonstrating a normal appearance of this segment).

Note: The screening imaging must provide sufficient anatomic detail to allow for a full and accurate assessment of all BEST-CLI Trial inclusion and exclusion criteria.

The following imaging strategies are encouraged to optimize image quality of CTA, MRA, and Arterial Duplex:

- For CTA: Utilization of non-contrast and contrast-enhanced arterial phase acquisitions from the renal arteries to the foot, of a resolution to permit multiplanar MIP and 3-D volumetric post-processing.

- For MRA: Utilization of contrast-enhanced 3-D MRA sequences from the renal arteries to the feet, with minimum post-processing into multiplanar MIP images in the coronal and oblique planes.
- For Arterial Duplex: Utilization of duplex ultrasound that includes continuous imaging of the following: common femoral artery, proximal deep femoral artery, superficial femoral artery, popliteal artery, anterior tibial artery, tibioperoneal trunk, posterior tibial artery, peroneal artery, and dorsalis pedis artery.

If the initial imaging is an Angiogram, CTA, or MRA, complete the Angiogram Case Report Form. If the initial imaging is an Arterial Duplex, complete the Arterial Duplex Case Report Form. These forms should be filled out at the time of the initial diagnostic imaging (i.e. screening Angiogram/ CTA/ MRA/ Arterial Duplex) (or at the time of the screening visit, if information from a prior diagnostic image is being used to determine eligibility). If a patient has additional imaging prior to randomization (e.g. if the clinical situation of the subject has changed or to perform an endovascular aortoiliac intervention prior to infrainguinal revascularization), an additional Angiogram Case Report Form should be filled out. If a CTA, MRA or Arterial Duplex is the sole diagnostic study utilized for study screening, the results of that study should be used to fill out the Baseline Angiogram CRF. An Angiogram Case Report Form should also be filled out at the time of any subsequent diagnostic or therapeutic Angiogram performed throughout the follow-up period. *Of note, it is not necessary to fill out an Angiogram CRF for “completion” angiograms performed at the conclusion of open surgical revascularization.*

Please note imaging of the non-index leg is not required.

5.5.3 Angiogram Case Report Form (CRF)

The following comments pertain to the Angiogram CRF:

Moderate occlusive disease is defined as a segment of artery that has a $\geq 50\%$ but $< 70\%$ stenosis in its most diseased portion. Severe occlusive disease is defined as a stenosis that is $> 70\%$ in its most diseased portion, but is not fully occluded. If there is an occlusion present within an arterial segment, that segment should be documented as “occluded.”

If a moderate stenosis and a severe stenosis are present in one arterial segment then the worst degree of stenosis should be recorded (e.g. If the *anterior tibial artery-proximal third* has a 60% stenosis and a 95% stenosis, then this arterial segment should be recorded as having a severe stenosis). If a stenosis and an occlusion are present in one arterial segment, then that segment should be recorded as occluded.

Subjects with patent arterial stents/stent-grafts in the index limb deployed more than 6 months prior to randomization may be included in the BEST-CLI Trial as per the criteria outlined in Section 4.1 of the Protocol (*Criteria for inclusion of previously created vessels*). Any stent(s) or stent-graft(s) noted on the initial diagnostic Angiogram that do not disqualify the subject from randomization eligibility should be recorded. If a stent or stent-graft crosses more than one arterial segment then involvement of both segments should be recorded as long as the stent/stent-graft involves more than 1/3 of the bordering segment.

On subsequent Angiograms, all arterial segments of the index limb should be assessed and all areas of stenosis within the index limb should be recorded. This should include both areas treated during the index procedure and any new areas of stenosis.

If an inflow bypass graft is noted on the initial screening or any subsequent Angiogram, its location should be recorded.

An Angiogram worksheet is available on the DCC administrative website. The worksheet can be completed by a study physician and is a helpful tool in the data entry of the Angiogram results.

Endovascular Aortoiliac interventions:

- If an endovascular aortoiliac intervention is performed at the same time as the initial screening Angiogram, the details of that intervention should be appropriately recorded in the Angiogram CRF.
- If an endovascular aortoiliac intervention is performed at the time of a subsequent pre- or post-randomization Angiogram, the details of that intervention should be recorded on an additional Angiogram CRF.
- If an endovascular aortoiliac intervention is performed concurrently with endovascular index revascularization (but at a separate time point than the original screening Angiogram form), the details of this intervention should be recorded on a new Angiogram CRF in addition to the Endovascular Procedure Details CRF.
- If an endovascular aortoiliac intervention is performed concurrently with open surgical index revascularization, a new Angiogram CRF should be filled out and the details of the aortoiliac intervention recorded.

The TransAtlantic Inter-Society Consensus (TASC) II classification system of arterial disease patterns will be used. Schematics of the TASC II system for assessing aortoiliac and femoropopliteal disease are provided below:

Figure 1: TASC II system for assessing aortoiliac disease

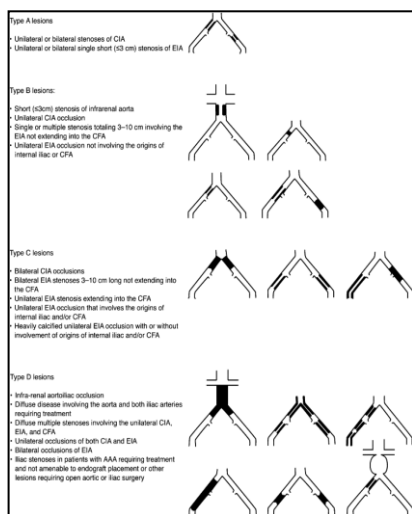
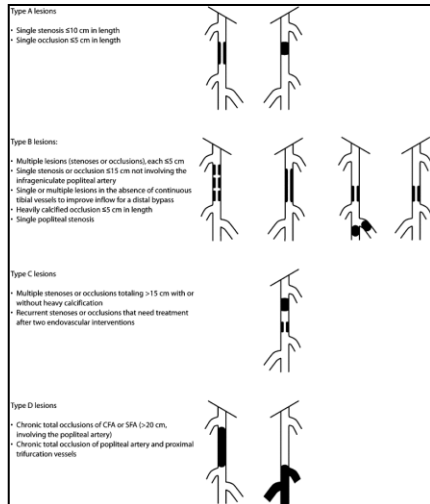


Figure 2: TASC II system for assessing femoral-popliteal disease



5.5.4 Final Eligibility Determination

Certain inclusion and exclusion criteria can be evaluated based on a review of available baseline data prior to the initial screening imaging. For those patients that do not have adequate imaging (i.e. Angiogram, CTA, MRA, or Arterial Duplex) within the prior 3 months, the final determination of eligibility for randomization cannot be made until the current diagnostic imaging is obtained and reviewed by the relevant members of the treating CLI team.

Criteria that require anatomic information obtained from the screening imaging study include:

Inclusion:

1. The subject remains a candidate for both open and endovascular infrainguinal revascularization.
2. Adequate aortoiliac inflow is either already present at baseline or to be established prior to or at the time of the index revascularization.
3. Adequate distal target for surgical bypass is present

Exclusion:

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).

Prior to randomization, at least two members of the CLI Team must review the results of the Angio and reach consensus that all of the inclusion and exclusion criteria have been met (see MOO Chapter 2).

Important note: *The trial was designed to allow for and facilitate subjects undergoing both the diagnostic imaging (required to fully determine eligibility) and the therapeutic angiogram, should they randomize to endovascular therapy, at the same setting, if the Investigator so chooses.*

5.5.5 Inclusion and Exclusion Criteria CRFs

The following comments pertain to the Inclusion Criteria and Exclusion Criteria CRFs:

Inclusion criterion 3 (CRF Section B, Question B3):

CLI in the trial will be measured according to the Rutherford classification of chronic limb ischemia (reference: Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997; 26(3):517) According to that classification, stages of chronic limb ischemia are defined by Categories based on both clinical presentation and hemodynamic assessment. Categories 1, 2, and 3 denote mild, moderate and severe claudication, respectively. Category 4 represents ischemic rest pain. Category 5 and 6 represent minor and major tissue loss, respectively. In the BEST-CLI Trial, subjects with Category 5 and 6 chronic ischemia will be grouped together. Therefore, it is not necessary to distinguish a difference between Rutherford Category 5 and Category 6.

Inclusion criterion 5 (CRF Section B, Question B3):

Adequate aortoiliac inflow is an important inclusion criterion for BEST-CLI as the purpose of the trial is to assess infrainguinal intervention. To that end, a worksheet has been developed to help with assessment of aortoiliac inflow (please see Appendix 1).

Exclusion criterion 3 (CRF Section B, Question B3):

The decision as to whether a patient is considered at prohibitively high risk for surgical revascularization is typically based on a variety of objective and subjective factors. Due to the lack of validated guidelines to inform this determination, this decision will be left to the Investigator and the CLI team.

Exclusion criterion 9 (CRF Section B, Question B9)

Subjects currently taking a chemotherapy agent or radiation therapy are excluded.

- Chemotherapy agents are defined as any systemic drug (not topical) that is used for the treatment of an active cancer. This includes cytotoxic agents, biologic agents (monoclonal antibodies) and kinase inhibitors or other signaling pathway inhibition such as VEGF, mTOR, PI3k, EGFR, etc.
 - Hormonal therapy for the treatment of active cancers or for prevention are allowed (e.g. tamoxifen, raloxifene, LHRH agonists, aromatase inhibitors)

5.5.6 Vein Mapping

Vein Assessment

Assessment of the adequacy of adequate single-segment greater saphenous vein (SSGSV) will be made by a surgical member of the treating CLI team. It is strongly preferred that saphenous vein mapping be obtained in a formal fashion through an Intersocietal Commission for the Accreditation of Vascular Laboratories (ICAVL), Intersocietal Accreditation Commission (IAC) or American College of Radiology (ACR) accredited vascular laboratory study. It is recognized that some vascular surgeons routinely perform vein assessment themselves using bedside duplex either prior to or at the time of surgery. Determination of saphenous vein adequacy in this manner will be accepted, provided it allows appropriate placement into Cohort 1 (adequate SSGSV present) or Cohort 2 (adequate SSGSV absent) prior to the time of randomization.

For example, intraoperative dissection of the saphenous vein to determine its suitability after randomization will not be allowable. On the other hand, assessment of the saphenous vein by bedside duplex in the operating room or angiography suite in patients brought for diagnostic angiography will be allowed provided it allows appropriate Cohort designation prior to randomization, even when the intention is to proceed with revascularization immediately following the angiogram.

Note: *Vein adequacy must be assessed prior to the time of randomization to allow appropriate Cohort designation.*

While the determination of what constitutes an “adequate vein” will be left to the treating surgeon, the undilated vein diameter should generally be >2.5 mm throughout the extent of the needed length.

Investigators will be asked to measure and record the vein size at the completion of the surgical bypass. This should be determined by measuring the minimal post-inflation diameter over the extent of the vein using a sterile ruler or caliper. For grafts tunneled superficially, this measurement can be performed once both the proximal and distal anastomoses have been constructed and flow through the graft has been re-established. For graft tunneled deeply, the measurement can be evaluated once the vein is pressurized with blood at the completion of the proximal anastomosis.

5.5.7 Randomization

Once the subject has consented and is determined to be eligible based on a review of all inclusion and exclusion criteria, randomization may be performed. Randomization will take place following the complete data entry of the following eCRFs. Note that all queries must be resolved in order to randomize a subject.

- General Information
- Informed Consent
- Inclusion Criteria
- Exclusion Criteria
- Vein Mapping
- Randomization

The results of the randomization will be displayed in the EDC system (i.e. open surgical procedure or endovascular procedure). The randomized procedure can always be checked by going to the Information tab, selecting “View Unblinding Information” or by selecting the Rand tab in eCOS.

5.5.8 Timing of eligibility determination, randomization and index procedure

As stated above, the trial is specifically designed to allow subjects to undergo endovascular therapy immediately following the screening diagnostic Angiogram (i.e. as part of the same procedure) if the determination is made based on review of the angiographic findings by the CLI Team that the subject: has met all of the inclusion and exclusion criteria, remains eligible for both therapies, and randomizes to endovascular therapy. Similarly, if the Angiogram is performed in a hybrid operating room or standard operating room setting, and the subject randomizes to surgical therapy, proceeding directly to surgical bypass as part of the same procedure is acceptable. All components of the inclusion/exclusion criteria must be satisfied in order to facilitate performing both the diagnostic Angiogram and the revascularization at the same time.

It is also acceptable to defer either endovascular or surgical revascularization to a later time (i.e. different than the time of the diagnostic angiography) if this is preferable.

5.6 Index Procedure

5.6.1 Staged Procedures

Planned staged infrainguinal revascularization procedures, in which components of the index revascularization are planned to be undertaken at two different time periods, will not be allowed. Unplanned staged endovascular procedures are strongly discouraged. However, if an Investigator feels compelled to discontinue index endovascular revascularization prior to fully completing the intended revascularization goals given the intraprocedural findings or situation (e.g. concerns about excessive contrast load or fluoroscopy time), he/she will be permitted to plan and carry out a second stage provided the second stage is undertaken within 4 days of the first stage. In such situations, the anatomic and treatment status must be clearly documented in the Endovascular Procedure Details CRF at the completion of the first stage. This documentation must include which stenotic lesions were treated during the first stage, and the outcome of all such treatments. It must also include a clear delineation of which anatomic lesions remain untreated, and a clearly outlined treatment plan for the second stage.

The patency status of any and all lesions that were treated during the first stage must be re-documented at the beginning of the second stage in a new Endovascular Procedure Details CRF. Retreatment of lesions treated during the first stage will not be allowed at the time of the

second stage. Retreatment during the second stage of any lesions treated during the first stage (presumably undertaken as believed to be in the best interest of the patient) will be considered a treatment failure and an appropriate outcome determination made. All such unplanned two stage endovascular procedures will be audited to ensure strict adherence to these rules.

5.7 Study Measurements

5.7.1 Medical History

A Medical History will be obtained at the baseline visit. All relevant medical conditions will be broadly assessed. The degree of daily exercise, ambulatory status and living status will also be recorded.

For patients who smoke, the number of pack-years smoked must be calculated. This is defined as the number of packs of cigarettes smoked per day multiplied by the number of years the person has smoked. For example, 1 pack-year is equal to smoking 20 cigarettes (1 pack) per day for 1 year, or 40 cigarettes per day for half a year, and so on.

5.7.2 Focused Peripheral Vascular History

At the baseline visit, any and all relevant elements of a subject's past vascular history should be reviewed and collected. Any prior open revascularization procedures, including bypass configurations and conduit used, should be reported. Similarly, prior endovascular procedures should be recorded. All amputations in both the index and non-index leg should be recorded.

5.7.3 Vascular Assessment

An assessment of the subject's CLI status will be recorded at baseline and at every in-person visit. The presence of ischemic rest pain (Rutherford 4) will be ascertained, based on appropriate symptomatology and corroborated by appropriate hemodynamic parameters. The presence of ischemic tissue loss (Rutherford 5/6) will be based on the presence of ulcerations felt to be secondary to arterial insufficiency (rather than ulcers of venous or neuropathic origin) or ischemic gangrene. All such lesions will be recorded at baseline, and will serve as the basis for determining any change in the subject's CLI status over the course of the trial. Given the lack of an accepted standard as to the difference between Rutherford Category 5 and Category 6 lesions, Rutherford 5 and 6 will combined into a designation Rutherford 5/6 throughout the trial duration.

During the baseline and all other in-person visits, a vascular physical examination needs to be performed by the Investigator and documented by the coordinator. This exam includes a careful assessment of bilateral femoral, popliteal, dorsalis pedis and posterior tibial pulses. On follow-up visits, a pulse in a bypass graft for patients randomized to open revascularization will also be assessed. Rather than using a numerical scale, pulses will be recorded as being absent, diminished, normal, or augmented. An index graft pulse will be recorded as palpable and non-palpable.

Presence of tissue loss will be assessed only in the index limb. An ulcer is defined as a wound without presence of tissue necrosis. Gangrene is defined as presence of any necrotic tissue involving the dermis or deeper tissue layers. Presence of an ulcer or gangrene will be recorded at the 5 toes, forefoot, hind foot, ankle, and above ankle.

Healing of tissue loss after following index revascularization will be monitored in every applicable patient. At every visit, all ulcers will be graded as being new (since previous visit), having healed or not having healed. Healing will be defined by the complete epithelialization of the ulcer.

If a patient undergoes a toe or foot amputation before, during or after index revascularization procedure, the amputation incision site will be monitored for healing at every visit. A toe or foot amputation site performed for tissue loss will be monitored for healing as a proxy for the initial wound. Breakdown or non-healing of a toe or foot amputation site will be counted as failure of wound healing. Those toe and minor foot amputations performed 7 days or sooner before the index revascularization and those performed within 1 month after the index revascularization will be counted as proxy for the initial wound.

Wound Classification:

Although there are many wound classification systems, none allow for accurate categorization of the extent of tissue loss, presence of infection and the degree of ischemia, all of which are factors that significantly bear on the likelihood of healing. To that end, the Society for Vascular Surgery has developed the Wlfi Classification, which combines the effects of wound grade, ischemia, and infection. An effort will be made to validate the Wlfi classification in the BEST-CLI Trial.

In the CRF, the domains of wound grade, infection, and ischemia will be assessed using a series of tools.

Wound Grade: Presence of an ulcer or gangrene will be assessed using one of four grades. Every patient with tissue loss will be assigned to one of these wound grades based on the best estimate on the part of the coordinator and Investigator.

- 0 No wound or gangrene
- 1 Small, shallow ulcer on distal leg or foot, with no exposed bone (unless limited to the distal phalanx) and no gangrene. These findings would be clinically consistent with minor tissue loss. Limb salvage would not require any procedure other than a simple amputation of one or two toes.
- 2 Deeper ulcer with exposed bone, joint or tendon; A shallow heel ulcer is allowed as long as there is no calcaneal involvement; If gangrene is present it needs to be limited to the toes. These findings would be consistent with major tissue loss that would at most require amputation of three or more toes or a transmetatarsal amputation.
- 3 Extensive deep ulcer or gangrene involving forefoot or mid foot; deep, full thickness heel ulcer with or without calcaneal involvement. Extensive gangrene involving forefoot and/or mid foot; full thickness heel necrosis with or without calcaneal involvement. These findings describe extensive tissue loss salvageable only by a complex foot reconstruction or a Chopart/Lisfranc amputation. Flap coverage may be needed.

Ischemia Grade: Presence of ischemia, for the purposes of the Wlfi classification, will be based on the following four categories which will be chosen based on arterial non-invasive imaging that will include Ankle Brachial Index (ABI), ankle systolic pressures and toe pressure (TP) or transcutaneous oximetry (TcPO₂) measurements.

- 0 ABI ≥ 0.8 ; ankle systolic pressure > 100 mm Hg; TP or TcPO₂ ≥ 60 mm Hg. These hemodynamic findings are consistent with no ischemia.
- 1 ABI 0.6-0.79; ankle pressure 70-100 mm Hg, TP or TcPO₂ 40-59 mm Hg. These hemodynamic findings are consistent with mild ischemia.

- 2 ABI 0.4-0.59; ankle pressure 50-70 mm Hg, TP or TcPO₂ 30-39 mm Hg. These hemodynamic findings are consistent with moderate ischemia.
- 3 ABI $\leq$.039; ankle pressure $<$ 50 mm Hg, TP or TcPO₂ $<$ 30 mm Hg. These hemodynamic findings are consistent with severe ischemia.

The highest ankle pressure in the index limb will be measured and ABI will be calculated. If the calf arteries are non-compressible or if ABI is $>$ 1.3 then TP or TcPO₂ will be obtained.

In diabetics TP should be measured. In subjects with arterial calcification measurement of accurate ankle pressure or ABI may not be possible. In such patients TP, TcPO₂, or pulse volume recordings (PVR) may be used to assess ischemia. If ABI and TP measurements result in different grades, TP will be the primary determinant of ischemia grade. Flat forefoot PVR are consistent with grade 3 ischemia.

Infection Grade: presence of clinical manifestation of infection in the index limb will be assessed.

- 0 No symptoms or signs of infection.
- 1 Infection is present as defined by at least 2 of the following:
 - a. Local swelling or induration
 - b. Erythema $>$.5 cm to $\leq$ 2 cm around ulcer
 - c. Local tenderness or pain
 - d. Local warmth
 - e. Purulent dischargeClinically this Grade would be consistent with a local, self-limited infection involving the skin and subcutaneous tissues only. Other causes of inflammatory skin conditions need to be excluded as being primarily responsible for the appearance of the wound (trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis or venous stasis).
- 2 Local infection (as described above) with erythema $>$ 2cm or involving structures deeper than the skin and subcutaneous tissue. This includes presence of an abscess, osteomyelitis, septic arthritis and fasciitis. There should be no evidence of a systemic inflammatory response syndrome (SIRS).
- 3 Local infection (as described above) with signs of SIRS, as manifested by two or more of the following;
 - a. Temperature $>$ 38°C or $<$ 36°C
 - b. Heart rate $>$ 90 beats per minute
 - c. Respiratory rate $>$ 20 breaths/min or PaO₂ $<$ 32 mm Hg
 - d. White blood cell count $>$ 12,000 or $<$ 4,000/mm³ or 10% immature (band) forms.

A 0-3 score will be assigned for the Wound, Ischemia and Infection domain and will be recorded as such in the Vascular Physical Exam CRF (Mills JL, Conte MS, Armstrong DG, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification based on wound, ischemia, and foot infection (Wlfi) J Vasc Surg 2014;59:220-34). Please see worksheet in Appendix 2.

In parallel with Wlfi, we will also collect the Wagner wound classification defined below

- 0 no open lesion, but may possess pre-ulcerative skin changes
- 1 superficial ulcer, not involving subcutaneous tissue

- 2 deep ulcer with penetration through the subcutaneous tissue, potentially exposing bone, tendon, ligament or joint capsule
- 3 deep ulcer with osteitis, abscess or osteomyelitis
- 4 partial foot gangrene
- 5 whole foot gangrene

5.7.4 Medications

Sites are to report medications (including dosages) that subjects report as currently taking at the time of each study visit, and will be recorded in the medication CRF at each visit.

- Anticoagulant agents
- Antihypertensive agents
- Antiplatelet agents
- Cholesterol-lowering agents (including statins)
- Diabetes medications (both oral and injectable)

5.7.5 Hemodynamic Assessment and Arterial Duplex

At every in-person visit, the subject will undergo hemodynamic monitoring of the index limb. Measurements of distal perfusion will be used at the initial visit to corroborate the presence of CLI, at the first post-index procedural visit to assess for the hemodynamic success of the revascularization and at follow visits to assess the presence or absence of continuous hemodynamic success. Ankle systolic pressures will be measured and the ABI will be calculated. If ankle pressures are not measurable or spuriously high due to arterial calcification that is often observed in the setting of diabetes and renal insufficiency, then toe pressures, TcPO₂, tibial waveforms, or PVRs should be measured. In some vascular labs, a hemodynamic vascular system (e.g. Parks) is used to assess distal perfusion. Such a system often allows for simultaneous measurement of ankle pressures, Doppler waveforms, PVRs, and toe pressures. If such a system is routinely used for hemodynamic assessment, then results of the above tests should be recorded in the CRF.

Arterial duplex is not mandatory for sites that do not perform this assessment as part of routine practice. However, at all sites that perform duplex as a standard means of post-operative bypass graft surveillance, results will be collected at indicated time points in all randomized patients and recorded in the CRF. Results will similarly be collected in all randomized subjects undergoing arterial duplex surveillance studies following endovascular treatment in all sites routinely performing such studies. Reports of endovascular duplex studies will not be recorded in the CRF but rather should be emailed (best@neriscience.com) or faxed (617.673.9517) to the DCC.

5.7.6 Pain Numeric Rating Scale

Using a scale of 0 to 10 (10 being the worst), subjects are asked to rate their level of pain at the time of the visit and during the previous week. This form can be printed for subjects to circle the number that best fits their level of pain (research staff can circle the number provided by the subject verbally as well). Once printed, completed, and initialed the form must be placed in the subject's study file to be used as source documentation.

5.7.7 Laboratory Assessment

Creatinine will be recorded at baseline, before the index procedure, and at follow-up visits (30 days post procedure, month 12, and month 24) according to the Schedule of Measurements outlined in the protocol. The creatinine will be valid for up to three months prior to

randomization. Any significant change in the subject's clinical status should prompt a repeat assessment of the creatinine. Note: BUN levels will not be recorded for the BEST Trial.

The following laboratory values should be recorded if available:

- Hemoglobin
- Albumin
- HgA1c
- Triglycerides, low density lipoprotein, high density lipoprotein

While hemoglobin, albumin, HgA1c and lipid levels are not required, please record the most recent value for each test that is available dating from 6 months prior to randomization. Beyond the baseline value, please record the most recent available value of each test since the time of the last study visit.

5.7.8 Six-minute Walk Test

The 6 Minute Walk Test will be administered at sites that perform this test as standard of care.. At those sites, the 6 Minute Walk Distance (6MWD) test will be administered per the guidelines available in Appendix 3. Please familiarize yourself with the 6MWD Guidelines before the study begins. A test administrator, apparatus and ideally a 100-foot straight distance must be readily available in order to perform the test.

The test should be deferred in subjects unable to ambulate secondary to their CLI or medical comorbidities. Reasons for test deferment should be indicated on the appropriate CRF. Subjects in whom walking capability has been restored following successful treatment of their CLI should be administered the 6 Minute Walk Test at the 6 month post-randomization visit regardless of whether or not a baseline test was performed.

5.7.9 Quality of Life Measurements

The following quality of life instruments must be administered:

- VascuQOL
- SF-12
- EQ-5D

These instruments are designed to be self-administered, although research staff, including the use of an interpreter, can help subjects complete them. These instruments can also be administered via phone (See Appendix 4 – BEST-CLI Telephone Scripts). After completion, the subject's responses should be recorded on the appropriate CRF. The original paper copies of the instruments must be kept in the subject's study file as source documentation.

5.7.10 Device Accountability

A device accountability form must be completed for cases where an endovascular procedure is performed AND the device is an implantable device between randomization and the end of the study. This includes the following devices:

- Bare metal stent
- Drug-eluting metal stent
- Covered metal stent (Stentgraft)

For each device implanted you must specify the device name, manufacturer, model, and lot number.

5.7.11 CLI Intervention/Procedure (Re-Intervention)

Index Limb

All interventions relevant to the subject's CLI (on the index limb) performed after the index procedure and before the subject completes the study must be reported on the CLI Intervention/Procedure (Re-Intervention) Form. This form must be completed in addition to the corresponding Adverse Event Form. If a device is implanted during an endovascular reintervention, the device must be reported on a Device Accountability form. If the subject is hospitalized for the reintervention, a Hospital Encounter Form must also be submitted.

Non-Index Limb

All interventions relevant to the subject's CLI on the non-index limb performed after the index procedure and before the subject completes the study will be recorded on the Non-Index Intervention log and then entered into the Non-Index Limb Intervention/Procedure eCRF at the end of study. Corresponding Adverse Event forms and hospitalization forms should be completed for applicable events that meet the criteria.

5.7.12 Amputations

An amputation form must be completed when a subject undergoes a new amputation. This form must be completed in addition to the corresponding Adverse Event Form.

5.7.13 Health Resources Utilization

All medical encounters that occur after the index procedure visit or hospitalization must be recorded. These include whether, and how many times, patients were rehospitalized, visited an emergency department, had outpatient diagnostic tests or procedures, and physician office visits. Information about whether outpatient rehabilitation services (and, if so, how many hours) and long-term care or inpatient rehabilitation/skilled nursing care services (and, if so, how many days patients were inpatients) were used must also be recorded. Finally, information about the number of hours of work that were missed by the patient for all outpatient services (including emergency department visits) since the last study visit and whether the patient has received any informal care from family or friends should be noted.

Information about re-hospitalization and ED visits will be captured in the Hospital Encounter Form. Each outpatient procedure or diagnostic test will be detailed on a separate Outpatient Procedure/Diagnostic Test form.

5.7.14 Case Report Form Completion

The following table provides the time points/visits when each of the measurements described in Section 5.7 must be completed/ reported.

Table 1: eCRF Completion Schedule

	Screening	Baseline	Index Procedure	30 Days Post Procedure	Months Post-Randomization							End of Study	Each Procedure/Test/Hospitalization/AE
					3	6	12	18	24	30, 42, 54, 66, 78	36, 48, 60, 72, 84		
General Information	X												
Demographics	X												
Informed Consent	X												
Inclusion Criteria	X												
Exclusion Criteria	X												
Randomization	X												
Angiogram		X											X*
Medical history		X											
Vital Statistics		X	X	X	X	X	X	X	X		X		
Amputation status													X*
Vascular Physical Assessment		X		X	X	X	X	X	X		X	X	
Peripheral vascular history		X											
Vein mapping	X												
Hemodynamic Assessment and Arterial Duplex		X		X	X	X	X	X	X		X		
Laboratory Results		X	x	X			X		X				
Medications		X	X	X	X	X	X	X	X	X	X	X	
Quality of Life Measurements (VascuQOL, SF12, EQ5D)		X		X	X		X		X		X		
Pain Scale (NRS)		X		X	X	X	X	X	X				
Six-Minute Walk Test		X*				X*							
Open Surgical Procedure			X										
Endovascular Procedure			X										
Device Accountability			X*										X*
Study Status Change Information												X	X*
Reintervention Details													X*
Smoking Status		X										X	
Utilization Form				X	X	X	X	X	X	X	X	X	
Hospital/ED Encounter Form												-	X*
Outpatient Procedure/Diagnostic Test												-	X*
Adverse Event													X*

X = Required per protocol

X* = Add as needed for each test/procedure/implanted device/event/hospitalization, etc.

5.8 Timing of Screening and Baseline Measurements

Screening measurements consist of the information needed to determine if the subject is eligible for BEST-CLI. Baseline data is information captured after consent and prior to the index procedure. The following table outlines the acceptable window for screening and baseline measurements. Where indicated, information in the subject's medical record that was obtained as part of routine care may be reported as a screening or baseline measurement. If a required screening measurement is not available in the medical record in the window indicated below it must be obtained after consent and prior to randomization. If a required baseline measurement is not available in the medical record in the window indicated below it must be obtained after consent and prior to the subject's index procedure. Failure to obtain a required measurement will result in a protocol violation. If multiple values are available within the window, report the most recent information available.

Table 2: Screening Measurements

Measurement	eCRF	Window
Inclusion Criteria	Inclusion Criteria	At randomization
Exclusion Criteria	Exclusion Criteria	At randomization
Vein mapping	Vein mapping	Up to 6 months prior to randomization
Cardiac Risk Stratification	Randomization	At randomization
Demographics	Demographics	Baseline visit, post-randomization

Table 3: Baseline Measurements

Measurement	eCRF	Window
Imaging (Angiogram, catheterization preferred; CTA, MRA, Arterial Duplex allowed)	Angiogram / Arterial Duplex Addable Form	Up to 3 months prior to randomization
Medical history	Medical History	Up to 1 month prior to randomization
Height, weight, heart rate, blood pressure	Vital statistics	Up to 1 month prior to randomization
Amputation status	Vascular Physical History	At randomization
Assessment of CLI symptoms	Vascular Physical Assessment	Up to 1 month prior to randomization
Peripheral vascular history	Vascular Physical History	At randomization
Hemodynamic assessment (ankle pressures; toe pressures; DW or transtalar pulse volume recording if ankle or toe pressures inaccurate)	Hemodynamic Assessment and Arterial Duplex	Up to 3 months prior to randomization
Renal function (creatinine)	Laboratory Results	Up to 3 months prior to randomization
Hemoglobin, albumin, HgA1c, lipid (if available)	Laboratory Results	Up to 6 months prior to randomization
Medications	Medications	At randomization
Quality of Life Measurements	VascuQOL, SF12, EQ5D	Post consent, prior to index procedure
Pain Scale (NRS)	Pain Scale (NRS)	Post consent, prior to index procedure
Six-Minute Walk Test	Six-Minute Walk Test	Post consent, prior to index procedure

5.9 Telephone Visits

The visits at 30, 42, 54, 66 and 78 months post-randomization are telephone visits. The subject does not need to return to the study center to complete these visits. The subject's medications, health care utilization, and adverse events must be reviewed over the telephone (see Telephone Script, Appendix 4). It is strongly encourage that all sites obtain complete contact information for the subject and at least one other person who is in contact with the subject. At least 5 attempts must be made to contact the subject for a telephone visit before the visit is considered missed. These attempts must be recorded in the subject's study record.

5.10 Study Status Change

All randomized subjects are expected to be followed as per the BEST-CLI protocol until they complete all of the study visits, even if they have already experienced a primary outcome event, unless they withdraw consent. Once all study visits are completed a Study Status Change Form must be data entered. In addition, a Study Status Change Form must also be submitted when any of the following events occur:

- Death: indicate date, time, and cause of death
- Withdrawal or change in level of study participation: indicate date and most recent study status. Please note:
 - A subject may decline future in-person visits but agree to telephone contact for study visits and vital status check
 - A subject may decline all future study visits, in-person or telephone, but agree to contact for vital status at the end of the study
 - A subject may decline all future study visits and contact but agree to a medical record review
 - A subject may decline all future study contact or data collection.
- Subject lost to follow-up: every attempt must be made to contact the subject. Documentation of such attempts must also be made to the subject's study file for review during monitoring visits.
- Study or site closure

Please note that a Study Status Change Form must be completed in addition to the Adverse Event form (if applicable). In addition, all expected CRFs for visits and events that occur prior to the status change must also be data entered.

5.11 End of Study

At the End of Study visit, the following will be collected:

- CLI symptoms
- Smoking Status (current status and smoking history over the course of the trial)
- Revascularization of Non-Index Limb (record of interventions that occurred on the non-index limb over the course of the trial)
- Medications
- Health Care Utilization
- Vital Status
- Final follow up on all on going Adverse Events

SECTION B – Trial Conduct

Trial Therapies

Index Revascularization:

All care rendered during the index revascularization and any reinterventions should be undertaken according to established standards of care and guidelines. The trial will be conducted in compliance with the BEST-CLI Trial protocol, Good Clinical Practice (GCP) guidelines and applicable federal regulatory requirements [Title 21 Code of Federal Regulations Parts 50, 54, 56, 812 and 45CFR46]. The trial is registered on ClinicalTrials.gov.

The BEST-CLI trial is designed to be a pragmatic trial. Inherent in the definition of a pragmatic trial, Investigators will not be limited to a particular treatment strategy or device platform. Rather, the exact modality or modalities of treatment rendered with regard to either surgical bypass or endovascular therapy will be left to the discretion of the treating physician, and should be guided by what the Investigator has come to believe in his or her own experience are best practices and optimal medical care.

While specific treatment strategies will be left to individual Investigators as stated above, recommendations are provided with regard to general principles of optimal therapy for both surgical bypass and endovascular treatment. Adherence to such recommendations is strongly encouraged.

Surgical revascularization – General and technical considerations:

Alternative conduit refers to anything other than a single segment of ipsilateral or contralateral greater saphenous vein. Alternative conduit (Cohort 2) specifically includes spliced ipsilateral and/or contralateral greater saphenous vein, single segment or spliced ipsilateral or contralateral lesser saphenous vein, single segment or spliced arm cephalic, basilic or brachial vein, prosthetic conduit, cryopreserved vein, and any composite of autogenous vein, prosthetic or cryopreserved conduit.

With regard to construction of the surgical bypass, all configurations of a venous conduit (reversed, non-reversed, in-situ) will be allowed. For non-reversed and in-situ grafts, use of any commercially available valvulotome is allowed. If a patch angioplasty is undertaken, the patch may be constructed with autogenous tissue (venous or arterial), bovine pericardium or prosthetic [polytetrafluoroethylene (PTFE) or Dacron] material.

General recommendations for optimal care for both surgical bypass and endovascular therapy:

1. In the setting of tissue loss (Rutherford Category 5/6), revascularization should result in in-line arterial flow to the foot.
2. In the setting of ischemic rest pain (Rutherford Category 4) without tissue loss and multi-segment disease (i.e. involving both the femoropopliteal and the tibial segments), revascularization of at least the femoropopliteal segment should be achieved. In such scenarios, leaving the tibial disease untreated is acceptable if in the view of the treating Investigator, the perfusion resultant from treating the femoropopliteal segment alone will likely result in resolution of the rest pain.
3. The decision as to which vessel or vessels should be revascularized should be based on thorough assessment of the anatomic disease pattern, available runoff and the likelihood

of successful clinical success. While recognizing the importance of and growing academic interest in angiosome-directed therapy, this strategy will not be mandated.

General recommendations for optimal care for surgical bypass:

1. The final open surgical bypass result should be assessed by one or more of the following completion modalities at the time of the index surgery: continuous wave Doppler, duplex, or angiography. Findings suggestive of a technical error or hemodynamic impairment that will likely impact graft patency should be addressed at the time discovered.
2. If a prosthetic conduit is grafted to a tibial distal anastomotic target, a prosthetic with a prefabricated cuff or an adjunctive vein patch, vein cuff, and/or arteriovenous fistula should be utilized.
3. Prosthetic conduit should not be used in the setting of a pedal distal anastomotic target.
4. Given inferior durability, cryopreserved conduit should only be used in the setting of infection or as a last resort when options for use of an alternative non-SSGSV autogenous or prosthetic conduit are unavailable. Although cryopreserved vein may have a role in helping heal distal tissue loss it should not be used to treat ischemic rest pain.
5. Patients with conduits considered high-risk (i.e. a prosthetic conduit to a below knee or tibial target, a spliced or non-SSGSV autogenous conduit, or a cryopreserved vein) should be considered for post-operative anticoagulation.

Endovascular Revascularization – General and technical considerations:

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.

The following technologies can be utilized either as stand-alone therapy or in combination.

- Balloon dilatation with a standard balloon
- Balloon dilatation with a cutting or scoring balloon
- Deployment of a bare metal stent, self-expanding or balloon-expandable
- Deployment of a drug-eluting metal stent, self-expanding or balloon-expandable
- Deployment of a covered metal stent, self-expanding or balloon-expandable
- Use of directional or rotational atherectomy device
- Use of excimer laser angioplasty
- Use of embolic protection device
- Use of luminal re-entry device

All of the devices listed above have been approved by the Food and Drug Administration (FDA) and the Health Canada's Therapeutic Products Directorate (HCTPD) for human use. The BEST-CLI Trial has been granted an Investigational Device Exemption (IDE) by the FDA to allow "off-label" application of all FDA-approved technologies that are routinely used for the treatment of CLI as part of current standards of care.

New technology and devices relevant to the treatment of CLI that are developed or become available over the course of the trial (e.g. drug-eluting balloons) will be formally evaluated by the Evolving Technology Committee on a case by case basis once FDA approval has been received. This committee will provide a recommendation to the BEST-CLI Trial Executive Committee, which will then determine suitability for potential use in the trial.

The use of cryoplasty balloons is prohibited in the BEST-CLI Trial.

General recommendations for optimal care for endovascular therapy:

1. Bailout or salvage stenting should be undertaken in the setting of persistent stenosis, recoil or dissection following angioplasty or atherectomy that results in a hemodynamically significant limitation of flow.
2. Strict attention should be given to avoiding injuring potential distal anastomotic surgical bypass targets.
3. A 0.014 or 0.018 wire platform should be utilized for tibial interventions.
4. During the intervention, and prior to endovascular treatment, an ACT of ≥ 225 seconds should be achieved.
5. Appropriate anti-platelet therapy should be continued or initiated post-procedure unless specifically contraindicated. Patients should be maintained on aspirin 81-325 mg per day indefinitely. Clopidogrel 75 mg per day should be used post-procedure for at least 4 weeks (or a suitable alternative in the event that clopidogrel is contraindicated, e.g. ticagrelor, prasugrel, or ticlopidine). If patient has been on at least 5 days of daily clopidogrel at the time of the endovascular procedure, then a loading dose is not necessary. The duration of clopidogrel therapy will be left to the judgment of the treating Investigator.

Wound care:

In the setting of tissue loss, all devitalized and non-viable tissue should be debrided in a timely and appropriate fashion according to acceptable standards of wound care. Following the index procedure, any planned readmissions for wound care of ischemic lesions should be indicated on the appropriate CRF. Similarly, any planned wound or ulcer debridement and/or toe or forefoot amputations should be indicated on the appropriate CRF.

Antibiotic therapy should be administered according to current standards of care. For surgical bypass, appropriate gram positive coverage should be administered within 60 minutes of the time of incision. For endovascular therapy, routine use of antibiotics is not indicated.

Technical failure:

Technical failure in the setting of a surgical bypass is defined as occlusion of the bypass graft or failure to achieve a patent bypass graft at the completion of the procedure. Abortion of the procedure prior to successful completion due to non-technical reasons (e.g. due to hemodynamic instability following a myocardial infarction) will still be considered a technical failure of bypass surgery.

Technical failure in the setting of endovascular therapy is defined as the inability to cross a stenosis or occlusion or a residual obstruction of $\geq 50\%$ in the SFA, popliteal and/ or all tibial arteries (from recoil, dissection, thrombosis, embolization or other complication) such that there is no in-line flow to the foot.

BEST-CLI Aortiliac Inflow Worksheet

Subject ID _____ - _____

- A1. Which leg is the trial leg? ☐ Right ☐ Left
- A2. Rutherford Category: ☐ Category 4: ischemic rest pain **without** tissue loss.
☐ Category 5 or 6: ischemic rest pain with tissue loss

A subject is confirmed to have adequate aortoiliac flow when the following criteria are met (see notes):

B1. Normal ipsilateral femoral pulse	☐ Yes ☐ No	At least one question B1-B4b must be YES
B2. Biphasic or triphasic Doppler waveform in the ipsilateral common femoral artery	☐ Yes ☐ No	
B3. Normal radiographic appearance of ipsilateral iliac artery	☐ Yes ☐ No	
B4. Radiographic evidence of ipsilateral common and external iliac artery occlusive disease:		
B4a. All lesions are of <50% severity	☐ Yes ☐ No	
B4b. There is ≤ 10 mmHg aortic to femoral mean pressure gradient	☐ Yes ☐ No	

C1. If Rutherford category 4 ischemia (ischemic rest pain):		C1a or C1b must be YES
C1a. <70% stenosis of the aorta or ipsilateral iliac arteries	☐ Yes ☐ No	
C1b. ≥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.	☐ Yes ☐ No	

D1. If Rutherford category 5 or 6 ischemia (tissue loss):		D1a must be YES
D1a. If patients with iliac or aortic stenosis or occlusion must undergo endovascular revascularization prior to or at the same time as the index infrainguinal revascularization.	☐ Yes ☐ No	

E1. Patients have not undergone contemporaneous open surgical inflow procedures (aorto-femoral, axillo-femoral, ilio-femoral, thoracofemoral, femorofemoral bypass).	☐ Yes ☐ No	E1 must be YES
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**Eligibility Determination: adequate inflow confirmed if
all of the following are true:**

☐	At least one question B1 – B4b is answered YES
☐	Rutherford category 4: C1a or C1b at least one question is YES <u>OR</u> Rutherford category 5 or 6: D1a must be YES
☐	Question E1 must be answered YES

Record eligibility determination on Inclusion Criteria CRF, question B5.

Appendix 2: Wound, Ischemia, and Foot Infection (WIFI) Score

Wound Grade Definitions

Grade	Ulcer	Gangrene	Description
0	No	No	ischemic rest pain (requires typical symptoms + ischemia grade 3); no wound.
1	Small, shallow ulcer on distal leg or foot; no exposed bone, unless limited to distal phalanx	No	Minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage
2	Deeper ulcer with exposed bone, joint, or tendon; generally not involving the heel; shallow heel ulcer, without calcaneal involvement	Limited to digits	Major tissue loss salvageable with multiple (≥ 3) digital amputations or standard TMA + skin coverage)
3	Extensive, deep ulcer involving forefoot and/or midfoot; deep, full thickness heel ulcer + calcaneal involvement	Extensive gangrene involving forefoot and/or midfoot; full thickness heel necrosis + calcaneal involvement	Extensive tissue loss salvageable only with complex foot reconstruction or nontraditional foot amputation (Chopart, Lisfranc); flap coverage or complex wound management needed for large soft tissue defect

Wound Grade Definitions

Grade	Ankle Brachial Index	Ankle Systolic Pressure	Toe Pressure/TcPO ₂
0 (none)	≥ 0.8	> 100 mmHg	≥ 60 mmHg
1 (mild)	0.6-0.79	70-100 mmHg	40-59 mmHg
2 (moderate)	0.4-0.59	50-70 mmHg	30-39 mmHg
3 (severe)	$\leq .39$	< 50 mmHg	< 30 mmHg

If ABI is incompressible (> 1.3) then use toe pressure or TcPo₂ measurements. In patients with diabetes toe pressures should be measured. If arterial classification precludes reliable ABI/ankle pressure measurements then ischemia should be documented using toe pressures, TcPO₂, or PVR. If toe pressure and ABI measurements result in different grades then toe pressures will be the primary determinant of grade. Flat forefoot PVR + grade 3.

Infection Grade Definitions

Grade	Clinical Manifestation	Severity
0	No symptoms or signs	Uninfected
1	Infection defined by at least 2 of the following: - Local swelling or induration - Erythema $> .5$ cm to ≤ 2 cm around ulcer - Local tenderness or pain - Local warmth - Purulent discharge	Mild

	Local infection involving only the skin and the subcutaneous tissue (without involving the deeper tissues and without systemic signs)	
2	Location infection (as defined above) with erythema > 2cm, or involving structures deeper than the skin and subcutaneous tissues (i.e. abscess, osteomyelitis, septic arthritis, fasciitis) and no systemic inflammatory response signs	Moderate
3	Local infection (as described above) with signs of SIRS, as manifested by two or more of the following; • Temperature > 38°C or < 36°C • Heart rate > 90 beats per minute • Respiratory rate > 20 breaths/min or PaO₂ < 32 mm Hg • White blood cell count > 12,000 or < 4,000mm³ or 10% immature (band) forms.	Severe

Appendix 3: 6-MINUTE WALK INSTRUCTIONS

Description: The 6-minute walk is a simple test for assessing exercise capacity as a measure of functional status. It also reflects the normal daily activity levels of patients.

Equipment Needed:

- Watch or clock with second hand
- Chairs
- Tape measure
- Tape
- 6-Minute Walk Worksheet and pen

Preparation:

1. Six minute walks will be administered by a registered RN or LPN, a study coordinator, or a trained exercise technician using a standardized approach using a 100 foot (30m) straight distance* in an enclosed corridor with a chair placed at each end of the course. Patients will be allowed to use any mobility aids they traditionally use. Patients will be instructed to walk from end to end at their own pace while attempting to cover as much ground as possible in the six minutes.
2. Provide patient teaching. Explain the test to the patient by using the suggested wording below. Answer any questions the patient may have.

*Ideally, you should use a 100 foot straight distance for the 6MWD. The minimum distance used should be 82 feet (25m). Regardless of the course used, the same course should be used for each test whenever possible.

Conducting the 6-Minute Walk Test:

1. Escort the patient to the start of the course. Show the patient the walking course and ask the patient to begin walking as you begin keeping time. Stay with the patient for the entire walk test and record the number of completed laps.
2. Provide encouragement to the patient. At 30 second intervals, encourage the patient using the examples provided below. Notify the patient when 2, 4, and 6 minutes (stop) have elapsed and what the remaining time is. Patients will be allowed to slow or stop and rest during the walk, but will be asked to resume walking as soon as they feel able. After 6 minutes, the distance walked will be measured to the nearest meter. Vital signs (heart rate and BP) will be obtained before and immediately after the test in the sitting position. Patients will indicate symptoms limiting the ability to walk during the test (angina, lightheadedness, syncope, dyspnea, fatigue, leg or joint pain, instability, other, none) and these should be recorded on the 6-Minute Patient Walk Worksheet.
3. Stop the test after 6 minutes. Mark the floor where the patient stops with a piece of tape.
4. Determine the total distance walked. Multiply the number of laps by the distance of each lap (round to the nearest meter). Add this figure to the distance covered in the last partial lap. Record the distance.

Suggested explanation of the 6-minute walk:

"The purpose of this test is to find out how far you can walk in 6 minutes. You will start from this point and walk back and forth between the two markers I showed you. You will go back and forth as many times as you can in the 6- minute period. If you need to, you may stop and rest. Just remain where you are until you can go again. However, the most important thing about the test is that you cover as much ground as you possibly can during the 6 minutes. I will tell you the time and I will let you know when the 6 minutes are up. When I say "stop", please stand right where you are."

"The aim at the end of the 6 minutes is for you to feel that you couldn't have covered more ground in the time provided. I will stay with you as you walk. We won't talk while you walk because this could affect your performance. I will say some things to you periodically, such as how much time is left."

"Please let me know if you are uncomfortable or have pain. The idea is for you to walk at a comfortable pace, but for you to cover as much ground as possible in the 6 minutes. Are you ready?"

To start: *"Begin walking"*

0:30 second intervals: *"You're doing well"... "keep up the good work"... "good job"...
"you're doing fine"*

2 minutes: *"You have been walking 2 minutes." "You have 4 minutes left to walk."*

4 minutes: *"You have walked 4 minutes." "You have 2 minutes left to walk."*

6 minutes: *"Stop."*

Encouragement statements if subject is resting:

1 minute: *"It's been ____ minutes. Rest as long as you need and let me know when we can get started again."*

2 minutes: *"____ minute(s) are left in the test. You can keep resting or begin walking again when you feel able."*

Repeat the last statement each minute if the subject continues to rest.

APPENDIX 4: BEST-CLI TELEPHONE SCRIPTS

INSTRUCTIONS TO INTERVIEWER

TEXT IN UPPERCASE CONTAINS INSTRUCTIONS FOR THE INTERVIEWER.
UNDERLINED TEXT INDICATES CALL-SPECIFIC INFORMATION. REVIEW ONGOING ADVERSE
EVENT REPORTS PRIOR TO TELEPHONE CONTACT.

ADVERSE EVENT REPORTING INSTRUCTIONS

AS A REMINDER, ALL SERIOUS ADVERSE EVENTS (SAEs) MUST BE DOCUMENTED ON THE
APPROPRIATE eCRF. SITE STAFF MUST NOTIFY THE DCC OF ANY SAEs BY COMPLETING
THE eCRF WITHIN 24-HOURS OF LEARNING OF THE EVENT. A SEPARATE FORM MUST BE
USED FOR EACH ADVERSE EVENT.

MONTH 30,42, 54, 66 and 78 TELEPHONE VISIT SCRIPT

INTRODUCTION TO TELEPHONE INTERVIEW

***Hello, my name is [your name] and I am calling from [name of your clinic].
Is [name of subject] available?***

IF NO, ASK FOR BETTER TIME TO CALL BACK AND NOTE ON CONTACT RECORD.
IF YES, CONTINUE.

I'm calling regarding your participation in the BEST-CLI Trial. I am calling you today to ask you a few questions about how you have been feeling and what medications you are taking. This should take about 15 to 30 minutes to complete depending on your responses. Is it OK to discuss this now?

IF NO, ASK FOR BETTER TIME TO CALL BACK AND NOTE ON CONTACT RECORD.
IF YES, READ CONFIDENTIALITY STATEMENT, AND THEN GO TO THE MEDICAL PROBLEM QUESTIONS

CONFIDENTIALITY STATEMENT

THE STATEMENT BELOW MUST BE READ TO ALL INTERVIEWS BEFORE EVERY TELEPHONE INTERVIEW.

Before we begin let me remind you as a mandatory part of all calls that all information is strictly confidential and that your name will not be used in any reports. Please answer each question as best as you can. This interview is completely voluntary and will not affect your medical care. You may decide to stop the interview at any time. If there is a question that you cannot or do not wish to answer, please tell me and I will go on to the next question. If you have any questions or concerns about this interview, you may call the Principal Investigator, [name of PI], at [PI telephone number]. If you have any questions about your rights as a research subject, you may call [IRB contact] of [name of site's] Institutional Review Board at [IRB telephone number].

I'd like start by asking you about medications you are currently taking. Do you have those medications?

IF RESPONDENT DOES NOT HAVE THEM: ***Could you please get them and bring them to the phone?***

Please look at the medication bottles you have brought to the phone. For each medication, please tell me the name of the medication and the total daily dose that you are taking. This information should be listed on the container.

COMPLETE MEDICATION eCRF FOR EACH MEDICATION.

MEDICATION: _____	TOTAL DAILY DOSE: _____
MEDICATION: _____	TOTAL DAILY DOSE: _____
MEDICATION: _____	TOTAL DAILY DOSE: _____
MEDICATION: _____	TOTAL DAILY DOSE: _____

MEDICATION: _____

TOTAL DAILY DOSE: _____

Now I would like to ask you some questions about how you have been feeling and whether you have seen any doctors since your last visit on [date of last visit]. Since your last visit have you:

1. Been admitted to the hospital?		☐ Yes	☐ No	☐ Don't Know	
1a. IF YES: How many times?		_____			
2. Been seen in an Emergency Department?		☐ Yes	☐ No	☐ Don't Know	
2a. IF YES: How many times?		_____			
3. Had any of the following tests or procedures done (other than when you were in the hospital)?					
Test	Yes	No	How Many?	Dates	Locations
a. Tracheostomy	☐	☐	_____	_____	_____
b. Feeding tube	☐	☐	_____	_____	_____
c. Gastrointestinal endoscopy	☐	☐	_____	_____	_____
d. Cardiac catheterization	☐	☐	_____	_____	_____
e. CT Scan	☐	☐	_____	_____	_____
f. MRI	☐	☐	_____	_____	_____
g. Ultrasound	☐	☐	_____	_____	_____
h. Echocardiogram	☐	☐	_____	_____	_____
i. Cardiac stress test	☐	☐	_____	_____	_____
j. Physical therapy	☐	☐	_____	_____	_____
k. Dialysis	☐	☐	Start date: _____	Stop date: _____	_____
4. Gone to see a doctor for an appointment?		☐ Yes	☐ No	☐ Don't Know	
4a. IF YES: How many times?		_____			
5. Used any outpatient rehabilitation services?		☐ Yes	☐ No	☐ Don't Know	
5a. IF YES: About how many hours?		_____			
6. Used any long-term care or inpatient rehabilitation/skilled nursing care services?		☐ Yes	☐ No	☐ Don't Know	
6a. IF YES: How many days were you an inpatient?		_____			
7. Missed any hours of work because of doctor visits, tests or days in the hospital?		☐ Yes	☐ No	☐ Don't Know	
7a. IF YES: About how many hours?		_____			

8. Received any care from family or friends?	☐ Yes	☐ No	☐ Don't Know	
5a. IF YES: About how many hours?				

IF SUBJECT SEEN IN THE ED OR ADMITTED TO A HOSPITAL, ASK THE FOLLOWING QUESTIONS 1-5 FOR EACH HOSPITAL ENCOUNTER:

Now I would like to ask you some questions about the times you were seen in the Emergency Department or were admitted to the hospital:

1. Where were you seen (name of facility)?				
2. Please describe what happened and what part of your body was affected?				
3. When did the problem, symptom, or illness begin?	___ / ___ / ___ (mm/dd/yyyy)			
4. Did you receive any treatment for this problem?	☐ Yes	☐ No	☐ Don't Know	
5. Are you still experiencing [problem]?	☐ Yes	☐ No	☐ Don't Know	
5a. IF YES: Has the problem:	☐ Improved	☐ Worsened	☐ Stayed the same	
5b. IF NO: When did the problem stop?	___ / ___ / ___ (mm/dd/yyyy)			

ONCE ALL HOSPITAL ENCOUNTERS ARE DOCUMENTED, ASK THE FOLLOWING:

6. Did you have any other problems, symptoms, or illnesses that we have not talked about?	☐ Yes	☐ No	☐ Refused	☐ Don't Know
---	------------------------------	-----------------------------	----------------------------------	-------------------------------------

IF YES: REPEAT QUESTIONS 1-5 ABOVE FOR EACH PROBLEM AS APPROPRIATE. IF NO, GO TO END SCRIPT.

ADVERSE EVENT FOLLOW-UP QUESTIONS

REVIEW PREVIOUSLY REPORTED ADVERSE EVENTS. IF THERE ARE NO ONGOING EVENTS GO TO THE END SCRIPT. IF THERE ARE ONGOING EVENTS, REVIEW EACH EVENT WITH THE SUBJECT/CONTACT.

I would like to ask you about medical problems that were still going on since a previous study visit.

ASK THE FOLLOWING QUESTIONS FOR EACH ONGOING EVENT.

1. Are you still experiencing [problem]?

IF YES: Has the problem:

☐ Improved ☐ Worsened ☐ Stayed the same

IF NO: When did the problem stop?

2. What was done to treat the problem?

3. Was a doctor seen to treat this problem?

4. Where were you treated (doctor's office, hospital visit, ER, etc.)

USE THIS INFORMATION TO COMPLETE A FOLLOW-UP ADVERSE EVENT FORM. ONCE ALL EVENTS ARE REVIEWED, GO TO THE END SCRIPT

END SCRIPT

The next time we speak with you will be for your in-person study visit in about 6 months on [date of next visit]. IF SUBJECT HAS NOT SCHEDULED THE NEXT IN-PERSON VISIT YET: Are you able to schedule your appointment now for around [approximate date of next visit]?

IF SUBJECT IS UNABLE TO SCHEDULE HIS/HER APPOINTMENT AT THIS TIME, ARRANGE FOR A TIME TO CONTACT THEM IN ORDER TO SCHEDULE THE VISIT.

As always, please feel free to contact me at [telephone number] if you have any ill effects, or have any questions or concerns. Thank you for your time today.

QUESTIONNAIRE SCRIPT

INTRODUCTION TO QUESTIONNAIRE INTERVIEW

***Hello, my name is [your name] and I am calling from [name of your clinic].
Is [name of subject] available?***

IF NO, ASK FOR BETTER TIME TO CALL BACK AND NOTE ON CONTACT RECORD.
IF YES, CONTINUE.

I'm calling regarding your participation in the BEST-CLI Trial. I am calling you today to ask you to answer some questions about your health. This should take about 30 minutes to complete depending on your responses. Is it OK to discuss this now?

IF NO, ASK FOR BETTER TIME TO CALL BACK AND NOTE ON CONTACT RECORD.
IF YES, READ CONFIDENTIALITY STATEMENT, AND THEN GO TO THE QUESTIONNAIRES

OPTIONAL SCRIPTS

ANSWERING MACHINE SCRIPT (IF LEAVING A MESSAGE ON AN ANSWERING MACHINE)

Hello, this is [your name] calling from [name of your clinic] regarding the BEST-CLI Study. If you would like to contact me, I can be reached at [your phone number] between the hours of [time for interviewee to call back]. Thank you.

TRACKING SCRIPT (IF CALLING A CONTACT PERSON IN ORDER TO LOCATE A SUBJECT)

I'm calling from [name of your clinic] regarding a research study that [name of subject] is participating in. [Name of subject] gave me your name in the event that I was unable to reach [him or her] at the time of our next scheduled telephone interview. Would you be able to give me any updated contact information for [name of subject] today?
IF NO: ***Can you take a message for [name of subject]? My name is [your name] calling from [name of your clinic] regarding the BEST-CLI Study. I can be reached at [your phone number] between the hours of [time for interviewee to call back].***

Thank you.

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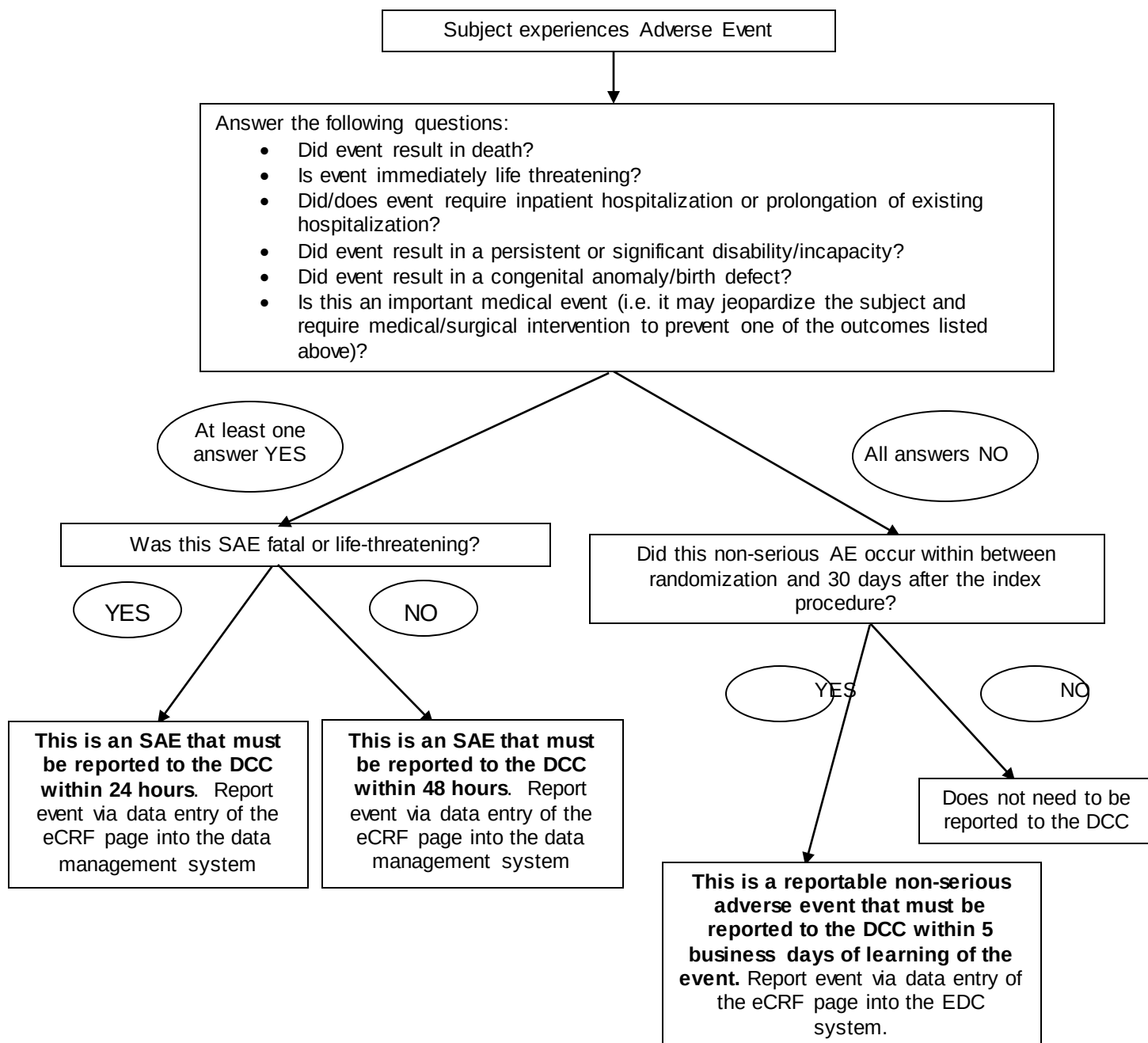
Chapter 6

ADVERSE EVENT REPORTING

6.0 Adverse Event Reporting

This section serves to discuss in further detail the Adverse Event section of the BEST-CLI protocol.

6.1 Adverse Event (AE) Reporting Flow and Reporting Timelines



6.2 AE Definition

An adverse event is any untoward/unfavorable medical experience occurring in a subject during participation in a clinical trial whether or not it is related to the procedure or device. An adverse event may include a concurrent illness, injury, or any other concomitant impairment of the subject's health, as well as abnormal laboratory findings if deemed to have clinical significance. Adverse events may also include worsening of an existing symptom or condition or post-treatment events that occur as a result of protocol-mandated procedures.

An Adverse Event (AE) may be a disease, a set of related symptoms or signs, or a single symptom or sign (including an abnormal laboratory finding). Note: While a procedure (e.g. PTA), action (e.g. hospitalization), or outcome (e.g. death) are considered AEs, they should not be listed as the AE term. Only signs, symptoms, or disease should be listed as the AE term.

For purposes of this trial, non-serious AEs will be collected only from randomization through 30-days after the index procedure.

Investigators must record all non-serious AEs in this time frame into the electronic data capture (EDC) system within 5 working days from learning of the event. All serious adverse events (SAEs), Unanticipated Adverse Device Effects (UADEs), or Unanticipated Problems (UPs) must be reported as outlined the sections below.

Adverse events information to be recorded will include the date and time of first occurrence, severity, and duration, as well as any treatment prescribed. Following randomization, all new adverse events that were not present at enrollment will be recorded. Any medical condition present at the initial visit, which remains unchanged or improves, will not be recorded as an adverse event at subsequent visits. However, *worsening of a medical condition that was present at the initial visit will be considered a new adverse event* and reported if it occurred within 30-days post-randomization. Abnormal laboratory values, if felt by the investigator to be clinically significant, will also be recorded on the AE Form and assessed in terms of severity and relationship to procedure/device. Laboratory values that are abnormal at study entry and that do not worsen will not be recorded on the AE Form, unless the same abnormality resolves and then recurs between randomization and 30 days after the index procedure. AEs are automatically reported to the DCC when the sites complete the AE Form in the EDC system. For patients who are hospitalized, the patient's discharge disposition (i.e. home, transfer to another hospital, short term rehabilitation, long term care facility or death) must also be recorded.

6.3 Serious Adverse Event (SAE)

A SAE is defined by regulation as any untoward medical occurrence or effect 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);
- results in 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, major safety finding from a newly completed animal study).

For purposes of the trial, serious AEs will be collected from the time of subject consent through the remainder of the subject's participation in the trial.

As well, an inpatient hospitalization will be defined as any admission to the hospital with at least one (1) overnight stay, even if the subject is considered to be under "observation" status for the purpose of billing or if the subject physically remains in an emergency department while waiting for a ward or ICU bed. Subjects who remain in an emergency department, even with an overnight stay, but who are not actually admitted (under observation or inpatient status) are not considered to have been hospitalized.

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.

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and require medical/surgical intervention to prevent one of the outcomes listed above.

Regarding reporting timelines, 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. SAEs are automatically reported to the DCC when the sites complete the AE Form in the EDC system. For fatal and life-threatening SAEs, the Site Principal Investigator (PI) must also electronically sign all SAEs forms within the 24-hour period (48 hours for all other SAEs).

6.4 Unanticipated Adverse Device Effect (UADE)

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

UADEs may occur in subjects undergoing endovascular treatment of CLI during the index procedure or a later procedure, for which a device is used as a part of treatment.

All UADEs must be reported in the EDC system within 24 hours of learning of the event. Clinic sites must report all UADEs to the DCC within 24 hours. UADEs are automatically reported to the DCC when the sites complete the AE Form in the EDC system. The Site PI must also electronically sign all UADEs within the 24-hour period.

6.5 Unanticipated Problem (UP)

An Unanticipated Problem 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, the investigators brochure, 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)

All UPs must be reported in the EDC system within 24-hours of learning of the event. UPs are automatically reported to the DCC when the sites complete the AE Form in the EDC system. The Site PI must also electronically sign all UPs within the 24-hour period.

6.6 Causality/Relatedness Assessment of AEs

For all AEs, the Investigator will make an initial determination of the causality of the AE. Causality assessment is the determination of whether there exists a reasonable possibility that the endovascular device or surgical procedure caused or contributed to an AE. If the determination of causality is unknown because the reviewer does not know whether or not the device or procedure caused the AE, then the AE will be handled as “related to device” or “related to procedure” for reporting purposes. If the final determination of causality is “unknown but not related to device”, this information should be clearly documented on trial records.

In addition, if the Investigator determines an SAE is associated with trial procedures, 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.

Causality is categorized as definitely-, probably-, possibly, or not- related to the endovascular device or surgical procedure:

- Not Related Event clearly related to other factors (e.g., clinical state, other therapies; concomitant drugs)
- Possibly Related Sequence of events is compatible with the device or procedure, but could have been produced by other factors as above
- Probably Related Sequence of events is compatible with the device or procedure and cannot be explained by other factors as above without much doubt
- Definitely Related Sequence of events is compatible with the device or procedure and beyond doubt cannot be explained by other factors as above

6.7 Severity/Intensity Assessment of AEs

Severity describes the intensity of a specific event:

- Mild - Symptom(s) barely noticeable to the subject or does not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
- Moderate - Symptom(s) of a sufficient severity/intensity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.
- Severe - Symptom(s) of a sufficient severity to cause the subject severe discomfort. Severity may cause cessation of treatment with the device (e.g. explant) or additional procedures (e.g. further endovascular or surgical intervention). Treatment for symptom(s) may be needed.

6.8 Documentation of Adverse Events

Any AEs, SAEs, UADEs, or UPs occurring during the study must be documented in the subject's source documents and on the appropriate CRF page. Information relating to the adverse event such as onset and cessation date and times, intensity, seriousness, relationship to study drug, and outcome is also to be documented in the CRF. Adverse events should be recorded using standard medical terminology. If several signs or symptoms are clearly related to a medically defined diagnosis or syndrome, the diagnosis or syndrome should be recorded on the CRF page, not the individual signs and symptoms.

All adverse events should be followed until resolution (or return to normal or baseline values), stabilization, or until they are judged by the investigator to no longer be clinically significant, whichever occurs first. All SAEs occurring during the study will be followed until resolution, stabilization, death, or subject withdrawal. Supplemental measurements and/or evaluations may be necessary to investigate fully the nature and/or causality of an adverse event or SAE. This may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. Additional CRF pages should be added to report any new or additional information as appropriate.

6.9 Institutional Review Board or Ethics Committee Reporting

Sites should follow their local or central IRB/EC adverse event reporting requirements. In addition to local reporting procedures, the Office of Human Research Protection (OHRP), DHHS issued a memorandum dated November 10, 2010, Guidance on Continuing Review (<http://www.hhs.gov/ohrp/policy/continuingreview2010.html>), which authorizes IRBs or ECs to rely on current statements from a DSMB monitoring a study. The statement will inform each participating center IRB or EC that the DSMB has reviewed study-wide adverse events, interim findings and any recent literature that may be relevant to the research.

In addition, the FDA issued Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Report to IRBs – Improving Human Subject Protection in January 2009 (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126572.pdf>). Section IV Reporting AEs to IRBs in Clinical Trials of Devices under the IDE Regulations specifies that all UADEs must be reported by the clinical investigator to the sponsor (in this case the DCC on behalf of the sponsor) and the reviewing IRB.

The DCC will report all events (AEs, SAEs, UADEs, and UPs) to the FDA and DSMB, during the required timeframes, as applicable. Unanticipated problems will be reported by the DCC to NHLBI, as per their requirements.

6.10 BEST-CLI Trial Hotline

For all study related medical questions (i.e. inclusion/exclusion questions, safety questions), please contact the BEST-CLI Trial Hotline via the toll free number, 844-237-8120. *The BEST-CLI Hotline is available - 24-hours a day, 7-days a week.* A member of the CCC will respond within 60 minutes.



BEST-CLI Manual of Operations

Chapter 7

DATA MANAGEMENT AND DATA FLOW

7.0 DATA MANAGEMENT AND DATA FLOW

7.1 ECLINICAL OS (ECOS): AN OVERVIEW

The BEST-CLI study will use eClinicalOS (eCOS), a web based electronic data capture (EDC) system owned and operated by IBM Clinical Development., eCOS is a fully integrated product suite including EDC, eDiary, Interactive Voice and Web randomization (IVR/IWR) and a Clinical Imaging Management System. eCOS can be used in a manner that is compliant with 21CFR11, FDA Guidance to Industry, HIPAA and EU Privacy regulations.

Among the many benefits of this system, eCOS allows sites with browser-equipped PCs or Macs to enter data directly onto the computer. Using eCOS, sites are able to view the status of all of their patients, and thus able to determine at the click of a mouse what forms are outstanding or incomplete. eCOS uses electronic case report forms, called pages, eliminating the need for paper forms.

No data is directly stored at NERI from eCOS. All data are stored in data bases at Merge's hosting facility. Five levels of security are provided at PEAK-10 – eClinicalOS' hosting facility. They include:

- Level 1: Proximity card access with PIN to enter the building (does not grant access to the data center)
- Level 2: Proximity card access with biometric scan required to enter the data center
- Level 3: Hardware is located in a secure cage or locked cabinet
- Level 4: Video surveillance throughout the facility
- Level 5: Staffed 24x7x365

Additionally, access to study data is only allowed via NERI approved users.

During the entry of pages, when saving, eCOS performs validity checks on each field, and the user is immediately notified of any out of range values or incomplete responses. As a result, the user has the option to respond to any edits on the spot, while the patient's medical record is in front of him or her, rather than waiting for paper edit reports to be generated and sent out by the Data Coordinating Center. Additional manual queries can be added as needed by the DCC data manager or CRA to address items found during external data cleaning, which can be resolved in eCOS in a similar manner to automatic queries.

7.2 GETTING STARTED: HARDWARE & SOFTWARE RECOMMENDATIONS

eClinical OS is designed to run on the majority of operating systems and browsers in addition to those listed below. Additional software may be required to use information downloaded or exported from the system, including Adobe Reader and Microsoft Excel.

eClinical OS is designed to run on the majority of operating systems and browsers in addition to those listed below:

- Internet Explorer (IE), version 8.0+
- Firefox, version 3.6+
- Chrome

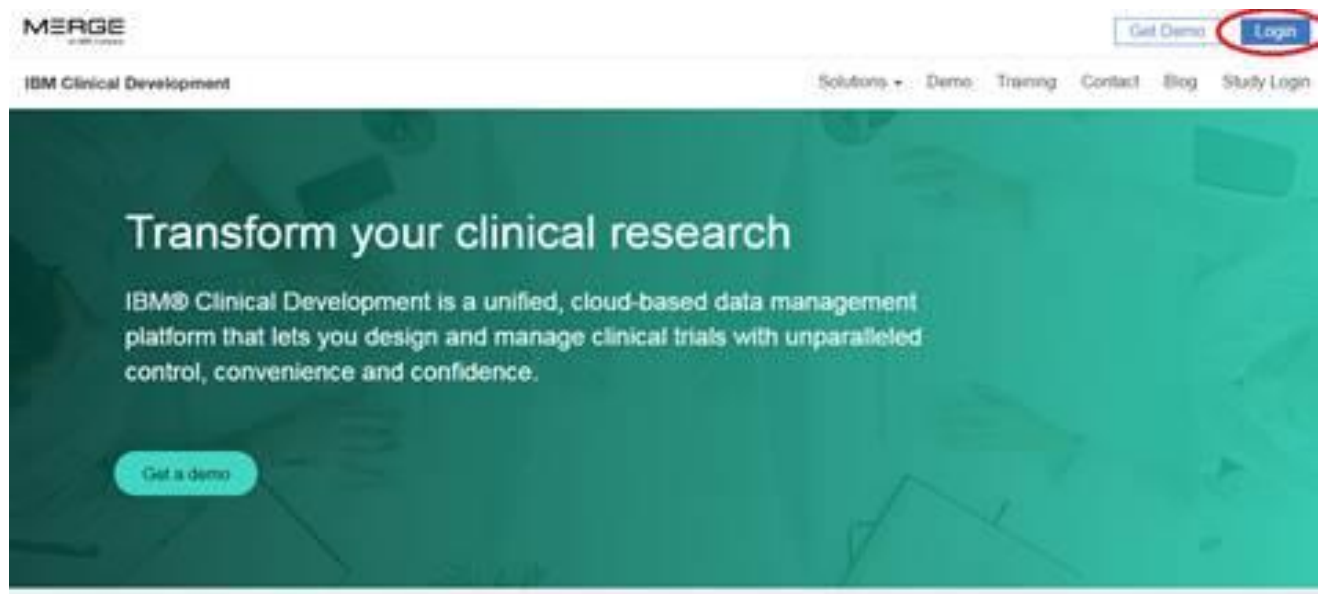
NOTES: eClinical OS does not block access using other Browsers or using older versions of the supported browsers; however, certain features may not behave as expected.

7.3 ACCESSING ECLINICAL OS

There are two steps to gaining access to eCOS. The first is to file a Data Access Authorization form with the DCC. The Data Access Authorization form must be completed for all staff needing access to the study database. This will be provided by the study Data Manager or CRA.

Next create an eCOS user account by going to the eCOS website at <https://eclinicalos.com>.

Figure 1: eClinical OS Login Pages



Select “LOGIN” and then “Sign up for free” on the login page.

Figure 2: Login Page

Secure Login

Please enter your eClinicalOS Username and Password to continue.

User ID

Password

Select Language: English (United States)

LOGIN TO ECOS

Need Help?

Forgot your password?

Need help logging in?

Don't have an account?

Create a user account, log in and request access to a study.

SIGN UP

eClinicalOS is now
IBM Clinical Development

HOME

Secure Login

Existing Users

Please enter your Username and Password to continue.

User ID

Password

Logout Successful

Forgot your password?

Language: English (United States)

LOGIN

Need help logging in?

Don't have an account?

Create a user account, log in and request access to a study.

SIGN UP

Start a sandbox trial and experience IBM Clinical Development firsthand. [Get Started Now](#)

NEED HELP?

Contact Support 24/7/365 days a year.

Phone: 888.500.4247 or International

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Complete all the setup screens including name, company, contact information, and security questions (Figure 3). Your user ID should be your first initial followed by last name, or first and second initial followed by last name. User your business email address, not a personal email address.

Click on the "Register" button to finalize your new account. eCOS will email confirmation of your username and a temporary password.

Figure 3: eClinical OS Initial New User Registration Screens

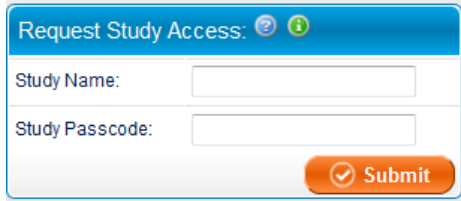
Once you complete the registration process you will receive an email from eCOS with login information. Upon logging in with your user ID and temporary password you will be asked to create your own password. The User ID and password combination is also used as an electronic signature in compliance with 21 CFR part 11. Please note that for security reasons, ***your password must be changed every 90 days*** or your login will expire.

Upon logging in you will be brought to the eCOS Landing Page. From this page you can access eCOS training materials, request access to specific studies and go to data for studies you already have access to.

Figure 4: eClinical OS Landing Page

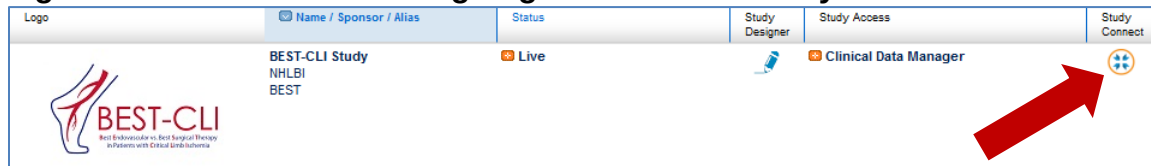
To request access to a specific study, navigate to the “Request Study Access” box and submit the “Study Name” and “Study Passcode” provided to you by the Data Coordinating Center.

Figure 5: eClinical OS Request Study Access window

A screenshot of a web form titled "Request Study Access:". It features two input fields: "Study Name:" and "Study Passcode:". Below these fields is an orange "Submit" button with a checkmark icon. The form has a blue header bar with a question mark and an information icon.

An email will be sent to the Data Coordinating Center alerting them about your request. You will receive an email once your account has been approved. Clicking on the “Study Connect” button will bring you to the Home Screen of your study.

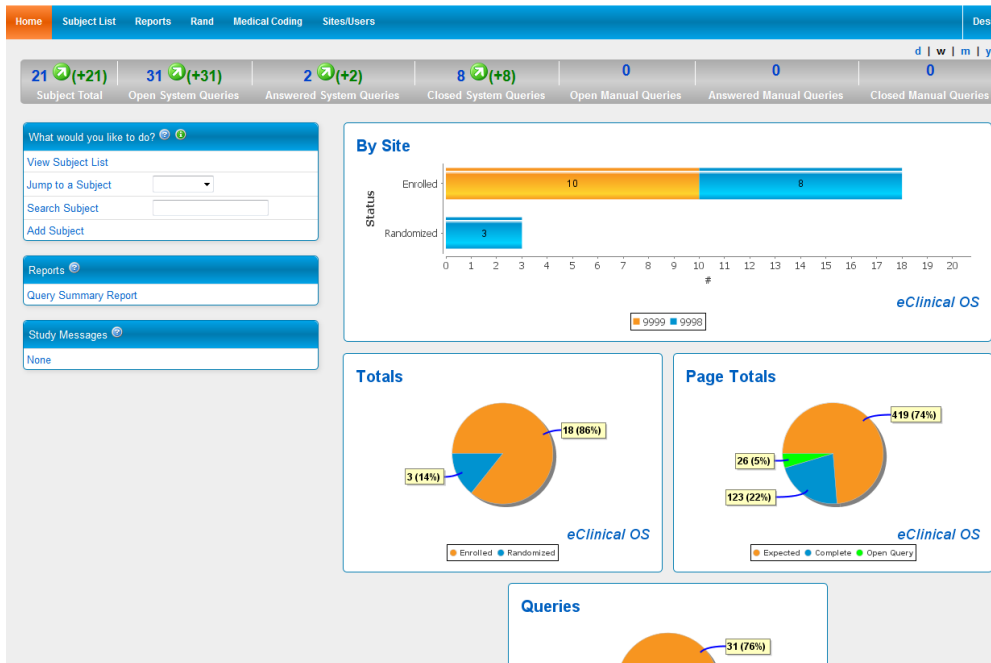
Figure 6: eClinical OS Landing Page – BEST-CLI Study Connect Icon



7.4 HOME SCREEN

Once you have successfully logged in, you will see the following on the home screen:

Figure 7: BEST-CLI eClinical OS Home Screen



The Home Screen consists of the following items:

- Blue Study Menu bar
- Grey Status Counts bar
- Actions Menu
- Study Reports and Diagrams
- Study Messages

Please note that you may return to the Home Screen at any time by clicking on “Home”, which will always be displayed at the top of the screen in the blue menu bar.

7.5 DATA MANAGEMENT SYSTEM (DMS) DESIGN AND SUBJECT DATA ENTRY

The DMS has been organized into a set of categories called “Visits.” These are the BEST-CLI Visit Categories):

- Screening
- Baseline
- Index Procedure
- 30 Days Post Procedure
- 3 Months
- 6 Months
- 12 Months
- 18 Months
- 24 Months
- 30 Months
- 36 Months

- 42 Months
- 48 Months
- 54 Months
- 60 Months
- 66 Months
- 72 Months
- 78 Months
- 84 months
- Addable Pages
- End of Study
- Adverse Event

Visits are displayed across the top of the grid. Data collection pages are displayed down the left side. To see an example of the subject grid, please see MOO, Chapter 5.

7.5.1 ADDING A NEW SUBJECT

Once a potential subject has been identified by medical record review or physician referral **AND** the patient has signed the Informed Consent Form (ICF) per proper study procedures, the subject may be added to the eCOS system and assigned a Study ID number. To add a new subject, click the Add Subject link from left menu on the Home Screen.

The Add Subject window will appear, automatically assigning the next sequential ID number at your site. The currently approved revision of the study will also be selected. Click “Add” to confirm the subject.

Figure 9: Add Subject Screen

Add Subject ?	
Site:	9999
Site Name:	New England Research Institutes
Number / Identifier:	9999006
CRF Revision:	1 -- Initial revision of study *
☐ (Remain at this screen to add more)	

7.5.2 DATA ENTRY

Adding a new subject will bring you to the main “Subject Grid” screen where all subject visits and forms will be displayed. You can also get to this screen by choosing a study ID number from the “View Subject List” or “Jump to a Subject” on the home screen or selecting a subject ID from the “Subject List” link at the top of the screen in the blue menu bar.

The Subject Grid will show available subject visits across the top and the list of available pages down the left column. The subject’s current status in the study will also be listed in

the top left corner of the grid. Data entry and data editing is accessed by clicking on the page status icon.

Figure 10: Subject Grid Screen

Home Subject List Reports Rand Medical Coding Sites/Users Designer

Subject 9998012 Reports Queries (0) Links / Attachments (0) Statuses Information

Subject 9998012: Grid Tree | Add Visit

Status: Initial Entry SCRN

General Information E

For new subjects, select “E” (Expected) next to the General Information page in the Screening visit (“SCRN”) and complete the page. Once this page is completed the Informed Consent page will appear, followed by the Inclusion Criteria, Exclusion Criteria, Vein Mapping and Randomization pages based on data entry of previous pages. Data entry is done by entering text or numeric values in each field, or selecting the correct choice from radio buttons or selection lists. Additional help text may be available on the screen or by hovering over any green information icon ⓘ. Use “Tab” or your mouse to go to the next field. New fields may appear based on data in previous fields. Click “Save” or “Save/Next” to save the data.

Figure 11: Data Entry Screen

Inclusion Criteria	
Section A: General Information	
A1. Subject ID	(9999999)
Section B: Inclusion Criteria	
B1. Male or female, age 35 years or older.	☐ Yes ☐ No
B2. Atherosclerotic, infrainguinal Peripheral Artery Disease (PAD)	☐ Yes ☐ No
B3. Critical Limb Ischemia (CLI), defined as arterial insufficiency with gangrene, non-healing ischemic ulcer, or rest pain consistent with Rutherford categories 4, 5 or 6.	☐ Yes ☐ No
B4. Candidate for both open and endovascular infrainguinal revascularization as judged by the treating investigator.	☐ Yes ☐ No
B5. Adequate aortoiliac inflow	☐ Yes ☐ No
B6. 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.	☐ Yes ☐ No
B7. Willingness to comply with protocol, attend follow-up appointments, complete all study assessments, and provide written informed consent.	☐ Yes ☐ No
All Inclusion Criteria Met:	(auto calculated) (9)
Save Save / Next	

7.6 RANDOMIZING A SUBJECT

Once all of the necessary screening pages have been entered (General Information, Informed Consent, Inclusion Criteria, Exclusion Criteria, Vein Mapping, and Randomization) and the subject is determined to be eligible, the subject can be randomized. Randomization is done as a special Subject Status change.

After data entering the Randomization page, click the subject ID number on the gray toolbar to go to the Subject Grid screen and select the blue “Randomized?” hyperlink:

Figure 12: Randomized? Subject Status Link

Subject 9998003: Grid			
Status: Enrolled	ENRL	SCRN	BASE
>> Randomized?			
General Information			
Informed Consent			
Inclusion Criteria			

Review the confirmation screen and click “GO.”

Figure 13: Special Status Move Confirmation Screen

Special Status Move	
Subject:	9998003
Current Status:	Enrolled
Move To:	Randomized
Notes:	• This action will Randomize the Subject. • This action is NOT typically reversible, please ensure it is desired at this time.
Go Cancel	

If randomization is successful, eCOS will bring you to the Information page for that subject and the status will be listed as “Randomized.” To view the randomization treatment arm you will have to click on the “View Unblinding Information” button.

Figure 14: Information Page for Randomized Subject

Subject 9998003: Subject Information:

Site:	9998 -- Test Site
Number / Identifier:	9998003
Status:	Randomized
Randomization #:	6
Marked Deleted?	No

View Unblinding Information

Subject 9998003: Unblinding Information

Stratification Group:	2-I
Randomization:	ENDO

OK

IMPORTANT: Randomization is contingent upon the subject meeting study eligibility requirements and screening data entry being complete. Please contact study staff for assistance if you receive an error message or have difficulty during the randomization process.

7.7 POST-RANDOMIZATION FOLLOW-UP VISITS AND TRIGGERS

Once the screening data have been entered and the subject's randomization eligibility has been determined, the Baseline and Index Procedure Visits will be triggered. The Procedure Details pages and subsequent post-procedure visits will be triggered upon data entry of specific pages.

7.7.1 PROCEDURE DETAILS PAGE TRIGGERS

In order to trigger the page needed to data enter the subject's index procedure details, the Index Procedure Summary Page will need to be entered first. The responses on this page will trigger the Open Surgical Procedure Details Page or the Endovascular Procedure Details Page. Data entry of the Index Procedure Summary Page will also trigger the next visit, "30 Days Post-Procedure."

Figure 15: Index Procedure Summary Page

Status: Randomized 	SCRN	BASE	INDEX	EOS
General Information				
Informed Consent				
Inclusion Criteria				
Exclusion Criteria				
Vein Mapping				
Randomization				
Demographics				
Angiogram				
Medical history				
Vital Statistics				
Vascular Physical Assessment				
Peripheral Vascular History				
Hemodynamic Assessment and Arterial Duplex				
Laboratory Results				
Medications				
VascuQOL				
SF-12				
EQ-5D				
Pain Scale (NRS)				
Six-minute Walk Test				
Index Procedure Summary				
Device Accountability				
Hospitalization/ED Encounter				
Study Status Change Information				
Health Care Utilization				

7.7.2 VISIT INFORMATION PAGE AND POST-PROCEDURE VISIT TRIGGERS

In order to trigger the pages within a post-procedure visit, the Visit Information Page must be entered first. This page will collect information on whether the visit was completed, and if any data was collected if the visit was missed. If the visit was completed or if partial data was obtained, the remaining pages within the visit will be triggered.

Data entry of the Visit Information Page will also trigger the next visit on the subject grid. For example, data entry of the Visit Information Page under the “30 Days Post-Procedure” visit will trigger the subsequent “3 Months” visit; data entry of the Visit Information Page under the “3 Months” visit then will trigger the “6 Months” visit and so on.

Figure 16: Visit Information Page

Status: Randomized 	SCRN	BASE	INDEX	30DAYS	ADDABLE	EOS
General Information						
Informed Consent						
Inclusion Criteria						
Exclusion Criteria						
Vein Mapping						
Randomization						
Demographics						
Angiogram						
Medical history						
Vital Statistics						
Vascular Physical Assessment						
Peripheral Vascular History						
Hemodynamic Assessment and Arterial Duplex						
Laboratory Results						
Medications						
VascuQOL						
SF-12						
EQ-5D						
Pain Scale (NRS)						
Six-minute Walk Test						
Index Procedure Summary						
Endovascular Procedure Details						
Device Accountability						
Hospitalization/ED Encounter						
Visit Information						
Reintervention Details						
Additional Procedure/Diagnostic Test						
Amputation Details						
Study Status Change Information						
Health Care Utilization						

7.8 ADDABLE PAGES

The BEST-CLI Study has implemented the use of addable, or repeating, pages in eCOS. Addable pages allow you to enter one or more copies of the same page, and are indicated by a  magnifying glass icon on the subject grid. The following pages are addable pages in the BEST-CLI Study:

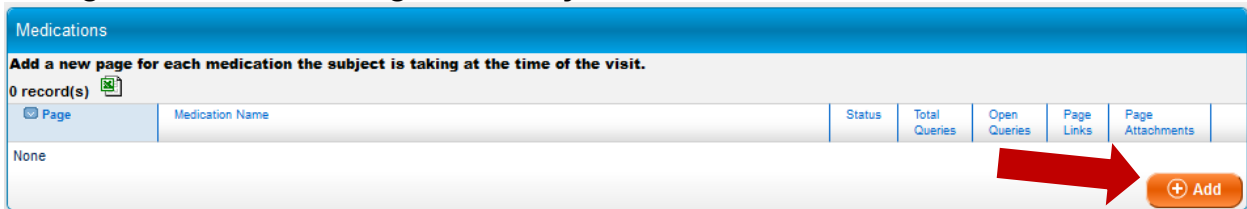
- Medications (reported within each visit)
- 6-Minute Walk Test (reported within the Baseline and 6 Month visits)
- Angiogram (post-baseline angiograms are reported within the Addable Pages visit)
- Device Accountability (reported within the Index Procedure Visit if endovascular procedure was performed and devices were used. Any post-index procedure devices are reported within the Addable Pages visit)
- Hospitalization/ED Encounter (any post-procedure hospital encounter is reported within the Addable Pages visit)
- CLI Intervention/Procedure (Re-Intervention) Details (reported within the Addable Pages visit)

- Additional Procedure/Diagnostic Test (reported within the Addable Pages visit)
- Amputation Details (post-baseline amputations are reported within the Addable Pages visit)
- Adverse Event Follow-Up (reported within the particular Adverse Event visit)
- Subjects who re/consent under protocol v5.0
- Arterial Duplex used for inclusion criteria

Here are the steps to follow to enter an addable page:

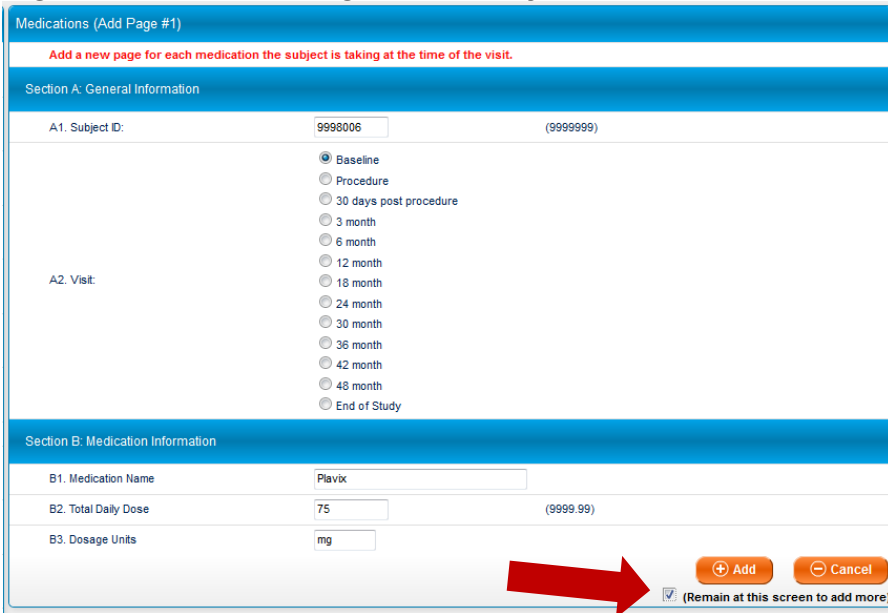
1. Click on the  magnifying glass icon on the subject grid to open up the Page Summary View.
2. Click on the “Add” button to add a page.

Figure 17: Addable Page Summary View



3. Data enter the page and then click the “Add” button to save the data. If you have more pages to add, you may check off the box “(Remain at this screen to add more)” first, and then click “Add.”

Figure 18: Addable Page Data Entry Screen



All pages that have been added will then show up on the Page Summary view, where you are able to access and view or edit the individual pages.

Figure 19: Completed Addable Page Summary View

Medications						
Add a new page for each medication the subject is taking at the time of the visit.						
2 record(s) 						
Page	Medication Name	Status	Total Queries	Open Queries	Page Links	Page Attachments
Medications (1)	Plavix		0	0	0	0
Medications (2)	Warafin		0	0	0	0
						

7.9 ADVERSE EVENT REPORTING

For the BEST-CLI Study, all 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 during the entire course of subject participation. Please refer to the Manual of Operations for specific reporting guidelines and deadlines.

7.9.1 FILING THE INITIAL REPORT

In order to add an Adverse Event, you must first add an Adverse Event visit by following these steps:

1. Click the “Add Visit” link in the top righthand corner of the subject grid.

Figure 19: Add Visit Link

Subject 9998006: Grid						
Tree Add Visit						
Status: Randomized 	SCRN	BASE	INDEX	30DAYS	ADDABLE	
General Information						
Informed Consent						
Inclusion Criteria						
Exclusion Criteria						

2. Select Adverse Event from the drop-down menu and click the “Add” button.

Figure 20: Add Adverse Event Drop-Down Menu

Study Instructions for Adding (Visit):

Visit	Instructions
Adverse Event	(none given)

Add:  

Adverse Event -- (1)

Status: Randomized 	SCRN	BASE	INDEX	30DAYS	ADDABLE
General Information					
Informed Consent					
Inclusion Criteria					

An “AE” visit will now be displayed next to the “EOS” visit and the Adverse Event Initial Report page will be “expected” for you to data enter.

Figure 21: Expected Adverse Event Initial Report Page

Index Procedure Summary			C				
Endovascular Procedure Details			E				
Device Accountability							
Hospitalization/ED Encounter			E				
Visit Information				E			
Reintervention Details							
Additional Procedure/Diagnostic Test							
Amputation Details							
Study Status Change Information							E
Health Care Utilization							E
Adverse Event Initial Report							E
Adverse Event Follow-up							

7.9.2 FILING FOLLOW-UP AE REPORTS

If an event is not resolved, a follow-up report should be filed during the study when the intensity/grade of the event, severity, or seriousness changes; upon resolution of an event; or discharge from the BEST-CLI study. Follow-up reports may be added to the particular Adverse Event visit by clicking on the  magnifying glass icon on the subject grid. Multiple follow-up pages may be added under the same Adverse Event visit.

Figure 22: Expected Adverse Event Follow-Up Page

Index Procedure Summary			C				
Endovascular Procedure Details			E				
Device Accountability							
Hospitalization/ED Encounter			E				
Visit Information				E			
Reintervention Details							
Additional Procedure/Diagnostic Test							
Amputation Details							
Study Status Change Information							E
Health Care Utilization							E
Adverse Event Initial Report							C
Adverse Event Follow-up							

7.10 QUERY MANAGEMENT

System queries will fire any time a page is saved. These involve empty field queries, range checks to detect errors in data entry, and Logic Checks which check individual responses against each other to detect contradictions in data.

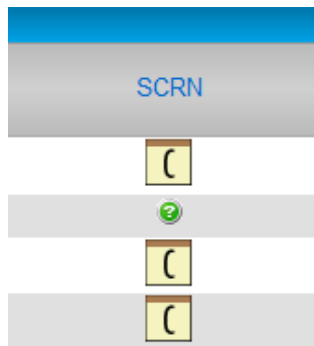
If a query is open, the field will have a red outline and a red query icon to the right of the gear. If you hover over the icon, you will see information about the query and be able to click on a link to open the query details. When a query has been answered or closed, the outline goes away and the query icon will change from red to green. The hover access to the query history remains.

Figure 23: Open Query

The screenshot shows a web form titled "Informed Consent". It has two main sections: "Section A: General Information" and "Section B: Informed Consent". In Section A, there is a field "A1. Subject ID" with the value "p998010" and a gear icon. In Section B, there is a field "B1. Was written Informed Consent obtained?" with radio buttons for "Yes" (selected) and "No". Below that is a field "B2. Date Informed Consent signed:" with the value "20-AUG-2014" and a calendar icon. To the right of the date field is a red gear icon. A tooltip is visible over this icon, displaying the following information: "#222 : System Query: SYSQ_3501", "Status: Open", and "Subject: ICF Date cannot be before the study start date." There is a "Next" button in the bottom right corner of the form.

When the system flags the item with a query, the page on the subject grid will appear with a green “?” icon (🟢).

Figure 24: Open Query Page Status



7.10.1 VIEWING A QUERY

You can access a query one of several ways. While in the page, hover over the red query icon to see the query summary. You can click the Query number or Query subject to access the Query Details screen (see Figure 23).

You can also access subject-specific queries from the All Subject Queries link in the options menu at the top of the page (Figure 25), or access all queries at your site by selecting “Reports” on the blue menu bar, then “Query Summary Report” (Figure 26).

Figure 25: Subject-Specific Queries Link

Figure 26: Query Summary Report

7.10.2 CORRECTING THE DATA

Changing the data to fit within the conditions will automatically resolve a query. Add missing data points, correct incorrectly entered data values or mismatched unit selection, and then resave the page to resolve data entry queries.

7.10.3 ANSWERING THE QUERY

The other method of answering the query is to provide a response. This is usually used when the data is recorded correctly, but recognized as outside the expected parameters for the study, or to confirm that an expected data value was not collected. In these cases, you cannot change the data, so you must provide an explanation in the 'More Details' box on the Query Details screen.

Figure 27: Answering a Query on Query Details Screen

Choose “Answered” from the status menu, provide a reason for the missing or discrepant value, and then click “Update” to resolve the query.

A Data Manager will review the query and close it if appropriate. Additional comments by the Data Manager may be added to the query if further action is required by the Study Coordinator, in which case the query status will return to “Open”. Continue to make comments and corrections on the Query until the query parameters are satisfied and the Query has been closed by the Data Manager.

7.11 ELECTRONIC SIGNATURES

Certain important pages require the signature of a Site Investigator with signing privileges. Users with the role “Site Investigator w/ Signature” have the ability to sign pages to indicate that they have reviewed and approved the data as correct and complete to the best of their knowledge.

In order to sign a form in eCOS, the investigator needs to have 1) access to eCOS, 2) access to BEST-CLI Study in eCOS and 3) authorization to Electronically sign the forms. Submission of the Electronic Signature Certification form (located on NERI Connect) is required prior to e-signature access. This form’s purpose is to acknowledge that your electronic signatures have the same legal significance as your traditional handwritten signatures.

Before signing a page, the investigator should check the following:

- Data are as complete as possible – no missing data that could feasibly be filled in
- Data are accurate
- All relevant source documentation has been attached for applicable Adverse Events
- All open queries have been answered and closed

If data are not accurate per investigator judgment, they should not sign the form. The Site Coordinator should be instructed to fix the data in eCOS. Once the data are correct then the page can be signed.

Signatures are considered a “Page Status Change”. There are two ways to perform signature:

- The investigator can batch sign all case report forms for a particular subject
- The investigator can sign pages individually

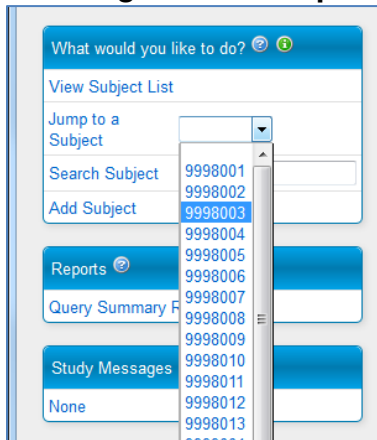
7.11.1 BATCH SIGNING ECRFS BY SUBJECT

Please follow these steps to review and sign multiple case report forms at once:

1. Log in to the eCOS system using the username and password previously provided.
2. Click on the Study Connect icon for the BEST-CLI Study.

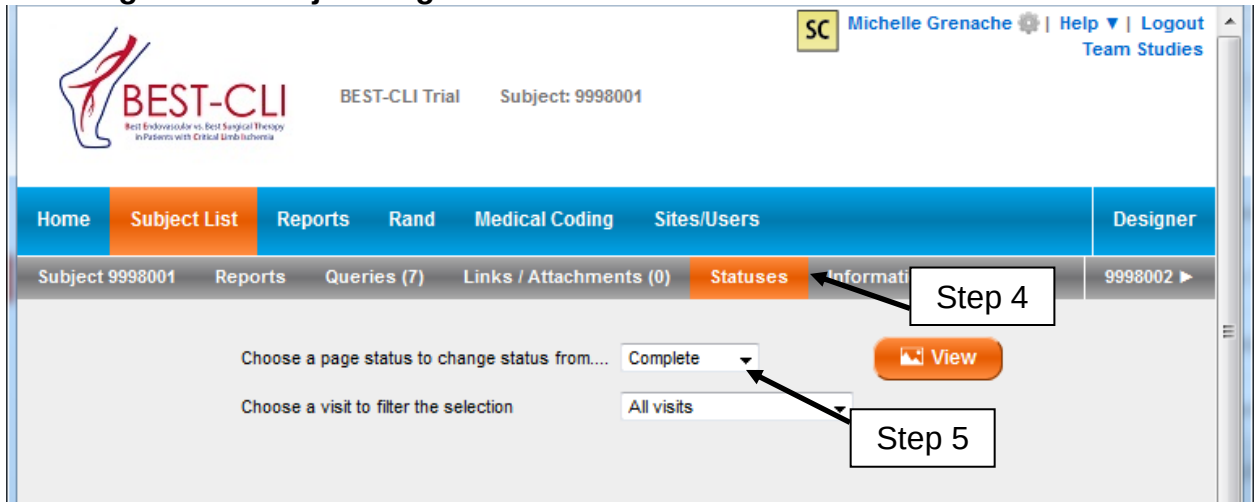
3. Select the desired BEST subject ID number from the list or use the “Search Subject” feature to access the subject data:

Figure 28: Jump To A Subject ID List and Search Subject



4. Click the Statuses link in the subject-level options menu (gray bar).
5. Select the “Completed” page status from the drop-down list and click View.

Figure 29: Subject Page Statuses Selection



6. Check the box to the right of the page(s) you want to sign.
7. In the Signatures column at the bottom (center), select the "Signed" page status from the drop-down list, enter your eCOS username and password, and review the statement provided.
8. Click the "Sign Selected" button.

Figure 30: Batch Signing eCRFs by Subject

Home Subject List Reports Rand Medical Coding Sites/Users Designer

Subject 9998001 Reports Queries (7) Links / Attachments (0) **Statuses** Information PDF 9998002 ▶

Choose a page status to change status from... Complete View

Choose a visit to filter the selection All visits

Subject 9998001: Statuses

Visit	Page	Status	
Screening	General Information	C	☐
Screening	Informed Consent	C	☐
Screening	Inclusion Criteria	C	☐
Screening	Exclusion Criteria	C	☐
Screening	Randomization	C	☐
Index Procedure	Index Procedure Summary	C	☐
30 Days Post Procedure	Visit Information	C	☐

Update Options

Status Updates Signatures Mark Deleted

Change Status To: Update Selected

Sign Status To: User ID: Password: Statement: I certify that I have reviewed source documentation, case report forms and all other study related documents for Sign Selected

(no permission to mark pages deleted)

Step 6 points to the checkbox in the table.

Step 7 points to the User ID field.

Step 8 points to the Sign Selected button.

NOTE : eSignature usernames and passwords in eCOS are case sensitive (even though the regular login screen is not case sensitive).

7.11.2 SIGNING ECRFS INDIVIDUALLY

1. Log in to eCOS and select the desired BEST subject ID number from the list or use the “Search Subject” feature to access the subject data.
2. Open the page you want to sign.
3. In the Status Change menu, select the “Signed” page status from the drop-down list and click “Update.”

Figure 31: Changing Individual Page Status to “Signed”

The screenshot displays the eCOS system interface for Subject 9998001. The top navigation bar includes tabs for Home, Subject List, Reports, Rand, Medical Coding, Sites/Users, and Designer. Below this, a sub-navigation bar shows Subject 9998001, Reports, Queries (7), Links / Attachments (0), Statuses, Information, and PDF. The main content area is titled 'Current Visit: Screening' and features a 'Status' dropdown menu with options: Complete, Complete, and Signed. A red arrow points to the 'Signed' option. The 'Update' button is located to the right of the status dropdown. The left sidebar contains a 'Visit Pages' section with links for General Information, Informed Consent, Inclusion Criteria, Exclusion Criteria, Vein Mapping, Randomization, and Demographics. Below this is a 'Queries' section with a link for 'All Page Queries' and a 'Run System Queries' button. The main content area is divided into 'Section A: General Information' and 'Section B: Inclusion Criteria'. Section A includes fields for A1. Subject ID (9998001) and (9999999). Section B lists seven inclusion criteria (B1-B7) with radio buttons for 'Yes' and 'No' and a gear icon for each. At the bottom, the 'All Inclusion Criteria Met' status is shown as '1' with a gear icon and '(9)'. The bottom right corner contains 'Save' and 'Save / Next' buttons.

4. In the Sign Page box enter your eCOS username and password, and review the statement provided.
5. Click “Update.”

Figure 32: Signing Individual eCRF

Once the pages are signed, their status will change to 'Signed'.

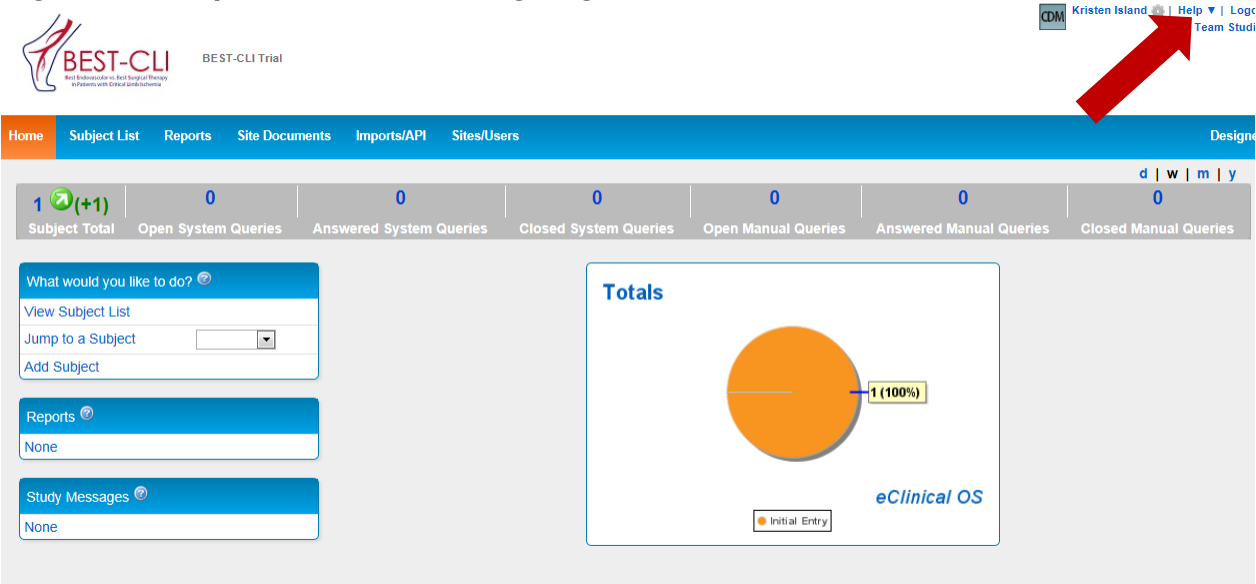
Once signed, a page will enter a Read-Only status where no modifications are permitted to the entered data. If for some reason a Study Coordinator needs change the data, they will need to request the DCC Data Manager to break the signature status. If this should occur, the page will need to be signed again to be considered complete.

7.12 ADDITIONAL RESOURCES

The Data Coordinating Center offers assistance with enrolling subjects into the study and to help facilitate any data entry questions that might arise during study conduct. The data managers can be reached by email at BEST-DM@neriscience.com.

Additionally, eClinical OS offers detailed End User manuals and videos available to you on the main Landing Page as soon as you activate your eCOS user account (Figure 4). They are also listed under the “Help” link on any study specific eCOS page. These can be viewed online or downloaded as PDFs for reference.

Figure 33: Help Manuals – Landing Page



BEST-CLI
Manual of Operations

Chapter 8

QUALITY ASSURANCE (QA) AND QUALITY CONTROL (QC)

8.0 Quality Assurance and Quality Control

The goal of Quality Assurance (QA) and Quality Control (QC) is to ensure standard and consistent implementation of the study protocol and all procedures by study staff at participating Clinical Centers in order to maximize completeness and accuracy of study data. When properly implemented, the QA/QC plan protects the scientific integrity of the study by maximizing the reliability and validity of the data collected.

Standard application of the protocol will be accomplished by the following methods:

- Comprehensive Manual of Operations (MOO)
- User-friendly electronic case report forms (eCRFs) and detailed instructions for each form
- Standardized, central training of site staff
- Regularly scheduled conference calls with Clinical Research Coordinators (CRCs) and other research staff
- Site monitoring visits
- On-going monitoring of data collection activities via analyses and reports

Each of these activities, as well as specific procedures for monitoring performance, is described in the following sections.

8.1 Protocol, eCRFs, and MOO

The Data Coordinating Center (DCC) and Clinical Coordinating Center (CCC) are responsible for developing the study protocol, eCRFs, and a study-specific MOO. The chapters of the MOO are maintained on the BEST-CLI SharePoint site (<http://connect.neriscience.com>). Each page is dated so that updated materials, with revision date, can be generated by the DCC and posted to the website. All study staff members are required to refer to the MOO to ensure a standardized application of the study protocol and procedures.

8.2 Training and Certification

An important component of data quality and consistency is a standardized, central training process. To obtain data of the highest quality, a centralized training and certification process will be implemented for all study staff. In addition, regular monitoring and re-training will be performed as required. Baseline training will include a comprehensive review of all study procedures including protocol and study design, eligibility assessment, study procedures, eCRF completion, and data management. This training will be organized by the DCC with expertise drawn from the CCC.

8.3 Study Coordination and Communication

Each participating Clinical Center will have a CRC who, along with the Principal Investigators (PIs), is responsible for ensuring the study protocol is properly implemented as outlined in the BEST-CLI MOO.

The CRC is responsible for the following:

- Participating in CLI Team meetings at his/her study site
- Ensuring that potential BEST-CLI subjects are provided with appropriate information about the study, including the informed consent form (ICF)
- Maintaining a study file for each subject containing the signed ICF, all completed worksheets (if used), and corresponding edit forms/queries
- Communicating with the DCC regarding subject enrollment, data collection and data entry
- Maintaining a file of correspondence with the DCC, IRB and NHLBI
- Maintaining a regulatory binder

- Maintaining an up-to-date BEST-CLI MOO and BEST-CLI Protocol
- Ensuring entry of eCRFs to the Electronic Data Capture system (eCOS) takes place in a regular and timely manner (i.e. within 5-days of a completed visit, or as specified in Chapter 6 for reporting of AEs, SAEs, UADEs, and UPs)
- Ensuring that subject names, social security numbers, and any other personal identifiers are removed from all materials sent to the DCC in compliance with privacy regulations (e.g. Health Insurance Portability and Accountability Act, HIPAA)
- Responding to data queries from the DCC in a timely manner
- Coordinating with the DCC to ensure that the personnel performing BEST-CLI procedures are properly trained and certified, as needed
- Assisting with the Protocol Monitor during site visits at his/her Clinical Center
- Maintaining study-related materials including regulatory documents and all source records
- Identifying and reporting irregularities or problems that may affect the data quality to the Contact PI and the DCC Clinical Research Associate (CRA) assigned to the Clinical Center

In order to foster a collaborative, mutually supportive atmosphere, the DCC will schedule regular conference calls among the CRCs, research staff, and the CCC. The conference calls will be used to address questions and share knowledge and techniques to facilitate the effective conduct of the study. Frank discussion of problems early in the process of data collection can improve the quality of the data and accelerate the learning curve.

8.4 Site Monitoring

Representatives of the DCC and CCC will conduct Site Monitoring Visits. All sites will be visited at least once during the trial. For monitoring purposes, “All sites” refers to all sites that enroll three or more subjects in the trial. The DCC will aim to conduct a minimum of one on-site monitoring visit and may conduct unscheduled monitoring visits as needed. Remote monitoring activities may also be utilized to supplement in-person monitoring as needed.

The purpose of the site visit is to: (1) review study procedures with the Site Contact PI and study staff; (2) assess the site's proficiency in executing the BEST-CLI protocol; and (3) assess the data quality by comparing source documents to the electronic case report forms. Additional, for-cause visits will be scheduled as needed.

Unscheduled visits or risk-based visits may be based upon reports or evidence of potential noncompliance with any Sponsor or regulatory requirements, significant increases in subject enrollment rates, or changes in protocol/personnel and training activities.

8.5 Ongoing Monitoring via Analyses and Reports

A number of procedures have been established to ensure that the BEST-CLI data is the highest quality possible. These include real-time data entry queries, data monitoring by the DCC, and on-site visits from the NHLBI and the DCC or their representatives. Several routine reports regarding the quality of study procedures and data are generated and distributed to study leadership by the DCC.

The DCC continuously reviews data to check for accuracy and congruency of information within and across all data forms for an individual participant. Sites are routinely notified and requested to review inconsistent data. The DCC prepares tabulations on data quality by site.

The DCC tracks and reports on the progress of study recruitment at each site. The DCC monitors the site's adherence to randomization and protocol procedures and deviations from the

protocol, including enrollment of ineligible subjects. Enrollment, protocol compliance, and violations are reported to NHLBI at least quarterly.

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Chapter 9

OPTIMAL MEDICAL THERAPY

9.0 Optimal Medical Therapy (OMT)

All subjects enrolled in BEST-CLI, by definition, have peripheral artery disease (PAD) caused by atherosclerosis. Subjects with PAD are at markedly increased risk for major adverse cardiovascular events (MACE), including myocardial infarction (MI) and stroke, and for premature all-cause mortality. It is therefore critical that subjects within BEST-CLI are provided optimal medical therapy throughout their participation in the trial.

The Optimal Medical Therapy Committee will provide these guidelines as well as develop tools to track adherence and offer feedback to sites regarding their need to follow the BEST-CLI OMT guidelines.

9.1 Anti-hypertensive Therapy Guidelines

9.1.1 Definition of Hypertension

The target for blood pressure control should follow current guidelines and depend on subject age and comorbid medical conditions.

Non-pharmacologic treatment will include behavioral interventions such as: 1) dietary sodium restriction, 2) weight loss, 3) increased physical activity, 4) smoking cessation, and 5) moderation of alcohol consumption.

The following are the recommendations for blood pressure treatment (JAMA. 2014; 311(5):507-20, <http://jama.jamanetwork.com/article.aspx?articleid=1791497>):

- Age ≥ 60 years: BP < 150/90
- Age < 60 years: BP < 140/90 (for both diabetic and non-diabetic patients)
- In subjects with intermittent claudication, angiotensin converting enzyme inhibitors should be considered as first line treatment if there are no other indications for other specific agents.

Subjects with a confirmed blood pressure above target for their age and comorbid medical conditions will be considered candidates for appropriate pharmacologic treatment in addition to behavioral treatment. It is likely that the majority of hypertensive subjects in BEST-CLI will require two or more drugs to attain this target blood pressure.

9.1.2 Criteria for BP Measurement

All subjects will be specifically questioned regarding prior history, duration and treatment of hypertension. Blood pressure will be measured using an appropriately sized cuff after 5 minutes of rest and recorded to the nearest 2mmHg for systolic and diastolic levels.

9.1.3 Treatment of Hypertension

All subjects will receive counseling on lifestyle modifications as noted in section 9.1. The approach to use of the various medications has been outlined based on the Joint National Committee VIII recommendations. The response to treatment should be assessed at each study visit.

9.2 Anti-diabetes Therapy Guidelines

A stepwise approach to the achievement of glycemic control will be strongly recommended at all sites. Though the treatment algorithm will be less stringently defined, medications prescribed and success in achieving the ideal treatment goal of hemoglobin A1c < 7% will be carefully

assessed. These results will be monitored by the Data Coordinating Center (DCC) with queries to investigators if subjects do not meet this target.

The recent American Diabetes Association (ADA) 2014 standards recommend liberalizing the hemoglobin A1C results to <8% for individuals with advanced macrovascular complications. Therefore, this will be considered an acceptable management standard for subjects enrolled in BEST-CLI.

9.2.1 Lifestyle Management

Comprehensive lifestyle management should focus on improving diabetes self-management skills, dietary intervention to promote weight loss for those who are overweight and increased physical activity as appropriate for patients' cardiovascular disease. These interventions should ideally be delivered by a Certified Diabetes Educator, preferably in the context of an ADA-recognized education program, unless prior comprehensive diabetes education can be documented. Further instruction on nutrition therapy should be prescribed as appropriate. These services are generally covered benefits for Medicare beneficiaries and most people with commercial insurance.

9.3 Lipid-lowering Therapy Guidelines

Individuals with PAD are considered at high risk for premature cardiovascular events and death, and therefore should be considered for intensive lipid lowering therapy. Despite the recent controversies regarding new guidelines for statin use, all subjects enrolled in BEST-CLI should be considered for statin therapy as noted here:

(Circulation. 2013 Nov 12 [Epub ahead of print] <https://circ.ahajournals.org/content/128/20/2241.full>, Ann Intern Med. 2014;160:339-343 <http://annals.org/article.aspx?articleid=1818923>):

- Age ≤75 years with no safety concerns: high-intensity statin
- Age >75 years or with safety concerns: moderate-intensity statin
- If a statin is not administered there must be documentation as to the reason.

High-, Moderate-, and Low-Intensity Statin Therapy*			
Statin	High intensity	Moderate intensity	Low intensity
Atorvastatin	>40-80 mg	20-40 mg	
Rosuvastatin	20-40 mg	5-10 mg	
Simvastatin		20-40 mg	10 mg
Pravastatin		40-80 mg	10-20 mg
Lovastatin		40 mg	20 mg
Fluvastatin		40 mg BID or 80 mg QD	20-40 mg
Pitavastatin		2-4 mg	1 mg

Specifically, the Committee recommends the use of atorvastatin 80 mg/d in subjects younger than age 75 years and atorvastatin 20-40 mg/d in subjects age 75 years or older.

*Note: Subjects should not be taking more than one statin.

9.4 Tobacco Cessation Strategies

(Circulation. 2013;127 (13):1425-43, <https://circ.ahajournals.org/content/127/13/1425.full>):

- In subjects who use tobacco, there must be a documented recommendation to quit smoking
- Subjects who express an interest in smoking cessation should be offered nicotine replacement, varenicline* or bupropion+
 - *0.5 mg po qd x 3 days, then 0.5 mg po bid for 4 days; then 1 mg po bid x 11 weeks; reduce dose if CrCl <30 cc/min
 - +100 mg po bid x 3 days, then 100 mg po tid.

If available, enrollment in formal tobacco cessation classes and/or support groups should be considered. In addition, at each visit, subjects must be reminded of the importance of continued abstinence from tobacco exposure.

9.5 Anti-platelet Therapy Guidelines

(Circulation. 2013;127(13):1425-43 <https://circ.ahajournals.org/content/127/13/1425.full>,
Chest. 2012;141(2 Suppl):e669S-90S
<http://journal.publications.chestnet.org/article.aspx?articleID=1159568>):

- Each subject should be considered for an antiplatelet agent
- Aspirin 81-325 mg or Clopidogrel 75 mg are appropriate first line options for BEST-CLI subjects. Clopidogrel is the treatment of choice in subjects who cannot tolerate aspirin.
- Subjects who have undergone endovascular treatment that included stent deployment should receive dual antiplatelet therapy for at least 1 month, and in some subjects longer, at the discretion of the investigator (see MOO Chapter 5).
- Subjects who have undergone infrainguinal bypass surgery should receive a single antiplatelet agent. Dual antiplatelet therapy may be used at the discretion of the Investigator.

9.6 Exercise

Each subject should have documented either a recommendation for exercise or a statement attesting that they cannot perform exercise, once their condition which initially described critical limb ischemia has resolved.

9.7 Achieving ideal weight

Each subject should undergo formal counseling by a registered nutritionist regarding a plan to achieve ideal body weight.

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Chapter 10

CLINICAL EVENTS COMMITTEE ADJUDICATION

10.1 Purpose of Clinical Event Review and Adjudication

Appropriate interpretation of results from the BEST-CLI trial will depend upon proper assessment and categorization of clinical events, outcomes, and primary and secondary endpoints for individual patients enrolled in the trial. The purpose of adjudication in BEST-CLI is to standardize the definition and interpretation of clinical events, ensure consistency across sites, reduce variability and bias, enhance trial integrity, and instill confidence in data quality.

BEST-CLI is an open-label trial, in which site investigators and coordinators are responsible for reporting events by completing case report forms (CRFs). Such self-reporting introduces the potential for subjectivity and bias regarding event type, category, and causality. Indeed, variability and unintentional bias in reporting is anticipated, based on the following contributing factors:

- Diverse training backgrounds and experience of investigators and study coordinators across sites
- Differing clinical practice patterns amongst investigators
- Variability in interpretation of events with respect to clinical relevance and causality, and relationship/importance to the trial itself
- Lack of standardized definitions and measures to evaluate clinical outcomes in CLI

These factors are to be addressed by formal adjudication processes incorporated into the BEST-CLI trial. Through the adjudication process, independent experts will consistently apply objective definitions and review methodology (including review of source documentation) to determine trial endpoint events and other specific clinical events. In performing assessments, adjudicators will be blinded or masked to treatment assignment whenever possible.

10.2 Personnel Involved in Review and Adjudication Processes

The adjudication processes will include the use of:

- Associate Project Managers and Clinical Research Associates (CRAs) - based at DCC
- Independent Medical Reviewer(s) (IMR)
- Clinical Events Committee (CEC) of physicians
- Myocardial Infarction (MI) subgroup (CEC +/- ad hoc physician reviewers)
- Stroke subgroup (CEC +/- ad hoc physician reviewers)

A CEC will be constituted that will function as an independent body. The CEC will be responsible for adjudicating major re-interventions, as well as those which are “possibly major”, based on IMR evaluation and CRF review. The committee will establish whether the occurrence represents a primary endpoint. In addition, the CEC will be responsible for adjudication of the secondary endpoints of MI and stroke.

The CEC will be a single team consisting of one chairperson and two or more members, with sufficient expertise in vascular disease to allow proper expert review of clinical events reported in the BEST-CLI trial. The CEC will function as an independent body. Its deliberations shall be carried out without bias or influence by CCC, DCC, IMRs, site investigators, or study participants.

10.3 Overview of Event Review and Adjudication Process

Sites will be responsible for thorough recording of events and relevant information on the case report forms (CRFs). Events to be reported are pre-specified (see MOO Chapter 5), and include primary endpoint events, serious adverse events, adverse events within the first thirty days after initial study procedures, re-interventions to treat CLI or PAD, MIs, and strokes.

When a clinical event is reported, the DCC APMs/CRAs will review all associated CRFs to ensure that the requested information is complete and consistent. Queries will be sent to sites when clarification or additional information is needed, or when information indicates that more than one event has occurred and additional clinical events should be reported on separate CRFs. The DCC will periodically send requests out to the clinical sites to upload into the DCC's secure SFTP site all the necessary source documents, reports, and hospital records required for review and/or adjudication.

The DCC will assemble all information (including CRFs and source documentation) required for IMR review and – if indicated – CEC adjudication. Based on pre-specified criteria, certain events will automatically trigger CEC review and adjudication. Examples include major re-intervention (a primary endpoint event) and MI and stroke (secondary endpoint events).

10.4 Role of Site Principal Investigator and Site Personnel

Site principal investigators, co-investigators and research coordinators are responsible for completing CRFs in a comprehensive fashion, adhering to the definitions associated with the trial, and identifying and reporting all relevant events and endpoints. Investigator and site perceptions of causality are deemed to be important elements of BEST-CLI. Accordingly, where CRFs request assignment and determination of causality, site personnel should delineate – to the best of their ability – the relationship of the event to trial procedures and treatments. In addition to causality, site personnel will report – through the CRFs – whether events were expected/anticipated and the level of seriousness. All CRFs should be completed fully, and clinical narrative explanations regarding events should be submitted whenever possible. Sites must also respond in a timely fashion to all requests for source documents, reports, and hospital records required for review and/or adjudication. Sites will be responsible for obtaining the documents, removing any patient identifiers, and labeling each document with the appropriate subject ID.

10.5 Definitions of Events and Source Documents to be Collected

10.5.1 All-Cause Mortality

All-cause mortality will be reported if it occurs at any time after randomization.

- Source documents to be provided (Note: DCC, IMR or CEC may request additional documentation)
 - o Death certificate or other vital status report
 - o Narrative regarding circumstances surrounding death
 - o Discharge summary

10.5.2 Amputation

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

- Source documents to be provided (Note: DCC, IMR or CEC may request additional documentation)
 - o Operative report
 - o Narrative regarding circumstances surrounding amputation
 - o Discharge summary

10.5.3 Major Re-intervention

Major Re-intervention is 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.

- Source documents to be provided (Note: DCC, IMR or CEC may request additional documentation)
 - o Operative Note or procedure reports
 - o Clinical narrative regarding circumstances leading to repeat intervention
 - o Discharge summary

10.5.4 Minor Re-intervention

Minor Re-intervention is 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.

- Source documents to be provided (Note: IMR or CEC may request additional documentation)
 - o Operative Note or procedure reports
 - o Discharge summary
 - o Narrative regarding circumstances leading to repeat intervention

10.5.5 Myocardial Infarction (MI)

- Source documents to be provided (Note: IMR, MI Adjudicators, or CEC may request additional documentation)
 - o Cardiac enzymes: Troponin, CK, CKMB (before, during, and after MI as available)
 - o Electrocardiogram (before, during, and after MI as available)
 - o Discharge summary
 - o Physician narrative as available

10.5.6 Stroke

- Source documents to be provided (Note: IMR, Stroke Adjudicators, or CEC may request additional documentation). The following source documents are requested for strokes:
 - o Neuro-imaging reports, if performed and available
 - o Neurology consult Notes, if performed
 - o Results of stroke scales: Barthel Index, NIH Stroke Scale, if performed and available
 - o Discharge summary
 - o Clinical narrative

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Chapter 11

ANCILLARY STUDY POLICY

11.1 Definition of an Ancillary Study

An ancillary study is defined as research using BEST-CLI trial participants (including their laboratory specimens or tests) to collect or derive *supplemental* data for purposes above and beyond those set forth in the BEST-CLI protocol. Of note, a proposal for data analysis of main trial data is not an ancillary study.

Ancillary study research might employ a technique, therapy, procedure, questionnaire, or observation that results in the acquisition of additional data. In addition, observational studies involving BEST-CLI Trial participants and/or resources, including registries, are considered ancillary studies and require approval according to the Ancillary Studies Policies and Procedures. All analyses of BEST-CLI main trial data are conducted at the Data Coordinating Center (DCC) according to the collaborative procedures described in the BEST-CLI Publications and Presentations policy.

The investigator responsible for the conduct of an ancillary study must be a member of the BEST-CLI trial group or work in close collaboration with a BEST-CLI investigator. If a research request is made by an individual external to the BEST-CLI trial group, a BEST-CLI investigator who is familiar with the main study must be identified in the study application to serve as a liaison to - and collaborate as a co-investigator of - the ancillary study.

11.2 Overall Principles

Ancillary studies will be evaluated with careful consideration of their potential impact on the objectives and performance of the BEST-CLI trial. Investigators and study participants are entitled to prior assurance that all ancillary studies are of high scientific merit and will not:

- cause a deviation from the protocol,
- confound interpretation of the BEST-CLI trial results (e.g., request premature release of BEST-CLI results; introduce an intervention or treatment that will affect interpretation of main trial results),
- adversely affect participant cooperation,
- jeopardize the public image of the BEST-CLI trial,
- create a significant diversion of the BEST-CLI resources at the clinical centers, at the coordinating center, or at any other level,
- negatively influence the cooperative spirit of the collaborating investigators, or
- otherwise compromise the scientific integrity of the BEST-CLI trial.

Ancillary studies that complement the objectives and thereby enhance the value of the study are encouraged. Such studies should augment and promote the continued interest of both participants and investigators. To protect the integrity of the main BEST-CLI trial, a proposal to conduct an ancillary study must be reviewed and approved by the Ancillary Studies Committee, the BEST-CLI Executive Committee (EC), and (if funded) the BEST-CLI Data and Safety Monitoring Board before its initiation. A major review criterion is the impact on the BEST-CLI protocol. No clinical center will be required to participate in an ancillary study.

11.3 Overview of Procedures

The Ancillary Studies Committee has established a stepwise system of proposal, review, and approval (see Figure 1). The system is designed to minimize effort by investigators for proposals that may be rejected. The steps are:

1. Investigators submit a preliminary concept proposal (3-6 pages) to the Ancillary Studies Committee. The proposal is reviewed by all members of the Ancillary Studies Committee, which votes to approve the concept, subject to review of full proposal (by majority vote).
2. The Ancillary Studies Committee submits the proposal to the BEST-CLI Executive Committee along with a summary of its review and recommendation to approve or not.
3. The BEST-CLI EC reviews the recommendation of the Ancillary Study Committee and votes to approve or disapprove the application according to voting rules outlined in the charter of the BEST-CLI Executive Committee.
4. The DCC sends the applicants the Ancillary Study Committee summary and BEST Trial EC approval or disapproval.
5. The investigators have a maximum of 6 months from Executive Committee approval to prepare a full proposal for review by the Ancillary Studies Committee. After 6 months, procedures start again at step 1.
6. A full proposal (up to 12 pages, with supporting documentation) is resubmitted to the Ancillary Studies Committee for review and approval and then to the CCC and DCC PIs for final approval and to ensure adequate funding, if applicable for coordinating center activities.
7. Only full proposals that are approved by the Ancillary Studies Committee and BEST-CLI PIs may be submitted to a funding agency. Investigators of such a proposal will receive an approval letter that they may present when submitting their application to a funding agency.

11.4 Funding

The BEST-CLI trial will not provide funds for ancillary studies. In particular, no funds are provided for central laboratory, central reading center, or coordinating center activities or services in support of ancillary studies. If funds are needed, the investigator must explore other avenues such as submission of a research grant application or use of other sources of funds (i.e., the National Institutes of Health, a foundation, departmental resources, drug or device company, etc.) to utilize the services of the BEST DCC for data management, statistical analysis, etc. The anticipated source of funds must always be identified.

11.5 Publication and Presentation of Results

All manuscripts, abstracts, or presentations for scientific meetings based on ancillary study data must follow the policies and procedures of the BEST-CLI Publications and Presentations Committee. Under no circumstances will the results of an ancillary study that contains post-baseline data of BEST-CLI Study subjects be submitted for publication or appear in presentation or in print prior to the release of the main trial results.

11.6 Participation by Clinical Centers

In general, for proposed ancillary studies open to all clinical centers, each clinical center principal investigator determines whether or not his/her center will participate. The Ancillary Studies Committee will also consider ancillary study submissions proposing participation of only one or a few centers if they can be shown to have adequate power (and potentially lower costs). In such cases, consultation with participating center PIs will be required prior to submission. The Ancillary Studies Committee retains the prerogative to request broader participation. Any

funding sought for ancillary studies should include a budget appropriate for each of the centers that have agreed to participate in the study, and for resource requests to be made to the CCC and/or DCC.

As noted in Section 11.1, a BEST-CLI investigator must be consulted and included as a co-investigator on an ancillary study application (and for the study, if approved). This individual will serve as a liaison who is familiar with the main trial policies and study design, and be particularly an important resource if the ancillary study PI is external to the BEST-CLI study group. In general, if a BEST-CLI clinical center agrees to provide participant data for the ancillary study, at least one member of that clinical center is included as a co-investigator.

11.7 Proposal Content

The preliminary concept proposal should be 3-6 pages and contain (see the BEST Ancillary Study Application form in the Manual of Operations for full details and format):

1. Investigators' and collaborators' name, role, and institutional affiliation. Include NIH biosketches for investigators and key personnel.
2. Planned start and end dates.
3. Estimated costs and plans for funding, including the anticipated source of funding.
4. Design and methods:
 - Statement of primary and secondary goals and objectives.
 - Brief background, significance, and rationale.
 - Sample size and justification (including power calculation).
 - Data needed (a) from the BEST-CLI trial central database and (b) from additional tests, surveys, etc.
 - Mechanism and timing of patient recruitment
 - Proposed mechanism of data or sample collection, and implementation plan.
 - Description of additional methods and procedures to be carried out on a study participant.
 - Plans for analysis.
 - Burden on participants.
 - Requirement for separate informed consent.
 - Impact on BEST-CLI trial.
 - Measures to be taken to ensure participant safety and confidentiality.
 - Payment or incentives to participants.
5. Coordinating center and other study resources requested.
6. Assurance of adequate facilities, equipment, etc to conduct the ancillary study.

11.8 Detailed Review Process

It is the responsibility of the investigators to allow adequate time for full review and approval by the BEST-CLI trial prior to a funding agency submission deadline according to the following review process.

1. The preliminary concept proposal must be submitted to the DCC. The CCC and DCC PIs are notified regarding new applications. If the study is being submitted for funding, then the preliminary concept proposal should be submitted to the Ancillary Studies Committee at least 12 weeks prior to a funding agency deadline. The DCC reviews the proposal for completeness and distributes a copy to each member of the Ancillary Study Committee. Each member of the Ancillary Study Committee completes the Ancillary Studies Evaluation Form (see last pages of policy).

2. The Ancillary Studies Committee may elect to use either e-mail exchange or conference call for its review. Minutes will be kept to summarize deliberations of meetings or conference calls (administrative help provided by CCC or DCC).
3. The Ancillary Studies Committee then votes to approve or disapprove. Approval or disapproval is based on a simple majority vote of the Ancillary Studies Committee. Highest priority will be given to studies that:
 - a. have the highest scientific merit,
 - b. produce the least burden on BEST-CLI participants,
 - c. have objectives closest to those of the BEST-CLI trial, and
 - d. require the unique characteristics of the BEST-CLI cohort.
4. The Ancillary Studies Committee chair prepares a summary evaluation form, which is based on the Ancillary Studies Evaluation Forms and the the consensus of the Committee after its deliberations. Included in this summary evaluation form are reservations or objections, and the decision to recommend approval or disapproval. The summary evaluation form is submitted to the DCC for distribution to the BEST-CLI EC.
5. Members of the BEST-CLI Executive Committee receive the preliminary concept proposal and the summary evaluation form, as well as written clarification if applicable. The BEST-CLI Executive Committee will need 1 month for review and vote on the preliminary concept proposal. The Executive Committee may elect to use either or both e-mail exchange and conference call in their review. The decision of the EC is acknowledged in a letter to the proposal PI from the DCC Statistical PI. The summary evaluation form from the Ancillary Studies Committee is also included with the letter.
6. At any point, the investigators making the proposal for an ancillary study may choose to:
 - a. withdraw the proposal,
 - b. modify the proposal based upon the feedback from the Ancillary Studies Committee or EC, and then re-submit for reconsideration, or provide written clarification in response to the Ancillary Studies Committee and to the BEST-CLI EC.
7. With approval of the preliminary concept proposal, the investigators may proceed to prepare a full proposal to the Ancillary Studies Committee with the intent (if applicable) of submitting a grant application to a funding agency based on the full proposal. At least 4 weeks in advance of the funding agency deadline (if applicable), the investigators should submit a full proposal up to 12 pages; see application for more details) to the DCC. The submission must be accompanied by a letter signed by the principal and all co-principal investigators in which they agree to abide by the policies for ancillary studies herein described, including those regarding publication or presentation of results.
8. The DCC will distribute the full proposal for review and approval by:
 - a. the Ancillary Studies Committee (The Ancillary Studies Committee is generally designated by the BEST-CLI EC to provide approval of the full proposal; however, the EC reserves the right to also review a full proposal, if desired.)

- b. the CCC and DCC PIs overseeing operations (to ensure that the requested budget and scope of coordinating center work put forth in the original application are intact)
9. If the full proposal has been significantly changed from the preliminary concept proposal, the Ancillary Studies Committee may request revisions and a full review by the EC. In such cases, it would be advisable for the investigators to submit their revised proposals at least 6 weeks in advance of a funding deadline.
10. After CCC and DCC PI approval, the investigators may proceed with the submission of the proposal to a funding agency. Funded proposals are submitted to the DSMB Chair for review and approval. The funded ancillary study begins according to the timetable delineated in the full final proposal.

11.9 Protocol Changes

In rare instances, if the Ancillary Studies Committee feels that the proposed ancillary study requires a change in the BEST-CLI main trial protocol or main informed consent form, such an amendment must be reviewed by the EC for benefit to the BEST-CLI trial and is subject to final vote of approval according to protocol amendment procedures (consensus of Executive Committee required to amend the BEST-CLI protocol).

11.10 Monitoring

The Ancillary Studies Committee will track and record the progress of approved ancillary studies. Central monitoring of studies is needed to ensure that the composite impact of the total number of active studies does not have unforeseen consequences. Monitoring will include evaluating the burden on participants and BEST-CLI staff, as well as the use of irreplaceable BEST-CLI resources. Investigators with approved ancillary studies will submit a semi-annual progress report to the DCC regarding the status of study funding, initiation and termination dates, success of data collection, and any presentations or publications derived from the ancillary study (i.e., the progress report should follow the same format as that for annual funding requests). These reports will be forwarded to the Ancillary Studies Committee and the DSMB. The Ancillary Studies Committee Chair will provide a summary of these reports to the EC. All presentations and publications must follow the BEST-CLI trial Publications and Presentations Policy.

11.11 Analysis

All BEST-CLI approved ancillary studies must include plans for data analysis, who will perform the analysis, and what their credentials are. Data analysis must be financed by the investigators submitting the proposal. Data analysis for the ancillary study may be performed at the BEST-CLI DCC with funding provided by the ancillary study investigators. A DCC budget is prepared at the proposal stage.

Ancillary study investigators may request selected data collected in the main trial on the ancillary study participants to integrate with the ancillary study data. The DCC will prepare an export for a small fixed fee. The DCC Statistical Principal Investigator should be contacted regarding such requests.

Following approval of an ancillary study by the BEST-CLI EC, there can be no substantial changes in the type or amount of main trial data requested from the DCC. If major changes are desired, the PI(s) of the Ancillary Study can submit a formal request to the DCC. This request for additional data or changes, or any other major change, will be reviewed and reconsidered by

the Ancillary Study Committee and then the EC, which will then vote to approve or disapprove, based on the merits and additional resources required.

11.12 Informed Consent

When required by federal regulation, separate informed consent must be obtained from all ancillary study participants for participation in the ancillary study. Any consent documents and associated communication with the participants should clearly identify the ancillary study as one being performed *in addition to* the main Trial and inform subjects that their participation in the ancillary study is not necessary for them to continue to be enrolled and involved in the BEST-CLI trial. Informed consent forms for an ancillary study will not be presented to a trial subject until after the main trial consent is signed and submitted.

All ancillary study protocols must be submitted to the relevant local Institutional Review Boards. Unless the ancillary study PI has hired the DCC to perform coordinating center duties, it is the responsibility of the ancillary study PI and his/her staff to collect all IRB approval letters and stamped consent forms before a clinical center participates in the study, and to ensure that renewals are on file.

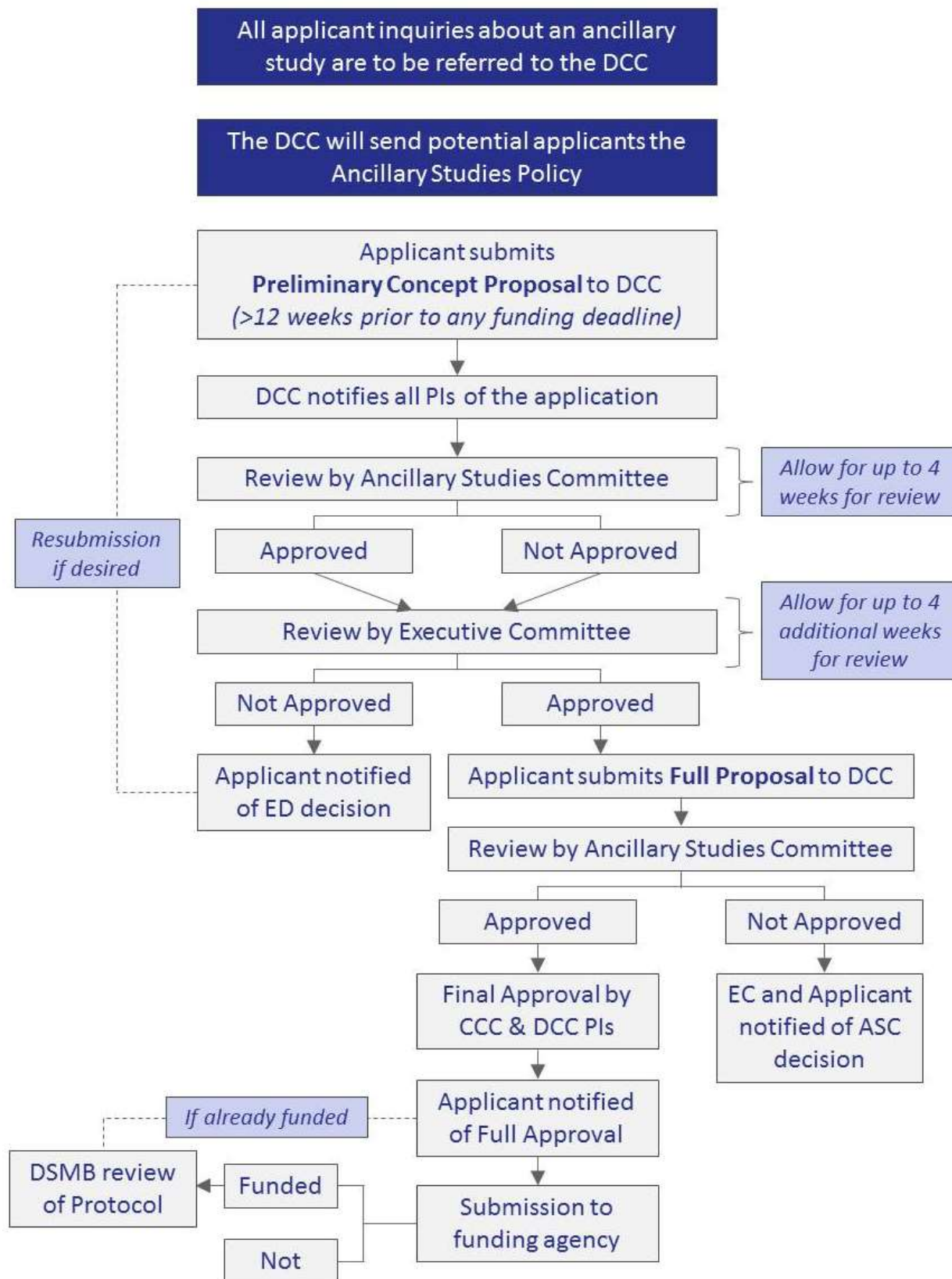
11.13 Incorporation of Additional Data Collection to BEST-CLI Trial Visit

If investigators propose to collect additional data from the participant—whether during a study visit or at another contact—they need to consider the impact of the burden of additional tests or survey questions on participation in the BEST-CLI trial. The proposal should address the potential impact of additional data collection on participation in the BEST-CLI trial.

11.14 Changes to Ancillary Studies Policies and Procedures

Any changes in the policies and procedures described in this document will require approval of the BEST-CLI trial EC, according to the parameters delineated in the EC Charter. Review of such proposed changes and recommendations in advance will be provided to the EC by the Ancillary Studies Committee.

Figure 1. BEST-CLI Ancillary Study Approval Process



Appendix 1: Ancillary Study Evaluation Form

Reviewer _____

1.	Title:																											
2.	Principal Investigator(s):																											
3.	Strengths and weaknesses of ancillary study Strengths: Weaknesses:																											
4.	This study has potential to... <table style="width: 100%; border: none;"> <tr> <td style="width: 70%;">a. cause a deviation from the protocol.</td> <td style="width: 15%; text-align: center;">☐ Yes*</td> <td style="width: 15%; text-align: center;">☐ No</td> </tr> <tr> <td>b. confound interpretation of BEST-CLI trial results.</td> <td style="text-align: center;">☐ Yes*</td> <td style="text-align: center;">☐ No</td> </tr> <tr> <td>c. adversely affect subject participation in the BEST-CLI trial.</td> <td style="text-align: center;">☐ Yes*</td> <td style="text-align: center;">☐ No</td> </tr> <tr> <td>d. jeopardize the public image of the BEST-CLI trial.</td> <td style="text-align: center;">☐ Yes*</td> <td style="text-align: center;">☐ No</td> </tr> <tr> <td>e. negatively influence the cooperative spirit among BEST-CLI clinical centers.</td> <td style="text-align: center;">☐ Yes*</td> <td style="text-align: center;">☐ No</td> </tr> <tr> <td>f. compromise the scientific integrity of the BEST-CLI trial.</td> <td style="text-align: center;">☐ Yes*</td> <td style="text-align: center;">☐ No</td> </tr> <tr> <td>g. raise concerns with the BEST-CLI DSMB.</td> <td style="text-align: center;">☐ Yes*</td> <td style="text-align: center;">☐ No</td> </tr> <tr> <td>h. add significant burden to subjects</td> <td style="text-align: center;">☐ Yes*</td> <td style="text-align: center;">☐ No</td> </tr> <tr> <td>i. add significant burden to BEST investigators/coordinators</td> <td style="text-align: center;">☐ Yes*</td> <td style="text-align: center;">☐ No</td> </tr> </table> *Explanation:	a. cause a deviation from the protocol.	☐ Yes*	☐ No	b. confound interpretation of BEST-CLI trial results.	☐ Yes*	☐ No	c. adversely affect subject participation in the BEST-CLI trial.	☐ Yes*	☐ No	d. jeopardize the public image of the BEST-CLI trial.	☐ Yes*	☐ No	e. negatively influence the cooperative spirit among BEST-CLI clinical centers.	☐ Yes*	☐ No	f. compromise the scientific integrity of the BEST-CLI trial.	☐ Yes*	☐ No	g. raise concerns with the BEST-CLI DSMB.	☐ Yes*	☐ No	h. add significant burden to subjects	☐ Yes*	☐ No	i. add significant burden to BEST investigators/coordinators	☐ Yes*	☐ No
a. cause a deviation from the protocol.	☐ Yes*	☐ No																										
b. confound interpretation of BEST-CLI trial results.	☐ Yes*	☐ No																										
c. adversely affect subject participation in the BEST-CLI trial.	☐ Yes*	☐ No																										
d. jeopardize the public image of the BEST-CLI trial.	☐ Yes*	☐ No																										
e. negatively influence the cooperative spirit among BEST-CLI clinical centers.	☐ Yes*	☐ No																										
f. compromise the scientific integrity of the BEST-CLI trial.	☐ Yes*	☐ No																										
g. raise concerns with the BEST-CLI DSMB.	☐ Yes*	☐ No																										
h. add significant burden to subjects	☐ Yes*	☐ No																										
i. add significant burden to BEST investigators/coordinators	☐ Yes*	☐ No																										
5.	Scientific merit score (standard NIH system) <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">☐ Outstanding (100-150)</td> <td style="width: 33%;">☐ Excellent (151-200)</td> <td style="width: 33%;">☐ Very good (201-250)</td> </tr> <tr> <td>☐ Good (251-300)</td> <td>☐ Fair (301-350)</td> <td>☐ Poor (> 350)</td> </tr> </table>	☐ Outstanding (100-150)	☐ Excellent (151-200)	☐ Very good (201-250)	☐ Good (251-300)	☐ Fair (301-350)	☐ Poor (> 350)																					
☐ Outstanding (100-150)	☐ Excellent (151-200)	☐ Very good (201-250)																										
☐ Good (251-300)	☐ Fair (301-350)	☐ Poor (> 350)																										
6.	Funding source and resource utilization <table style="width: 100%; border: none;"> <tr> <td style="width: 70%;">a. Sufficient funds are available to complete the study.</td> <td style="width: 15%; text-align: center;">☐ Yes</td> <td style="width: 15%; text-align: center;">☐ No*</td> </tr> </table> *Explanation:	a. Sufficient funds are available to complete the study.	☐ Yes	☐ No*																								
a. Sufficient funds are available to complete the study.	☐ Yes	☐ No*																										

b. The study will create a significant diversion of BEST-CLI resources.

☐ Yes* ☐ No

*Explanation:

7 Recommendation

☐ Approve

☐ Approve with the following modifications: _____

☐ Disapprove

8. Additional comments:

BEST-CLI
Manual of Operations

Chapter 12

PUBLICATION & PRESENTATION

12.0 Publication & Presentation Overview

The BEST-CLI Trial is a unique scientific investigation that will be conducted according to the protocol under the guidance of the National Heart Lung and Blood Institute (NHLBI). Because of the great effort that goes into such a study and the large amount of resources used, study investigators have the responsibility to communicate their findings to the scientific community and to the public at large.

To minimize the probability of inaccurate data in published materials, it is the policy of the BEST-CLI Trial that all data and text considered for all papers, and all abstracts, oral presentations, and posters for presentation at scientific meetings, be submitted to the Publications & Presentations Committee (PPC) for review and approval prior to presentation or publication. Members of the PPC are constituted from the Executive Committee with at least one member from the Clinical Coordinating Center (CCC), one member from the Data Coordinating Center (DCC), and one member from NHLBI.

Given the policy noted above, the overall objectives of the PPC committee are:

1. To review and set priorities for publications and presentations
2. To ensure that all NHLBI policies pertaining to publications and presentations are followed
3. To assure and expedite orderly and timely presentations to the scientific community of all pertinent data resulting from the BEST-CLI study
4. To assure scientifically accurate presentations and papers from BEST-CLI investigators
5. To assure that all investigators, particularly those of junior rank, have the opportunity to participate in the study-wide presentations and publications of BEST-CLI data
6. To assure that press releases, interviews, presentations, and publications are accurate and objective, and do not compromise the scientific integrity of this collaborative trial
7. To establish procedures that allows the Executive Committee, including NHLBI, to exercise review responsibility in a timely fashion for BEST-CLI publications and presentations
8. To maintain a complete up-to-date list of BEST-CLI presentations and publications, and to distribute such lists to all BEST-CLI investigators and the DSMB on a regular basis

12.1 Definitions

Main Papers and Presentations are those reporting results dealing with the main hypotheses of the randomized controlled trial (i.e., primary and secondary endpoints, the design and baseline data of the trial) as well as papers and presentations using the complete trial data sets. In general, main papers and presentations refer to use of trial data from all sites and report by randomized arm.

Other Papers and Presentations are those not encompassed by the above category. They relate to secondary hypotheses and work done in ancillary studies (studies not relating to the original main hypotheses).

12.2 TYPES OF MANUSCRIPTS

There are three types of manuscripts and anticipated authorships:

1. Main results papers based on core BEST-CLI data and study aims/hypothesis. Main results papers will be outlined by the PPC and reviewed through the process described below early in the study.
2. Other BEST-CLI investigator authored manuscripts developed in response to an approved manuscript proposal after approval by the PPC.
3. Ancillary study results led by investigators bringing external funding into BEST-CLI for a specific project.

12.3 PROPOSAL AND APPROVAL PROCESS

Investigators may lead or join a writing committee to prepare a manuscript on a topic of interest using data from the entire trial.

To initiate the process that might lead to a presentation at a scientific meeting, or writing a paper for publication, all BEST-CLI investigators and professional staff are invited to submit written proposals for abstracts or for papers to the PPC.

Proposals for publication or presentation of data from one site, or a subset of sites, must provide a rationale for not including data from all sites. Such proposals will require formal approval by the PPC before the proposal can move forward with selection of a writing group (WG).

Any given proposal should:

- clearly state the research question or hypothesis;
- include a brief background statement to clarify the purpose and importance of the research question; and,
- provide a preliminary description of the analysis plan, proposed collaborators, and plans for presentation and publication (see BEST-CLI Writing Topic Proposal Form in Appendix 1).

Investigators are required to consult with the PPC in developing proposals to ensure feasibility and to reduce overlap with ongoing analyses. If approved to go forward, a WG will be formed, as specified below.

BEST-CLI Trial endpoint data, particularly involving primary and secondary endpoints, will not be analyzed prior to the planned end of the study. These restrictions have the following exceptions:

- Group sequential analyses of the primary trial outcome and all-cause mortality for review by the DSMB
- Additional analyses of efficacy and safety outcomes, adverse events, and other data required by the DSMB to fulfill their trial monitoring responsibilities
- Comparison of baseline subject characteristics by trial arm for presentation at the Operations Committee, Executive Committee, and DSMB meetings
- Baseline subject characteristics of trial for presentation by approved Investigators at invited sessions with approval by the PPC (after enrollment is complete and baseline data has been cleaned)

12.4 SELECTION OF WRITING GROUP (WG)

Ideas for abstracts or papers may be initiated by the PPC which will outline a plan for relevant manuscripts. As soon as the concept for an abstract or paper has been identified and approved by the PPC, the PPC Chair will communicate with sites requesting nominees of qualified and interested investigators to participate as members of a WG for that paper, as well as seeking the rationale for each nominee for the WG. The request for nominees will include a specific date (deadline) for submission of nominations. In general, membership of WGs is restricted to BEST-CLI investigators and professional staff, including the CCC, DCC, and the project office at the NHLBI. Others not formally associated with BEST-CLI may become involved in some aspects of publication if sponsored by a BEST-CLI principal investigator, and approved by the PPC. The PPC will select from the submitted list of nominees the WG membership for each paper. The CCC and DCC will be represented on the WG.

An idea for a manuscript may be proposed by a BEST-CLI investigator. In that case, the investigator must contact the PPC and submit a proposal for an abstract and manuscript. The

PPC will evaluate the proposal and if is approved the PPC will constitute a WG. The PPC will also identify a lead person for the WG, so that the group may expeditiously proceed with the task. In general, the proposer of the idea for the paper or abstract will be the lead person.

If an NHLBI staff member is being considered for authorship on a BEST-CLI article, approval of the NHLBI staff member's participation must be obtained from NHLBI before publication.

It is the responsibility of the lead person to communicate with other WG members, to collaborate with the WG members (including the DCC statistician) to develop a detailed project analysis plan and manuscript outline, to collaborate with the DCC statistician to identify any additional needed data and analyses, and to assume leadership in writing the manuscript. In general, the lead person will be the first author of the paper.

To expedite publication, one or more meetings of the WG may be necessary. These meetings may be telephone conferences and will be organized by the DCC.

The PPC is charged with the task of periodic systematic review of the work of all WGs; aiding and encouraging members as appropriate; and revising their membership or reconstituting the group membership, with written notification, when indicated. It is the intent that selection of writing committee members is equitable and fair to all groups and individuals participating in this collaborative program, including encouragement of participation by younger professional colleagues, with due regard paid to exceptional efforts of groups or individuals.

12.5 PREPARATION AND SUBMISSION OF PAPERS

The following steps should be followed in the preparation of BEST-CLI manuscripts. The lead person of each WG should:

1. Contact each writing committee member and review the specific charge to the group;
2. Draft dummy tables which the WG considers appropriate for the manuscript;
3. Be aware that the DCC (based on EC guidance) will process all requests for data analysis according to the overall priorities of the BEST-CLI Study;
4. Collate comments and dummy tables, solicit opinions of the WG, and when a consensus is reached, submit the dummy tables (or data analysis requests) to the DCC with copies to the PPC Chair;
5. Obtain input from every member of his/her group. If any member of the WG does not respond to the lead person's request, or does not contribute to the writing of the paper, the lead person may request a replacement from the PPC. Members of each BEST-CLI WG should participate actively in the writing, and review of the paper assigned to that group. Input from every member of the WG should be encouraged;
6. Approve the final version of the paper before its submission to the PPC. All members of the WG should have reviewed the final draft before submission to the PPC;
7. The lead person will be required to submit a final draft of each BEST-CLI paper to the DCC for a final check of data accuracy.
8. Perform his/her duties under the review of the PPC. If in the judgment of the PPC a WG is not working well, and if there is an unjustifiable delay in writing the paper assigned to it, the PPC may change either the lead person or the entire membership, if in the PPC's judgment this action will expedite the writing of that particular paper.

12.6 AUTHORSHIP AND CLEARANCE

For main papers and presentations, names of members of the WG shall be listed as authors in the masthead, followed by the phrase "for the BEST-CLI Trial Investigators." The order of authorship will be determined by the lead person of the WG and the PPC, with concurrence of, other members of the group. A major criterion for order of authorship shall be the effort and

contribution made by each author in preparation of the manuscript, and the contribution to enrollment at the investigator's site, as appropriate. Membership in a WG without substantive contribution to the manuscript does not justify authorship. In general, "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (NEJM 1991; 324: 424-428) shall be adhered to with regard to authorship. Disagreement about the order of authors will be resolved by the PPC.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Numbers U01HL107407, U01HL107352, and U01HL115662. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health."

When applicable, financial and in-kind support of all non-federal sources will be acknowledged at the end of each manuscript.

The phrase "for the BEST-CLI Trial Investigators" added after the names of the authors in the masthead is optional in papers reporting local data, or ancillary studies using local data.

A credit roster of all major committees, units, and BEST-CLI centers with their members (generally no more than 5 persons from each site) is to appear at the end of each main paper (printed as an appendix). It is the responsibility of the CCC to solicit, obtain and prepare the final list for inclusion in each BEST-CLI paper. An electronic copy of the publication and any online supplemental material should be supplied to the CCC and DCC. All requests for reprints of main papers should be directed to the CCC.

The DCC staff will be requested to submit their review within a reasonable time limit (generally not to exceed one month) after the lead person submits the final draft, and provide feedback to the lead person and PPC Chair as soon as possible.

The EC shall have the final authority to review and approve all BEST-CLI papers including papers on ancillary studies, sub-studies, or local center data. It is the responsibility of the PPC Chair to present the recommendation of the PPC to the EC in a timely fashion, and to solicit the approval of that body without delay.

Every effort should be made to accommodate the expression of differing interpretations and alternate analyses within the body of each manuscript, so that all points of view are represented to the satisfaction of every author.

Since not all circumstances that might cause disagreement among BEST-CLI investigators on a given paper can be foreseen, these disagreements should be resolved by the PPC, and ultimately by the EC (if there is disagreement between the WG and PPC).

12.7 PREPARATION AND SUBMISSION OF ABSTRACTS FOR MEETINGS

The DCC will maintain a current list of all relevant meetings and their deadlines for submission of abstracts.

Any BEST-CLI Investigator may prepare an abstract on a subject appropriate to the BEST-CLI investigation. Such an abstract should be based on the topic already assigned to a WG and the person preparing the abstract should be a member of that WG.

Submission of any abstract must be approved by the PPC and the relevant WG.

An idea for an abstract may be suggested by a BEST-CLI investigator. In that case, the investigator must contact the PPC who will evaluate the proposal. If the PPC approves the proposal then it will constitute a WG. The CCC and DCC and NHLBI should have a representative on this WG, as with other BEST-CLI WGs, to expedite communication and facilitate timely analysis of data.

All data analysis requests for the preparation of an abstract for a national or international meeting must be submitted to the PPC at least 12 weeks prior to the abstract deadline if the abstract is to be based on analyses already in progress for a manuscript (see Figure 1). For new topics, the requests must be submitted to the PPC at least 20 weeks prior to the abstract deadline, to allow time for WG formation, clarification of required analyses, and performance of those analyses. If resources do not allow all analysis requests for a particular meeting to be fulfilled, the PPC or EC will prioritize the requests.

All abstracts of main, other, and ancillary study papers must be approved by the PPC before they are submitted to any national or international organizations. Abstracts submitted to the PPC for review should be accompanied, if appropriate, by copies of tables and graphs to support the conclusions of the abstract. It is understood that some descriptive abstracts may not require data submission or the data may be contained in the abstract. Only tables which relate to the major topics of the abstract should be requested from the DCC. These tables will be provided to the senior author of the abstract at least 4 weeks prior to the abstract deadline. Detailed tabulations dealing with special topics should be reserved for the preparation of the text for meeting presentations or for the manuscript for publication. Generally, 5-6 tables should be sufficient. On rare occasions, examination of these 5-6 tables may necessitate 1-2 additional tables. In these situations, the DCC should meet these additional requests in a timely fashion, if at all possible.

In general no abstract shall be submitted to any national or international organization for consideration prior to approval of the PPC and all co-authors. If the PPC disapproves of an abstract already submitted, then the author(s) must withdraw that abstract immediately. The PPC should be notified in a timely manner if the abstract/presentation is accepted.

The selection of the person who will present the material in the abstract at the respective national or international meeting will be at the discretion of the respective WG. In general, this will be the person proposing the abstract. Regardless of who selects the presenter, the selection must be approved by the PPC.

12.8 DISSEMINATION OF INFORMATION

Prior to abstract presentation, the responsible WG is required to submit a copy of visual aids, including slides or posters to the PPC and DCC for review at least 4 weeks before a particular meeting. Unless these materials are approved by the PPC and DCC, that material shall not be presented, even though the abstract may have been approved for presentation. Also, it is desirable to submit to the PPC a copy of the text for presentation, if available. Each presentation shall have a sentence at the beginning identifying it as the work of the BEST-CLI Investigators, and that it is presented by that particular member "for the BEST-CLI Investigators". Likewise, the presenters of BEST-CLI ancillary studies are required to share their visual aids and text of their presentations with the PPC. These presentations need not include the phrase "for the BEST-CLI Investigators" but if appropriate may be required to include the phrase "for the XX ancillary study investigators"

Once a main result has been presented at a scientific meeting, the tables used should be available to BEST-CLI investigators and may be used by them at other scientific meetings. However, such subsequent presentations should not appear in published form unless the data in the original paper has been published.

In the case of results scheduled for presentation before an organization issuing press releases, the presenter may submit, for release to the press, the text of the presentation after it has been approved by the PPC. If the presentation is based on a manuscript not yet accepted for publication in a peer review journal, a sentence must be included on the front page indicating the preliminary nature of the results. If release of the results is embargoed until a conference presentation or manuscript publication, this must be explicitly stated in the prepared materials.

A standard set of slides, representing the major results of BEST-CLI, will be produced by the DCC for each study center after the results have been presented publicly at a national or international meeting or in a published manuscript. A standard set of slides representing the major results of an ancillary study may be prepared for each study center by the ancillary study lead investigator.

12.9 INVITATIONS TO INVESTIGATORS FOR BEST-CLI PRESENTATIONS

The BEST-CLI Investigators welcome opportunities to participate and present reports at national and international scientific meetings. When an invitation is received by a BEST-CLI Investigator, BEST-CLI policies with regard to publications and presentations must be followed.

1. Personal invitations received by BEST-CLI investigators for presentations should be sent to the PPC for review and approval.
2. When an invitation is extended to more than one investigator, or if it comes to the EC or PPC, requesting a representative of the BEST-CLI trial, the PPC shall decide who is to represent the BEST-CLI Trial.
3. All presentations in response to such invitations are to be based on published or previously presented BEST-CLI reports unless approved beforehand by the PPC.
4. Any presentation of unpublished BEST-CLI data must be reviewed and approved by the PPC prior to the date of presentation.
5. Requests received by PIs or their staff, to present or discuss at local meetings (city, state or regional) any previously published BEST-CLI data, need no prior clearance by the PPC. All local presentations must be reviewed and approved by the Contact PI at the site making the presentation. BEST-CLI Investigators should be encouraged to accept such invitations. It is requested that PIs receiving such requests notify the DCC for record keeping purposes.

12.10 USE OF BEST-CLI MATERIAL FOR GRADUATE/MEDICAL STUDENT THESES OR DISSERTATIONS

1. All requests for use of BEST-CLI data by students will be reviewed by the PPC.
2. The student requesting BEST-CLI data must be associated with an investigator in the BEST-CLI study. The BEST-CLI investigator shall act as the student's "sponsor" with regard to the data request.
3. If the PPC recommends approval for the use of the requested data, a review group will be established and will include the student as convener of the group.
4. The review group will take no action regarding the paper until the student has completed and defended the thesis or dissertation, provided this occurs in a reasonable length of time. (The student's sponsor will report on the student's progress to the PPC).
5. The students must include in the completed thesis the following:
 - a. a statement acknowledging BEST-CLI study for use of the data;
 - b. a statement indicating that opinions, ideas, and interpretations included in the thesis or dissertations are those of the student alone and not necessarily those of the BEST-CLI Investigators.
6. When the thesis/dissertation has been completed as determined by the sponsor, the dissertation review group will proceed to prepare the paper(s) for publication. A WG will be formally constituted and composed primarily of review group members. The student should be given the opportunity to take the lead on the paper.
7. The standard BEST-CLI publication policy will apply to any material published from the thesis or dissertation.
8. The BEST-CLI Investigators reserve the right to proceed with preparing a paper for publication on the thesis or dissertation topic if, in the view of the PPC, the student has not made reasonable progress on completing the thesis or dissertation.

12.11 OTHER PAPERS AND PRESENTATIONS, AND OTHER MATTERS

If a specific WG decides that the topic or charge to that WG is too broad and should be divided into 2 or more papers rather than the one paper originally assigned, the WG (through its lead person) shall communicate with the PPC Chair indicating the WG's recommendation for the division of the paper into two or more components. The WG is to identify which of the components it believes are its responsibilities, and to suggest titles and outlines for the other components. The PPC shall consider these recommendations and, as appropriate, redefine the charge to the WG, following which the above specified policy and procedure will apply.

If, in its deliberation, any WG identifies other topics or papers, either directly or indirectly related to the charge of that WG, the lead person of the WG is to communicate these suggestions to the PPC Chair, following which above specified policy and procedures are to apply.

12.12 BEST-CLI ANCILLARY STUDY PUBLICATIONS AND PRESENTATIONS

Proposals for publications & presentations from approved ancillary studies will be submitted in writing to the PPC for review and approval. The responsible proposer must be identified.

The principal proposer of the ancillary study publication will serve as the lead person of the WG for papers based on approved ancillary studies. The proposer will notify the PPC of the intent to prepare a paper or presentations on the ancillary study.

The selection of a WG, preparation and submission of papers, and submission of abstracts will follow guidelines for other BEST-CLI papers as outlined in the preceding sections.

Papers and presentations being developed, based on special data sets by sites involved in sub-studies or ancillary studies, are to be reviewed by the PPC. In general, the WG, preparing such

a report, must consist of individuals designated by the participating center(s), plus a representative of the DCC. The authorship of such a report is designated in the usual manner for a scientific report, with the order of names appearing after the title to be decided upon by the participating center(s). The PPC may act as referee, if requested, to help resolve the order of names of authors. In addition to a statement of authorship, such a paper is to have a clear statement that this work was a substudy or ancillary study of BEST-CLI and the appropriate grant support is to be acknowledged.

At the end of the list of the paper's authors, an asterisk is to appear for a footnote designating that this work was performed as part of the BEST-CLI Trial as a substudy or an ancillary study. Where appropriate, a listing of participating centers and participants who are not authors (generally not more than four persons from each center) is to be included. This decision is to be made by the participating centers and is to be reviewed by the PPC.

12.13 PRIVATE SECTOR PARTICIPATION IN A CLINICAL TRIAL

The PPC and BEST-CLI Trial will adhere to NHLBI guidelines regarding private sector participation in a clinical trial.

Appendix 1: BEST-CLI Writing Topic Proposal Form

The purposes of this form are to provide the information needed by the PPC for review of proposals for manuscripts, abstracts, and presentations, and also to provide sufficient detail to the DCC to permit informed allocation of statistical resources. The form should be completed by the main proposer(s) of the writing topic, and forwarded to the PPC Chair.

Contact Information
Lead proposer:
Site:
Phone:
Fax:
E-mail:

Working Title: _____

Type of Task: ☐ **Publication**
☐ **Presentation**
☐ **Other (specify):** _____

Nature of Work: ☐ **Descriptive**
☐ **Inferential (Comparisons/Associations)**

Date of Request: ____ / ____ / ____

Introduction/Background:

Please provide a brief description of the proposed work, including the scientific context and interest in this research topic.

Literature Review:

List references that will provide useful background to the PPC and the DCC statisticians

Primary Aim(s):

If the proposed work is descriptive in nature, then outline the major objectives. Otherwise, if the proposed work is inferential in nature, then describe the major research questions that are to be investigated.

Specific Hypotheses:

If the proposed work is inferential in nature, list the specific hypotheses to be tested. Each hypothesis should be written as a declarative, falsifiable statement

Inclusions/Exclusions:

Indicate which subjects/participants to use in the analysis. Please specify any special restrictions to be placed upon the data.

Variables to be used (from eCRFs):

Form	Item Numbers or Variable Names

Outline of Analysis:

Provide a brief outline of the analysis to be conducted. This may include specific relations among variables that you would like investigated, statistical methods that you think would be most appropriate, variables or variable selection procedures to be used for adjusting the results, as well as any recoding, rescaling, or collapsing of variables that may be desired/necessary. Drafts of tables and/or figures are often useful and may be attached as supplements to this document. (This section is meant primarily to guide the statistician toward an analysis that will be meaningful, understandable, and useful to the investigator. The statistician may supplement or alter the analysis plan to enhance the analysis or to ensure a statistically rigorous approach)

Additional Comments: