INVESTIGATIONAL PLAN

Percutaneous Deep Vein Arterialization for the Treatment of Late-Stage Chronic Limb-Threatening Ischemia

The PROMISE II Trial

LF-CA-PR-3, Revision 2

03 February 2021

Product Name:

LimFlow System™

Sponsor:
LimFlow, Inc.
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Santa Clara, CA 95054
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Contents

1. Protocol Synopsis

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Independent Review Committee, Clinical Events Committee, Data Monitoring Committee, Wound Core Lab, & Statistical Analysis	Syntactx 4 World Trade Center; 44th Floor 150 Greenwich St. New York, NY 10006 Phone: (212) 228-9000 Fax: (646) 375-3183
Study Title	Percutaneous Deep Vein Arterialization for the Treatment of Late-Stage Chronic Limb-Threatening Ischemia (The PROMISE II Trial)
Investigational Device	LimFlow System™
Indication for Use	The LimFlow System is indicated to treat chronic limb-threatening ischemia by creating an arteriovenous (AV) connection in the below-the-knee vasculature for treatment of chronic limb-threatening ischemia (CLTI).
Intended Use	The LimFlow System is intended for endovascular, minimally invasive procedures in patients who have a clinical diagnosis of chronic limb-threatening ischemia and who have been determined to have no surgical or endovascular treatment option (i.e., “no option”).
Study Objective	The objective of this US pivotal trial is to investigate the safety and effectiveness of the LimFlow System for creating an AV connection in the Below The Knee (BTK) vascular system using

	an endovascular, minimally invasive approach to arterialize the pedal veins for the treatment of chronic limb-threatening ischemia in subjects ineligible for conventional endovascular or surgical limb salvage procedures.
Study Population	The study population is comprised of subjects who are confirmed as "no option" (ineligible for conventional endovascular or surgical limb salvage procedures) by the Independent Review Committee (IRC). "No option" is defined as either a) absence of a usable pedal artery target (endovascular or surgical approach), or b) the presence of a pedal artery target with absence of a viable single-segment vein in either lower extremity or either arm that could be used for autogenous vein conduit.
Study Design	A prospective, single-arm, multi-center pivotal study designed to confirm the safety and effectiveness of the LimFlow System. The study will consist of a minimum of 60 and up to 120 subjects. This study utilizes a Bayesian Goldilocks adaptive design for sample size determination.
Number of Sites	Up to 25 sites in the United States, United Kingdom, and Japan
Primary Endpoint	Amputation Free Survival (AFS) defined as freedom from major amputation and death (defined below) at 6 months, compared to a historical performance goal. **Major Amputation:** above-ankle amputation of the index limb *and* **Death:** all-cause mortality
Secondary Endpoints	**Primary Patency:** Defined as absence of occlusion of the endovascular intervention that is maintained without the need for additional or secondary surgical or endovascular procedures, at 30 days and 6 months. **Primary Assisted Patency:** Defined as absence of occlusion of the endovascular intervention maintained with the use of additional or secondary surgical or endovascular procedures, as long as occlusion of the primary treated site has not occurred, at 30 days and 6 months. **Secondary Patency:** Defined as absence of occlusion of the endovascular intervention that is maintained with the use of additional or secondary surgical or endovascular procedures after occlusion occurs, at 30 days and 6 months. **Limb Salvage:** Defined as percentage of subjects with freedom

from above-ankle amputation of the index limb, evaluated at 30 days, 3 and 6 months.

Change in Rutherford Classification: Defined as a change of one class or greater, as evaluated at 30 days, 3 and 6 months.

Technical Success: Defined as the successful creation of an arteriovenous fistula in the desired limb location with immediate morphological success.

Procedural Success: Defined as the combination of technical success, and absence of all-cause death, above-ankle amputation or clinically driven major re-intervention[1] of the stent graft at 30 days.

Target Wound Healing: Defined as complete healing of the patient's target wound as evaluated at 30 days, 3, 6, 9 months, and 1 year.

All Wound Healing: Defined as complete healing of the patient's wounds as evaluated at 30 days, 3, 6, 9 months, and 1 year.

All Wound Area Reduction: Defined as reduction in area of the patient's wounds as evaluated at 30 days, 3, 6, 9 months, and 1 year.

Freedom from Contrast-Induced Nephropathy: Defined as subjects without acute (within 72 hours after intravenous contrast administration) impairment of renal function, measured as an absolute ≥0.5 mg/dL (44 μmol/L) increase compared to baseline SCr value that results in a value above the upper limit of the normal range.

Procedure Time: Defined as the time of the first puncture (venous or arterial) to when the last catheter is removed.

Radiation Exposure: Defined as patient radiation exposure (in milligray) during the procedure.

Contrast Volume: Defined as the total volume of contrast media (in milliliters) given during the procedure.

[1] The creation of a new surgical bypass, the use of thrombectomy or thrombolysis (i.e., procedures done in the setting of lost primary-assisted patency), or major surgical revision such as a jump graft or an interposition graft performed for occlusion of the stent graft.

Inclusion Criteria

1) Subject must be ≥ 18 and ≤ 95 years of age

2) Clinical diagnosis of chronic limb-threatening ischemia, defined as any of the following clinical assessments: previous angiogram or hemodynamic evidence of severely diminished arterial inflow of the index limb (e.g., ABI ≤ 0.39, TP / TcPO2 < 30 mm Hg) and

   a) Rutherford Classification 5, ischemic ulceration *or*

   b) Rutherford Classification 6, ischemic gangrene

3) Subject has been assessed by the Principal Investigator, reviewed by the Independent Review Committee (IRC), and determined that no conventional distal bypass, surgical or endovascular therapy for limb salvage is feasible due to either a) absence of a usable pedal artery target (endovascular or surgical approach), or b) the presence of a pedal artery target with absence of a viable single-segment vein in either lower extremity or either arm that could be used for autogenous vein conduit.

4) Proximally, the Target In-flow Artery at the cross-over point must fall within the recommended vessel diameter ranges for the LimFlow stent graft by visual estimation.

5) Prior stent(s) to the infrainguinal arteries (e.g., iliac, SFA, and popliteal) are allowed.

6) Planned minor amputation (e.g., partial toe, ray or proximal foot/transmetatarsal) of target extremity within 30 days after the index procedure is allowed.

7) Subject is willing and able to sign the informed consent form.

8) Subject is enrolled in an acceptable wound care network and has an adequate support network to ensure that subject is compliant with medication regimen and follow-up study visits.

9) Prior to enrollment (7-day window), women of childbearing potential must have a negative pregnancy test.

10) Primary wound is stable (e.g., not rapidly deteriorating and/or showing signs of healing).

11) Stable glycemic control, HbA1C < 10% (<269mg/dL)

12) Subjects requiring dialysis may be included, provided they meet *all* the following requirements:
    - On dialysis for > 6 months
    - Autologous arteriovenous (AV) fistula or peritoneal access used for hemodialysis
    - Serum albumin $\geq$ 30 g/liter
    - BMI $\geq$ 20

Exclusion Criteria

Subjects will be excluded from participating in this study if they meet any of the following criteria prior to initiation of the endovascular procedure:

1) Concomitant hepatic insufficiency, thrombophlebitis in the target limb, or non-treatable coagulation disorder within the past 90 days.

2) Active immunodeficiency disorder or currently receiving immunosuppressant therapy for an immunodeficiency disorder.

3) Prior peripheral arterial bypass procedure above or below the knee which would inhibit proximal inflow to the stent graft or interventional revascularization procedure within 30 days.

4) Previous major amputation of the target limb or presence of a wound requiring a free flap or absence of adequate viable tissue.

5) Life expectancy less than 12 months.

6) Documented myocardial infarction or stroke within previous 90 days.

7) Active infection (e.g., fever, significantly elevated WBC count >20.0 x 10^9/L, and/or positive blood culture) at the time of the index procedure that may preclude insertion of a prosthesis or require major amputation (e.g., osteomyelitis proximal to metatarsals).

8) Known or suspected allergies or contraindications to aspirin or $P2Y_{12}$ inhibitors, heparin, stainless steel, nitinol or contrast agent that cannot be adequately pre-treated.

9) Subject is currently taking anti-coagulants, which in the opinion of the investigator, interferes with the subject's ability to participate in the study (i.e., intermittent interruption of therapy for procedure may compromise subject's safety).

10) Lower extremity vascular disease that may inhibit the procedure and/or jeopardize wound healing (e.g., vasculitis, Buerger's disease, significant edema in the target limb, deep venous thrombus in the target vein, hyperpigmentation, or medial ulceration above the ankle).

11) Significant acute or chronic kidney disease with a serum creatinine of > 2.5 mg/dl in subjects not undergoing dialysis.

12) Severe heart failure (e.g., NYHA Class IV), which in the opinion of the investigator may compromise subject's ability to safely undergo a percutaneous procedure.

13) Any significant concurrent medical, psychological, or social condition, which may significantly interfere with the subject's optimal participation in the study, in the opinion of the investigator.

14) The subject is currently participating in another investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the endpoints of this study.

15) Subject is unwilling, unable, or unlikely for cognitive or social reasons to comply with any of the protocol or follow-up requirements.

Duration of Study

Each enrolled subject will be followed for up to 3 years (± 4 weeks) post-procedure. The primary endpoint assessments will be completed by 6 months (± 2 weeks), and secondary endpoint assessments will be completed by 12 months (+/- 1 month) post-procedure.

Follow-Up Schedule

Measures of safety and effectiveness will be assessed through hospital discharge, at 14 (+/- 3) days, 30 (+/- 7) days, at 2, 3, 6, and 9 months (+/- 2 weeks), at one year (+/- 4 weeks), two years (+/- 4 weeks), and three years (+/- 4 weeks). The study will be completed and closed after all subjects have either met a primary endpoint or completed the 3-year follow-up requirements.

Independent Review:

An Independent Review Committee (IRC), a Clinical Events Committee (CEC), a Data Monitoring Committee (DMC), and a Wound Core Lab will provide independent oversight per their respective charters.

2. Introduction and Background

Chronic limb-threatening ischemia (CLTI) is the most advanced form of peripheral arterial disease (PAD). CLTI is defined as PAD with a clinical syndrome including ischemic rest pain, nonhealing ulceration, and gangrene (Rutherford categories 4 to 6; Fontaine stages III to IV) attributable to objectively proven arterial occlusive disease.[2,3] Within this definition, there is a broad spectrum of severity, from milder degrees of vascular insufficiency to "no option" situations where occlusive lesions are so complex, that currently available surgical and endovascular techniques are not sufficient and amputation is considered the only solution. Long-term prognosis for patient survival and limb loss are directly related to the extent of disease, and therapeutic choices have a profound impact on both life and limb. It is the highest risk and worst prognosis population—"no-option patients"—that LimFlow treats with deep vein arterialization.

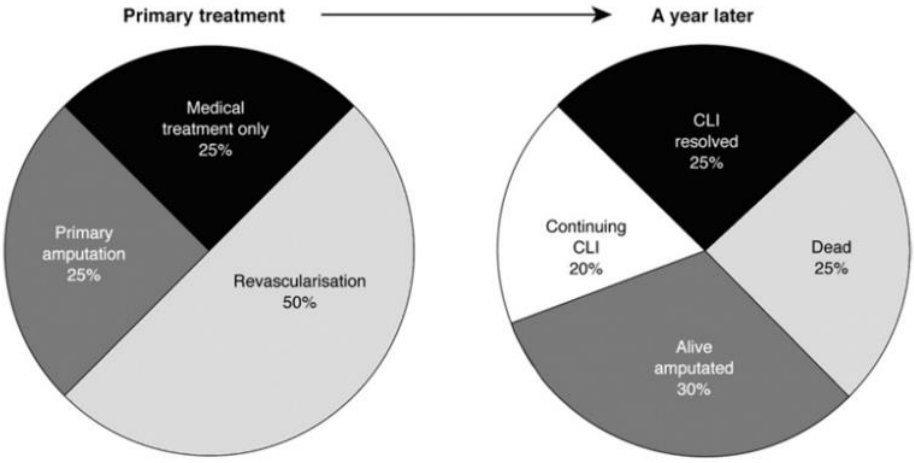

Fig. A5. Fate of the patients presenting with chronic critical leg ischemia. CLI – critical limb ischemia.

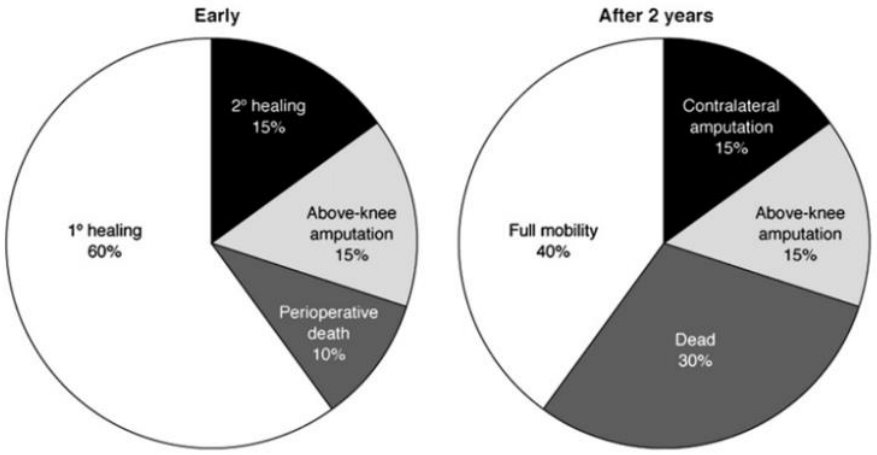

Fig. A6. Fate of the patient with below-knee amputation.

Source: Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease. Intern Angiol. 2007;26(2):81–157.

Figure 1: CLI Primary Treatment and One Year Status

[2] Conte MS. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) and the (hoped for) dawn of evidence-based treatment for advanced limb ischemia. *J Vasc Surg*. 2010 May;51(5 Suppl):69S-75S.

[3] Conte MS, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. J Vasc Surg. Volume 69, Issue 6, 3S - 125S.e40

CLTI populations are difficult to study and many data sets are incomplete due to large lost to follow-up and death in longitudinal studies, but it is expected that there will be approximately between 500 and 1000 new cases of CLTI per million every year in the European and North American populations.[4] The natural history of patients with CLTI is difficult to track as the majority of these patients receive some form of active treatment, with approximately half the patients undergoing some type of revascularization. Of those patients in surveys cited in the Inter-Society Consensus for the Management of Peripheral Arterial Disease, only a quarter who were actively being treated for CLTI had a positive resolution at one year, and in those patients who underwent amputation, two-year outcomes were even less promising (see Figure 1).

Considering the outcomes of amputation, limb salvage remains the primary goal of contemporary CLTI treatment.[5] Even with the current opportunities for treatment, the therapeutic options in CLTI patients are limited: approximately 40% of the patients are not eligible for surgical or radiological revascularization, either due to the extent or location of atherosclerotic lesions or due to extensive co-morbidity.[6,7] Wound healing is intractable in most CLTI patients who have reduced blood flow in the skin; therefore even with aggressive local wound care, patients with severe limb ischemia and chronic ulceration who do not or cannot undergo revascularization often progress to amputation.[8]

Interventionalists have been aggressively trying to treat CLTI by attempting to open Chronic Total Occlusions (CTOs) or bypassing them in the sub-intimal space using such products as the Medtronic Pioneer catheter which tunnels a wire into the sub-intimal space at the CTO and then attempts to re-enter the vessel after the occlusion. Once a wire is in place, one can place a stent to provide a bypass conduit past the occlusion. More conventional approaches to treating PVD are also used in CLTI treatment once (if) a wire gets across the occlusion. These conventional methods include PTA, stenting, and, more recently, drug-coated balloons and drug-eluting stents. Less conventionally, laser treatment and atherectomy have been used.

The LimFlow approach to treating CLTI involves the concept of venous arterialization, which has been performed surgically for many years with first clinical surgical cases reported in the early 1900s.[9,10]

Numerous small series of clinical trials have been published using a surgical approach and recent publications summarized this work.[11,12,13,14]

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[4] Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease. Intern Angiol. 2007;26(2):81–157.
[5] Sprengers RW, Lips DJ, Bemelman M, et al. Lower leg amputation due to critical limb ischaemia: morbidity, mortality and rehabilitation potential. *Dutch Journal of Medicine*. 2007;151:2185e91.
[6] Guidelines for percutaneous transluminal angioplasty. Standards of Practice Committee of the Society of Cardiovascular and Interventional Radiology. *Radiology* 1990;177:619e26.
[7] Valentine RJ, Myers SI, Inman MH, Roberts JR, Clagett GP. Late outcome of amputees with premature atherosclerosis. *Surgery*. 1996;119:487e93.
[8] Slovut DP, Sullivian TM. Critical limb ischemia: medical and surgical management. *Vasc Med*. 2008;13:281–291.
[9]Halstead AE, Vaughan R. Arteriovenous anastomosis in the treatment of gangrene of the extremities. *Trans Am Surg Ass*. 1911; 29: 265-315.
[10] Kum S, Tan YK, Tang T, Schmidt A, Scheinert D, Ferraresi R. Percutaneous Deep Venous Arterialization. *Endovascular Today*. 2015: 80-83.
[11]Lu XW, Idu MM, Ubbink DT, Legemate DA. Meta-analysis of the clinical effectiveness of venous arterialization for salvage of critically ischaemic limbs. *Eur J Vasc Endovasc Surg*. 2006; 31(5): 493-499.
[12]Schreve MA, Minnee RC, Bosma J, Leijdekkers VJ, Idu MM, Vahl AC. Comparative study of venous arterialization and pedal bypass in a patient cohort with critical limb ischemia. *Ann Vasc Surg*. 2014; 28(5): 1123-1127.
[13]Schreve MA, Vos CG, Vahl AC, et al. Venous Arterialisation for Salvage of Critically Ischaemic Limbs: A Systematic Review and Meta-Analysis. *Eur J Vasc Endovasc Surg.* 2017; 53(3): 387-402
[14] Kum S, et al. Midterm Outcomes From a Pilot Study of Percutaneous Deep Vein Arterialization for the Treatment of No-Option Critical Limb Ischemia. *J Endovasc Ther.* 2017 Oct;24(5):619-626.

Non-randomized prospective pilot studies have been conducted with the LimFlow System in Singapore and in Europe. A non-randomized prospective pilot study and a CE Mark study have been conducted with the LimFlow System. These studies supported the CE Mark approval of the device on October 17, 2016. The subjects continue to be followed through 2 years post-procedure, and the results continue to be encouraging. Subjects were enrolled under an early feasibility (EFS) trial in the United States beginning in July 2017 and, while not statistically powered, the results are also promising.[15]

3. Test System

3.1 Device manufacturer

Contract Medical International GmbH
Lauensteiner Strasse 37
01277 Dresden
Germany

3.2 System Components

The LimFlow System consists of the following components:

- Ultrasound System
  - Transceiver
  - Control Mechanism
- Arterial/Venous Catheter Set
  - Arterial Catheter
  - Venous Catheter
  - Extension Cables (may be provided separately)
- Stent Graft System
  - Conical Stents: 3.5 & 4.0 x 5.5 x 60 mm
  - Cylindrical Stents: 5.5 x 60, 100, 150, & 200 mm
- Valvulotome

4. Study Overview and Methodology

LimFlow, Inc. (Sponsor) plans to conduct a clinical trial to investigate the safety and effectiveness of the LimFlow System for creating an AV connection in the Below The Knee (BTK) vascular system using an endovascular, minimally invasive approach to arterializing the pedal veins for the treatment of chronic limb-threatening ischemia (CLTI) in subjects ineligible for conventional endovascular or surgical limb salvage procedures.

4.1 Study Design

A prospective, multi-center pivotal study consisting of up to 120 subjects designed to confirm the safety and effectiveness of the LimFlow System.

4.2 Name of Investigational Device

LimFlow System™

[15] Mustapha JA, Saab FA, Clair D, Schneider P. Interim Results of the PROMISE I Trial to Investigate the LimFlow System of Percutaneous Deep Vein Arterialization for the Treatment of Critical Limb Ischemia. *J Invasive Cardiol*. 2019;31(3):57-63

4.3 Number of Centers

Subjects may be enrolled at up to 25 sites. A complete listing of all clinical sites will be maintained by the Sponsor and will be available upon request.

4.4 Study Population

The study population is comprised of subjects who are confirmed as "no option" (ineligible for conventional endovascular or surgical limb salvage procedures) by the Independent Review Committee (IRC). "No option" is defined as either a) absence of a usable pedal artery target (endovascular or surgical approach), or b) the presence of a pedal artery target with absence of a viable single-segment vein in either lower extremity or either arm that could be used for autogenous vein conduit.

4.5 Number of Subjects

The study will enroll at least 60 and up to 120 subjects, based upon the planned adaptive trial design sample size re-estimation during enrollment.

4.6 Loss to Follow-up Considerations

It is estimated that the overall general loss to follow-up will be 10% at the time of primary analysis, and a true loss to follow up rate <10% will incur censoring while a loss >10% will require various sensitivity analyses.

4.7 Primary Endpoint

Amputation Free Survival (AFS) defined as freedom from major amputation and death at 6 months compared to a historical performance goal:

Major Amputation: above-ankle amputation of the index limb

and

Death: all-cause mortality

4.8 Secondary Endpoints

Primary Patency: Defined as absence of occlusion of the endovascular intervention that is maintained without the need for additional or secondary surgical or endovascular procedures, at 30 days and 6 months.

Primary Assisted Patency: Defined as absence of occlusion of the endovascular intervention that is maintained with the use of additional or secondary surgical or endovascular procedures, as long as occlusion of the primary treated site has not occurred, at 30 days and 6 months.

Secondary Patency: Defined as absence of occlusion of the endovascular intervention that is maintained with the use of additional or secondary surgical or endovascular procedures after occlusion occurs, at 30 days and 6 months.

Limb Salvage: Defined as percentage of subjects with freedom from above-ankle amputation of the index limb, evaluated at 30 days, 3 and 6 months.

Change in Rutherford Classification: Defined as a change of one class or greater, as evaluated at 30 days, 3 and 6 months.

Technical Success: Defined as the successful creation of an arteriovenous fistula in the desired limb location with immediate morphological success.

Procedural Success: Defined as the combination of technical success, and absence of all-cause death, above-ankle amputation or clinically driven major re-intervention of the stent graft at 30 days.

Target Wound Healing: Defined as complete healing of the patient's target wound as evaluated at 30 days, 3, 6, 9 months, and 1 year.

All Wound Healing: Defined as complete healing of the patient's wounds as evaluated at 30 days, 3, 6, 9 months, and 1 year.

All Wound Area Reduction: Defined as reduction in area of the patient's wounds as evaluated at 30 days, 3, 6, 9 months, and 1 year.

Freedom from Contrast-Induced Nephropathy: Defined as subjects without acute (within 72 hours after intravenous contrast administration) impairment of renal function, measured as an absolute ≥ 0.5 mg/dL (44 μmol/L) increase compared to baseline SCr value that results in a value above the upper limit of the normal range.

Procedure Time: Defined as the time of the first puncture (venous or arterial) to when the last catheter is removed.

Radiation Exposure: Defined as patient radiation exposure (in milligray) during the procedure.

Contrast Volume: Defined as the total volume of contrast media (in milliliters) given during the procedure.

4.9 Enrollment Criteria

4.9.1 Inclusion Criteria

1) Subject must be ≥ 18 and ≤ 95 years of age
2) Clinical diagnosis of chronic limb-threatening ischemia, defined as any of the following clinical assessments: previous angiogram or hemodynamic evidence of severely diminished arterial inflow of the index limb (e.g., ABI ≤ 0.39, TP / TcPO2 < 30 mm Hg) and
    a) Rutherford Classification 5, ischemic ulceration *or*
    b) Rutherford Classification 6, ischemic gangrene
3) Subject has been assessed by the Principal Investigator, reviewed by the Independent Review Committee (IRC), and determined that no conventional distal bypass surgical or endovascular therapy for limb salvage is feasible due to either a) absence of a usable pedal artery target (endovascular or surgical approach), or b) the presence of a pedal artery target with absence of a viable single-segment vein in either lower extremity or either arm that could be used for autogenous vein conduit.
4) Proximally, the Target In-flow Artery at the cross-over point must fall within the recommended vessel diameter ranges for the LimFlow stent graft by visual estimation.
5) Prior stent(s) to the infrainguinal arteries (e.g., iliac, SFA, and popliteal) are allowed.

6) Planned minor amputation (e.g., partial toe, ray or proximal foot/transmetatarsal) of target extremity within 30 days after the index procedure is allowed.
7) Subject is willing and able to sign the informed consent form.
8) Subject is enrolled in an acceptable wound care network and has an adequate support network to ensure that subject is compliant with medication regimen and follow-up study visits.
9) Prior to enrollment (7-day window), women of childbearing potential must have a negative pregnancy test.
10) Primary wound is stable (e.g., not rapidly deteriorating and/or showing signs of healing)
11) Stable glycemic control, HbA1C < 10% (<269mg/dL)
12) Subjects requiring dialysis may be included, provided they meet *all* the following requirements:
    - On dialysis for $\geq$ 6 months
    - Autologous arteriovenous (AV) fistula or peritoneal access used for hemodialysis
    - Serum albumin $\geq$ 30 g/liter
    - BMI $\geq$ 20

4.9.2 Exclusion Criteria

1) Subjects will be excluded from participating in this study if they meet any of the following criteria prior to initiation of the endovascular procedure: Concomitant hepatic insufficiency, thrombophlebitis in the target limb, or non-treatable coagulation disorder within the past 90 days.
2) Active immunodeficiency disorder or currently receiving immunosuppressant therapy for an immunodeficiency disorder.
3) Prior peripheral arterial bypass procedure above or below the knee which would inhibit proximal inflow to the stent graft or interventional revascularization procedure within 30 days.
4) Previous major amputation of the target limb, presence of a wound requiring a free flap, or absence of adequate viable tissue.
5) Life expectancy less than 12 months.
6) Documented myocardial infarction or stroke within previous 90 days.
7) Active infection (e.g., fever, significantly elevated WBC count >20.0 x 109/L, and/or positive blood culture) at the time of the index procedure that may preclude insertion of a prosthesis or require major amputation (e.g., osteomyelitis proximal to metatarsals).
8) Known or suspected allergies or contraindications to aspirin or P2Y12 inhibitors, heparin, stainless steel, nitinol or contrast agent that cannot be adequately pre-treated.
9) Subject is currently taking anti-coagulants, which in the opinion of the investigator, interferes with the subject's ability to participate in the study (i.e., intermittent interruption of therapy for procedure may compromise subject's safety).
10) Lower extremity vascular disease that may inhibit the procedure and/or jeopardize wound healing (e.g., vasculitis, Buerger's disease, significant edema in the target limb, deep venous thrombus in the target vein, hyperpigmentation, or medial ulceration above the ankle).
11) Significant acute or chronic kidney disease with a serum creatinine of > 2.5 mg/dl in subjects not undergoing dialysis.
12) Severe heart failure (e.g., NYHA Class IV), which in the opinion of the investigator may compromise subject's ability to safely undergo a percutaneous procedure.

13) Any significant concurrent medical, psychological, or social condition, which may significantly interfere with the subject's optimal participation in the study in the opinion of the investigator.
14) The subject is currently participating in another investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the endpoints of this study.
15) Subject is unwilling, unable, or unlikely for cognitive or social reasons to comply with any of the protocol or follow-up requirements.

4.10 Key Contributors

4.10.1 Study Sponsor - LimFlow, Inc.

2934 Scott Boulevard
Santa Clara, CA 95054
Telephone: (888) 478-7705
Facsimile: (408) 898-1459
Email: PROMISE@limflow.com

4.10.2 Independent Review Committee (IRC)

The IRC will review potential study candidates to evaluate their eligibility for the study, specifically to determine that no conventional distal bypass surgical or endovascular therapy for limb salvage is feasible due to the absence of a suitable distal target artery. The IRC will operate according to an IRC Charter, which will detail the scope and purpose of the committee.

4.10.3 Core Laboratory

An independent core laboratory will be utilized in this clinical study for the reporting of technical success and wound-related clinical data. Wound data (e.g., images and measurements) collected by the sites will be compiled, reviewed, and analyzed for healing of target and all wounds (progression, completion, confirmation) by the core laboratory. A Core Lab Manual of Operations and Procedures will be maintained by the core lab.

4.10.4 Data Monitoring Committee (DMC)

The DMC will act in an advisory capacity to the Sponsor to monitor participant safety and evaluate the progress of the study and will alert Sponsor to possible concerns related to the conduct of the Study, as appropriate. DMC members will consist of at least three independent medical professionals who are not PROMISE Trial Investigators and without any conflict of interest. The committee members may include experts in the fields of interventional cardiology, vascular surgery, interventional radiology, and biostatistics. The DMC will operate according to a DMC Charter, which will detail the scope and purpose of the committee.

4.10.5 Clinical Events Committee (CEC)

The CEC will assess important endpoints of a trial and determine whether each meet protocol-specified criteria. CEC members will be independent medical professionals qualified by training and experience, with expertise in the fields of interventional cardiology, vascular surgery, and interventional radiology without conflict of interest. The CEC will operate according to a CEC Charter, which will detail the scope and purpose of the committee. A medical monitor (MM) will be responsible for training the CEC members on the protocol, the CEC Charter, and on the standard definitions and Protocol/Charter defined terms used for event adjudication. The MM will review each adverse event to determine whether it meets the criteria for adjudication.

4.11 Data Management

Electronic Case Report Forms (eCRF) will be collected in an electronic database (EDC) used to capture data for the safety and effectiveness analysis. Sites will be required to maintain source documentation, in accordance with GCP guidelines, 21 CFR 812, and ISO 14155 to substantiate all data collected. Primary data collection based on source-documented chart reviews will be performed by the clinical research team. The Sponsor will provide adequate source document worksheets for capture of study-specific data during the procedure and follow-up visits that may not normally be collected during routine procedures or visits.

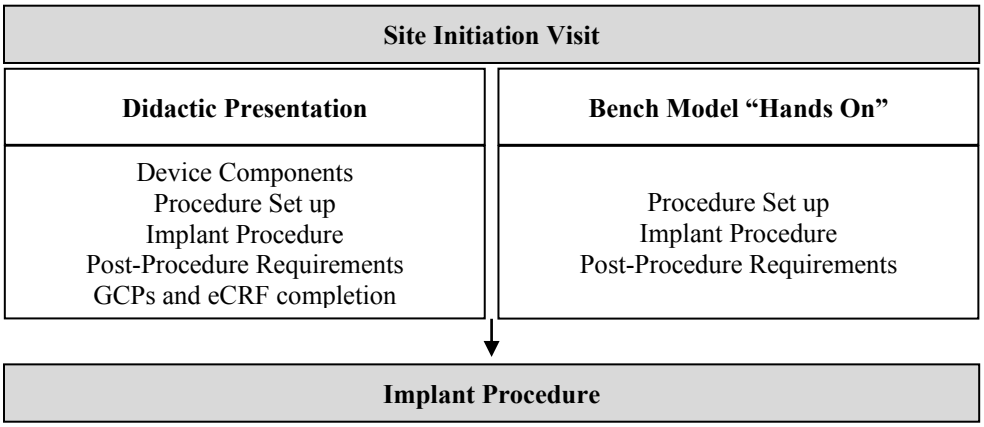
4.12 Monitoring

The clinical site will be monitored periodically by the Sponsor's personnel, or Sponsor's designee, for protocol adherence, accuracy of eCRFs, and compliance to applicable regulations. Any observations of non-compliance will be reviewed with the Principal Investigator. Any evident pattern of ongoing non-compliance may result in corrective actions by the Sponsor, including potential study suspension, as deemed appropriate by the Sponsor. The Sponsor will review significant new information, including unanticipated adverse device events and ensure that such information is provided to the appropriate regulatory agencies, the investigators and to all reviewing investigational review boards (IRBs) or Ethics Committees (ECs) as required by applicable regulations.

4.13 Training

The implanting physician(s) will receive training prior to their first case. A didactic presentation will cover the following areas: device components, procedure setup, implant procedure, post procedure requirements, protocol and regulatory requirements, screening procedures, and the Independent Review Committee approval process. The primary investigators and research coordinators will attend the didactic training session. All primary investigators will be required to attend the detailed bench model training and session. Research coordinators and ancillary staff will be encouraged to attend.

A LimFlow System implant procedure may be performed following the formal training.



A LimFlow proctor will attend all implant procedures.

4.14 Subject Recruitment

Subjects who have a clinical diagnosis of chronic limb-threatening ischemia and have been determined by their physician to have no surgical or endovascular treatment possible (i.e., "no option") will be recruited.

4.15 Subject Compensation

Subjects may be compensated for expenses associated with attending study sessions (e.g., travel costs) in

this study.

5. Study Procedures and Evaluations

5.1 Screening and Enrollment

5.1.1 Preliminary Screening

Prior to obtaining written informed consent, the subject's existing medical records may be reviewed to determine whether or not the subject might be an acceptable candidate for this study. If initial review of the medical records indicate that the subject may be eligible, the informed consent process may commence.

5.1.2 Informed Consent

The Investigator or a designated member of his/her staff should approach the subject to obtain written informed consent. As much as possible, non-technical language shall be used that is understandable to the subject. If the family of the subject is available, they should also be consulted. The background of the proposed study and the benefits and risks of the procedures and study should be explained. The subject will be given the plain language study specific Informed Consent Form (ICF) which describes all information that is relevant to study participation. The subject should be provided with ample time to read the consent form and discuss it with their family and physician. The subject must sign the consent form prior to enrollment or upload of any protected health information to IRC for screening. This form or a modification of it must have prior approval of the study site's Institutional Review Board (IRB) or Ethics Committee (EC). Subjects may not be consented after receiving any medication that might alter their ability to comprehend the consent form (*e.g.,* sedatives, narcotics, etc.).

The subject and the authorized study personnel obtaining informed consent must sign and date the ICF. A copy must be given to the subject. It is not expected that enrollment into this study will be under emergency circumstances; therefore, emergency consenting procedures do not apply. **Written informed consent must be obtained prior to performing any *protocol driven* tests or procedures that are not standard of care.** Once written consent has been obtained, the subject will be entered on a screening log which will be maintained at each site. All subjects *who provide written informed consent* will be entered on the screening log regardless of whether or not they continue on to enrollment in the study. Subjects who provide written informed consent and remain interested in study participation will begin the screening process. As appropriate, important and new information will be provided to new and existing subjects throughout the duration of the study.

If a subject is unable to make the decision to participate (e.g., mentally ill, demented or otherwise cognitively handicapped person), the subject will be excluded.

Table 1: Study Assessment Schedule

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
	Baseline and Screening (-6M to proc)	Treatment (Day 0) to Discharge	2 Weeks (+/- 3 Days)	1 Month (+/-1 week)	2 Month (+/- 2 weeks)	3 Month (+/- 2 weeks)	6 Month (+/- 2 weeks)	9 Month (+/- 2 weeks)	1 Year (+/- 4 weeks)	2 Year (+/- 4 weeks)	3 Year (+/- 4 weeks)
Written Informed Consent	√										
Baseline imaging[1] that establishes pedal artery target	√										
Inclusion / Exclusion criteria, including IRC, assessment that subject is not a candidate for conventional surgical or endovascular limb salvage procedures	√										
Demographic data, medical history, medication review, physical exam, and pregnancy test (if applicable)	√										
Additional exams if required to confirm eligibility[2]	√										
Pedal vein assessment for case planning	√										
Review of medications / dual anti-platelet regimen[3]	√	√	√	√		√	√	√	√	√	√
Rutherford Classification (RCC)	√			√		√	√	√	√	√	√
WIfI Classification (ischemia measured via $TcPO_2$[4] or Toe Pressure)	√		√	√		√	√	√	√	√	√
Wound healing assessment, and photographs[5]	√		√	√		√	√	√	√	√	√
Wound culture, if suspected infection[6]	√	√	√	√		√	√	√	√	√	√
Pulse evaluation via hand-held continuous wave Doppler distal to the stent graft[7]		√[8]	√	√		√	√	√	√	√	√
Serum Creatinine	√			√			√				
Numeric Pain Scale Rating (1-10)	√			√		√	√	√	√	√	√
Procedural angiogram[8] and device performance data		√									
Procedure time, defined from sheath insertion to final catheter removal		√									
Fluoroscopy and Contrast for the index procedure		√									
Device- or procedure-related AE and SAEs[9,10]		√	√	√	√	√	√	√	√	√	√
Assessment of amputation and/or re-intervention of the Stent Graft			√	√		√	√	√	√	√	√
Duplex Ultrasound Exam to assess Stent Graft patency[11]				√	√	√	√	√	√	√	√
All-cause mortality		√	√	√	√	√	√	√	√	√	√

[1] E.g., an angiogram without procedure or angiogram from a failed recanalization
[2] Including an MRI, if there is suspected osteomyelitis and bypass conduit vein mapping if there is a pedal artery target and the ipsilateral saphenous vein has not been previously harvested
[3] Dual antiplatelet therapy is recommended for 3 months post-procedure. At a minimum, all subjects are recommended to be started on DAPT at least one week before procedure or adequately pre-loaded with DAPT as per institution practice.
[4] $TcPO_2$ will be measured at 2 constant points on the dorsum of the midfoot through the 12-month follow-up at sites who perform $TcPO_2$.
[5] Prior to any re-intervention of the stent graft, an angiogram/image and wound photograph should be obtained for adjudication purposes.
[6] Optional; Sponsor will reimburse for culture any time there is a suspected infection.
[7] Hand-held continuous wave Doppler will be performed immediately post-procedure and again between 4 and 30 hours post-procedure to assess for acute thrombosis; any findings of acute thrombosis in this time frame must be reported to the Sponsor within 24 hours of the exam.
[8] Must include pre- and post-index arteriogram showing vasculature from hip to foot
[9] Review of any hospitalizations or procedures involving the index limb, and/or potentially related to the device or procedure; all SAEs through 6 months. For subjects out of area or who refuse to come in for a visit, a telephone assessment should be conducted to capture as much information as possible at the time point.
[10] If any LimFlow device is introduced but stent-graft implantation is either not attempted or unsuccessful, subjects will be followed for safety for 30 days with a minimum of phone calls to assess AFS.
[11] May be performed at any additional non-study visit as standard of care, as indicated by clinical symptoms.

5.2 Baseline and Screening (within 6 months prior to index)

Baseline evaluation will be performed after the subject has provided written informed consent in order to ensure that the subject is an appropriate candidate for this study and to obtain baseline values for study endpoint evaluation. If the subject continues to meet the study's enrollment criteria and continues to be willing and able to participate in the study protocol, the subject undergoes baseline evaluation and continued assessment for eligibility.

Baseline visit and data collection can occur anytime within six months before the LimFlow procedure up to the time of procedure (unless otherwise indicated). Subjects not eligible per the angiographic requirements (determined at the time of the screening) will be screen-failed from the study and the reason for exiting documented in the screening and enrollment logs.

5.3 Unique Study Identification Code Assignment

Each subject will be assigned a unique study identification code in an effort to protect subject confidential information. The unique study ID will be used to link study data and other study information to the subject in lieu of the subject name. The Subject Name Log will be used to link the unique study ID to the subject. This log will remain confidential and will not be provided to the Sponsor, but only used for reference when monitoring at the study site.

5.4 Medication Regimen

It is recommended that subjects be started on dual anti-platelet therapy (DAPT) at least 1 week before the procedure or adequately pre-loaded with DAPT according to the institution's practice. Administration of anticoagulation medication and monitoring of activated clotting time (ACT) per institution guidelines is to be performed throughout the procedure. It is recommended that an Activated Clotting Time of at least 200 seconds is maintained for the duration of the index procedure. It is recommended that dual anti-platelet and/or anti-coagulant therapy be prescribed for a minimum of 3 months post-procedure.

5.5 Enrollment (Day 0)

Once any component of the LimFlow System is introduced into the body, the subject will be considered to be enrolled in the study. If any LimFlow device is introduced but stent-graft implantation is either not attempted or unsuccessful, subjects will be followed for safety for 30 days with a minimum of phone calls to assess Primary Endpoint of AFS.

5.6 Intra-operative

For consented subjects that meet the pre-operative eligibility criteria, the following data regarding their endovascular procedure will be recorded:

- Target In-Flow Artery (cross-over point), including proximal reference vessel diameter (RVD) and assessment of calcification or any other abnormalities
- Target Out-Flow Vein (cross-over point) characteristics
- Intra-operative anticoagulants administered, and corresponding ACT levels
- Pre- and post-procedural angiographic images showing flow to the foot
- Procedure start and finish times
- Total contrast amount given
- Total fluoroscopic milligray for the procedure

- Documentation of any device- or procedure-related adverse events
- Technical Success

At the end of the endovascular procedure, with the procedural sheath in place and under fluoroscopic visualization, an injection of contrast may be made to assess the anatomy, placement, and patency of the proximal, body and distal ends of the LimFlow stent graft.

5.7 Post-Operative

After the LimFlow System is successfully placed, the access site and peripheral extremity should be closely monitored. All subjects will undergo a continuous wave Doppler exam distal to the stent graft immediately following the completion of the procedure and again between 4 and 30 hours post-procedure. The exam is intended to verify the patency of the LimFlow stent graft and assess for acute stent graft thrombosis. Any findings of acute stent graft thrombosis must be reported as an adverse event within 24 hours.

5.8 Follow-up

Study subjects will be asked to undergo evaluation prior to and during the course of the clinical trial. Such tests and procedures are outlined in the Study Assessment Schedule.

Subjects should return to the clinic at 14 days (+/- 3 days), 1 month (+/- 1 week), at 2, 3, 6, and 9 months (+/- 2 weeks), and then annually (+/- 4 weeks) for up to 3 years following their endovascular procedure and the peripheral limb/wound should be assessed. For the purposes of this study, 1 “month” will equal 30 calendar days, e.g., 3 months would be equivalent to 90 days. For the purposes of this study, 1 “year” will equal 365 calendar days, e.g., 2 years would be equivalent to 730 days.

Visits or tests occurring outside of the specified date range will be considered protocol deviations. All protocol deviations, including visits outside of the protocol allowable window, will be documented and reported. Subject compliance with follow-up is critical. Lack of or incomplete follow-up may present a risk to the subject and may compromise study results. For subjects out of area or who refuse to come in for a follow-up visit, a telephone assessment should be conducted to capture as much information as possible at this time point.

Routine surveillance of the wound and index limb will be performed during each follow-up visit, in accordance with ACC/AHA 2006 Peripheral Disease Guidelines. Examinations will include assessments of pulse, pain, Rutherford Classification, WIfI Classification, wound healing status, medication regimen (antiplatelets, anticoagulants, antibiotics, and other pertinent medications that may affect wound healing) and any procedures or complications related to the index limb occurring since the last visit. In the event of a major amputation of the target limb, the LimFlow Stent Grafts may be harvested for evaluation.

The limb/wound will be photographed by trained personnel using the eKare Insight® system. Refer to the eKare Insight Training for photograph protocol. The eKare inSight digital wound management platform (eKare, Inc., Fairfax, Virginia, United States of America) will be used for photographing, scanning, and assessing wounds at screening and follow-up visits. eKare inSight will be provided to sites for use during the study by the Sponsor. eKare is ISO 13485 certified and is fully compliant with FDA 21 CFR Part 820, Part 11.

5.9 Study Exit or Premature Withdrawal

Subjects will be exited from the study by completion of a Study Exit eCRF. Subjects will be exited upon completion of the follow-up visits, withdrawal of consent, or instance of meeting a primary study endpoint (major amputation or death). Following study exit, the subject will undergo the standard medical care for their condition as determined necessary and appropriate by their physician.

Subjects may be prematurely exited or withdrawn from the study for, including but not limited to, the following reasons:

- Voluntary withdrawal – meaning that the subject voluntarily chooses not to further participate in the study
- Lost to follow-up – meaning that the subject is more than 14 days out of window of a study visit and 3 documented attempts to contact the subject are unsuccessful. A subject who misses two consecutive study visits, including phone contact, will be considered lost to follow-up. A missed visit will be considered a protocol deviation and the deviation will be documented and reported.
- In the physician's opinion, it is not in the best interest of the subject to continue study participation.

All subjects enrolled (including those withdrawn or lost to follow-up) shall be accounted for and documented.

6. System Accountability

Access to LimFlow System inventory will be controlled and will be housed in a secure location. Records will be maintained to document the physical location of inventory from shipment/removal from Sponsor facility through use and/or return or disposal.

The site will be responsible for keeping the Device Accountability Logs up to date, which record receipt, use, return and/or disposal of each investigational device.

If there is a product malfunction or other need to return the system or system components to the Sponsor, the Sponsor should be contacted for safe product disposal and/or return. Specific instructions will be provided in the Manual of Operations.

7. Safety Oversight

7.1 Independent Review Committee (IRC)

The Independent Review Committee specific criteria to be evaluated in the determination of patient eligibility include, but may not be limited to:

- Baseline angiograms/images to evaluate the status and patency of the distal arterial bed (i.e., anterior /posterior projections of below the knee and foot views of tibial and peroneal arteries, dorsalis pedis artery, and plantar arteries).
- Wound photographs of all wounds
- Additional exams if required to confirm eligibility

7.2 Clinical Events Committee (CEC)

The Clinical Events Committee (CEC) will be responsible for the review of all device- or procedure-related adverse events and adjudication of study endpoint events according to the CEC charter. The details of the CEC objectives, scope of responsibilities, meeting schedule, record keeping, and other committee

administration details will be outlined in the CEC Charter and further agreed to by the committee members. CEC adjudicated events will be used in the analysis of study endpoint data.

The CEC will adjudicate the events related to the endpoints as listed below and all UADEs. The CEC will also review other events when requested to do so by Sponsor.

Events reviewed by the CEC:

Outcomes Adjudication: Reports of endpoint event components will be reviewed and adjudicated, including but not limited to:

- Target Limb amputation documented at ankle or above
- Target Limb Occlusion (via DUS and/or angiographic documentation)
- Target Limb Thrombosis (via DUS and/or angiographic documentation)
- Death
- Major and minor re-interventions of the index limb
- Contrast-induced nephropathy within 72 hours of the index procedure

The CEC will also review safety data while the study is in progress, including reports of any serious device- or procedure-related adverse events and/or any reports of device malfunction or failure.

7.3 Data Monitoring Committee (DMC)

The Data Monitoring Committee (DMC) will make a recommendation to the sponsor regarding sample size re-estimation. This will be based upon the information provided to them by the independent statistician that will implement the adaptive sample size re-estimation. During the study, the DMC will be asked to ensure that the rights and welfare of the subjects are protected by providing recommendations concerning the continuation, modification, or termination of the study based on review of safety data. Additional DMC details will be outlined in the DMC Charter and further agreed to by committee members.

7.4 Study Termination

If the Sponsor determines that an event, or event rate presents an unreasonable risk to subjects, then the investigation or parts of the investigation presenting that risk shall be immediately revised or terminated. Termination shall occur not later than 5 working days after the Sponsor makes this determination and not later than 15 working days after the Sponsor first received notice of the event. The Sponsor will notify all participating investigators, and IRB/ECs and the FDA of the termination of the investigation.

8. Adverse Event and Incident Reporting

Adverse events (AEs) may occur during the investigational procedure or during the follow-up phase. Existing medical conditions prior to patient enrollment will be documented in the subject's medical record but should not be reported as adverse events that are related to the investigational device or procedure unless significant exacerbation of the pre-existing medical condition resulted directly from the device or the procedure. Adverse Events determined to be relevant to the indication being studied will be recorded and reported to the Sponsor.

At each evaluation, the investigator (or designee) will determine whether any adverse events (AEs) relevant to the indication being studied have occurred. Subjects are encouraged to report AEs spontaneously or in response to general, non-directed questioning (e.g., How has your health been since the last visit?). If it is determined that a relevant AE has occurred, the investigator should obtain all the information required to complete the AE Case Report Form (CRF).

Each adverse event will be judged by the Investigator as to its relationship and level of relatedness to the investigational devices and/or investigational procedure. In addition, the Investigator will identify the date of onset, any required treatment or intervention, severity and duration. All adverse events will be monitored until they are adequately resolved or explained. The CEC will be the final arbiters of AE seriousness, severity, classifications, relatedness, and anticipatedness.

For purposes of this study, the following events are not considered adverse events, because they are normally expected to occur in conjunction with endovascular procedures / post-procedure, or are associated with customary, standard care of subjects undergoing these procedures:

- Early post-operative pain (within 24 - 48 hours post-index procedure) at the access site and/or related to position on procedure table
- Post-anesthesia/conscious sedation emesis, nausea, or headache (within 24 - 48 hours post-index procedure)
- Chest pain without associated ECG changes
- Hematocrit decrease from baseline not associated with hemodynamic changes, remaining above 30% and not requiring transfusion
- Electrolyte/fluid imbalance without clinical sequelae following endovascular procedure, even if requiring correction
- Low grade temperature increase (<38.3ºC/101ºF)
- Sinus bradycardia/tachycardia that does not require treatment or intervention
- Systolic or diastolic blood pressure changes that do not require treatment or intervention
- Standard wound care for this patient population (e.g., debridement, minor amputations, etc.) including those instances wherein the patient stays overnight for observation

This listing of events is intended to provide guidance to the investigational sites for purposes of adverse event reporting. The investigator at the investigational site should utilize his/her own clinical judgment in evaluating adverse experiences and may decide that the above events should be reported as adverse events.

8.1 Adverse Event Follow-up

After the occurrence of an AE, the investigator is required to follow the subject proactively and provide further information on the subject's participation. Any device- or procedure-related SAEs, or SAEs involving the index limb will be followed up until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up. Non-serious AEs that are relevant to the indication being studied, and other SAEs will be followed until adequately resolved or explained. The investigator will ensure that all follow-up information is provided to the Sponsor including results from any laboratory tests, investigations or consultations with other health care professionals that serve to clarify the nature of the event and/or cause of the event.

8.2 Adverse Event Reporting

All adverse events will be reported to the Sponsor as indicated in Table 2 below:

Table 2: Overview of AE Reporting Timelines, Investigator/Site to Sponsor

Type of Report	Submission Schedule
Acute Thrombosis Post Procedure	Verbal or written report within 24 hours of finding
Adverse Device Effect (ADE)	Written report within 5 working days
Unanticipated Adverse Device Effect (UADE)	Written report within 10 working days
Serious Adverse Event/Serious Adverse Device Effect (SAE/SADE)	Written report within 5 working days
Subject Death	Written report within 5 working days

The Investigator will report adverse events to the reviewing IRB/EC *(as applicable)* according to the institutional reporting requirements.

8.3 Other Incident Reporting

Incidents that occur during a clinical investigation must also be reported to the Sponsor. Table 3 below indicates potential incidents requiring reporting. There are unforeseen circumstances that may occur. Any item of incident or note must be reported to the Sponsor regardless of whether or not the item is listed. Reports must identify subjects using the study's unique identifier to protect subject's confidentiality.

Table 3: Overview of Other Incident Reporting Timelines, Investigator/Site to Sponsor

Type of Notification	Time Constraints
Withdrawal of IRB/EC Approval	Verbal report within 24 hours followed by a written report within 5 working days
Informed Consent NOT Obtained	Verbal or written report within 5 working days

8.4 General AE Definitions

An AE is defined as any undesirable clinical occurrence in a subject whether or not it is considered to be device related. In addition, the definition of AE applies to any event with an onset post study procedure or to any underlying diseases, present at baseline that exacerbate in severity post study procedure. Therefore, an underlying disease that was present at the time of enrollment is not reported as an AE, but any increase in the severity of the underlying disease is to be reported as an AE.

The following definitions for rating severity of adverse events will be used:

Mild: Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs or symptoms are transient. Consider whether these events are clinically significant and relevant to report.

Moderate: Interferes with the subject's usual activity and/or requires symptomatic treatment.

Severe: Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

Serious adverse event (SAE) is defined as an event:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolonged hospitalization
- Necessitates an intervention to prevent a permanent impairment of a body function or permanent damage to a body structure (i.e. revascularization of LimFlow System)
- Results in persistent or significant disability/incapacity
- Results in congenital abnormality

Adverse Device Effect (ADE) / Device-Related Adverse Event: an adverse effect on health or safety caused by or associated with the study device. An adverse event is considered to be device-related when, in the judgment of the investigator, the clinical event has a reasonable time sequence associated with use of the investigational device and is unlikely to be attributed to concurrent disease or other procedures or medications. It is reasonable to believe that the device directly caused or contributed to the adverse event.

Procedure-Related Adverse Event: an adverse event is considered to be procedure-related when it occurs within 30 days of the study procedure, and in the judgment of the investigator it is reasonable to believe that the event is associated with the study procedure and is not specific to the investigational device used. Other products, surgical techniques, or medications required specifically for the procedure are likely to have contributed to the occurrence of the event.

Concomitant Medication-Related Adverse Event: an adverse event is considered to be concomitant medication related when, in the judgment of the investigator, it is reasonable to believe that the event is associated with concomitant medications used in conjunction with the investigational device and is not otherwise specific to the investigational device (e.g., bleeding associated with anticoagulation medication).

Pre-Existing Condition-Related Adverse Event: an adverse event is considered to be related to a pre-existing condition when, in the judgment of the investigator, it is reasonable to believe that the event is associated with the subject's pre-existing condition and is not specific to the investigational device or procedure. Pre-existing conditions that are aggravated or become more severe during or after the procedure should be evaluated on a case-by-case basis to determine if the event may be more appropriately classified as device-related or procedure-related.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with the study device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the Investigational Plan or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The Sponsor, or its designee, will assess all adverse events considered to be serious and device-related for potential reportability to the FDA and other regulatory authorities as an Unanticipated Adverse Device Effect (UADE).

When reporting AEs, the presenting condition should be reported as the AE; any procedures performed would be reported as "treatment", and any deaths would be reported as outcomes. Example:

- Adverse Event: arterial or venous occlusion
- Treatment: re-interventions or amputation
- Outcome: resolved

8.5 General Reporting Requirements (Serious & Non-Serious Adverse Events)

All potentially device- and/or procedure-related adverse events (AE) and all serious adverse events (SAE) will be reported and monitored from the time of treatment through the 6-month follow-up visit. Any SAEs related to the index limb will be reported and monitored throughout the 3-year follow-up visit. The report should include: severity, duration, action taken, treatment outcome and relationship of the adverse experience to the study device, procedure, concomitant medications, pre- existing condition, etc. (i.e., unrelated, related or relationship unknown).

In the case of device- and/or procedure-related adverse events that require adjudication by the CEC, medical record source documentation (e.g., procedure notes, operative notes, discharge summary, relevant progress notes, imaging, photos, or lab studies) must be provided to Sponsor or its designee.

It is the responsibility of the investigator to inform their IRB/EC of serious adverse events as required by their IRB/EC procedures and in conformance with FDA and local regulatory requirements.

8.6 Reporting to Sponsor

All serious device- and/or procedure-related adverse events and any device malfunctions or failures should be reported by the investigator (or designee) to the Sponsor, within 5 working days of learning of the adverse event or failure via phone or email contact. The Sponsor contact information for reports and questions is:

Sponsor Contact:
LimFlow, Inc.
Phone: (888) 478-7705
Fax: (408) 898-1459

9. Protocol Deviations

Investigators must obtain prior approval from the Sponsor's clinical study management and in some cases, where applicable, the reviewing IRB/EC, before initiating *major* deviations from the protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval shall be documented in writing and maintained in the clinical study management and Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g., subject was not available for scheduled follow-up office visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation and will be reported on the appropriate CRF.

Deviations must be reported to Sponsor regardless of whether medically justifiable, outside the control of the Investigator, pre-approved by Sponsor, or taken to protect the subject in an emergency. Subject-specific deviations and other deviations (e.g., unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator agreement or not been trained in the use of the device, etc.) will be reported in the eCRF. Investigators will adhere to procedures for reporting study deviations to their IRB/EC in accordance with their specific reporting policies and procedures. AE source document worksheets (SDW) will be provided for documentation of Investigator's assessments/signature/date, which will be used to monitor relatedness data.

Regulations require that Investigators maintain accurate, complete, and current records, including documents showing the dates of and reasons for each deviation from the protocol. For reporting purposes, Sponsor classifies study deviations as major and minor:

***Major deviation*:** Any deviation from subject inclusion and exclusion criteria, subject informed consent procedures, or unauthorized device use.

***Minor deviation*:** Deviation from a protocol requirement such as incomplete/inadequate subject testing procedures, follow-ups performed outside specified time windows, etc.

Minor Deviations that continue to occur at an investigational site may be classified as Major Deviations if corrective action is not taken to secure future compliance to the protocol. Periodic listings of site-specific protocol deviations will be provided to the respective clinical sites throughout the course of the study.

10. Risk/Benefit Assessment

10.1 Potential Benefits

The potential benefit to the subjects enrolled in this study is improved blood flow to the foot, but not necessarily eliminating the need for major amputation. The potential benefit of improved wound healing greatly outweighs the standard endovascular/surgical risks associated with this procedure in this "no-hope" patient population who will have a major amputation if the LimFlow procedure is not attempted. However, the actual benefits are not known and are the subject of this investigational study. There may be no direct benefits of study participation. However, subject participants will undergo an enhanced level of clinical scrutiny of health compared to routine clinical care, which may provide some indirect health benefits.

10.2 Risk Analysis

The benefit to the subjects enrolled in this study is the potential for improved blood flow to the foot, reducing or eliminating the need for major amputation. The proposed clinical investigation is designed to gather evidence to support preliminary risk assessment and the subjects to be enrolled may be subject to both anticipated and unanticipated adverse events.

10.3 Anticipated Adverse Events

The following adverse events may occur as a result of anesthesia, use of contrast or the use of the investigational device. Listed below are the events that are considered to be anticipated when performing any percutaneous endovascular intervention and may be attributable to the use of the LimFlow System:

- Allergic response
- Arterial / venous occlusion
- Arterial / venous thrombus formation
- Arterio-venous fistula (unplanned)
- Bleeding / oozing from the puncture site
- Bruising at wound site
- Compartment syndrome
- Congestive cardiac failure
- Contrast-induced nephropathy and renal failure
- Death
- Device failure / malfunction
- Edema
- Embolization (air, tissue, device)
- Hematoma
- Infection
- Inflammatory response
- Intimal tear / dissection
- Lower extremity ischemia
- Occlusion of the stent graft
- Perforation of the vessel wall
- Peripheral nerve injury
- Pseudoaneurysm
- Requirement for major amputation of index limb
- Retroperitoneal bleeding
- Systemic infection, sepsis
- Vascular injury requiring repair
- Vasospasm
- Vasovagal response
- Wound dehiscence
- Wound site pain

The LimFlow System was reviewed in accordance with a risk management process that complies with the international standard on the application of risk management to medical devices EN ISO 14971:2012. The risk management process entailed an analysis of potential risks and an evaluation of their acceptability in the light of the intended therapeutic use of the system. The purpose of the risk analysis was to identify and characterize undesirable events that could result in harm. For each identified hazard the risks were estimated by factoring in the probability of occurrence and severity of the harm. The design verification report was reviewed to verify that all risk control measures identified as necessary to reduce risk to acceptable levels had been implemented and that no risks would arise from the implementation of control measures. It was concluded that all risks associated with the identified hazards had been reduced to acceptable levels and that the overall risk of the use of the LimFlow System was determined to be acceptable. The LimFlow System received CE-mark in October 2016.

10.4 Potential Risks to Subject Confidentiality

In all clinical studies, confidentiality of protected health information may be breached due to study-related activities beyond those of routine clinical care. This risk will be minimized by not collecting personally identifying information on Case Report Forms (CRFs) or other study related documentation to be provided to the study Sponsor. Such documentation will be linked to the subject using a unique study identification code.

10.5 Minimization of Anticipated Risks

The following steps have or will be taken by LimFlow, Inc. to control or mitigate the risks during the course of this study:

- The use of standard medical grade materials that have been thoroughly characterized and tested to assure biocompatibility.
- Extensive pre-clinical evaluation including in vitro bench testing, animal and cadaver study.
- The well-established, standard nature of the endovascular procedures and techniques to be used.
- The ability to quickly and safely remove the LimFlow System from the procedure; the physician may elect to discontinue the use of the device at any time in favor of alternate devices.
- Monitoring of angiographic and hemodynamic parameters during placement of the device to evaluate for any compromise of the subject's condition.
- Conducting frequent follow-up visits in the first year post-operatively to allow for systematic monitoring and surveillance of the index limb, allowing for early detection of hemodynamically significant stenosis in the graft that may occur in the absence of obvious symptoms.
- Screening of potential subjects by an independent committee to ensure that all subjects meet defined eligibility criteria.
- Selecting only qualified, experienced Investigators who have participated in an extensive training program to assure thorough knowledge of the Investigational Plan and proper technique for use of the LimFlow System.
- Providing clinical support for device related guidance during the implant procedure.
- Providing safety oversight by an independent group of physicians (the CEC and DMC) for individual subjects as well as across the entire study population.
- Attending to arterial and venous access techniques to minimize the trauma to vascular structures.
- Ensuring that treatment and follow-up of subjects is consistent with standard and current medical practice.
- If the DMC determines a negatively high rate for a particular safety issue across the subject population, a termination assessment will be performed, and the DMC may recommend enrollment in the study be stopped.
- PHI protection measures such as use of a unique study identification code and a commitment from all participants to protect subject confidentiality at every step during the investigation.

11. Statistical Analysis Plan

A single treatment arm will be enrolled to confirm the safety and effectiveness of the LimFlow System. The study will consist of a minimum of 60 and up to 120 subjects. This study utilizes a Bayesian Goldilocks[16] adaptive design for sample size determination.

[16] Broglio KR, Connor JT, Berry SM., "Not too big, not too small: a goldilocks approach to sample size selection," J Biopharm Stat. 2014;24(3):685-705

11.1 Analysis Overview

This design utilizes a Bayesian Goldilocks[17] adaptive design for sample size determination. The pivotal cohort will consist of a minimum of 60 subjects and a maximum of 120 subjects. When N=60 subjects have been enrolled in this cohort, enrollment may stop based on a Bayesian predictive probability calculation of whether the study is likely to pass its primary endpoint hypothesis test. If enrollment does not stop, 15 more subjects will be enrolled (N=75 total in the pivotal cohort), and the process will be repeated. The repetition may continue up to a maximum of N=120 subjects in the pivotal cohort. Once enrollment stops, six months of follow-up will ensue, at the end of which the only primary endpoint hypothesis test will occur.

11.2 Statistical Hypotheses for the Primary Endpoint

The null and alternative hypotheses for the primary endpoint are:

$$H_0: \phi \leq 0.54$$

$$H_a: \phi > 0.54$$

where ϕ is the proportion of subjects that are amputation-free at 180 days (i.e., AFS at 180 days).

11.2.1 Criterion for Success

The value specified for Ψ in this study is $\Psi = 0.977$. Achieving probability $Pr(\phi > 0.54 \mid data) > \Psi$ at the final analysis will imply acceptance of the alternative hypothesis and will constitute evidence of study success.

11.2.2 Determining the Performance Goal

The following is a summary of a report prepared for LimFlow by the Yale Cardiovascular Research Group, *Meta-Analytic Report for the LimFlow System Version 3* dated 10 March 2020.

A literature search was undertaken to identify published data on the long term (6 months or longer) clinical outcomes. Specifically: amputation-free survival or the composite of all-cause mortality or major [above-the-knee] amputation, all-cause mortality, major amputation, and wound healing) of patients with unintervened lower extremity critical limb ischemia (CLI) treated per the standard of care. Also, a literature search was performed to identify clinical data regarding the relative hazard of high-risk CLI patients (Rutherford category 5 or 6) in comparison with low-risk CLI patients (Rutherford category 4) for the outcomes of amputation-free survival, all-cause mortality, and major amputation.

The literature search was performed according to a pre-specified protocol, and the search methods and results have been documented in a Literature Search Report ("Literature Search Report for the LimFlow System" Version 2.0 dated 25 February 2020). The literature search identified 42 publications meeting inclusion criteria that reported amputation-free survival (AFS), the composite of all-cause death or major (above-the-knee) amputation, all-cause mortality, major amputation, or wound healing in no-option CLI patients.

Double data entry was performed to abstract the data into a Microsoft Excel spreadsheet, including study design variables, sample size, treatment arms, enrollment timeframe (month and year range), medical management (type, duration, and dose), patient demographics, baseline disease characteristics, and the selected clinical outcome measures at 6 and 12 months.

[17] Broglio KR, Connor JT, Berry SM., "Not too big, not too small: a goldilocks approach to sample size selection," *J Biopharm Stat.* 2014;24(3):685-705.

Of the 42 publications, 33 publications reported the 6- or 12-month rate of amputation free survival (or the composite of all-cause mortality or major amputation, which was converted into amputation free survival) and contributed to the meta-analysis. Of these, 29 studies reported AFS at six months, and 25 reported AFS at 12 months.

The observed event rates were extracted from each of the relevant studies and combined via a meta-analytic approach to arrive at an estimated historical AFS event rate for patients with no-option CLI. The pooled AFS rate estimate was calculated by taking the meta-analytic average using inverse variance weighting and a random-effects approach to account for the variability in the estimates and the potential heterogeneity of the studies. Confidence intervals around the pooled estimate were also calculated.

Table 4 shows details for each article included in the meta-analysis. The column labeled *Included Rutherford Categories* shows that many studies in Rutherford 4 (R4) as well as Rutherford 5 and 6 (R5, R6). The columns labeled *Observed Proportion R 5/6* shows the proportion of R5 and R6 patients in the study. Several studies did not report the proportion of R5 and R6, the proportion of patients in each Rutherford category, the proportion of high-risk patients was imputed based on the average of all studies that reported this proportion.

For studies only reporting patient classification by Fontaine Stage, and enrolled only Fontaine IV patients, it was not possible to determine the proportion of patients with Rutherford category four versus Rutherford category 5/6 disease. Some Fontaine IV patients would be classified as Rutherford category four because they did not meet both clinical and objective criteria for Rutherford category 5. The proportion of patients in each Rutherford category; the proportion of high-risk patients was, was also imputed based on the average of all studies that reported this proportion.

The proportions, either imputed or observed, are shown in the column labeled *Imputed or Observed Proportion R 5/6*.

The last column shows the risk-adjusted AFS rates. The risk adjustment was necessary since most studies reporting amputation-free survival in no-option CLI patients include subjects with R4, 5, and 6, and the OPG is based on R5/R6. Therefore, it was necessary to adjust the observed historical event rates to match that of the target patient population.

The initial approach to determining the adjustment factor was to perform another literature search for papers reporting the hazard ratios (HR) for AFS, all-cause mortality, or major amputation by Rutherford category in patients with CLI (regardless of revascularization status). Thirteen publications were identified, but only 3 provided the unadjusted HR for Rutherford category 5/6 versus Rutherford category four patients. An adjustment factor for AFS rates was calculated from the HRs reported in Table 5 by the following methodology. First, the HR was log-transformed, and a weighted average of the log HR was calculated and then inverted back to the arithmetic scale. The resulting risk adjustment factor for AFS rates was 2.18.

The adjustment factor was then applied to the observed AFS rates in the applicable studies of no-option CLI patients according to the proportion of high-risk (Rutherford category 5/6) and low-risk (Rutherford category ≤4) patients in each study to arrive at an adjusted AFS rate by using the following three equations and solving for the High-Risk AFS rate:

Equation 1: ***Adjustment Factor = Hazard Rate for death or major amputation for the high- risk patients ÷ Hazard Rate for death or major amputation low-risk patients = (1 - High-Risk AFS) ÷ (1 - Low-Risk AFS) = Low Risk AFS ÷ High Risk AFS***

Equation 2 ***Observed AFS Rate = High Risk % * High Risk AFS + Low Risk % * Low Risk AFS***

Equation 3 ***Low Risk AFS = High Risk AFS/adjustment***

The adjusted AFS rate for each paper is reported in the last column of Table 4.

The pooled AFS rate estimate was calculated by taking the meta-analytic average using inverse variance weighting and a random-effects model. This approach accounts for the variability in the estimates and the potential heterogeneity of the studies (see Meta-Analytic Average at the bottom of the last column in Table 4. Confidence intervals around the pooled estimate were also calculated. The meta-analytic estimate of the historical rate of AFS at six months in no-option patients with Rutherford category 5 or 6 CLI was 42.3% (95% CI, 33.5-51.1).

The performance goal is set at 54%, which is 2.9% higher than the upper 95% confidence limit of 51.1%.

Table 4: Meta-analysis of 6-month AFS rate in no-option patients with Rutherford category 5 or 6 CLI Original from Version 3.0 of Meta-Analytic Report)

Study	N	Event-free survivors (n)	Observed AFS Rate	Included Rutherford Categories	Observed Proportion R4	Observed Proportion R 5/6	Imputed or Observed Proportion R 5/6	Adjusted AFS Rate
Brass et al 2006[3]	177	146	82.5%	4, 5, 6	NR	NR	66.0%	58.9%
Teraa et al. 2015[4]	79	66	83.5%	3, 4, 5, 6	31.6%	63.3%	63.3%	58.3%
Dubsky et al. 2013[5]	22	10	45.5%	4, 5, 6	NR	NR	66.0%	32.4%
Iafrati et al. 2016[6]	34	22	64.7%	5	0.0%	100.0%	100.0%	64.7%
Anghel et al. 2011[11]	14	3	21.4%	4,5	50.0%	50.0%	50.0%	13.5%
Li et al. 2013[12]	29	22	75.9%	4, 5, 6	NR	NR	66.0%	54.1%
Benoit et al. 2011[13]	14	9	64.3%	4,5	50.0%	50.0%	50.0%	40.4%
Gupta et al. 2013[14]	10	8	80.0%	4, 5, 6	20.0%	80.0%	80.0%	64.7%
Szabo et al 2013[17]	10	4	40.0%	4, 5, 6	NR	NR	66.0%	28.5%
Belch et al. 2011[18]	259	196	75.7%	4, 5, 6	NR	NR	66.0%	54.0%
Losordo et al. 2012[19]	12	8	66.7%	4,5	41.7%	58.3%	58.3%	44.7%
Nikol et al. 2008[20]	56	34	60.7%	4, 5, 6	NR	NR	66.0%	43.3%
Powell et al. 2012[21]	24	17	70.8%	4, 5, 6	NR	NR	66.0%	50.5%
Idei et al. 2011[22]	30	3	10.0%	4, 5, 6	27.0%	73.0%	73.0%	7.6%
Pignon et al. 2017[16]	19	14	73.7%	4,5	35.0%	65.0%	65.0%	52.1%
Wang et al. 2018[24]	36	28	77.8%	4,5	66.7%	33.3%	33.3%	43.5%
Lindeman et al. 2018[25]	25	21	84.0%	3.4,5,6	8.0%	56.0%	56.0%	55.3%
Faglia et al. 2010[26]	27	3	11.1%	4,5,6	37.0%	63.0%	63.0%	7.7%
Dalla Paola et al. 2019[27]	84	50	59.5%	4,5,6	NR	NR	66.0%	42.5%
Dubsky et al. 2019[28]	44	31	70.5%	4,5,6	NR	NR	66.0%	50.3%
Faglia et al. 2012[29]	12	3	25.0%	5.6	0.0%	100.0%	100.0%	25.0%
		Simple Average	59.2%				**Simple Average**	42.5%
		Weighted Average	68.6%				**Weighted Average**	49.0%
		Meta-Analytic Average	**59.7%**				**Meta-Analytic Average**	**42.3%**
		Min	10.0%				**Min**	7.6%
		Max	84.0%				**Max**	64.7%
		SD	24.0%				**SD**	17.4%

Table 5: Publications reporting unadjusted HR for Rutherford Category 5/6 v. Rutherford Category 4

Study	N	Patient Risk Profile	Variable	Event	Unadjusted Hazard Ratio	95% CI
Chung et al. 2013[18]	98	Rutherford 4/5/6	R 5/6 vs. R4	AFS	1.56	1.01 - 2.41
Soga et al. 2014[19]	995	Rutherford 4/5/6	R 5 vs. R 4	Death	2.3	1.6 - 3.3
Spreen et al. 2016 [20]	281	Rutherford 4/5/6	Rutherford 5/6 vs. Rutherford 4	Major Amputation	2.03	1.28 - 3.21

11.3 Determination of Sample Size

Although the analysis methods are Bayesian, the following frequentist scenarios are used to guide the determination of minimum and maximum sample size.

- According to PASS 13, when using $\alpha = 0.025$ (one-sided) in an exact binomial test, achieving 90% power to test the hypotheses in Section 7.1 when the true AFS = 0.70 would require a sample size of 101 subjects. Allowing for 10% missing data would require a sample size of N=113 subjects
- If the true AFS = 0.68, a sample size of 101 subjects would achieve 81% power. Allowing for 10% missing data would require a sample size of N=113 subjects
- If the true AFS = 0.75, 90% power requires a sample size of N=56 subjects. Allowing for 10% missing data would require a sample size of N=63 subjects.

There is considerable uncertainty in the true AFS rate ϕ. Consequently, it is desirable to utilize a study design that achieves at least 80% power when AFS $\geq$ 0.68 and 90% power when AFS $\geq$ 0.70, while allowing early stopping of enrollment if the AFS rate proves to be very high (e.g., 0.75) or very low ($\leq$ 0.54). Therefore, the study design was selected wherein the sample size is adaptively determined, with a minimum value of 60 and a maximum value of 120.

11.4 Populations for Analysis

Modified Intention-To-Treat Population: mITT is defined as all subjects where a LimFlow device was introduced into the patient, regardless of technical or procedural success or major protocol deviation.

Per Protocol Population: The Per-protocol (PP) population is defined as all subjects who met all inclusion/exclusion criteria and had a successful procedure.

Untreated Population: This population consists of all consented subjects who met all inclusion and exclusion criteria but are not included in the mITT population.

[18] Chung J, Timaran DA, Modrall JG, et al. Optimal medical therapy predicts amputation-free survival in chronic critical limb ischemia. J Vasc Surg. 2013;58(4):972-980.

[19] Soga Y, Iida O, Takahara M, et al. Two-year life expectancy in patients with critical limb ischemia. JACC Cardiovasc Interv. 2014;7(12):1444-1449.

[20] Spreen MI, Gremmels H, Teraa M, et al. Diabetes Is Associated With Decreased Limb Survival in Patients With Critical Limb Ischemia: Pooled Data From Two Randomized Controlled Trials. Diabetes Care. 2016;39(11):2058-2064.

11.5 Statistical Analyses

11.5.1 General Approach

Descriptive statistics for continuous variables will include mean, standard deviation, median, quartiles, minimum, maximum, and sample size for each treatment group. Categorical variables will be summarized using counts and percentages. Proportions will be calculated using known non-missing values. Unless otherwise indicated, all statistical tests will be performed at α= 0.05 (2-sided), and confidence/credible intervals will be at level 95%.

11.5.2 Primary Endpoint Interim and Final Analyses

This study utilizes a Bayesian adaptive Goldilocks[21] design, in which several interim analyses are conducted to assess sample size adequacy, dring the only analysis that tests the alternative hypothesis that occurs once enrollment has stopped. All enrolled subjects have had the opportunity to be followed for six months (180 days). The schedule of analyses is as follows.

The set of possible sample sizes are $\{N_i = 60, 75, 90, 105, 120\}$. At the i^{th} interim analysis (when Ni subjects have been enrolled, i = 1,2,3,4), two predictive probabilities are calculated:

- PP_{win} = Pr(Eventual Win | observed and predicted outcomes, $N=N_i$ is the final sample size)
- PP_{fut} = Pr(Eventual Win | observed and predicted outcomes, N=120 is the final sample size)

Stopping of Accrual is based on the following criteria:

- Criterion for stopping accrual for expected success: PP_{win} exceeds a suitably high threshold W_i.
- Criterion for stopping accrual for futility: PP_{fut} is less than a suitably low threshold F_i.

In either case, follow-up will continue until all enrolled subjects have had the opportunity to be followed for six months, and the final analysis (i.e., a test of whether $\phi > 0.54$) will occur. If neither of these conditions holds at the i^{th} interim analysis, enrollment will continue to the next larger sample size, subject to a maximum of N=120 subjects. The set of possible sample sizes are $\{N_i = 60, 75, 90, 105, 120\}$. **Figure** displays this as a flowchart.

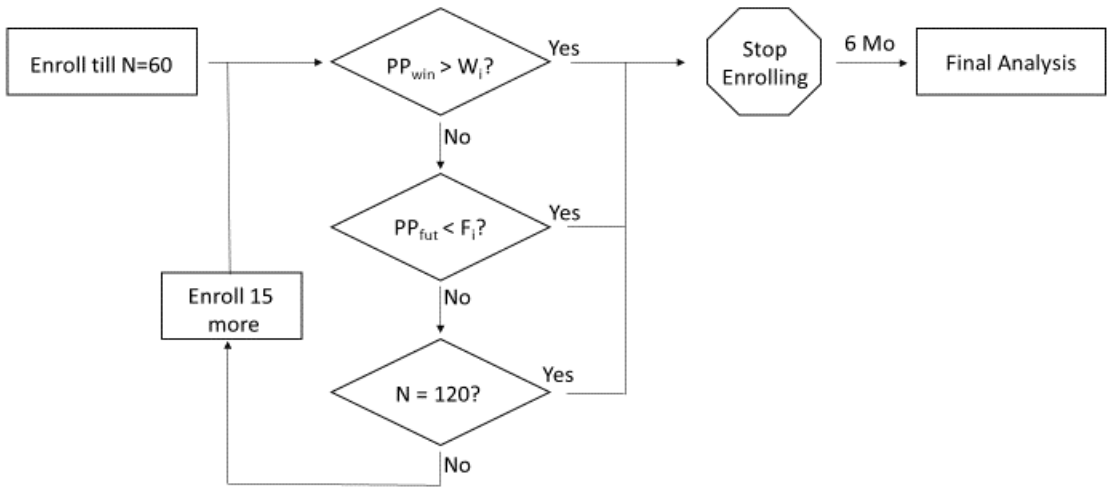


Figure 2: Flowchart of Sampling Plan

[21] Broglio KR, Connor JT, Berry SM., "Not too big, not too small: a goldilocks approach to sample size selection," *J Biopharm Stat*. 2014;24(3):685-705.

The predictive probability thresholds W_i and F_i are shown in Table 6.

Table 6 Predictive Probability Thresholds for Stopping Accrual at Interim Analyses

Interim Analysis	Sample size (N_i)	Threshold for Stopping Accrual for Promising Trend (Wi)	Threshold for Stopping Accrual for Futile Trend (F_i)
1	60	0.98	0.05
2	75	0.95	0.10
3	90	0.90	0.15
4	105	0.90	0.15

To compute the predictive probabilities PP_{win} and PP_{fut} at each interim analysis, any subject with a missing 6-month outcome will have that outcome imputed via a Bayesian predictive probability model that incorporates observed follow-up to date. The set of imputed outcomes X^* is then combined with the set of observed 6-month outcomes X_{obs} to become a "completed" dataset, with a resulting posterior probability $P(\phi > 0.54 \mid X^*, X_{obs})$ that is easily calculated from the conjugate beta posterior distribution. This process is then repeated to obtain many completed datasets. The proportion of these completed datasets that result in $P(\phi > 0.54 \mid X^*, X_{obs}) > \Psi$ is the quantity PP_{win} defined above.

To calculate PP_{fut}, the dataset is augmented with $(120 - N_i)$ yet-to-be-enrolled subjects (who have 0 days of follow-up and no event), and outcomes for all subjects with a missing 6-month outcome will have that outcome similarly imputed via a Bayesian predictive probability model that incorporates observed follow-up to date. By combining imputed and observed 6-month outcomes, a "completed" dataset X^* is obtained. This process is then repeated to obtain many completed datasets, and the proportion of these completed datasets that result in $P(\phi > 0.54 \mid X^*, X_{obs}) > \Psi$ is the quantity PP_{fut} defined above.

When follow-up is complete, the final posterior distribution is computed via Bayesian multiple imputations. The imputation will use the same predictive model that is used in the interim analyses. Each "completed" dataset implies a value for $P(\phi > 0.54 \mid X^*, X_{obs})$; averaging these probabilities over the many completed datasets integrates out the uncertainty in the imputation model and produces the final posterior probability $P(\phi > 0.54 \mid X_{obs})$. (See SAP Appendix 2 for mathematical details.) This final posterior probability is then compared to the threshold ψ to determine whether the alternative hypothesis should be accepted.

Special Considerations for COVID-19

It is possible that COVID-19 will impact the incidence of AFS. To obtain data that adequately assesses this impact, subject accrual will not actually be stopped for futility unless both of the following criteria are met:

I. $PP_{fut} < F_i$, using AFS as the endpoint
II. $PP_{fut} < F_i$, using a modified definition of AFS as the endpoint. In this modified definition, deaths documented to be caused by COVID-19 will be excluded from the definition of AFS, and subjects who die of COVID-19 will be censored on their death dates.

If both of the above conditions are met, then accrual will stop for futility. However, if Condition I is met but Condition II is not met, then accrual of subjects will continue to the next larger sample size, subject to the maximum of N=120.

At the conclusion of the trial, analyses will be presented in two ways:

1. Analyses resulting from the dataset obtained when strictly following Condition I. This analysis will exclude all data from subjects accrued after Condition I was met and will likely indicate failure to meet the performance goal. This is the principal analysis.
2. Analyses resulting from all accrued data. This analysis will include data from subjects accrued after

Condition I was met. This is a sensitivity analysis. Other planned sensitivity analyses are presented in Section 11.5.3.

Predictive Model

This section describes the prediction model that is used to predict the 6-month outcomes for subjects who have not yet reached six months. This model enables computation of predictive probabilities that form the basis for the sample size decisions in the Goldilocks design; it also serves as the "imputer's model" in the Bayesian multiple imputations that are used in the final inference.

Outcomes at six months are binary and are denoted "E" (for having experienced a primary outcome Event) or "N" (for not having experienced an event). At any analysis, it is expected that some subjects will not have completed six months, and the 6-month outcomes for those subjects will be imputed based on a statistical model, as described below.

At the time of analysis, subjects will fall into one of three categories:

A. Status E or N has been observed at 180 days. For example, subject is known to be event-free at 180 days (N), or subject has had a primary event before 180 days, and at least 180 days have elapsed since that subject entered the analysis cohort (E). (Note: an event at exactly 180 days will count as an event.)

B. Subject is known to have had an event at time < 180 days, but the subject has not yet had the opportunity to be followed for 180 days. For example, the subject dies at Day 100, but the data cutoff date for analysis is only 25 days later before the subject has the opportunity to be followed for 180 days.

C. Subject is censored without known event at time < 180 days.

Subjects in Group A have observed 180-day event status and need no imputation. Subjects in Group B will have their 180-day status set to E (with probability 1). Subjects in Group C will have their 180-day outcome imputed to be E with a probability that is subject-specific. It will be based on how long that subject has been followed and also on the event-free survival experience of other subjects, calculated via a Bayesian piecewise exponential survival model, as follows.

In this imputation model, the hazard function h(τ) is piecewise constant over the intervals [0, 30 days], (30 days, 60 days], (60 days, 90 days], and (90 days, 180 days]. Specifically, let each subject's time to an event be modeled such that the survivor function is

$$S(t) = e^{-\int_0^t h(\tau)d\tau}, \text{ where}$$

$$h(\tau) = \begin{cases} \lambda_1, & \tau \in [0, 30\ days] \\ \lambda_2, & \tau \in (30, 60\ days] \\ \lambda_3, & \tau \in (60, 90\ days] \\ \lambda_4, & \tau \in (90, 180\ days] \end{cases}$$

and let $\Lambda = \{\lambda_1, \lambda_2, \lambda_3, \lambda_4\}$. We assign each λ_i (i = 1, 2, 3, 4) an independent vague Gamma(0.001, 0.001) prior distribution (i.e., mean = 1 and variance = 1000), and because of the well-known Poisson-Gamma conjugacy, the posterior distribution f(λ_i | data) is a Gamma(0.001 + D_i, 0.001 + T_i) distribution, where D_i is the number of events that occurs within interval *i* and T_i is the total amount of follow-up over all subjects in interval *i* (in days). Moreover, because these are non-overlapping intervals, the posterior distributions of λ_1, λ_2, λ_3, and λ_4 are independent. Samples from the posterior distributions of λ_1, λ_2, λ_3, and λ_4 can be drawn directly, without the need for Markov chain Monte Carlo techniques.

For a subject j followed for $Q_j < 180$ days without a known event (i.e., censored at $Q_j < 180$ days), the probability θ_j that this subject has an event by Day 180 can be computed as

$$\begin{aligned}\theta_j &= \text{Prob}[T \le 180 \mid T > Q_j] \\ &= \text{Prob}[Q_j < T \le 180] \,/\, \text{Prob}[T > Q_j] \\ &= (\, S(Q_j) - S(180) \,) \,/\, S(Q_j)\end{aligned}$$

where S(t) = exp(-H(t)) and H(t) is the cumulative hazard function

$$H(t) = \int_0^t h(\tau)d\tau = \begin{cases} \lambda_1 t, & t \in [0,30]\ days \\ 30\lambda_1 + (t-30)\lambda_2, & t \in (30,60]\ days \\ 30\lambda_1 + (60-30)\lambda_2 + (t-60)\lambda_3, & t \in (60,90]\ days \\ 30\lambda_1 + (60-30)\lambda_2 + (90-60)\lambda_3 + (t-90)\lambda_4, & t \in (90,180]\ days \end{cases}$$

The distribution of θ_j can thus be easily computed from the piecewise constant form of $h(\tau)$ to be a function of Λ and Q_j. The distribution can be easily and quickly accomplished multiple times by first drawing samples from the gamma posterior distributions of λ_1, λ_2, λ_3, and λ_4 and subsequently transforming these into samples from the subject-specific distribution of θ_j for subject j. The missing 180-day binary event status for subject j is then imputed multiple times from a Bernoulli distribution with parameter θ_j (once for each sampled value of θ_j).

Operating Characteristics of the Design

The design described above has been subjected to extensive simulation to evaluate its anticipated performance in a variety of scenarios. In the simulation, the proportion of simulated trials that result in accepting the alternative hypothesis is the estimated power when $\phi > 0.54$ and the estimated type I error rate when $\phi \le 0.54$. The estimated operating characteristics are based on 10,000 simulated trials per scenario, with predictions for each subject with the unobserved final outcome (for each of the 10,000 trials) based on 10,000 draws from the relevant posterior predictive probability distribution.

Table 7 displays the operating characteristics and summarizes the performance of the adaptive sample size determination algorithm under various assumptions about the amputation-free rate (ϕ). Column headings are:

- ϕ^* -– The amputation-free survival rate (at 180 days) for which data were simulated
- **Power** — The power of the study. I.e., the proportion (out of 10,000 simulated trials per row) that resulted in a determination that $\phi > 0.54$.
- **Average N** — the average sample size achieved (for the pivotal cohort) in each row (of the 10,000 simulated trials per row)
- **N=60 (Futile, Promise)** — the proportion of the 10,000 trials that stopped accrual at N=60, by reason
- **Futile** — study success is unlikely, even with the maximum sample size because $PP_{fut} < F_i$
- **Promise** — study success is likely to be established with this sample size because $PP_{win} > W_i$
- **N=75 (Futile, Promise)** — analogous information about the N=75 sample size analysis
- **N=90 (Futile, Promise)** — analogous information about the N=90 sample size analysis
- **N=105 (Futile, Promise)** — analogous information about the N=105 sample size analysis
- **N=120 (Max)** — The proportion of the 10,000 trials that did not stop accrual until the maximum sample size was reached (N=120)

Table 7 Operating Characteristics of the Design

Expected Accrual Rate (5/mo)			Probability for Stopping Enrollment (by Reason)				
ϕ^*	Power	Average N	At N=60 (Futile, Promise)	At N=75 (Futile, Promise)	At N=90 (Futile, Promise)	At N=105 (Futile, Promise)	At N=120 (Max)
0.54	0.0244	76.0	0.4647	0.2317	0.1379	0.0688	0.0810
			0.0019	0.0033	0.0049	0.0058	
0.65	0.6336	95.2	0.0529	0.0594	0.0594	0.0466	0.3166
			0.0911	0.1159	0.1287	0.1294	
0.66	0.7130	94.3	0.0355	0.0422	0.0478	0.0357	0.2967
			0.1181	0.1336	0.1475	0.1429	
0.67	0.7810	92.3	0.0260	0.0314	0.0374	0.0238	0.2614
			0.1486	0.1578	0.1654	0.1482	
0.68	0.8423	90.3	0.0208	0.0228	0.0235	0.0180	0.2222
			0.1726	0.1865	0.1786	0.1550	
0.69	0.8879	87.9	0.0112	0.0158	0.0171	0.0118	0.1890
			0.2190	0.2049	0.1783	0.1529	
0.70	0.9253	84.6	0.0093	0.0099	0.0133	0.0080	0.1384
			0.2654	0.2287	0.1846	0.1424	
0.75	0.9945	71.7	0.0005	0.0004	0.0011	0.0001	0.0227
			0.5219	0.2699	0.1316	0.0518	

In Table 7, the type I error rate (when $\phi^* = 0.54$) is 0.0244, and the average achieved sample size is 76.0. In this scenario,

- the trial stopped accruing at N=60 46.66% of the time (46.47% for futility, 0.19% for promising trend),
- at N=75 23.50% of the time (23.17% for futility, 0.33% for promising trend),
- at N=90 14.28% of the time (13.79% for futility, 0.49% for promising trend),
- at N=105 7.46% of the time (6.88% for futility, 0.58% for promising trend, and
- at N=120 8.10% of the time.

When $\phi^* = 0.70$, the estimated power is 0.9253, and the average achieved sample size is 84.6. In this scenario, the trial stopped accruing at N=60 27.47% of the time (0.93% for futility, 26.54% for promising trend), at N=75 23.86% of the time (0.99% for futility, 22,87% for promising trend), at N=90 19.79% of the time (1.33% for futility, 18.46% for promising trend), at N=105 15.04% of the time (0.80% for futility, 14.24% for promising trend), and at N=120 13.84% of the time. Overall, the design performs as intended, with type I error rate ≤ 0.025, high power when $\phi^* \geq 0.68$, and smaller sample sizes when the simulated amputation-free survival rate ϕ is particularly high (e.g., $\phi^* = 0.75$) or particularly low (e.g., $\phi^* = 0.54$).

Simulation details and sensitivity of the operating characteristics to assumptions made about the data mechanism can found in the SAP for the study.

11.5.3 Sensitivity Analyses for the Primary Endpoint

At the conclusion of the study, several planned analyses will assess sensitivity to specific analytical and data features.

Sensitivity to Missing Data

All reasonable efforts will be undertaken to minimize missing data. However, some missingness is inevitable, and the study is designed with the expectation that there may be up to 10% missing primary data at six months. The reasons for missing data will be described in detail and evaluated for assessment of possible bias.

By design, the analysis of the primary endpoint multiply imputes 6-month outcomes for any subjects without measured 6-month outcomes, based on available follow-up and the imputation model previously described (Section 0). Several additional analyses are planned that will explore the sensitivity of the main conclusions, specifically:

- A completers-only analysis of binary outcomes will be conducted. This analysis will exclude subjects with a missing final primary outcome, presenting the posterior probability that $\phi > 0.54$ based on those subjects whose status is known at Day 180. The prior for ϕ will be Beta(1,1).

- A tipping-point analysis of binary outcomes will be conducted. This analysis will systematically consider each subject with a missing outcome at Day 180 as an Event or a Non-Event at 180 days, in all combinations. Posterior probabilities (that $\phi > 0.54$) will be presented for each combination. The prior for ϕ will be Beta(1,1).

- A multiple-imputation analysis, similar to the primary analysis, will be conducted. This sensitivity analysis will use a piecewise exponential prediction model with six pieces (rather than four), with the time axis from 0 to 180 days partitioned such that there are approximately equal numbers of events in each piece. Specifically, if a total of V events are observed within [0, 180 days], the k^{th} piece (k=1, …, 5) in the partition will end with a cutpoint equal to the smallest integer day D such that $D \geq k \times V/6$. The 6^{th} piece ends at 180 days.

Sensitivity to COVID-19 deaths

By definition in this study, AFS includes deaths documented to be caused by COVID-19. The following additional analyses are planned to assess the sensitivity of the study's conclusions to the handling of deaths related to COVID-19.

- An analysis wherein all deaths due to COVID-19 are censored on the date of death.

- A tipping point analysis in which COVID-19 deaths are included, or not, in the definition of AFS, in every combination. This analysis will use methods similar to the principal analysis but will conduct the imputation/prediction for subjects with missing final status as if they are similar to the cohort of subjects who did not die of COVID-19. In other words, if k subjects die of COVID-19, the parameters of the piecewise exponential model in the imputation model will be estimated while removing the k subjects who died of COVID-19. The final posterior probability will be computed by re-inserting the COVID deaths (in separate analyses) as follows:

    - k COVID deaths count as deaths at Day 180.
    - (k–1) COVID deaths count as deaths at Day 180, 1 counts as a non-AFS event at Day 180
    - (k–2) COVID deaths count as deaths at Day 180, 2 counts as a non-AFS event at Day 180
    - Etc.
    - 0 COVID deaths count as deaths at Day 180, k count as non-AFS events at Day 180
- A frequentist competing risk survival model in which deaths due to COVID-19 are considered competing risks will be performed. Cause-specific cumulative incidence functions (CIF) will be estimated, and confidence intervals for the CIF at 180 days will be reported. The levels of confidence will be 95% (two-sided) and 97.7% (one-sided, analogous to the Bayesian posterior

threshold $\psi = 0.977$).

- Other analyses suggested by patterns of observed data may be conducted.

11.6 Subgroup Analyses for the Primary Endpoint

Descriptive statistics and Bayesian posterior distribution summaries (e.g., mean, median, 95% credible interval) will be computed for the amputation-free rate parameter ϕ when computed separately according to each of the subgroups defined below. Pre-specified subgroups are:

- Sex (Male/Female)
- Dialysis status (Yes/No)
- Age (≤ 70, > 70)
- Diabetes (Type I, Type II, None)
- Race/Ethnicity
- Rutherford Category

11.7 Demographic and Clinical Characteristics

Tables of baseline characteristics will be summarized using descriptive statistics. For continuous measures, the number of observations, mean, median, quartiles, minimum, and maximum will be reported for each measure. For categorical measures, the proportion, numerator, and denominator for each category will be reported.

Untreated subjects will be described with similar descriptive statistics and with a listing.

The proportion of subjects screened and enrolled will be tabulated by site, along with measures of compliance with follow-up visits.

11.8 Tabulation of Individual Participant Data

Patient data listings, including demographics, baseline characteristics, safety data, adverse events, procedural data, and endpoints, will be provided.

11.9 Heterogeneity

Heterogeneity across sites will be assessed as follows. Based on completers, a (frequentist) Cox proportional hazards regression will be conducted, with a term for site included in the model. If there is not a significant site effect ($p > 0.10$), data will be considered poolable across sites. If there is a significant site effect ($p < 0.10$), an investigation will be conducted into whether subject baseline characteristics explain this difference. Candidate baseline characteristics include those that (1) significantly predict AFS, (2) significantly differ across sites, or (3) are deemed to be clinically important. If a baseline characteristic (or set of characteristics) explains the difference (in that inclusion of the characteristic(s) in the proportional hazards regression model causes the site effect to become non-significant, $p > 0.10$), a summary Bayesian analysis of AFS adjusting for the characteristic(s) will be conducted. If baseline characteristics do not explain the difference, results will be presented by site and in various groupings of sites as appropriate (e.g., perhaps removing any markedly different sites).

The summary Bayesian analysis will be a Bayesian piecewise exponential survival regression that adjusts for the baseline characteristic(s) described above. Summaries of the posterior distribution of the 180-day AFS rate (e.g., posterior mean/median, 95% credible interval, the posterior probability that $\phi > 0.54$) will be presented.

In these analyses, small sites (contributing < 5 subjects) will be combined into one or more larger pseudo-sites of size ≥ 5 but ≤ 10. An analysis omitting small sites will also be presented. Descriptive statistics will

be presented for all sites regardless of size.

- Heterogeneity analyses across the following factors (in addition to sites) will be conducted similarly:
- US/OUS
- Sex (Male/Female)
- Dialysis status (Yes/No)
- Age (≤ 70, > 70)
- Diabetes (Type I, Type II, None)
- Race/Ethnicity

12. Study Management

For this study, the Sponsor will have direct responsibilities and will delegate other responsibilities to appropriate and qualified consultants, contractors, and/or Contract Research Organizations (CROs).

Together, the Sponsor, consultants, and CROs will ensure that the study is conducted according to the Clinical Investigational Plan and all applicable and governing regulations. All personnel to participate in the conduct of this clinical trial will be qualified by education, training and/or experience to perform their tasks.

12.1 Source Data Verification

At a minimum, source data verification will be performed on all primary endpoint and secondary endpoint and safety data points for each subject enrolled in the study. However, it is the intent of the Sponsor to perform an appropriate risk-based monitoring approach.

12.2 Insurance

The Sponsor will maintain the appropriate and necessary insurance coverage for the duration of the study.

12.3 Regulatory & Ethical Considerations

This study will be conducted in compliance with ICH E6 Consolidated Good Clinical Practice Guidance, 21 CFR Parts 11, 50, 54, 56, and 812; 45 CFR Part 164, ISO 14155, and any requirements imposed by the U.S. Food and Drug Administration (U.S. FDA) or reviewing IRB/EC. The study will not commence until the necessary government and IRB/EC approvals have been obtained.

It is expected that all parties will share in the responsibility for ethical conduct in accordance with their respective roles in the investigation. The Sponsor and the Investigator(s) shall avoid improper influence or inducement of the subject, monitor, the clinical investigator(s) or other parties participating in or contributing to the clinical investigation.

12.4 Quality Assurance and Supervision by Authorities

All documents and data shall be produced and maintained in such a way to assure control of documents and data to protect the subject's privacy as far as reasonably practicable. The Sponsor and representatives of the FDA or other regulatory authorities are permitted to inspect the study documents (e.g., study protocol, CRFs, and original study-relevant medical records/files) as needed. All attempts will be made to preserve subject confidentiality.

All clinical sites are subject to audit by study Sponsor personnel or designee for protocol adherence, accuracy of CRFs and compliance with applicable regulations. Any evident pattern of non- compliance with respect to these standards may be cause for corrective action.

Clinical sites are also subject to an independent clinical Quality Assurance audit by Sponsor, its designee, or health authorities.

12.5 Corrective and Preventative Action

Aside from an official site audit, non-compliance may be discovered through other means such as monitoring, site management, general communication or site visits. As with non-compliance discovered during an audit as outlined above, any evident pattern of non-compliance with respect to governing regulations, guidelines, the investigational plan or other governing requirements may be cause for corrective action. Such corrective action may range from communication of the non-compliance, to the site being placed on probation until corrective action is taken. In more serious circumstances, enrollment may be terminated at the site. Corrective actions will be followed through resolution and any resulting documentation surrounding the corrective and preventative action will be housed in the central study files.

12.6 Institutional Review Board (IRB)/ Ethics Committee (EC) Approval

IRB/EC approval is required prior to study commencement. The Investigator must also obtain renewal of IRB/EC approval for any protocol amendments or as dictated by local requirements during the entire duration of the study. The Investigator is responsible for fulfilling any conditions of approval imposed by the reviewing IRB/EC, such as safety or routine reporting. The Investigator will provide the study Sponsor with copies of such approvals and reports.

12.7 Amendment to the Investigational Plan

The Sponsor is responsible for management, processing and approval of any amendment to the Investigational Plan. Should the site consider an amendment necessary, the Sponsor will work with the site to make the appropriate changes. The Sponsor will manage documentation of such changes through the existing document control system. A history of changes and a redline version of the documentation will be maintained per the applicable quality system procedures. The proposed amendment will be submitted to the reviewing IRB/ECs and government agency as applicable. Any necessary approvals will be received in writing before the requested change is implemented.

The Sponsor may make certain administrative changes to the protocol without prior approval of the FDA or IRB. The Sponsor will notify all investigative sites of such changes to ensure the study continues to be conducted consistently across all sites. The site IRBs will be notified of these changes.

12.8 Approved Informed Consent

The reviewing Institutional Review Board or Ethics Committee must review and approve an Informed Consent Form (ICF) specific to this study. The Sponsor will provide each study center with an example ICF. The study center, to meet specific requirements, may modify this example ICF; however, the ICF to be used for subject consent under this protocol must contain all of the elements required by the study Sponsor and the governing regulatory requirements for informed consent (21 CFR Part 50 and ISO 14155) and be approved by the Sponsor in writing prior to IRB/EC submission. Each investigational site will provide the Sponsor with a copy of the IRB/EC approved ICF - as well as any amendments - for the duration of the study. The original, signed and dated ICF must be retained by the investigational site for monitoring, and a copy provided to the subject.

12.9 Sponsor Responsibilities

LimFlow, Inc, the Sponsor of this study, has the overall responsibility of the study and will:

- Select qualified Principal Investigators, clinical investigators, and study sites
- Select qualified monitors
- Provide the Investigational Plan and any subsequent amendments
- Provide appropriate information and LimFlow System training to Investigators and study site staff
- Ensure that all deviations from the Investigational Plan are reviewed with the appropriate Investigator(s) and reported in the eCRF and the final report and that any necessary preventative or corrective action is taken
- Ensure that all adverse events and all adverse device effects (ADEs) are reported and reviewed with the Investigator(s), and where appropriate, that all serious adverse events (SAEs) and all serious adverse device effects (SADEs) are appropriately reported
- During the course of the investigation, inform in writing all Investigators about unanticipated adverse events/device effects that have been reported to Sponsor (this information shall be sent to each Investigator based on perceived risk)
- Promptly inform the Investigators and where applicable, any regulatory authorities or IRB/EC, if the study is prematurely terminated or suspended and the reason for the termination or suspension
- Ensure proper device usage, uniform data collection and protocol compliance
- Provide protocol initiation training to include review of LimFlow System instructions for use, the Investigational Plan, eCRF completion guidelines, and guidelines for obtaining informed consent
- Provide investigational product to participating study sites, in quantities sufficient to support study activities
- Coordinate ongoing communication with CRO(s), consultants and study sites to resolve any problems concerning the protocol or data collection
- Every effort will be made to ensure compliance with the protocol
- Retain ownership of all clinical data generated in this study, and control the use of the data for purposes of regulatory submissions to the US and other governments
- Protect subject confidentiality
- Collect, store and keep secure relevant regulatory and training documents.

12.10 **Monitor Responsibilities**

Study site monitoring will be performed by the Sponsor or their designee(s). Each site will be visited regularly to ensure that the study is conducted in compliance with governing regulations and guidelines. The monitor will also ensure that the data reported in the eCRFs are consistent with the information found in the subject's medical records (source data verification). Monitoring will also include the assessment of the site's overall progress, including but not limited to the site's ability to keep accurate records and to report study related data to the study Sponsor in a timely fashion. In order to appropriately monitor the progress of the study, the monitor will have access to the source documents and other information necessary to ensure Investigator compliance with the Investigational Plan and applicable rules and regulations, and to assess the progress of the clinical investigation.

The study monitor(s) will maintain personal contact with the Investigator and staff throughout the study by

phone, e-mail, mail and on-site visits. The monitor will compile and file a monitoring report for each visit. Monitoring will ensure continued protocol compliance, adequate subject enrollment and accurate data reporting and device accountability.

12.11 Investigator Responsibilities

The Investigator is responsible for ensuring that the investigation is conducted according to all signed agreements, the study protocol, governing regulations, data protection regulations, the medical device laws, and any other conditions imposed by the U.S. FDA, reviewing IRB/EC or other regulatory authority. In addition, each Investigator must sign an Investigator Agreement and submit a Financial Disclosure Form (FDF) to the Sponsor prior to the recruitment of subjects.

The Investigator(s) shall be responsible for the day to day conduct of the investigation as well as for the safety and well-being of the human subjects involved in the clinical investigation.

To ensure proper execution of the study protocol, each Investigator should identify a study coordinator for this study. Working with and under the authority of the Investigator, the study coordinator assures that all study requirements are fulfilled and is the contact person at the site for all aspects of study administration.

The Investigator is aware of the likelihood of audit and will allow auditing of their clinical investigation procedure(s) as required by the U.S. Food and Drug Administration or another agency. The Investigator is responsible for maintaining medical and study records for every subject participating in the clinical study (including information maintained electronically such as digital imaging). The Investigator will also maintain source documents from which study-related data are derived.

The Investigator must ensure that all study subject records are stored for at least 2 years after the investigation is completed or terminated. To avoid error, the study site should contact the Sponsor prior to the destruction of study records to ensure that they no longer need to be retained. In addition, the Sponsor should be contacted if the Investigator plans to leave the investigational site so that arrangements can be made for the handling or transfer of study records.

13. Data Management

13.1 Data Management Responsibilities

Electronic Case Report Forms (eCRFs) will be developed for data collection during the course of the study and must be completed for all subjects enrolled into the study. It is the responsibility of the investigator to ensure the quality of the data collected and recorded in the eCRFs. The eCRFs will be reviewed for errors, omissions, internal consistency, and to ensure that the investigator has signed the appropriate sections; entered data will be audited for verification and validation purposes.

Data collection will include clinical data, as well as medical images based on the clinical endpoints outlined above. Images will be centrally analyzed by independent committees.

The EDC Platform and wound management platform (eKare insight) are compliant with FDA 21 CFR Part 11 requirements. All information and data concerning subjects or their participation in this study will be considered confidential. Only authorized personnel will have access to this confidential information. All data used in the analysis and reporting of this evaluation will be without identifiable reference to individual subjects.

13.2 Data Entry

Data entry into the eCRFs will be performed by the study sites. Data entry will be performed by qualified personnel that have undergone appropriate training. Data entry and verification will be handled according to the applicable data handling and audit procedures defined in the Data Management Plan.

13.3 Data Cleaning

All eCRF pages will be subject to review for omitted data, gross data inconsistencies, illegible data and deviations. Any deficiencies or deviations will be reviewed, and any necessary action determined (e.g., data query, communication to the study center).

Data review (including crosschecks) will be performed and any discovered errors will be reported to the study site using the data correction and query process (as necessary). The study site will be expected to review the query, respond and make any necessary corrections or comments. The data cleaning cycle will be repeated until all data are considered clean.

13.4 Confidentiality and Security

Unique usernames and passwords will be utilized by data entry, data verification and other personnel who have database access to insure confidentiality and protection of data.

13.5 Data Retention

eCRF data, queries, and the locked database will be archived for a minimum of 2 years following the end of the study. The database will be managed on a secure server and backed up intermittently per the Data Management Plan.

14. Study Closeout

At the time of the site closeout visit, the site monitor or designee will collect all outstanding study documents, ensure that the Investigator's files are accurate and complete, review record retention requirements with the Investigator, make a final accounting of all study supplies, and ensure that all applicable requirements are met for the study. The observations and actions made at this visit will be documented in a closeout visit report.

Once all sites are considered closed, the study may be closed.

14.1 Study Suspension or Early Termination

The study can be discontinued at the discretion of the Investigator or study Sponsor for reasons including, but not limited to, the following:

- Occurrence of adverse events unknown to date in respect to their nature, severity, or duration, or the unexpected incidence of known adverse events (Sponsor may terminate the study immediately)
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Insufficient recruitment of subjects
- Persistent non-compliance with the protocol
- Persistent non-compliance with IRB/EC or other regulatory requirements

If the study is discontinued or suspended prematurely, the Sponsor shall promptly inform all clinical investigator(s) / investigational center(s) of the termination or suspension and the reason(s) for this. The

IRB/EC shall also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the clinical investigator / investigation center(s). Regulatory authorities and the personal physicians of the subjects may also need to be informed if deemed necessary.

14.2 Final Report

A Final Report will be prepared even if the study is prematurely terminated. The Final Report will be submitted to the FDA, as required.

14.3 Publication Policy and Trial Registration

At the conclusion of the trial, a multi-center abstract reporting the results will be prepared and may be presented at a major meeting(s). A multi-center publication may also be prepared for publication in a reputable scientific journal. The publication of results from any single center experience within the trial is not allowed until the aggregate study results have been published, unless there is written consent from the study Sponsor.

"The study will be registered on Clinicaltrials.gov in compliance with 42 CFR Part 11 and ISO 14155. Results of the study, including an unanticipated early termination of the trial, will be posted to the Clinicaltrials.gov database at the conclusion of the study. In the event that the study is terminated early, the posting of these results will be completed within 30 days of completion of data analysis."

15. Definitions

ACUTE STENT THROMBOSIS REQUIRING IMMEDIATE REPORTING

Identification of thrombus within the stent graft/segment, as assessed by duplex ultrasound (DUS) exam, continuous wave Doppler exam, or angiogram. Any findings of acute thrombosis during the treatment to discharge phase must be reported to the Sponsor within 24 hours of the exam.

ALL-CAUSE DEATH, divided into 2 categories:

Cardiac death: death due to any of the following:

- Acute myocardial infarction.
- Cardiac perforation/pericardial tamponade.
- Arrhythmia or conduction abnormality.
- Cerebrovascular accident within 30 days of the procedure or cerebrovascular accident suspected of being related to the procedure.
- Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery.
- Any death in which a cardiac cause cannot be excluded.

Non-cardiac death: death not due to cardiac causes (as defined above).

ALLERGIC RESPONSE

Hypersensitive response of the immune system of an allergic individual to a normally harmless substance (allergen).

AMPUTATION

Major amputation: amputation of the index limb at the level above the ankle.

Minor amputation: amputation(s) of the index limb/metatarsals at the level below the ankle.

Pre-planned amputation: minor amputation(s) that are prospectively anticipated as part of the overall procedure and care plan for a subject. These anticipated procedures should be documented in the medical record prior to the index procedure.

AMPUTATION-FREE SURVIVAL

Freedom from major amputation and death:

Limb Salvage: Freedom from above-ankle amputation of the index limb AND

Survival: Freedom from all-cause mortality

ARTERIAL / VENOUS OCCLUSION

Narrowing or blockage of an artery or vein.

ARTERIAL / VENOUS THROMBOSIS FORMATION

Formation or development of a blood clot or thrombus, specifically in the arterial or venous system of the ipsilateral distal extremity.

ARTERIO-VENOUS (AV) FISTULA (UNPLANNED)

An unplanned, anatomical connection between the access artery and the adjacent vein that is demonstrated by arteriography or ultrasound, most often characterized by a continuous bruit.

BLEEDING / OOZING FROM THE PUNCTURE SITE

Bleeding or oozing of blood at the location of incision for the endovascular procedure.

BRUISING AT WOUND SITE

Pooling of blood at the location of incision for the endovascular procedure.

CLINICALLY DRIVEN MAJOR RE-INTERVENTION OF THE STENT GRAFT

The creation of a new surgical bypass, the use of thrombectomy or thrombolysis (i.e., procedures done in the setting of lost primary-assisted patency), or major surgical revision such as a jump graft or an interposition graft performed for occlusion of the stent graft. Definition per Conte, MS et al., Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia, *J Vasc Surgery,* vol. 50, no. 6, pp. 1462.e1–1473.e-3, 2009.

CLINICALLY DRIVEN MINOR RE-INTERVENTION OF THE STENT GRAFT

Include endovascular procedures (PTA, atherectomy, stenting) without thrombectomy/thrombolysis, and minor surgical revisions (patch angioplasty). Definition per C Conte, MS et al., Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia, *J Vasc Surgery,* vol. 50, no. 6, pp. 1462.e1–1473.e-3, 2009

COMPARTMENT SYNDROME

Increased compartment pressure within a confined space compromises the circulation and viability of the tissues within that space.

CONTRAST-INDUCED NEPHROPATHY AND RENAL FAILURE

Acute (within 72 hours after intravenous contrast administration) impairment of renal function, measured

as an absolute ≥0.5 mg/dL (44 μmol/L) increase compared to baseline SCr value that results in a value above the upper limit of the normal range.

CONGESTIVE CARDIAC FAILURE (CONGESTIVE HEART FAILURE)

Inability of the heart to maintain adequate circulation of blood in the tissues of the body or to pump out the venous blood returned to it by the venous circulation.

DEATH

Irreversible cessation of circulatory and respiratory functions, or irreversible cessation of all functions of the entire brain, including the brain stem.

DEVICE FAILURE / MALFUNCTION

An occurrence of equipment not functioning or operating as intended.

EDEMA

The abnormal accumulation of fluid in certain tissues within the body.

EMBOLISM (AIR, TISSUE, DEVICE)

The sudden blocking of an artery by a clot or other material that has been brought to its site of lodgment by the blood current (embolus). Potential sources of emboli include blood clots, fat globules, air bubbles, tissue, clumps of bacteria, thrombus or foreign material.

HEMATOMA

A localized collection of extravasated blood in subcutaneous tissue, usually clotted. A metric ruler should be used to measure the widest portion of the hematoma.

INFECTION

Invasion and multiplication of microorganisms in body tissues.

INFLAMMATORY RESPONSE

A response of the body to an injurious agent, characterized by cardinal signs such as swelling, pain, heat, loss of function, or reddening of the skin.

INTIMAL TEAR / DISSECTION

Disruption of an arterial wall resulting in splitting and separation of the intimal (subintimal) layers.

IPSILATERAL DEEP VEIN THROMBOSIS

Presence of a thrombus in the peripheral venous system of the ipsilateral limb. May be a complication of phlebitis or may result from injury to a vein or from prolonged bed rest. Symptoms include a feeling of heaviness, pain, warmth, or swelling in the affected part.

IPSILATERAL LOWER EXTREMITY ARTERIAL EMBOLI

Presence of emboli in the peripheral arterial system of the ipsilateral limb.

LOWER EXTREMITY ISCHEMIA

Inadequate blood supply to the lower extremities (from hip to toes).

NO OPTION

Either a) absence of a usable pedal artery target (endovascular or surgical approach), or b) the presence of a pedal artery target with absence of a viable single-segment vein in either lower extremity or either arm that could be used for autogenous vein conduit.

NYHA HEART FAILURE CLASSIFICATIONS

I: Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or angina pain.

II: Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina pain.

III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or angina pain.

IV: Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of heart failure or the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

OCCLUSION OF THE STENT GRAFT

Complete absence of flow on color Doppler, or absence of sound and/or waveform by bedside doppler, and/or absence of flow on angiographic images (conventional or CT).

PERFORATION OF VESSEL WALL

A hole or break in the arterial or venous wall (e.g., from insertion/advancement of a percutaneous device) as seen on angiography, which may or may not require intervention.

PERI-OPERATIVE DEATH

All-cause death that occurs within the peri-operative period of 30 days post-procedure.

PERIPHERAL NERVE INJURY

Injury to the peripheral nerves that may occur because of trauma (blunt or penetrating) or acute compression and may result in loss of motor function, sensory function, or both.

PERIPHERAL PULSE ASSESSMENT SCALE (IF PALPABLE)

0 = absent; not palpable; 1 = diminished; 2 = expected; 3 = full, increased; 4 = bounding.

PSEUDOANEURYSM

A blood vessel abnormality resembling an aneurysm (localized abnormal dilatation of a blood vessel) but consisting of a collection of blood with persistent flow outside an artery, contained by surrounding tissue and due to a leaking hole through all layers of the arterial wall. The leaking hole is due to injury of (e.g., rupture of or trauma to) the arterial wall. The pseudoaneurysm is usually identified by angiography or ultrasound.

RETROPERITONEAL BLEEDING

Bleeding from an injured vessel, with deposition of blood into the retroperitoneal space (between the

peritoneum and the posterior abdominal wall).

SERIOUS ADVERSE EVENT (SAE)

An event that:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolonged hospitalization
- Necessitates an intervention to prevent a permanent impairment of a body function or permanent damage to a body structure (i.e. revascularization of LimFlow System)
- Results in persistent or significant disability/incapacity
- Results in congenital abnormality

SUBJECT

An individual who participates in a clinical investigation.

SYSTEMIC INFECTION, SEPSIS

The presence of bacteria, other infectious organisms, or toxins created by infectious organisms in the bloodstream with spread throughout the body.

VASCULAR INJURY REQUIRING REPAIR

Injury to the access site, and/or target vessel arterial or venous vessel wall resulting in persistent bleeding and requiring repair (via surgery, angioplasty, ultrasound-guided compression, thrombin injection, or other means).

VASOSPASM

The sudden, but transitory constriction of a blood vessel, potentially causing discomfort and limitation of distal blood flow.

VASOVAGAL RESPONSE

Development of inappropriate cardiac slowing and arteriolar dilatation.

WOUND DEHISCENCE

Wound rupture along a surgical incision

WOUND SITE PAIN

Pain at the location of incision for the endovascular procedure.