A PILOT STUDY TO INVESTIGATE THE SAFETY, EFFECTIVENESS, AND FEASIBILITY OF THE LIMFLOW STENT GRAFT SYSTEM FOR CREATING AN AV FISTULA FOR THE TREATMENT OF CRITICAL LIMB ISCHEMIA

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Sponsor:

LimFlow, Inc.

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Protocol Signatures

A PILOT STUDY TO INVESTIGATE THE SAFETY, EFFECTIVENESS, AND FEASIBILITY OF THE LIMFLOW STENT GRAFT SYSTEM FOR CREATING AN AV FISTULA FOR THE TREATMENT OF CRITICAL LIMB ISCHEMIA

I have read and agree to the final version of the protocol **ECO-02527-009**:

I am aware of my responsibilities as an Investigator under the guidelines of 21 CFR Parts 50, 56, and 812, and local IRB requirements.

I agree to perform and conduct the study as described in the protocol. In addition, when applicable, I agree to enlist sub-investigators who also agree to perform and conduct the study as described in the protocol.

Investigator Name:

Institution Name:

Signature:_____ Date: _____

PROTOCOL SYNOPSIS:

A PILOT STUDY TO INVESTIGATE THE SAFETY, EFFECTIVENESS, AND FEASIBILITY OF THE LIMFLOW STENT GRAFT SYSTEM FOR CREATING AN AV FISTULA FOR THE TREATMENT OF CRITICAL LIMB ISCHEMIA

Primary Objective	The objective of this pilot clinical investigation is to investigate the safety, effectiveness and feasibility of the LimFlow Stent Graft System for creating an AV fistula in the Below The Knee (BTK) vascular system using an endovascular, minimally invasive approach for the treatment of Critical Limb Ischemia (CLI) in subjects ineligible for conventional endovascular or surgical limb salvage procedures.
Test Device	The LimFlow Stent Graft System
Indication for Use	The LimFlow Stent Graft System is intended to treat critical limb ischemia by creating an AV fistula in the below-the-knee vasculature for treatment of CLI.
Study Design	A prospective, multi-center pilot study consisting of up to 35 subjects designed to confirm the safety, effectiveness and feasibility of the LimFlow Stent Graft System
Number of Subjects	Up to 35 consecutively enrolled subjects
Principal Investigator	Dr. Jihad Mustapha, MD Metro Health Hospital 5900 Byron Center Ave, SW Wyoming, MI 49519
Number of Sites	Up to 7 U.S. sites
Duration of Study	Each enrolled subject will be followed for up to 2 years (± 4 weeks) post-procedure. The primary endpoint assessment will be completed by 30 (+/- 7) days, and secondary endpoint assessments will be completed by 12 (+/- 1 month) post-procedure.
Primary Safety Endpoint	**Amputation-Free Survival at 30 days, defined as the percentage of subjects with:** • **Limb Salvage:** Freedom from above-ankle amputation of the index limb AND • **Survival:** Freedom from all-cause mortality
Secondary Safety Endpoint	**Amputation-Free Survival Survival at 6 months, defined as the percentage of subjects with:** • **Limb Salvage:** Freedom from above-ankle amputation of the index limb AND • **Survival:** Freedom from all-cause mortality

Secondary Effectiveness Endpoints	• **Primary Patency at 30 days:** Defined as the absence of occlusion of the stent graft[1] without prior clinically-driven major re-intervention[2] of the stent graft at 30 days. • **Primary Patency at 6 months:** Defined as the absence of occlusion of the stent graft[1] without prior clinically-driven major re-intervention[2] of the stent graft at 6 months. • **Secondary Patency at 6 months:** Defined as the absence of occlusion of the stent graft[1] with or without prior clinically-driven major re-intervention[2] of the stent graft at 6 months. Occlusion is determined by duplex ultrasound data. • **Limb Salvage at 3, 6, 9 and 12 months:** Defined as percentage of subjects with freedom from above-ankle amputation of the index limb. • **Wound Healing at 3, 6, 9, and 12 months:** Defined as percentage of subjects with completed index wound healing • **Deterioration in Renal Function at 6 months:** Defined as a ≥ 25% increase in serum creatinine after using iodine contrast agents, without another clear cause for kidney injury. • **Technical Success:** Defined as percentage of subjects with technical success, defined as completion of the endovascular procedure and immediate morphological success with successful placement of the arterial and venous catheters in the desired location in the limb, and ability to place the stent graft. • **Procedural Success:** Defined as percentage of subjects with a procedural success, defined as combination of technical success, and absence of all-cause death, above-ankle amputation or clinically driven major re-intervention[2] of the stent graft at 30 days. [1] Occlusion is defined as absence of flow on color Doppler, and/or absence of flow on angiographic images (conventional or CT). [2] Clinically-driven major re-intervention is defined as 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.
Follow-Up Schedule	Measures of safety and effectiveness will be assessed through hospital discharge, at 30 and 60 (+/- 7) days, at 3, 6, and 9 months (+/- 2 weeks), and at one year (+/- 4 weeks) and 2 years (+/- 4 weeks) post-procedure. The study will be completed and closed after all subjects have either met a primary endpoint, or completed the 2 year follow-up requirements.
Primary Patient Population	In this first pilot study, the patients selected will be the “no hope” CLI patients, those that have been determined to be ineligible for conventional surgical or endovascular options due to severe vascular disease.

Pre-Operative Inclusion Criteria	1. Subject must be ≥ 21 and ≤ 95 years of age 2. Clinical diagnosis of symptomatic critical limb ischemia, defined as any of the following clinical assessments coupled with hemodynamic evidence of severely diminished arterial inflow of the index limb (e.g., absent pulse(s), TcPO2 < 30 mm Hg): a. Rutherford Classification 5, ischemic ulceration b. Rutherford Classification 6, severe ischemic ulcers or frank gangrene 3. Subject has been assessed by the principal investigator, and reviewed by the Independent Safety Committee (ISC), and it was determined that no conventional distal bypass surgical or endovascular therapy for limb salvage is feasible due to the absence of a suitable distal target artery. 4. Proximally, the Target In-flow Artery at the cross-over point must be treatable with a 3.5 – 4.0 mm stent after pre-treatment (by visual estimate), and be <50% stenosed. 5. Prior stent(s) to the Target In-flow Artery are allowed. 6. Planned minor amputation 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 has an adequate support network to ensure that subject is compliant with medication regimen and follow-up study visits.
Pre-Operative 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, deep venous thrombus, or coagulation disorder. 2. Pre-existing immunodeficiency disorder or receiving immunosuppressant therapy. 3. Prior peripheral arterial bypass procedure above or below the knee which could inhibit proximal inflow to the stent graft. 4. Previous major amputation of the target limb. 5. Life expectancy less than 12 months. 6. Documented myocardial infarction or stroke within previous 90 days. 7. Known or suspected active infection at the time of the index procedure that may preclude insertion of a prosthesis. 8. Known or suspected allergies or contraindications to aspirin / dual antiplatelet therapy, heparin, stainless steel, nitinol or contrast agent that cannot be adequately pre-treated. 9. Subject is currently taking warfarin, 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 venous disease with significant edema in the target limb that may inhibit the procedure and/or jeopardize wound healing, in the investigator's opinion. 11. Significant acute or chronic kidney disease with a serum creatinine of > 2.5 mg/dl, and/or requiring dialysis. 12. Severe heart failure, which in the opinion of the investigator may compromise subject's ability to safely undergo a percutaneous procedure

	(e.g., known ejection fraction of ≤ 40%, NYHA Classification III-IV). 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 or unable to comply with any of the protocol or follow-up requirements. 16. Prior to enrollment, women of childbearing potential must have a negative urine pregnancy test.	
Study Administration		
Study Sponsor	LimFlow, Inc. 2934 Scott Blvd. Santa Clara CA 95054 United States	Contact: Thomas Engels Vice President Clinical Affairs LimFlow, Inc. Phone: (888) 478-7705, ext. 101 Fax: (408) 898-1459 e-mail: tengels@limflow.com
CRO, United States (Clinical)	Chellew Clinical Outsourcing, LLC 7844 E. Riverdale St. Mesa, AZ 85207 Marlys Chellew, BSN Mobile: 916-303-0879 mchellew@chellewclinical.com	
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Data Management	TBD	

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1.0. Introduction

1.1 Background and Rationale

In the absence of treatment, Peripheral Vascular Disease (PVD) may progress to critical limb ischemia (CLI), which is characterized by profound chronic pain, and extensive tissue loss that restricts revascularization options and frequently leads to amputation. CLI is estimated to have an incidence of approximately 50 to 100 per 100,000 per year and is associated with mortality rates as high as 20% at 6 months after onset.

Interventional radiologists have been aggressively trying to treat CLI by attempting to open up Chronic Total Occlusions (CTO's) 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 passed the occlusion. More conventional approaches to treating PAD are also used in CLI treatment once (if) a wire gets across the occlusion. These conventional methods include PTA, Stenting and more recently drug eluting balloons and stents.

From the amputee-coalition.org website, the following are some statistics regarding the CLI problem:

- There are nearly 2 million people living with limb loss in the United States
- The main causes of limb loss are dysvascular disease – including diabetes (54%), trauma (45%), and cancer (less than 2%).
- Approximately 185,000 amputations occur in the United States each year.
- Hospital costs associated with having a limb amputated totaled more than $6.5 billion in 2007
- Survival rates after an amputation vary based on a variety of factors. Those who have amputations due to vascular disease (including peripheral arterial disease and diabetes) face a 30-day mortality rate reported to be between 9 -15% and a long-term survival rate of 60% at 1 year, 42% at 3 years, and 35-45% at 5 years.
- Nearly half of the people who lose a limb to dysvascular disease will die within 5 years. This is higher than the 5-year mortality rate experienced by people with colorectal, breast, and prostate cancer.

Of people with diabetes who have a lower-limb amputation, up to 55% will require amputation of the second leg within 2 to 3 years.

The LimFlow approach to treating CLI involves the concept of venous arterialization and this procedure has been performed surgically for many years and the first clinical surgical cases were reported in the early 1900's. Numerous small series of clinical trials have been published over the year using a surgical approach and a recent meta-analysis article summarized this work. The 2006 Meta Analysis article from the European Journal of Vascular and Endovascular Surgery titled:

"Meta-analysis of the clinical effectiveness of venous arterialization for salvage of critically ischemic limbs."

Had the following results and conclusions:

Results: A total of 56 studies were selected for comprehensive review. No RCTs were identified. Seven patient series, comprising 228 patients, matched the selection criteria. Overall 1-year foot preservation was 71% (95% CI: 64-77%) and 1-year secondary patency was 46% (95% CI: 39-53%). The large majority of patients in whom major amputation was avoided experienced successful wound healing, disappearance of rest pain and absence of serious complications.

Conclusions: On the basis of limited evidence, venous arterialization may be considered as a viable alternative before major amputation is undertaken in patients with 'inoperable' chronic critical leg ischemia.

The purpose of this first pilot clinical study is to test the LimFlow concept for creating an Arterio-Venous (AV) fistula in the Below The Knee (BTK) vascular system using an endovascular, minimally invasive approach.

1.2 Summary of Findings from Previous Studies

1.2.1. Pre-clinical studies:

Extensive in vitro bench, in vivo animal, and cadaver studies have been successfully performed with the LimFlow System and verification testing for the catheter has been completed. Testing on the device included comprehensive design verification and validation testing. The following testing was completed on the LimFlow devices:

- Biocompatibility testing
- Mechanical testing
- Packaging testing
- Shelf-life testing
- Sterilization validation
- Preclinical animal studies

These tests were successfully completed and are described in more detail in the Investigator Brochure.

1.2.2. Clinical studies:

A non-randomized prospective pilot study and a CE Mark study have been conducted with the LimFlow System, see Report of Prior Investigations in the Investigator Brochure for details on the study and patient outcomes. 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.

1.3 Risks and Benefits

The associated risks proposed in this study are similar to risks posed by other interventional and vascular surgery procedures. 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 potential benefit of reduced or no amputation of the foot 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.

1.3.1. Risks

The associated risks proposed in this study are similar to risks posed by other interventional and vascular surgery procedures.

Adverse events that may possibly be caused by or associated with the use of the investigational device or the related procedures, and which may or may not require endovascular or surgical treatment in this clinical trial include:

- Allergic response
- Arterial occlusion
- Arterial thrombus
- Arterio-venous fistula (unplanned)
- Bleeding/oozing from the puncture site
- Bruising at wound site
- Contrast-induced nephropathy and renal failure
- Compartment syndrome
- Congestive cardiac 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
- Peripheral nerve injury
- Perforation of the vessel wall
- Pseudoaneurysm
- Retroperitoneal bleeding
- Venous thrombus formation
- Vasovagal response
- Vasospasm
- Vascular injury
- Wound dehiscence
- Wound site pain
- Systemic infection, sepsis

- Requirement for major amputation of index limb

1.3.2. Benefits

The benefit to the subjects enrolled in this study is the potential for improved blood flow to the foot reducing, 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.

Specifically, risks to the patient are minimized due to:

- 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.
- Frequent follow-up visits are conducted in the first year post-operatively to allow for systematic monitoring and surveillance of the index limb, allowing for early detection of hemodynamically significant stenoses in the graft that may occur in the absence of obvious symptoms.
- Potential subjects will be screened by the Independent Safety Committee to ensure that all subjects meet defined inclusion/exclusion criteria.
- Investigators will receive device training and will be proctored for their first case, and then for as many cases as they deem necessary to perform the procedure proficiently.

2.0 Device Description

2.1. Intended Use

The LimFlow Stent Graft System is intended to treat the critical limb ischemia by creating an arterio-venous fistula in the below-the-knee vasculature.

The LimFlow Stent Graft System consists of:

- Arterial Ultrasound Catheter w/needle
- Venous Ultrasound Catheter
- Covered Nitinol Stent in 7 Fr delivery system
- Valvulotome
- Ultrasound system with laptop computer

For the initial procedures, commercially available GORE VIABAHN stents will also be used as extension stents.

2.2 Device Labeling

A copy of the Instructions for Use (IFU) will be included with the devices. The LimFlow Stent Graft System labels contain the following information:

- LimFlow Stent Graft System Model Number
- Lot or Serial number
- Expiration (use before) date
- For Investigational Use Only

3.0 Study Objectives

The objective of this study is to evaluate the feasibility, safety and effectiveness of the LimFlow Stent Graft System in creating a below-the-knee AV-fistula for venous arterialization in subjects with critical limb ischemia.

4.0 Study Design

4.1 Overview

This study represents a prospective, non-randomized, single arm, multi-center pilot study to evaluate the feasibility, safety and effectiveness of the LimFlow Stent Graft System. Measures of safety and efficacy will be assessed through hospital discharge, at 30 +/- 7 days, at 3, 6, and 9 months +/- 2 weeks post-procedure, and then annually (+/- 4 weeks) for up to 2 years post-procedure.

4.2 Sample Size

Up to 35 subjects will be enrolled in this study.

4.3 Investigational Sites

The study will be conducted at up to 6 clinical sites in the United States.

5.0 Study Population

5.1 Selection Criteria

The following section outlines the specific inclusion and exclusion criteria for the study. Before enrollment, a patient must meet all of the inclusion and exclusion criteria.

5.1.1. Pre-operative Inclusion Criteria

1. Subject must be $\geq$ 21 and $\leq$ 95 years of age
2. Clinical diagnosis of symptomatic critical limb ischemia, defined as any of the following clinical assessments coupled with hemodynamic evidence of severely diminished arterial inflow of the index limb (e.g., absent pulse(s), TcPO2 < 30 mm Hg):
   a. Rutherford Classification 5, ischemic ulceration
   b. Rutherford Classification 6, severe ischemic ulcers or frank gangrene
3. Subject has been assessed by the principal investigator, and reviewed by the Independent Safety Committee (ISC), and it was determined that no conventional distal bypass surgical or endovascular therapy for limb salvage is feasible due to the absence of a suitable distal target artery.
4. Proximally, the Target In-flow Artery at the cross-over point must be treatable with a 3.5–4.0 mm stent after pre-treatment (by visual estimate), and be <50% stenosed
5. Prior stent(s) to the Target In-flow Artery are allowed

6. Planned minor amputation 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 has an adequate support network to ensure that subject is compliant with medication regimen and follow-up study visits

5.1.2. Exclusion Criteria

1. Concomitant hepatic insufficiency, thrombophlebitis, deep venous thrombus, or coagulation disorder
2. Pre-existing immunodeficiency disorder or receiving immunosuppressant therapy
3. Prior peripheral arterial bypass procedure above or below the knee which could inhibit proximal inflow to the stent graft.
4. Previous major amputation of target limb
5. Life expectancy less than 12 months
6. Documented myocardial infarction or stroke within previous 90 days
7. Known or suspected active infection at the time of the index procedure that may preclude insertion of a prosthesis
8. Known or suspected allergies or contraindications to aspirin / dual antiplatelet therapy, heparin, stainless steel, nitinol or contrast agent that cannot be adequately pre-treated
9. Subject is currently taking warfarin, 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 venous disease with significant edema in the target limb that may inhibit the procedure and/or jeopardize wound healing, in the investigator's opinion.
11. Significant acute or chronic kidney disease with a serum creatinine of > 2.5 mg/dl, and/or requiring dialysis.
12. Severe heart failure, which in the opinion of the investigator may compromise subject's ability to safely undergo a percutaneous procedure (e.g., known ejection fraction of < 40%, NYHA Classification III-IV)
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 or unable to comply with any of the protocol or follow-up requirements
16. Prior to enrollment, women of childbearing potential must have a negative urine pregnancy test

6.0 Study Procedures and Enrollment

6.1. Duration of Subject Participation

Subjects enrolled in the study will participate for up to 2 years (+/- 4 weeks).

6.2. Screening, Written Informed Consent and Independent Safety Committee Review

All subjects considered for the treatment of the critical limb ischemia by creating an arterio-venous fistula in the below-the-knee vasculature, and eligible for treatment as determined by the study investigator should have the study explained to them, be given the IRB-approved informed consent form and allowed adequate time to consider whether or not they wish to take part in the study. The

investigator or a member of his/her staff should inform the patient about the study's purpose and risks/benefits.

Written informed consent must be obtained for all patients who are potential study candidates before any study-specific tests or procedures are performed. The wound shall be photographed, to include a metric ruler for adequate evaluation of the index wound/limb.

Once the principal investigator concludes that all inclusion criteria and no exclusion criteria are met, the patients will be reviewed by an Independent Safety Committee (ISC) consisting of at least 2 independent physicians with expertise in treatment of CLI patients. Once the ISC determines that a subject is not a candidate for conventional surgical or endovascular procedures for limb salvage, they may be enrolled in the study. See Section 10.2 Screening Responsibilities.

Patients who give consent to take part in the study and subsequently do not meet the eligibility criteria will not be enrolled.

6.3. Visit Schedule

The study coordinator at the site should schedule the 30-day follow-up visit before the subject is discharged post-procedure. Obtain contact information for subject's significant other or caretaker(s) to ensure that subject will be able to comply with follow-up study visits. Study assessments to be performed at each visit are summarized in Table 1.

TABLE 1: Study Assessment Schedule	**Visit 1 Day -1 -21 to -2** (Screen-ing & Baseline)	**Visit 2 Day 0** (Treat-ment- dis charge)	**Visit 3 30 (+/- 7) Days**	**Visit 4 60 (+/- 7) Days**	**Visit 5 (3 mo. +/- 2 wks) & Visit 7 (9 mo. +/- 2 wks)**	**Visit 6 6 months (+/- 2 weeks)**	**Visit 8 1 Year (+/- 4 weeks)**	**Visit 9[5] 2 Year (+/- 4 weeks)**
Written Informed Consent	√							
Baseline angiogram/images for screening	√							
Inclusion / Exclusion criteria assessment, including enrollment concurrence by an Independent Safety Committee that subject is not a candidate for conventional surgical or endovascular limb salvage procedures	√							
Demographic data, medical history, medication review, & physical exam	√							
Review of medications / dual anti-platelet regimen[1]	√	√	√		√	√	√	√
Rutherford Classification (RCC)	√		√		√	√	√	√
Wound healing assessment (completed or not), and photographs[2]	√		√		√	√	√	√
Index limb oxygenation measurement – $TcPO_2$[3]	√		√		√	√	√	
Pulse evaluation via continuous wave doppler assessment of grafted area (proximal, graft, and distal to outflow vessels)[4]	√ (target location)	√[8]	√		√	√	√	√

TABLE 1: Study Assessment Schedule (cont)	**Visit 1 Day -1 -21 to -2** (Screen-ing & Baseline)	**Visit 2 Day 0** (Treat-ment-discharge)	**Visit 3 30 (+/- 7) Days**	**Visit 4 60 (+/- 7) Days**	**Visit 5 (3 mo. +/- 2 wks) & Visit 7 (9 mo. +/- 2 wks)**	**Visit 6 6 months (+/- 2 weeks)**	**Visit 8 1 Year (+/- 4 weeks)**	**Visit 9[5] 2 Year (+/- 4 weeks)**
Serum Creatinine	√		√			√		
Numeric Pain Scale Rating (1-10)[5]	√		√		√	√	√	√
Procedural angiogram and device performance data		√						
Technical Success		√						
Procedural Success		√	√					
Procedure time, defined from sheath insertion to final catheter removal		√						
Fluoroscopy time and Contrast Load for the index procedure		√						
Device- or procedure-related AE/SAE's[6]		√	√		√	√	√	√
Assessment of amputation and/or major re-intervention of the Stent Graft			√		√	√	√	√
Duplex Ultrasound Exam to assess Stent Graft patency[7]			√	√	√[9]	√		
All-cause mortality			√		√	√	√	√

[1] Dual antiplatelet therapy is required for 3 months post-procedure. At a minimum, all subjects must be started on DAPT at least 1 week before procedure or adequately pre-loaded with DAPT as per institution practice.
[2] Prior to any re-intervention of the stent graft, an angiogram/image and wound photograph should be obtained for adjudication purposes.
[3] TcPO2 will be measured at 2 constant points on the dorsum of the midfoot through the 12 month follow-up.
[4] Per ACC/AHA 2006 Peripheral Arterial Disease Guidelines
[5] McCaffery, M., Beebe, A., et al. (1989). Pain: Clinical manual for nursing practice, Mosby: St. Louis, MO.
[6] 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 patients out of area or who refuse to come in for this visit, a telephone
assessment should be conducted to capture as much information as possible at this time point.
[7] May be performed at any visit as standard of care, as indicated by clinical symptoms.
[8] Continuous wave doppler must be performed between 4 and 30 hours post-procedure to assess for acute thrombosis; any findings of acute thrombosis must be reported to the Sponsor within 24 hours of the exam. The sponsor must notify the FDA via email of any cases of acute stent graft thrombosis within 5 days of the event.
[9] 3 Month visit only

6.4 Study Procedures

6.4.1 Enrollment

Once any component of the LimFlow Stent Graft System is introduced into the body, the subject will be considered to be enrolled in the study and subject to all follow-up requirements. If the device is introduced but implantation is either not attempted or unsuccessful, subjects will be followed through 30 days for safety only, or through resolution or stabilization of any device- or procedure- related adverse events, whichever is longer. Those subjects will then be exited from the study and will not be replaced.

6.4.2. Intra-operative

At a minimum, all subjects must 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. For consented subjects that meet the pre-operative eligibility criteria, record the relevant data regarding their endovascular procedure. Record the following information:

- 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 fluoroscopy time 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 will be made to assess the anatomy, placement and patency of the proximal, body and distal ends of the Stent Graft.

6.4.3. Post-operative

After the LimFlow Stent Graft System is successfully placed, the access site and peripheral extremity should be closely monitored. Dual anti-platelet therapy should be prescribed for a minimum of 3 months post-procedure.

All subjects will undergo a continuous wave doppler exam of the stent graft 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 to Sponsor within 24 hours of the exam and reported as an adverse event. The sponsor must notify the FDA by email of any cases of acute stent graft thrombosis within 5 days of the event.

6.5 Follow-up

Subjects should return to the clinic at 30 and 60 days (+/- 7 days), at 3, 6, and 9 months (+/- 2 weeks), and then annually for up to 2 years following their endovascular procedure and the peripheral limb/wound should be assessed.

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, $TCP0_2$, wound healing status, medication regimen and any procedures or complications related to the index limb occurring since the last visit. The limb/wound will be photographed, displaying a metric ruler in the frames, and in enough detail to capture any change in wound status. Photographs are to include Anterior-Posterior (AP) photos of the dorsum of the foot including toes, medial and lateral projections and plantar.

Duplex Ultrasound Exam Guidelines: A duplex ultrasound exam will be performed at 1, 2, 3, and 6 month visits to assess the following:

- Presence of any significant stenotic or occlusive lesions proximal to the AV fistula that may compromise in-flow
- Diameter of the stent graft proximal to the crossing point, just distal to the crossing point, proximal upper tibial, mid tibial and lower tibial
- Flow volume measurements based on Diameter and Time Averaged Mean Velocity (TAMV) at the identical points stated above where diameter measurements were made
- Presence of flow in the outflow veins of the foot and flow volume measurements if possible
- Standard duplex ultrasound of the tibial arteries with particular reference to the presence of reverse flow.

Subjects should be instructed to promptly notify the investigator regarding any outside surgical referrals initiated by referring physicians caring for the subject's wounds.

NOTE: In the event that an index limb is determined to need a re-intervention or major amputation, a photograph of the wound and angiogram/images should be collected prior to the procedure for event adjudication by the ISC.

6.6 Study Exit

Once the subject has a) completed the follow-up visits; b) has withdrawn consent to participate in the study; c) has met a primary study endpoint, or d) was enrolled but not able to have the device implanted, they will be exited from the study provided they do not have any conditions that require continued follow-up. The date of exit, reason, and subject status should be recorded.

7.0 Assessment of Safety and Effectiveness

7.1 Primary Safety Endpoint

Amputation-Free Survival at 30 days, defined as the percentage of subjects with:

- **Limb Salvage:** Freedom from above-ankle amputation of the index limb AND
- **Survival:** Freedom from all-cause mortality

7.2 Secondary Safety Endpoint

Amputation-Free Survival at 6 months, defined as the percentage of subjects with:

- **Limb Salvage:** Freedom from above-ankle amputation of the index limb AND
- **Survival:** Freedom from all-cause mortality

7.3 Secondary Effectiveness Endpoints

There are multiple secondary effectiveness endpoints to be evaluated in the study:

- **Primary Patency at 30 days:** Defined as the absence of total occlusion[1] of the stent graft without prior clinically driven major re-intervention[2] of the stent graft at 30 days.
- **Primary Patency at 6 months:** Defined as the absence of total occlusion[1] of the stent graft without prior clinically driven major re-intervention[2] of the stent graft at 6 months.
- **Secondary Patency at 6 months:** Defined as the absence of total occlusion[1] of the stent graft with or without prior clinically-driven major re-intervention[2] of the stent graft at 6 months.

- **Deterioration in Renal Function at 6 months:** Defined as a 25% increase in serum creatinine after using iodine contrast agent without another clear cause for kidney injury.

- **Limb Salvage at 3, 6, 9, and 12 months:** Defined as percentage of subjects with freedom from above-ankle amputation of the index limb.
- **Wound Healing at 3, 6, 9, and 12 months:** Defined as percentage of subjects with completed index wound healing.
- **Technical Success:** Percentage of technical success, defined as completion of the endovascular procedure and immediate morphological success with successful placement of the arterial and venous catheters in the desired location in the limb, and ability to place the stent graft.
- **Procedural Success:** Percentage of subjects with a procedural success, defined as combination of technical success, and absence of all-cause mortality, above-ankle amputation or clinically-driven major re-intervention of the stent graft through 30 days.

[1] Occlusion is defined as absence of flow on color Doppler, and/or absence of flow on angiographic images (conventional or CT).
[2] Clinically-driven major re-intervention is defined as 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 critical occlusion of the stent graft.

8.0 Statistical Considerations

8.1 Analysis Populations and Data Handling Conventions

8.1.1. Safety

All subjects who receive any portion of the LimFlow Stent Graft System will be included in safety analysis, as Intent to Treat population (ITT).

8.1.2. Effectiveness

All enrolled subjects meeting all inclusion and exclusion criteria that receive the LimFlow Stent Graft System (e.g., implanted) will be included in the effectiveness analyses, as Per Protocol population (PP).

8.1.3. Missing Data

Missing data will not be imputed by any method. All subject data will be collected on standardized case report forms.

8.2 Data Analysis

8.2.1. Baseline Subject Characteristics

Subject demographics, baseline characteristics and medical history will be summarized descriptively. Mean and standard deviation will generally be reported for continuous variables; median and range may be reported instead if the data distribution is skewed. Frequencies and proportions will be reported for categorical variables.

8.2.2. Safety

8.2.2.1. Primary Safety Analysis

The primary safety analyses will be based on the 30-day incidence rate of Amputation-Free Survival for the safety study sample per 8.1.1. Survival rates, 95% confidence intervals, and Kaplan-Meier analyses will be reported.

8.2.2.2. Secondary Safety Endpoints Analyses

The secondary safety endpoint will be similarly summarized as described in 8.2.2.1.

Additionally, all serious and non-serious adverse events that are potentially device- and/or procedure-related, and/or related to the index limb will be summarized by type of event, severity, relationship to the device and/or procedure, and timing of event relative to the procedure date.

8.2.3. Effectiveness

8.2.3.1. Secondary Effectiveness Analysis

The secondary effectiveness endpoints will be summarized for the effectiveness study sample per 8.1.2. Summary statistics for the Composite (rate and 95% confidence interval) will be reported. The proportion of LimFlow Stent Graft subjects who are converted to other treatment means due to technical failure will also be reported.

8.3 Sample Size Justification

It is generally recognized that a minimum of 10 completed subjects is sufficient to satisfy the goals of pilot studies such as the study described herein. Subjects will be carefully screened and followed to ensure all efforts are made to secure follow-up compliance in this frail subject population.

9.0 Data Management and Monitoring

9.1. Study Data Collection

Electronic Case Report Forms (eCRF) will be used to capture data for the safety and performance analysis. Sites will be required to maintain source documentation, in accordance with GCP guidelines and 21 CFR 812 to substantiate all data collected.

9.2. Site Data Monitoring and Quality Control

Primary data collection based on source-documented hospital chart reviews will be performed by the clinical research team, which may include sponsor or sponsor's designees. CRFs will be completed and forwarded to the sponsor within 14 days of the procedure or scheduled visit. 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.

The clinical site will be monitored periodically by the sponsor's personnel, or sponsor's designee, for protocol adherence, accuracy of CRFs, 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 serious adverse events and ensure that such information is provided to the appropriate regulatory agencies, the investigators and to all reviewing IRBs as required by applicable regulations.

10.0 Safety Oversight

10.1. Safety: Complication Analysis and Acceptance

Revascularization catheter procedures are known to have inherent risks of complications. No new or additional complications or adverse events are expected due to the LimFlow portion of the procedure.

10.1.1 Procedural Complications

If serious procedural complications or adverse events are observed, the events will be individually analyzed for root cause relative to the complete treatment procedure and then evaluated by the Independent Safety Committee and the Principal Investigator. The sponsor will assess these events for expedited reporting requirements.

10.1.2 Post-Procedural Complications

If serious complications or adverse events related to the procedure or device are observed during and through the 6 month follow-up, the events will be individually analyzed for root cause relative to the complete treatment procedure and then evaluated by the Independent Safety Committee and Principal Investigator. The sponsor will assess these events for expedited reporting requirements.

10.2. Independent Safety Committee (ISC)

An Independent Safety Committee will act as the medical monitor for this early Pilot Study. The ISC will consist of at least two (2) physicians with experience in surgical and/or endovascular treatment of CLI patients, who are independent from the Sponsor and are not investigators in the study. Whenever possible, the ISC will review data in a blinded fashion (i.e., blinded to site and subject ID, follow-up period, etc.) to minimize any potential bias. Specific roles, responsibilities and processes will be described in a Safety Charter, which will be agreed upon by ISC members and published prior to commencement of the study.

Screening Responsibilities:

The ISC 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. Specific criteria to be evaluated by the ISC in this determination include, but may not be limited to:

- Baseline angiograms/images to evaluate the status and patency of the distal arterial bed (i.e., tibial and peritoneal arteries, dorsalis pedis artery, and plantar arteries)
- Wound photographs
- Medical history, including Rutherford Classification
- Clinical evidence of severe hemodynamic compromise in the index limb (e.g., TcPO2, pulse assessments)

Endpoint Assessment/Adjudication:

Technical Success: The ISC will review the procedural angiograms to assess stent graft/limb patency post-procedure to determine Technical Success.

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

- Major amputation of the index limb
- Stent graft occlusion and/or acute stent thrombosis (via DUS and/or angiographic documentation)
- Death
- Major and minor re-interventions of the index limb
- Contrast-induced nephropathy
- Wound healing (progression, completion, confirmation).

Ongoing Safety Overview:

The ISC 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. During the study, the ISC 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.

10.3 Study Termination

If LimFlow and/or the ISC and/or principal investigator determine 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. LimFlow will notify all participating investigators, and IRBs and the FDA of the termination of the investigation.

11.0 Adverse Event Reporting

11.1. General 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.

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.

A serious adverse event (SAE) is defined as an event which leads to:

- Death due to any cause
- Life-threatening condition
- Results in persistent or significant disability/incapacity
- 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
- Results in congenital abnormality

All SAE's will be reported.

***Device-Related Adverse Event**:* 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, in the judgment of the investigator; it is reasonable to believe that the event is associated with the assigned 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.

LimFlow, or its designee, in cooperation with the investigator, 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).

The investigator should follow all unresolved serious adverse events until the events are resolved, the subject is lost to follow-up, the subject has withdrawn consent, or the adverse event is otherwise explained.

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 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 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 imbalance without clinical sequelae following endovascular procedure, even if requiring correction
- Low grade temperature increase (≤38.3°C/≤101°F)
- Sinus bradycardia/tachycardia that does not require treatment or intervention
- Systolic or diastolic blood pressure changes that do not require treatment or intervention

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.

11.2. Reporting of Serious and Non-Serious Adverse Events

11.2.1. 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 2 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 serious adverse events, procedure and/or device observations and malfunctions, medical record documentation (e.g. procedure notes, operative notes, discharge summary, relevant progress notes, imaging or lab studies) must be provided to sponsor or its designee.

The following criteria must also be adhered to by the investigator in the case of serious adverse events:

- The Adverse Event eCRF must be signed by the investigator.
- It is the responsibility of the investigator to inform their IRB of serious adverse events as required by their IRB procedures and in conformance with FDA and local regulatory requirements.

11.2.2. 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 24 hours of learning of the adverse event or failure via phone or email contact. The LimFlow contact information for reports and questions is:

Sponsor Contact:	LimFlow, Inc. Contact: Thomas Engels Vice President Clinical Affairs Phone: (888) 478-7705, ext. 101 Fax: (408) 898-1459 e-mail: tengels@limflow.com
Monitor Contact:	Marlys Chellew, BSN, RAC Mobile: 916-303-0879 mchellew@chellewclinical.com

11.3. Device Failures and Malfunctions

Device performance will be evaluated by the treating physician. All performance data will be captured on the electronic case report forms.

Device Failure: A device has failed if it does not perform according to labeling and negatively impacts the treatment while used according to the labeling.

Device Malfunction: A device malfunction is an unexpected change to the device that is contradictory to the labeling and may or may not affect device performance.

All reported device malfunctions or failures of the LimFlow Stent Graft System are required to be documented in the eCRF. In the event of a suspected observation or device problem, refer to the Manual of Operations for further instructions. Device failures and malfunctions should also be documented in the subject's medical record.

NOTE: Device failures or malfunctions are NOT to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded in the CRF.

12.0 Quality Control and Quality Assurance

12.1. Site Training

To ensure accurate, complete, and reliable data, the Sponsor or its representative will provide instructional material to the study site, as appropriate:

- Instruct the investigators and study personnel on the protocol, the completion of the CRFs, and study procedures
- Communicate regularly with site personnel via mail, email, telephone, and/or fax
- Make periodic visits to the study site.

12.2. Physician Training

All investigators participating in this clinical trial are skilled in vascular interventional procedures and the use of the competitors' endovascular catheters. The Site Initiation will include procedural relevant workflow and instruction for the LimFlow System. All treating physicians will have experience with the LimFlow system in cadaver and animal labs prior to treating the first subject, or LimFlow will provide a trained physician or clinical specialist to proctor the investigator's first cases, until the investigator is comfortable with the procedure.

12.3. Audits and Inspections

The principal investigator for the site will also allow representatives of the governing IRB, the United States Food and Drug Administration (FDA), and other applicable regulatory agencies to inspect all study records, CRFs, and corresponding portions of the subject's office and/or hospital medical records at regular intervals throughout the study. These inspections are for the purpose of verifying adherence to the protocol, completeness and exactness of the data being transcribed onto the CRF, and compliance with FDA or other regulatory agency regulations.

The principal investigator for the site will inform the sponsor or sponsor's designee in advance if they are to be audited or inspected by any regulatory agencies. The sponsor will also inform the site if they are made aware of a pending audit or inspection by a regulatory agency.

12.4. Independent Safety Committee (ISC) Member Training

All ISC members will be trained to the protocol, the procedure/device, the Safety Charter, and the documentation requirements prior to commencement of duties for this trial.

13.0 Ethical Considerations

13.1. Trial Conduct & the Declaration of Helsinki

The study will be performed in accordance with the relevant parts of Title 21 CFR Parts 812, 50, 54, and 56, and the ICH Guidelines for Good Clinical Practices (E6).

13.2. Institutional Review Board (IRB)

A copy of the protocol, proposed Informed Consent form, other written patient information and any proposed advertising material must be submitted to the Institutional Review Board (IRB) for written approval prior to use. A copy of the written IRB approval of the protocol and Informed Consent form must be received by the sponsor, before recruitment of patients into the study and shipment of investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB as well as any required regulatory agencies, for all subsequent significant protocol amendments and significant changes to the Informed Consent form. The investigator should notify the IRB of deviations from the protocol or SAEs and UADEs occurring at the site and other SAE/UADE reports received from the sponsor in accordance with local procedures.

The investigator will be responsible for obtaining annual IRB approval and renewal throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be sent to the sponsor.

13.3. Provisions for Maintaining Confidentiality

Confidentiality of subjects will be maintained throughout the study. A unique identification code will be assigned to each subject participating in this study. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity. The Sponsor and their CRO representative will make every reasonable effort to protect the confidentiality of the subjects participating in the study.

13.4. Provisions for Compensation in Case of Injury

On the conditions that a subject follows the directions of the study investigators in charge of this study, and in a case a subject is physically injured due to the trial procedure given under the plan for this study, the sponsor will pay the medical expenses for the treatment of that injury.

The sponsor will not provide payment for management of the normally expected consequences of the treatment of a subject. Subjects will not be reimbursed or compensated for participating in the study, except for modest reimbursement for travel costs related to attendance of follow-up visits.

By signing the Informed Consent Form, a subject will not waive any of his/her legal rights or release the parties involved in this study from liability for negligence.

13.5. Emergency Actions

The sponsor accepts the right of the investigator to deviate from the protocol in an emergency when necessary to safeguard the life or the physical well being of a study subject. The investigator must give notice of any emergency deviations and justification for the deviation to the sponsor and the IRB as quickly as possible after the episode, in any event no later than 24 hours after the emergency.

13.6. Informed Consent Form

A sample Informed Consent form is provided in Attachment 1 for the investigator to prepare for use at his/her site. The written Informed Consent documents should be prepared in the language(s) of the potential patient population at a reading level that the subjects can understand.

The reviewing IRB and the sponsor must first approve the Informed Consent forms that are used. The Informed Consent forms that are used should be in accordance with the current guidelines as outlined by the relevant parts of Title 21 CFR Parts 812, 50, 54, and 56, and the ICH Guidelines for Good Clinical Practices (E6).

Prior to participation in the clinical study, each patient must give written Informed Consent after the context of the study has been fully explained to the patient in language that is easily understood by the patient. The patients must also be given the opportunity to ask questions and have those questions answered to their satisfaction.

Written Informed Consent must be recorded appropriately by means of the patient's dated signature. The patient will receive a copy of the Informed Consent form.

14.0. Study Administration

The sponsor will make necessary efforts to ensure that this study is conducted in compliance with GCPs and all applicable regulatory requirements.

14.1. Pre-Study Documentation Requirements

Prior to shipment of investigational product, the following documents must be provided to the sponsor:

- Signed and dated Investigator Agreement, contract and budget
- Completed Financial Disclosure form(s) for all Investigators
- A copy of the written IRB approval of the protocol
- A copy of the written IRB approval of the Informed Consent Form
- A copy of the curriculum vitae of the Principal Investigator and Co-Investigator (if applicable).

14.2. Source Documentation

The principal investigator must maintain detailed source documents on all study subjects who are enrolled in the study or who undergo screening. Source documents include subject medical records, hospital charts, clinic charts, investigator's subject study files, as well as the results of diagnostic tests (e.g., laboratory tests).

The following minimum information should be recorded in the subject's medical records:

- The date the subject entered the study and the subject number
- The study protocol number and the name of the Sponsor
- The date that informed consent was obtained and a statement of informed consent process

- Evidence that the subject meets study eligibility requirements (e.g., medical history, study procedures and/or evaluations)
- The dates of all study related subject visits
- Evidence that required procedures and/or evaluations were completed, including required photographs, angiographic images, and DUS images
- Use of any concurrent medications
- Documentation of specific device used, if any
- Occurrence and status of any Adverse Events
- The date the subject exited the study, and a notation as to whether the subject completed the study or was discontinued, including the reason for discontinuation.

14.3. Record Retention

The investigator will maintain all essential study documents and source documentation, in original format, that support the data collected on the study subjects in compliance with the ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product.

14.4. Criteria for Terminating Study

The sponsor reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators and associated IRBs will be notified in writing in the event of termination.

Possible reasons for study termination include:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of the sponsor to suspend or discontinue development of the device.

14.5. Criteria for Suspending/Terminating a Study Center

The sponsor reserves the right to stop the enrollment of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled or if the center has multiple or severe protocol violations without justification or fails to follow remedial actions.

Possible reasons for suspending/terminating a study center include:

- Repeated failure to complete case report forms prior to scheduled monitoring visits
- Failure to obtain written Informed Consent prior to treatment
- Failure to report SAE/UADE to sponsor within 24 hours of knowledge
- Loss of (or unaccounted for) investigational product inventory

14.6. Amending the Protocol

An investigator may not make protocol changes without prior approval by the sponsor. All significant protocol changes that may affect the following must be submitted and approved by the IRB before initiating the change:

- validity of the data or information resulting from the completion of the approved protocol;
- relationship of the likely subject risk to benefit relied upon to approve the protocol;
- scientific soundness of the investigational plan, or;
- rights, safety, or welfare of the human subjects involved in the investigation.

The sponsor will submit a copy of any protocol amendment to the investigators for their IRB to review and ensure the study continues to be conducted consistently across all sites. The investigative site must send sponsor a copy of the IRB approval letter for the protocol amendment.

The sponsor may make certain administrative changes to the protocol without prior approval of the IRB, and will notify all investigative sites of such changes to ensure the study continues to be conducted accordingly.

14.7 Publication Policy

The existence of this clinical study is confidential, and it should not be discussed with persons outside of the study. Additionally, the information in this document and regarding this study contains trade secrets and commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by regional or national law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, but all such persons must be instructed not to further disseminate this information to others. These restrictions of disclosure will apply equally to all future information provided that is indicated as confidential.

The data generated by this clinical study are the property of the sponsor, and should not be disclosed without their prior written permission. These data may be used by the sponsor now and in the future for presentation or publication at sponsor's discretion or for submission to governmental regulatory agencies. The principal investigator may publish or present the study results with prior consent of the sponsor, but will not disclose confidential information. Prior to submission by a principal investigator for publication or presentation, the sponsor will be provided with the opportunity to review the submission for confidential information and accuracy.

15.0 Regulatory Considerations

15.1. Sponsor's Responsibilities

15.1.1 General

The sponsor of this clinical study has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the United States Food and Drug Administration (US FDA). Together, both the sponsor and its designees will ensure adherence to the sponsor's general duties, selection of investigators, monitoring, supplemental applications, maintaining records, and submitting reports.

The sponsor's general duties consist of obtaining IRB approval prior to shipping the devices, selecting qualified investigators and shipping devices only to those qualified investigators. The sponsor is also required to obtain signed study agreements, to provide the investigators with the information

necessary to conduct the study and adequate on-site training to conduct the study, to ensure proper clinical site monitoring, and to provide the required reports to the investigators, IRBs and appropriate regulatory agencies.

The sponsor will be responsible for providing quality data that satisfies appropriate regulations and informing of serious unanticipated adverse events and deviations from the protocol. Written progress reports and a final report will be prepared.

15.1.2. Investigational Device Distribution

LimFlow will control the distribution of the investigational devices. The investigator is responsible for ensuring that the devices are ordered for shipment to arrive at the hospital before the procedure date.

Devices will be shipped with an Investigational Device Shipment Record. This form is to be used by LimFlow and the investigational site to record any shipments of the investigational device. A copy is to be retained by the shipper and the recipient.

15.2 Investigator Responsibilities

15.2.1. Investigator Agreement

The investigator must:

- Agree to sign and adhere to the Investigator Agreement
- Be willing to provide required assessments for analysis
- Be willing to perform and be capable of performing treatment procedures as outlined in this protocol
- Comply with all required elements of this protocol (e.g., perform testing and follow-up as specified, especially during personnel transitions) and supply material suitable for quantitative analysis
- Agree to obtain written Informed Consent before any study specific procedures are performed in accordance with GCP
- Complete all case report forms prior to scheduled monitoring visits
- Be willing to change hospital routine if required by protocol (as long as subject safety and well-being is not compromised).

15.2.2. Required Reports

Table 2 displays a list of the reports that are the principal investigator's responsibility to generate. The local IRB may have additional reporting requirements.

Table 2: Reports Required From Clinical Investigators

Type of Report	Prepared By Investigator For:	Time Constraints of Notification
Acute stent thrombosis	Sponsor	Within 24 hours of knowledge of event; LimFlow will report to FDA within 5 working days
Subject death during investigation	Sponsor	Within 24 hours of knowledge of event
Unanticipated adverse device effect	Sponsor	If serious or life-threatening, within 2 calendar days; otherwise

		within 10 working days
Report of subject enrollment	Sponsor	Within 2 working days
Subject withdrawal	Sponsor	Within 5 working days
Withdrawal of IRB or Ethics Committee approval	Sponsor	Within 5 working days
Deviations from investigational plan (emergent)	Sponsor	Within 5 working days
Informed consent not obtained	Sponsor	Within 5 working days
Final summary report	Sponsor	Within 3 months

15.2.3 Investigational Device Accountability

The investigator shall maintain adequate records of the receipt and disposition of all investigational devices. The investigator is responsible for ensuring that the investigational devices are used only under the investigator's supervision and are only used according to this protocol and any approved amendments. The investigator will not supply an investigational device to any person not authorized to participate in the LimFlow study. The investigator shall document in the operative notes and CRF's the lot number of the devices used during a case. In addition, the investigator shall keep complete and accurate records of all devices used or unused that have been returned to LimFlow in a Device Accountability Log provided by the sponsor.

After the cases are completed, all unused devices must be accounted for and returned to LimFlow. Instructions for device return to LimFlow will be reviewed at the site initiation visit.

16.0 Glossary of Terms

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. Sponsor must be notified within 24 hours of findings, and Sponsor will subsequently report findings to the FDA via email within 5 working days of the event.

ALL-CAUSE DEATH, divided into 2 categories:

Cardiac death is defined as death due to any of the following:

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

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

AMPUTATION

Major amputation is defined as amputation of the index limb at the level above the ankle.

Minor amputation is defined as amputation(s) of the index limb/metatarsals at the level below the ankle. Indication for minor amputations should be documented in the CRF.

Pre-planned amputation is defined as 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

Defined as the percentage of subjects with:

- **Limb Salvage:** Freedom from above-ankle amputation of the index limb AND
- **Survival:** Freedom from all-cause mortality

ARTERIAL / VENOUS THROMBOSIS

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

ARTERIOVENOUS (AV) FISTULA

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.

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.

CLINICALLY-DRIVEN MINOR RE-INTERVENTION OF THE STENT GRAFT

Endovascular procedures (PTA, atherectomy, stenting) without thrombectomy / thrombolysis, and minor surgical revisions (patch angioplasty) performed to prevent occlusion of the stent graft.

DETERIORATION IN RENAL FUNCTION / CONTRAST-INDUCED NEPHROPATHY

An increase of $\geq$ 25% in serum creatinine after using an iodine contrast agent, without another clear cause for kidney injury.

EMBOLISM

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.

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.

LOCALIZED ACCESS SITE INFECTION
Infection occurring at the access site requiring treatment with oral or intramuscular antibiotic therapy. Does not include administration of prophylactic antibiotic regimens.

MAJOR BLEEDING COMPLICATION
Defined as blood loss resulting from the percutaneous revascularization procedure or adjunctive drug therapy requiring transfusions of blood products.

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
Absence of flow on color Doppler, and/or absence of flow on angiographic images (conventional or CT).

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

PERFORATION OF VENOUS VESSEL WALL
A hole or break in the venous wall (e.g., from insertion/advancement of a percutaneous device).

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

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)
Any untoward medical occurrence that results in death, is life threatening, requires subject hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity.

STROKE
A stroke is any sudden development of neurological deficits, such as vertigo, numbness, aphasia, or dysarthria due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm.

SUB-INVESTIGATOR / CO-INVESTIGATOR
Any individual member of the clinical investigation team designated and supervised by the Investigator at an investigational site who performs critical investigation-related procedures and/or makes important investigation-related observations. See also Investigator.

SUBJECT
An individual who participates in a clinical investigation.

TRANSIENT ISCHEMIC ATTACK (TIA)

Focal neurologic abnormalities of sudden onset and brief duration (i.e., lasting less than 24 hours) that reflect dysfunction in the distribution of the affected artery. TIAs include transient monocular blindness (e.g., amaurosis fugax defined as a transient episode of monocular blindness, or partial blindness, lasting ten minutes or less) and transient hemispheric attacks.

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.

17.0 Informed Consent Template

18.0 Revision History

Rev.	Change	Date
01	Original Issue of protocol for US Pilot study.	30Jan2017
02	FDA-requested revision to acute stent thrombosis reporting requirements, and post-procedural continuous wave doppler evaluation.	03Mar2017
A	US Sponsor information added; updated to Rev. A according to new Clinical Document Control procedures.	28Mar2017
B	Increased number of subjects from 10 to 25. Increased number of sites from 3 to 6.	27Dec2017
C	Increased number of sites from 6 to 7. Added Pulse evaluation of the target location via continuous wave doppler to the baseline assessment. Added Duplex Ultrasound Exam at 2 months and 3 months.	18May2018
D	Increased number of subjects from 25 to 35.	27June2018