Percutaneous Deep Vein Arterialization

PROMISE UK

Post-market study

Clinical Investigation Plan

Version 4.4-UK

21 July 2022

PROTOCOL SIGNATURE PAGE

Percutaneous Deep Vein Arterialization

PROMISE UK

Post-market study

I have read and agree to the final version of the post-market study protocol (version 4.4-UK, dated 21 July 2022).

I am aware of my responsibilities as an investigator under the ISO 14155:2020 standard *"Clinical investigation of medical devices for human subjects—Good clinical practice"*, local regulations (as applicable), and the clinical investigation plan.

I agree to conduct the study accordingly and to appropriately direct and assist the personnel under my control who will be involved in the study.

Investigator name: _____

Institution name: _____

Date (dd/mm/yyyy): _____/_____/_____ Signature: _____

0. Table of contents

1. General information

1.1. Identification

Title PROMISE UK

Version Version 4.4-UK

Date 21 July 2022

History Please refer to Table 1 below

Table 1. Revision history

Version	Date	Changes
Version 4-UK	28 November 2018	Initial version (adapted from PROMISE International version 4)
Version 4.1-UK	01 June 2020	Update product reference numbers, device description, and manufacturer Refer to IFU for procedural steps Clarify reporting of planned interventions for pre-existing conditions Update clinical data section to reference latest published information
Version 4.2-UK	31 May 2021	Update to study anticipated enrolment and completion timelines due to delays experienced due to the coronavirus pandemic. Update to current standard: ISO 14155:2020 Clarification on exiting of patients who met main study endpoint of amputation. Note that some patient follow-up imaging assessment may be unnecessary in cases where earlier occlusion endpoint had been reached, to be discussed with the study sponsor.
Version 4.3-UK	29 November 2021	Update to study anticipated enrolment and completion timelines due to impacts due to the coronavirus pandemic.
Version 4.4-UK	21 July 2022	Ongoing update to study anticipated enrolment and completion timelines due to impacts due to the coronavirus pandemic.

1.2. Sponsor

LimFlow SA
95 bis, boulevard Pereire
75017 Paris
France

1.3. Contract research organization

MedPass International
95 bis, boulevard Pereire
75017 Paris
France

1.4. Independent committee

Syntactx
4 World Trade Center
150 Greenwich Street, 44th Floor
New York, New York 10007
United States of America

1.5. Principal investigators and investigation sites

The list of principal investigators and investigation sites is provided in Annex A to this protocol.

1.6. Overall synopsis of the clinical investigation

1.6.1. Objectives

The objective of this post-market study is to collect *"real-life"* clinical data among a population of patients treated with the commercially-available LimFlow System in order to evaluate the **safety and effectiveness** of the LimFlow System in creating a below-the-knee arterio-venous fistula for venous arterialization in subjects with critical limb ischaemia.

1.6.2. Design

This study is a single-arm, open-label, prospective, post-market follow-up study to be conducted on up to 25 eligible patients (roll-in subjects plus 20 analysis subjects) with a twelve-month follow-up period. This study was designed and is to be conducted in compliance with the ISO 14155 standard.

1.6.3. Endpoints

Primary endpoint

- Amputation-free survival

Secondary endpoints

- Complete wound healing
- Primary and secondary patency
- Limb salvage
- Technical and procedural success

1.6.4. Visits and exams

Patients should be followed at regular intervals during one year after the initial percutaneous deep vein arterialization procedure. The protocol follow-up schedule is intended to align with the standard of care as seen with patients who are treated with surgical bypass or endovascular revascularization. Visits and exams scheduled for this post-market study are presented in Table 2 below (keys: ■ mandatory, ☐ optional).

Table 2. Visits and exams

Exams	Baseline	Treatment	Week 02	Month 01	Month 02	Month 03	Month 06	Month 09	Month 12
Eligibility	■								
Demographics	■								
Infection status[†]	■								
Venous mapping[‡]	■								
Angiogram	■	■							
Ultrasound		Duplex		Duplex	Duplex	Duplex	Duplex	Duplex	Duplex
Medication	■	■	■	■	■	■	■	■	■
Creatinine	■								
Rutherford	■			■	■	■	■	■	■
WIfI	■			■	■	■	■	■	■
Wound pictures	■		■	■	■	■	■	■	■
Pain	■		■	■	■	■	■	■	■
Perfusion	☐		☐	☐	☐	☐	☐	☐	☐
Quality of Life	■					■	■	■	■

Adverse events		■	■	■	■	■	■	■	■

[†]Wound culture and/or blood analysis (WBC, CRP, ESR)

[‡]Phlebography, duplex ultrasound, MRV or CTV, depending on what is available

1.6.5. Inclusion criteria

I-1. Subject must be > 21 and < 95 years of age

I-2. Clinical diagnosis of symptomatic critical limb ischaemia, defined as Rutherford category 5 or 6

I-3. Assessment that no conventional surgical or endovascular treatment is possible

I-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

I-5. Subject is willing and has adequate support to comply with protocol requirements, including medication regimen and follow-up visits

1.6.6. Exclusion criteria

E-1. Concomitant hepatic insufficiency, deep venous thrombus in target limb, uncorrected coagulation disorders, or current immunodeficiency disorder

E-2. Life expectancy less than 12 months

E-3. Patient currently taking coumarin/warfarin which, in the opinion of the attending physician, interferes with the patient's treatment

E-4. Any significant medical condition which, in the attending physician's opinion, may interfere with the patient's optimal treatment

E-5. Patient 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 treatment

E-6. Patient unable to give consent

E-7. Pregnant or breastfeeding women

E-8. Documented myocardial infarction or stroke within previous 90 days

E-9. Patients suffering from renal insufficiency (GFR value less than 30 ml/min/1.73 m^2) who are not on haemodialysis

E-10. Patients with vasculitis and/or untreated popliteal aneurysms

E-11. Patients with acute limb ischaemia

E-12. Prior peripheral arterial bypass procedure above or below the knee which could inhibit proximal inflow to the stent graft

E-13. Lower extremity venous disease with significant oedema in the target limb that may inhibit the procedure and/or jeopardize wound healing, in the investigator's opinion

E-14. Known or suspected systemic or severe infection (*e.g.*, WIfI foot Infection grade of 3)

E-15. Known or suspected allergies or contraindications to stainless steel, nickel, or contrast agent that cannot be adequately pre-treated, or patients who cannot receive anticoagulation or antiplatelet aggregation therapy

E-16. 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)

2. Identification and description of the medical device

2.1. Summary description and intended purpose

The medical device is the LimFlow System, which is CE-marked and intended to treat critical limb ischaemia by minimally invasively creating an arterio-venous bypass graft to produce the venous arterialization procedure in the below-the-knee vasculature.

2.2. Populations and indications for which the device is intended

The LimFlow System is indicated for endovascular, minimally invasive procedures in patients who have a clinical diagnosis of symptomatic critical limb ischaemia, have been assessed by a vascular surgeon and interventionalist and it was determined that no surgical or endovascular treatment is possible, and are clearly indicated for major amputation—also referred as "no-option" patients.

2.3. Device identification and materials used

The LimFlow System consists of five (5) medical device components: the ultrasound system, the extension cable set, the arterial and venous catheter set, the valvulotome, and a series of stent grafts with delivery systems. Below in Table 3 is a listing of all medical device components including whether or not the devices are sterile, reusable, or in contact with patient blood, along with device names and current identification numbers (subject to change).

Table 3. Device identification

Catalogue Number	Device	Materials	Sterile	Reusable	Blood contact
LF-US-EU-XX	Ultrasound system	Aluminium (outside enclosure of transceiver box) plus computer notebook	No	Yes	No
LF-EX-EU-XX	Extension cable set	Plastic cable isolation	Yes	No	No
LF-XX-EU-XX	Arterial and venous catheters	Various plastics and metals (nitinol and stainless steel)	Yes	No	Yes
LF-VT-EU-XX	Valvulotome	Nitinol, stainless steel, and various plastics (polyimide, pebax, etc.)	Yes	No	Yes
LF-SG-DDDDLL-EU-XX	Stent grafts in lengths 60 – 200 mm	Nitinol, PTFE, and various plastics (PEEK, polyimide, pebax, etc.)	Yes	No	Yes

The materials used to construct the LimFlow System including all components are well characterized with a long history of clinical use in, and similar in form to, approved and marketed medical devices. The LimFlow System contains no medicinal products, human and/or animal tissues or their derivatives, or other biologically active substances.

2.4. Device manufacturer

LimFlow SA
95 bis, boulevard Pereire
75017 Paris
France

Contract Manufacturer:
Contract Medical International GmbH
Lauensteiner Strasse 37
01277 Dresden
Germany

2.5. Traceability

Traceability shall be achieved during the clinical investigation by assignment of lot or serial numbers on all LimFlow System components. Catalogue numbers and lot or serial numbers of all devices used will be collected and recorded on the Case Report Forms (CRFs). LimFlow SA will supply the device; any requests for additional materials,

equipment, service, or information shall be directed to LimFlow SA. An inventory of materials will be taken at monitor site visits.

2.6. Device description

The LimFlow System comprises the following five (5) components:

- **Ultrasound system**

  The LimFlow ultrasound system consists of a power supply, a laptop computer, and a transceiver box. The system produces a short electrical pulse which is applied to the transmit catheter. The signal received by the receive catheter is amplified, filtered, and digitized. The received signal is then displayed on the laptop as a waveform, giving a visual display of the strength of the received pulse and hence permitting orientation of the two catheters. Software running on the laptop permits the gain of the receiver and other parameters to be adjusted.

- **Extension cable set**

  The LimFlow extension cables carry power between the LimFlow ultrasound system and the LimFlow arterial and venous catheters.

- **Arterial and venous catheter set**

  The arterial catheter is placed over a standard 0.014" guide wire through a sheath in the femoral artery and advanced to the target artery up to the point of total arterial occlusion. The arterial catheter allows for the following:

  1. **Locating** neighbouring veins via ultrasound (if applicable): a small single directed ultrasonic transmitter as its tip allows to detect the venous catheter in a neighbouring vein. The handle design and the catheter body allow for an easy torque and push-pull to find the correct location.
  2. **Connecting** to a neighbouring vein by advancing a crossing-needle: the catheter has a handle which advances the crossing needle from artery to vein. The catheter is placed into the artery with the needle retracted inside the catheter shaft. A standard 0.014" guide wire can be placed through the advanced needle from the proximal hub (this wire is referred to as the *"crossing wire"*).

  The venous catheter acts as a target in the vein for aligning the needle of the arterial catheter via ultrasound or fluoroscopy. The catheter is placed over a standard 0.014" guide wire and is placed through a sheath in the corresponding target vein and advanced up to and parallel to the arterial catheter. The venous catheter is left in place and the arterial catheter is rotated and moved longitudinally to facilitate creation of the arterio-venous connection.

  Both arterial and venous catheters are intended to be used in a catheterization laboratory in consenting patients under fluoroscopy guidance. Both catheters are supplied sterile, removed at the end of the procedure, and intended for single use only.

- **Valvulotome**

  The valvulotome is intended to make venous valves incompetent. The valvulotome is a device that is inserted over the crossing wire, passing the crossing section into the venous vessel. A push-pull deployment mechanism allows to deploy a nitinol cutting basket mounted at the distal tip. This cutting element self-centres in the venous vessel up to a maximum diameter of 4.5 mm. The actual cutting blades are arranged at a lower diameter as the maximum diameter of the cutting element, this prevents cutting the venous vessel but allows cutting of the vein vales ones the cutting element is pushed through the valves. The device (undeployed cutting element) has a total outside diameter of 4 Fr. The valvulotome is supplied sterile and intended for single use only.

- **Stent grafts**

  To facilitate constant blood flow through the newly-created crossing from artery to vein, a stent graft needs to be inserted. The LimFlow stent grafts product line consists of different self-expanding stent graft sizes and shapes, in order to meet physiological variations in anatomy of patients, and one delivery system, which is compatible for each stent size. The blank laser-cut nickel-titanium alloy (nitinol) stent serves as a base for additional forming and electro spun PTFE encapsulation procedures to obtain a final stent graft.

  The stent graft delivery system comprises of inner tubing, compatible with a 0.018" guide wire lumen and a flushing lumen, which is proximally accessible through a check valve. Design input specifications require 7-Fr sheath compatibility for the delivery device. In order to achieve excellent mechanical properties and functional pushability the outer shaft was designed with a special braid pattern. Two radiopaque markers are attached to the distal end of the delivery device where the stent is crimped in between. Unintended stent movement during sheath retraction is restricted by the delivery device.

2.7. Training and experience needed

The procedure itself should be performed by vascular surgeons and/or interventionalists experienced in interventional techniques such as complex percutaneous transluminal angioplasty and stenting in the lower limb. Study investigators will be selected based on their experience in performing below-the-knee interventions and duly trained by LimFlow SA on the percutaneous deep vein arterialization specific medical procedure. In order to avoid a learning curve bias, each study investigator will be required to first perform at least one (1) successful revascularization in a *"roll-in"* subject. *"Roll-in"* subjects will be included the study but excluded from the endpoint analysis. In addition, a LimFlow SA representative will attend the treatments performed in each site in order to assist the physician on technical issues as well as to ensure that treatment characteristics and potential complications are duly recorded.

2.8. Medical procedures involved

For the LimFlow procedure, please refer to the product instructions for use (IFU).

3. Justification for the design of the clinical investigation

3.1. Results of the preclinical testing

The LimFlow System has undergone extensive verification and validation testing. This includes device and packaging specific performance specifications, as well as transit, sterility, pre-clinical, biocompatibility and accelerated aging testing. Test samples were manufactured in accordance with a Device Master Record (DMR) using trained operators to nominal specifications and documented within a Design History Record (DHR).

Extensive *in vitro*, *in vivo*, and *ex vivo* 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 System:

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

3.2. Clinical data

In the absence of treatment, Peripheral Vascular Disease (PVD) may progress to critical limb ischaemia (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 (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 passed the occlusion. More conventional approaches to treating PVD 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.

The LimFlow approach to treating CLI involves the concept of venous arterialization, which has been performed surgically for many years with first clinical surgical cases reported in the early 1900s.[1,2] Numerous small series of clinical trials have been published using a surgical approach and recent publications summarized this work.[3-5] In conclusion, venous arterialization was considered as a viable alternative before major amputation is undertaken in "no-option" patients with critical limb ischaemia.

Several clinical studies have been conducted with the LimFlow System in Europe, Singapore, and the United States.[6] Results from these studies supported the CE-mark approval of the device in October 2016 and on-going investigation in the United States. The results from these studies have been presented at international congresses and published, demonstrating safety and feasibility of percutaneous deep vein arterialization. The most recent publication demonstrates the long-term viability of the therapy by presenting two year follow-up data.[7]

4. Risks and benefits

4.1. Anticipated clinical benefits

The patients designated for percutaneous deep vein arterialization have critical limb ischaemia with no treatment option other than major amputation. These patients have had repeated percutaneous procedures to use angioplasty to open up the below-the-knee vessels, but the re-occlusion rate is high and once the foot is deserted (lack of blood circulation to the foot), ischaemia and necrosis quickly set in. Necrotic tissue has to be cut away to allow healthy tissue a chance to heal. Infection is a major complication that can rapidly become systemic leading to mortality. Critical limb ischaemia patients are desperate as all medical experts have told them that there are no more possible treatments. The lack of options highlights percutaneous deep vein arterialization is a last hope treatment for these patients, who have exhausted all other possibilities. For this reason, the benefits of percutaneous deep vein arterialization with the LimFlow System far outweigh the known risks associated with this device and readily available percutaneous angioplasty equipment.

4.2. Anticipated adverse device effects

The following adverse events are considered to be anticipated when performing any percutaneous catheterization and will be assessed during the course of the study:

- Allergic reaction, including anaphylactic shock and Quincke's oedema
- Vascular complications at access site, including bleeding events and hematoma
- Arterial and venous thromboembolic events, including angina or myocardial infarction, stroke or transient ischaemic event, pulmonary embolism, deep vein thrombosis, and limb ischaemia
- Contrast-induced nephropathy and renal failure
- Local or systemic infection
- Oedema
- Pain

4.3. Residual risks associated with the device

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.

4.4. Risks associated with participation in the clinical investigation

In addition to the risks associated with the device, risks associated with participation in the clinical investigation are limited to the risks associated with the exams required for the clinical investigation. Those have been reduced to minimal levels by complying with standard of care procedures and not requiring any invasive measurement or exam.

4.5. Possible interactions with concomitant medical treatments

Possible interactions with concomitant medical treatments have been reduced by excluding patients with medical conditions necessitating medical treatments that could potentially interfere with the percutaneous deep vein arterialization procedure. Please refer to Section 6.3.2 *"Exclusion criteria"* on page 15.

4.6. Steps that will be taken to control or mitigate the risks

The following steps have or will be taken by LimFlow SA to control or mitigate the risks during the course of this post-market 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 favour 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 an independent committee to ensure that all subjects meet defined eligibility 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.

4.7. Risk-to-benefit rationale

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-option" patient population. It is therefore concluded, from the information currently available, that the risks inherent in the use of the device are in line with the generally accepted state of the art, have been reduced to a level as low as reasonably practicable and are outweighed by the anticipated benefits. The proposed clinical investigation is designed to gather evidence to support this preliminary risk assessment. The subjects to be enrolled in the clinical investigation are thus not expected to be exposed to any undue risks.

5. Objectives and hypotheses of the clinical investigation

5.1. Objectives

The objective of this post-market study is to collect "real-life" clinical data among a population of patients treated with the commercially-available LimFlow System in order to evaluate the **safety and effectiveness** of the LimFlow System in creating a below-the-knee arterio-venous fistula for venous arterialization in subjects with critical limb ischaemia.

5.2. Hypotheses

Results of the LimFlow System risk assessment indicated that device-related risks had been reduced to levels as low as reasonably practicable and comparable with the state of the art. However, although the risks associated with the use of the LimFlow System were comparable with the state-of-the-art, the clinical experience was insufficient to completely characterize the nature and incidence of device-related procedural complications or late clinical complications. Therefore, post-market clinical follow-up was indicated to more precisely assess the nature and incidence of potential risks or to confirm that their prevalence lied below the threshold of concern.

5.3. Claims and intended performance to be verified

The LimFlow System is intended to treat critical limb ischaemia by minimally invasively creating an arterio-venous bypass graft to achieve venous arterialization. The objective of this post-market study is to evaluate the **safety and effectiveness** of the LimFlow System in creating a below-the-knee arterio-venous fistula for venous arterialization in subjects with critical limb ischaemia.

5.4. Risks and anticipated adverse effects to be assessed

The following adverse events are considered to be anticipated when performing any percutaneous catheterization and will be assessed during the course of the study:

- Allergic reaction, including anaphylactic shock and Quincke's oedema
- Vascular complications at access site, including bleeding events and hematoma
- Arterial and venous thromboembolic events, including angina or myocardial infarction, stroke or transient ischaemic event, pulmonary embolism, deep vein thrombosis, and limb ischaemia
- Contrast-induced nephropathy and renal failure
- Local or systemic infection
- Oedema
- Pain

6. Design of the clinical investigation

6.1. General

6.1.1. Type of clinical investigation

This study is a single-arm, open-label, prospective, post-market follow-up study to be conducted on up to 25 eligible patients (roll-in subjects plus 20 analysis subjects) with a twelve-month follow-up period. This study was designed and is to be conducted in compliance with the ISO 14155:2020 standard.

6.1.2. Measures to be taken to minimize or avoid bias

In addition to the screening and enrolment of consecutive patients, an independent committee will act as a medical monitor in order to minimize or avoid bias during the course of the study. The independent committee will consist of at least two (2) physicians with experience in surgical and/or endovascular treatment of critical limb ischaemia patients, who are independent from LimFlow SA and are not investigators in the study. Furthermore, members of the independent committee are neither past or current users of the LimFlow System nor involved with the manufacturer supplying the LimFlow System. Specifically, the independent committee will be responsible for performing the following tasks:

- **Screening**: review of all potential patients for compliance with key eligibility criteria I-2 and I-3
- **Endpoints**: assessment of technical success, patency, and wound healing
- **Adverse events**: two-step process involving (1) independent review of all adverse events by a medical monitor and (2) adjudication of relevant adverse events following a 2 + 1 algorithm

6.1.3. Primary and secondary endpoints

Primary endpoint

- Amputation-free survival

Secondary endpoints

- Complete wound healing
- Primary and secondary patency
- Limb salvage
- Technical and procedural success

6.1.4. Methods and timing for assessing, recording, and analysing variables

Timing for performing visits and assessing variables during the study follow-up period are presented in Table 4 below. Additional post-treatment evaluations performed outside of the follow-up window will be considered "unscheduled".

Table 4. Time windows

Visit	Target	Interval	Minimum	Maximum
Two (2) weeks	15 days	± 5 days	10 days	20 days
One (1) month	30 days	± 7 days	23 days	37 days
Two (2) months	60 days	± 10 days	50 days	70 days
Three (3) months	90 days	± 14 days	76 days	104 days
Six (6) months	180 days	± 14 days	166 days	194 days
Nine (9) months	270 days	± 14 days	256 days	284 days
Twelve (12) months	360 days	± 28 days	332 days	388 days

All variables will be recorded on electronic Case Report Forms (eCRFs) specifically designed for the study and provided by LimFlow SA to the investigational centres. Collected variables will be analysed using IBM SPSS statistics software, version 17 or later.

6.1.5. Equipment to be used for assessing the clinical investigation variables

Standard evaluation tools such as the Rutherford classification[8] or the SVS WIfI (Wound – Ischaemia – foot Infection) classification system[9] will be used for the overall assessment of critical limb ischaemia at baseline and follow-up visits. Pain will be evaluated using a numerical rating scale and the EuroQol (EQ-5D) questionnaire[10] will be used to assess the patients Quality of Life.

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® is an FDA registered Class 1 medical device and is CE marked. Additionally, eKare is ISO 13485 certified and is fully compliant with FDA 21 CFR Part 820, Part 11. One (1) eKare insight platform will be provided by LimFlow to each participating clinical site for the purpose of the study.

6.1.6. Any procedures for the replacement of subjects

Patients who have signed a consent form and have not undergone the procedure will be replaced; however, patients who drop-out during the trial or withdraw their consent after the procedure will not be replaced.

6.2. Device(s) used and comparator(s)

6.2.1. Description of the exposure to the device(s)

Exposure to the medical devices is described in Section 2.8 *"Medical procedures involved"* on page 10 as well as in Section 6.4.3 *"Treatment"* on page 19.

6.2.2. Justification of the choice of comparator(s)

Not applicable as this post-market study is a single-arm study performed in a population of patients with no therapeutic option (other than amputation).

6.2.3. List of any other medical device or medication to be used

Other medical devices or medications to be used are similar to those used when performing a transcatheter, percutaneous intervention in the below-the-knee vasculature. The treatment is to be delivered under general anaesthesia or conscious sedation with regional block, therefore anaesthetic medications will be administered to the patient prior to the intervention. In addition, anticoagulant medication (heparin) will be administered in order to attain and maintain appropriate systemic anticoagulation as verified by ACT or other similar testing. Iodine contrast media will also be injected intravascular to visualize the vasculature under fluoroscopy.

6.2.4. Number of device(s) to be used

The ultrasound system is a reusable device therefore one (1) unit can be used to perform several interventions. The extension cable set, the arterial and venous catheter set, and the valvulotome are single-use devices; at least one (1) unit of each should be used for every patient treated. Several stent grafts may be implanted in every patient depending on the vasculature—typically one (1) stent graft used as a "crossing stent" and at least one (1) stent graft used as an "extension stent".

6.3. Subjects

6.3.1. Inclusion criteria

I-1. Subject must be > 21 and < 95 years of age

I-2. Clinical diagnosis of symptomatic critical limb ischaemia, defined as Rutherford category 5 or 6

I-3. Assessment that no conventional surgical or endovascular treatment is possible

I-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

I-5. Subject is willing and has adequate support to comply with protocol requirements, including medication regimen and follow-up visits

6.3.2. Exclusion criteria

E-1. Concomitant hepatic insufficiency, deep venous thrombus in target limb, uncorrected coagulation disorders, or current immunodeficiency disorder

E-2. Life expectancy less than 12 months

E-3. Patient currently taking coumarin/warfarin which, in the opinion of the attending physician, interferes with the patient's treatment

E-4. Any significant medical condition which, in the attending physician's opinion, may interfere with the patient's optimal treatment

E-5. Patient 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 treatment

E-6. Patient unable to give consent

E-7. Pregnant or breastfeeding women

E-8. Documented myocardial infarction or stroke within previous 90 days

E-9. Patients suffering from renal insufficiency (GFR value less than 30 ml/min/1.73 m^2) who are not on haemodialysis

E-10. Patients with vasculitis and/or untreated popliteal aneurysms

E-11. Patients with acute limb ischaemia

E-12. Prior peripheral arterial bypass procedure above or below the knee which could inhibit proximal inflow to the stent graft

E-13. Lower extremity venous disease with significant oedema in the target limb that may inhibit the procedure and/or jeopardize wound healing, in the investigator's opinion

E-14. Known or suspected systemic or severe infection (*e.g.*, WIfI foot Infection grade of 3)

E-15. Known or suspected allergies or contraindications to stainless steel, nickel, or contrast agent that cannot be adequately pre-treated, or patients who cannot receive anticoagulation or antiplatelet aggregation therapy

E-16. 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)

6.3.3. Point of enrolment

Once any component of the LimFlow 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. In addition, *"roll-in"* subjects performed to avoid a learning curve bias will be included the study but excluded from the endpoint analysis. In some instances, *"roll-in"* subjects within the study may not be required for any study site who has performed LimFlow System procedures outside the study in the commercial setting.

6.3.4. Criteria and procedures for subject withdrawal or discontinuation

Patients are withdrawn from study if signed informed consent is withdrawn or when lost to follow-up (if a patient is not able to be contacted within three phone calls, the site shall send a letter requesting response from the subject and contact the patient general practitioner in order to check on the patient's condition; if the site or service receives no response, the patient may be considered lost-to follow-up at that time). Early study exit will also occur if the patient reaches the primary study endpoint either in death, or major amputation of the treated limb. Reason for the study discontinuation must be recorded in the source documentation and on the electronic Case Report Form (eCRF).

6.3.5. Number of subjects and expected duration

The number of subjects required to be included in the clinical investigation was set to up to 25 eligible subjects, which includes any *"roll-in"* subjects and 20 subjects for analysis. The time needed to select this number (*i.e.*, the enrolment period) was initially estimated to be twelve (12) months, however due to the worldwide pandemic and impact it has had to study enrolment, the study recruitment and enrolment period will be extended. The enrolment period is extended to allow the full cohort of subjects which is anticipated to be by the end of October 2022.

Following enrolment in the clinical investigation, each subject's participation to this post-market study is expected to last twelve (12) months.

Therefore, this post-market clinical study is expected to last approximately four years, from the actual starting date in December 2019.

6.4. Procedures

6.4.1. Overview

Patients should be followed at regular intervals during one year after the initial percutaneous deep vein arterialization procedure. The protocol follow-up schedule is intended to align with the standard of care as seen with patients who are treated with surgical bypass or endovascular revascularization. Visits and exams scheduled for this post-market study are presented in Table 5 below (keys: ■ mandatory, ☐ optional).

Table 5. Visits and exams

Exams	Baseline	Treatment	Week 02	Month 01	Month 02	Month 03	Month 06	Month 09	Month 12
Eligibility	■								
Demographics	■								
Infection status[†]	■								
Venous mapping[‡]	■								
Angiogram	■	■							
Ultrasound		Duplex		Duplex	Duplex	Duplex	Duplex	Duplex	Duplex
Medication	■	■	■	■	■	■	■	■	■
Creatinine	■								
Rutherford	■			■	■	■	■	■	■
WIfI	■			■	■	■	■	■	■
Wound pictures	■		■	■	■	■	■	■	■
Pain	■		■	■	■	■	■	■	■
Perfusion	☐		☐	☐	☐	☐	☐	☐	☐
Quality of Life	■					■	■	■	■
Adverse events		■	■	■	■	■	■	■	■

[†]Wound culture and/or blood analysis (WBC, CRP, ESR)

[‡]Phlebography, duplex ultrasound, MRV or CTV, depending on what is available

6.4.2. Screening and baseline

The subject screening and recruitment process will be performed by the site medical personnel and should follow the steps below:

1. Critical limb ischaemia patients with no endovascular or surgical treatment options (inclusion/exclusion criteria are aligned with the CE-marked indications/contraindications, as per the IFU) are initially identified by the site investigators
2. No-option patients meeting the LimFlow System indications and contraindications (as provided in the instructions for use since the LimFlow System is commercially available) can be scheduled for a percutaneous deep vein arterialization
3. Patients scheduled for a LimFlow intervention are asked whether they would be willing to participate to the study (to collect the data associated to the surgical procedure and standard of care follow-up).
4. Patients candidate to the study are subsequently enrolled, treated, and followed as per standard of care (the study protocol does not require more visits than what is considered standard of care)

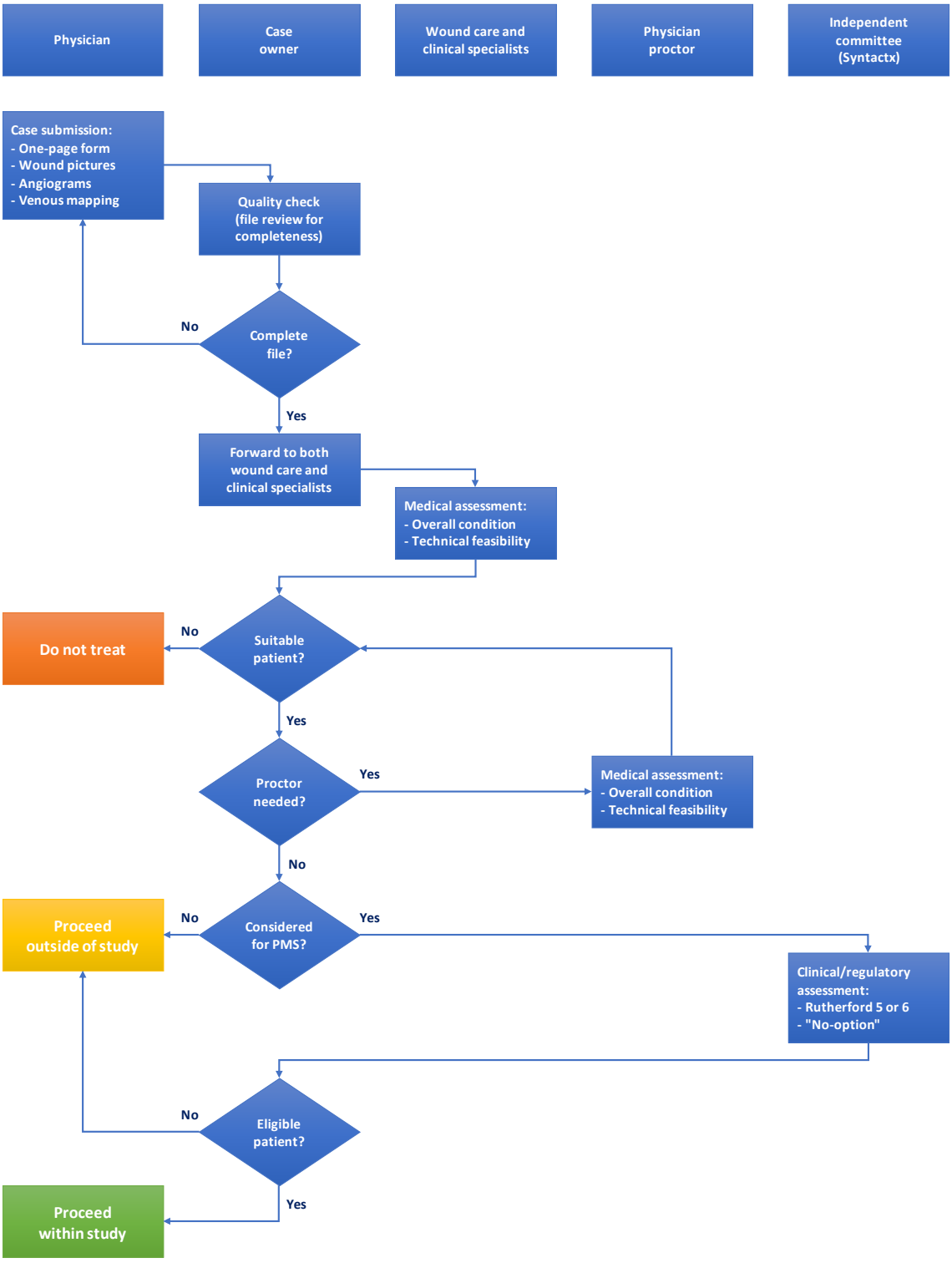
◆ ◆ ◆

Once the patients have agreed to participate to the study (*i.e.*, once the informed consent has been obtained), the following exams will be collected:

- Demographics, medical history, and peripheral assessment
- Infectious status, *i.e.*, wound culture and/or blood analysis (WBC, CRP, ESR)
- Venous mapping of the foot, *i.e.*, phlebography, duplex ultrasound, MRV, or CTV
- Arterial angiogram from the common femoral artery to the foot (two views)
- Serum creatinine level
- Rutherford classification
- WIfI (Wound – Ischaemia – foot Infection) classification
- Wound pictures and assessment
- Pain assessment
- Perfusion assessment ($TcPO_2$, ICG i.v. injection, white-light spectroscopy with laser Doppler, etc.—optional)
- Quality of Life (EQ-5D)
- Review of medications (antiplatelets/anticoagulants and antibiotics regimen)

A dedicated website (decidemedical.com platform provided by ClinFlows) will be used during the screening process to assess the eligibility of the candidates identified by the investigators. Baseline radiological images (*e.g.*, arterial angiograms, phlebography, duplex ultrasound, MRV, or CTV) as well as wound pictures should be uploaded by the investigators in order for the patients' eligibility to be confirmed. The eligibility screening process that will be followed for this post-market study is presented in detail on Figure 1 below.

Figure 1. Eligibility screening process for LimFlow cases



6.4.3. Treatment and discharge

A LimFlow representative will attend the interventions performed in order to assist the physician on technical issues as well as to ensure that treatment characteristics and potential complications are duly recorded.

Primary steps of the percutaneous deep vein arterialization intervention are described in Section 2.8 *"Medical procedures involved"* on page 10. Refer to the *"Instructions for Use"* for proper preparation and use of the devices.

In addition to the procedure images (angiography and/or ultrasound), the following intra-procedure parameters will be specifically recorded:

- Target artery and target vein
- Procedural steps
- Technical success
- Medical devices used
- Total procedure time
- Total fluoroscopy time
- Total volume of contrast media
- Any adverse event or device deficiency

Patients should receive adequate antiplatelet and anticoagulation therapy for a minimum of three (3) months post-procedure as per institution practice.

6.4.4. Follow-up visits

Sites shall maintain a contact log recording the attempted follow-up visits, scheduled at one month, three months, six months, nine months, and twelve months. If a patient is not able to be contacted within three phone calls, the site shall send a letter requesting response from the subject and contact the patient general practitioner in order to check on the patient's condition. If the site or service receives no response, the patient may be considered lost-to follow-up at that time.
Follow-up and wound care are to be performed on-site under direct supervision of a study investigator. Patient wounds should be treated in accordance with the TIME guidelines or following similar recommendations.[11-17] An arteriography should be performed in case of suspected stent graft occlusion, as per standard practice.

Day 015: two weeks

At 15 days post-treatment, subjects will be examined during a clinic visit and the following assessment will be performed:

- Wound pictures and assessment
- Pain assessment
- Perfusion assessment ($TcPO_2$, ICG i.v. injection, white-light spectroscopy with laser Doppler, etc.—optional)
- Adverse events
- Review of medications (antiplatelets/anticoagulants and antibiotics regimen)

Day 030: one month

At 30 days post-treatment, subjects will be examined during a clinic visit and the following assessment will be performed:

- Rutherford classification
- WIfI (Wound – Ischaemia – foot Infection) classification
- Wound pictures and assessment
- Pain assessment
- Perfusion assessment ($TcPO_2$, ICG i.v. injection, white-light spectroscopy with laser Doppler, etc.—optional)
- Duplex ultrasound
- Adverse events
- Review of medications (antiplatelets/anticoagulants and antibiotics regimen)

Day 060: two months

At 60 days post-treatment, subjects will be examined during a clinic visit and the following assessment will be performed:

- Rutherford classification
- WIfI (Wound – Ischaemia – foot Infection) classification
- Wound pictures and assessment
- Pain assessment
- Perfusion assessment ($TcPO_2$, ICG i.v. injection, white-light spectroscopy with laser Doppler, etc.—optional)
- Duplex ultrasound
- Adverse events
- Review of medications (antiplatelets/anticoagulants and antibiotics regimen)

Day 090: three months

At 90 days post-treatment, subjects will be examined during a clinic visit and the following assessment will be performed:

- Rutherford classification
- WIfI (Wound – Ischaemia – foot Infection) classification
- Wound pictures and assessment
- Pain assessment
- Perfusion assessment ($TcPO_2$, ICG i.v. injection, white-light spectroscopy with laser Doppler, etc.—optional)
- Quality of Life (EQ-5D)
- Duplex ultrasound
- Adverse events
- Review of medications (antiplatelets/anticoagulants and antibiotics regimen)

Day 180: six months

At 180 days post-treatment, subjects will be examined during a clinic visit and the following assessment will be performed:

- Rutherford classification
- WIfI (Wound – Ischaemia – foot Infection) classification
- Wound pictures and assessment
- Pain assessment
- Perfusion assessment ($TcPO_2$, ICG i.v. injection, white-light spectroscopy with laser Doppler, etc.—optional)
- Quality of Life (EQ-5D)
- Duplex ultrasound
- Adverse events
- Review of medications (antiplatelets/anticoagulants and antibiotics regimen)

Day 270: nine months

At 270 days post-treatment, subjects will be examined during a clinic visit and the following assessment will be performed:

- Rutherford classification
- WIfI (Wound – Ischaemia – foot Infection) classification
- Wound pictures and assessment
- Pain assessment

- Perfusion assessment ($TcPO_2$, ICG i.v. injection, white-light spectroscopy with laser Doppler, etc.—optional)
- Quality of Life (EQ-5D)
- Duplex ultrasound (Note: if previous ultrasound assessment revealed a total occlusion of the stent graft and no further intervention was performed or planned, duplex ultrasound assessment at this timepoint may be unnecessary. This will be handled on a case-by-case basis and will be discussed between the site and Sponsor ahead of the follow-up and documented accordingly.)
- Adverse events
- Review of medications (antiplatelets/anticoagulants and antibiotics regimen)

Day 360: twelve months

Finally, at 360 days post-treatment, subjects will be examined during a clinic visit and the following assessment will be performed:

- Rutherford classification
- WIfI (Wound – Ischaemia – foot Infection) classification
- Wound pictures and assessment
- Pain assessment
- Perfusion assessment ($TcPO_2$, ICG i.v. injection, white-light spectroscopy with laser Doppler, etc.—optional)
- Quality of Life (EQ-5D)
- Duplex ultrasound(Note: if previous ultrasound assessment revealed a total occlusion of the stent graft and no further intervention was performed or planned, duplex ultrasound assessment at this timepoint may be unnecessary. This will be handled on a case-by-case basis and will be discussed between the site and Sponsor ahead of the follow-up and documented accordingly.)
- Adverse events
- Review of medications (antiplatelets/anticoagulants and antibiotics regimen)

6.5. Monitoring plan

Under the supervision of LimFlow SA, monitors will conduct investigational site monitoring to ensure that all investigators are in compliance with the Declaration of Helsinki (*"Ethical Principles for Medical Research Involving Human Subjects"*, 18th World Medical Association General Assembly, Helsinki, Finland, June 1964), the standard ISO 14155:2020 (*"Clinical investigation of medical devices for human subjects—Good clinical practice"*), the Clinical Investigation Plan, and the Investigator's Agreement. Sites and source documents will be monitored to ensure that completed CRFs match medical records and to resolve any differences. The monitors and LimFlow SA will evaluate circumstances where an investigator deviates from the Clinical Investigation Plan.

The monitor's responsibilities include: maintaining regular contact with each investigational site, through telephone contact and on-site visits, to ensure that the investigational plan is followed; ensure that complete, timely and accurate data are submitted; ensure that problems with inconsistent and incomplete data are addressed; and that the site facilities continue to be adequate.

The monitor shall have access to the source documents and other information needed to ensure investigator compliance with the clinical investigation plan and applicable rules and regulations, and to assess the progress of the clinical investigation. The clinical investigators shall allow auditing of their clinical investigation procedures.

LimFlow SA will review significant new information and ensure that such information is provided to the investigators, and to the Ethics Committees and Competent Authorities, as appropriate.

7. Statistical considerations

7.1. Statistical design, method and analytical procedures

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.

The design of this post-market study (PMS) is mirroring that of the early feasibility study (EFS) conducted in the United States of America, allowing for both datasets to be pooled in order to perform a statistical analysis on a larger cohort of patients.

7.2. Sample size

In the absence of formal statistical hypotheses for this single-arm, post-market study, the planned sample size could not be derived statistically. It was however estimated that a cohort of approximately twenty (20) subjects would provide sufficient data in order to meet the objectives defined in the study.

7.3. Provision for an interim analysis

Interim analyses may be performed at any time if deemed necessary to fulfil the sponsor's or manufacturer's reporting requirements and/or update the evaluation of the side effects and of the acceptability of the benefit/risk ratio, as required in Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.

7.4. Specification of subgroups for analysis

If relevant, subgroup analyses may be performed based on baseline or treatment parameters—Student's (or Wilcoxon's according to the normality of the distribution) and Chi-2 (or Fisher's) between-group tests will then be used for quantitative and qualitative parameters, respectively.

In particular, renal function characteristics at baseline (GFR value and/or dialysis status) may be used to define subgroups for the purpose of the analysis. Specifically, patients on dialysis are excluded from the early feasibility study (EFS), which will be taken into consideration when pooling datasets from both cohorts. Safety and effectiveness results from dialysis and non-dialysis patients will be compared.

7.5. Treatment of missing, unused, or spurious data

The number of missing data will be presented for each variable as part of the descriptive statistical analysis. Subjects withdrawn and/or lost to follow-up will be presented in a patient tree showing detailed patient accountability at each follow-up visit.

8. Data management

Electronic Case Report Forms (eCRFs) will be specifically developed on the IBM Clinical Development platform for the study. The eCRFs will be used for data collection during the course of the study and must be completed for all patients 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 and dated 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 analysed by the independent committee. Specifically, the role of the core laboratory will be (1) to assess the anatomical eligibility of all candidates at baseline and (2) to assess the safety endpoint at follow-up timepoints.

The eCRFs are compliant with FDA 21 CFR Part 11 requirements. All information and data concerning patients 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 patients. Patients will be identified using a six-character sequence (ISO 3166-1 α-2 country code; two-letter site code; two-digit patient number).

The investigator must retain paper copies of study records. LimFlow SA will maintain copies of correspondence, data, and other records related to the study. LimFlow SA will maintain records related to the signed Investigator's Agreements.

LimFlow SA will provide devices only to participating investigators, obtain a signed Investigator's Agreement, and provide the investigator with the information necessary to conduct the study. The training of appropriate clinical site personnel will be the joint responsibility of the Sponsor and the Monitor. To insure uniform data collection and Clinical Investigation Plan compliance, the Sponsor and/or the Monitor will present a formal educational session to study site personnel which will review the Clinical Investigational Plan, techniques for the identification of eligible patients, instructions on in hospital data collection, methods for soliciting data from alternative sources, schedules for follow-up with the study site coordinators, and regulatory requirements.

9. Amendments to the clinical investigation plan

The investigator will not implement any changes without the prior agreement of LimFlow SA and review by the Ethics Committee with documented approval/favourable opinion, except when the change involves logistical or administrative aspects of the investigational site.

10. Deviations from clinical investigation plan

The investigator is not allowed to deviate from the clinical investigation plan, except under emergency circumstances to protect the rights, safety and well-being of a study subject. Such deviations shall be documented and reported to LimFlow SA and the Ethics Committee as soon as possible depending on local regulatory requirements.

11. Device accountability

Each component of the LimFlow System will be traceable via lot and serial number. Records of device shipments will be maintained at the LimFlow facility in accordance with LimFlow's quality system and internal procedures. Product Details will be captured on the case report forms for each subject receiving treatment with the LimFlow System to provide traceability.

LimFlow SA will supply the device; any requests for additional materials, equipment, service, or information shall be directed to LimFlow SA. An inventory of materials will be taken at monitor site visits.

12. Statements of compliance

This post-market study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (*"Ethical Principles for Medical Research Involving Human Subjects"*, 18th World Medical Association General Assembly, Helsinki, Finland, June 1964) and in compliance with the standard ISO 14155:2020 (*"Clinical investigation of medical devices for human subjects—Good clinical practice"*) as well as any regional or national regulations, as appropriate.

This post-market study shall not begin until the required approval/favourable opinion from the Ethics Committee or regulatory authority have been obtained, if appropriate. Any additional requirements imposed by the Ethics Committee or regulatory authority shall be followed, if appropriate

LimFlow SA subscribed to an insurance that shall be provided for all study subjects, in accordance with regional or national regulations, as appropriate.

13. Informed consent process

The sponsor will provide centres with a sample informed consent document that the centre may modify to meet individual Ethics Committee requirements. Any modifications of the informed consent document must be submitted to LimFlow SA for approval prior to submission to the Ethics Committee.

An informed consent form must be signed by each patient prior to study enrolment and implant of the study device. Informed consent will be obtained according to the Declaration of Helsinki (*"Ethical Principles for Medical Research Involving Human Subjects"*, 18th World Medical Association General Assembly, Helsinki, Finland, June 1964), requirements of the standard ISO 14155:2020 (*"Clinical investigation of medical devices for human subjects—Good clinical practice"*), and individual institution guidelines. Patient informed consents will be audited to ensure they have been signed prior to the treatment procedure and that the correct version was used.

The subject screening and recruitment process will be performed by the site medical personnel and should follow the steps below:

1. Critical limb ischaemia patients with no endovascular or surgical treatment options are initially identified by the site investigators
2. No-option patients meeting the LimFlow System indications and contraindications (as provided in the instructions for use since the LimFlow System is commercially available) can be scheduled for a percutaneous deep vein arterialization
3. Patients scheduled for a LimFlow intervention are asked whether they would be willing to participate to the study (inclusion/exclusion criteria are aligned with the CE-marked indications/contraindications)
4. Patients candidate to the study are subsequently enrolled, treated, and followed as per standard of care (the study protocol does not require more visits than what is considered standard of care)

14. Adverse events, adverse device effects and device deficiencies

14.1. Definitions

The ISO 14155:2020 *"Clinical investigation of medical devices for human subjects—Good clinical practice"* definitions will be used for this post-market study and are provided in Table 6 below.

Table 6. Definitions of adverse events and adverse device effects

Adverse event (AE)	Adverse device effect (ADE)
Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device	Adverse event related to the use of an investigational medical device or procedure
Serious adverse event (SAE)	**Serious adverse device effect (SADE)**

Adverse event that
▪ led to death,
▪ led to serious deterioration in the health of the subject, that either resulted in
  ▪ a life-threatening illness or injury, or
  ▪ a permanent impairment of a body structure or a body function, or
  ▪ in-patient or prolonged hospitalisation, or
  ▪ medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
▪ led to foetal distress, foetal death or a congenital abnormality or birth defect
	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
	▪ **Anticipated serious adverse effect (ASADE):**
	SADE which by its nature, incidence, severity or outcome has been identified in the risk analysis report
	▪ **Unanticipated serious adverse effect (USADE):**
	SADE which by its nature, incidence, severity or outcome has **not** been identified in the risk analysis report

Note: a planned hospitalisation or intervention for a pre-existing condition without deterioration in health is not considered to be an adverse event.

Device deficiency is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance, including malfunctions, use errors, and inadequate labelling.

14.2. Reporting

All adverse events will be documented in the case report forms, including date of onset, symptoms, treatment, duration (or the fact that it is still continuing), resolution, and assessment of both the seriousness and the relationship to the device. Similarly, all device deficiencies will be documented in the case report forms. In addition, all serious adverse events and serious adverse device effects must be reported immediately after discovery by any site member to LimFlow SA.

LimFlow SA will report such an event and the results of an investigation to the appropriate regulatory authorities in compliance with applicable regulatory requirements. If LimFlow SA and the investigator determine that the events present an unreasonable risk to the subjects, LimFlow SA will terminate all or parts of the study.

The reporting of any serious adverse events and/or serious adverse device effects to the Ethics Committee is the sole responsibility of the site's Principal Investigator.

All adverse events will be adjudicated by the independent committee in order to assess the procedure or device relatedness as well as the event seriousness.

14.3. Foreseeable events

The following adverse events may occur when performing percutaneous deep venous arterialization and will be specifically assessed during the course of the study:

- Allergic reaction, including anaphylactic shock and Quincke's oedema

- Vascular complications at access site, including bleeding events and hematoma
- Arterial and venous thromboembolic events, including angina or myocardial infarction, stroke or transient ischaemic event, pulmonary embolism, deep vein thrombosis, and limb ischaemia
- Contrast-induced nephropathy and renal failure
- Oedema
- Local or systemic infection
- Pain

14.4. Management

If the investigator determines that an adverse event occurs the investigator will manage the subject as he/she would if a similar event occurred during a standard interventional procedure. The investigator will formulate an appropriate management plan for the subject using only conventional, non-investigational methods. Medical management of the subject is the responsibility of the investigator and/or other trained, licensed medical personnel. It is at the discretion of the investigator as to whether the percutaneous deep vein arterialization procedure should be continued.

All subjects with adverse events will be followed with the appropriate treatment and medical supervision until either the end of the study (*i.e.*, 12 months) or resolution of the adverse event (whenever possible), whichever is the longer follow-up.

14.5. Emergency contact details

Serious adverse events and serious adverse device effects must be reported to the sponsor LimFlow SA. Contact details are as follows:

LimFlow SA
Vincent Cabane
Director of European Clinical Affairs
E-mail: vcabane@limflow.com
Cell phone: +33 (0) 6 03 86 17 13

15. Vulnerable population

Not applicable for this post-market study.

16. Suspension or premature termination of the investigation

In the event of unforeseen or increased risks to subjects encountered during the course of the study, LimFlow SA, the Ethics Committee, the Competent Authority, or the Investigator may decide to suspend or terminate the clinical study. Such decision would be made after discussion with all parties.

If the investigator terminates or suspends the study without prior agreement with LimFlow SA, he/she will promptly provide all details to the institution, LimFlow SA, and the Ethics Committee. If the investigation is terminated or suspended by LimFlow SA, the investigator will be promptly informed, who must then inform the Ethics Committee. If the Ethics Committee terminates or suspends the study, the investigator will promptly inform LimFlow SA with written explanation.

Subjects will continue to be followed per the clinical investigational protocol unless it has been determined by the investigator that the continued follow-up may jeopardize the rights, safety, and/or welfare of the subject.

17. Publication policy

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. The possibility of a publication in a peer-reviewed journal will be sought.

18. Definitions

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 (including metatarsals) at the level below the ankle.
Amputation-free survival	Defined as the percentage of subjects with limb salvage and survival.
Arteriovenous 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	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.
Deterioration in renal function	Defined as a ≥ 25% increase in serum creatinine after using iodine contrast agents, 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.
Limb salvage	Freedom form major amputation.
Myocardial Infarction (MI)	The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Specifically, the criteria provided by the universal definition of myocardial infarction will be used for diagnostic purposes.
Occlusion	Absence of flow on colour Doppler ultrasound and/or absence of flow on angiographic images (conventional or CT-scan).
Patency	**Primary patency** is defined as the absence of occlusion of the stent graft without prior clinically-driven major re-intervention of the stent graft. **Secondary patency** is defined as the absence of occlusion of the stent graft with or without prior clinically-driven major re-intervention of the stent graft.
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).
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 haemorrhage, embolism, thrombosis, or rupturing aneurysm.
Success	**Technical success** is 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** is defined as combination of technical success, and absence of all-cause death, above-ankle amputation or clinically driven major re-intervention of the stent graft.
Survival	Freedom from all-cause mortality.
Thrombosis	Formation or development of a blood clot or thrombus, specifically in the arterial or venous system of the ipsilateral distal extremity.
Transient Ischaemic Attack (TIA)	Focal neurologic abnormalities of sudden onset and brief duration that reflect dysfunction in the distribution of the affected artery. Transient ischaemic attack is characterized by fully reversible symptoms of short duration.

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20. Annex A: list of investigators and investigational sites