A prospective, multicentre observational study to evaluate the BioMimics 3D Self-Expanding Stent System in the treatment of peripheral arterial disease: MIMICS-3D

Protocol Number: MIMICS-3D

Revision: 02
Date: 03 August 2016

Sponsor:

Veryan Medical Ltd
Block 11, Galway Technology Park
Parkmore, Galway,
Co. Galway, Ireland
Telephone: +353 (91) 750 040
Facsimile: +353 (91) 750 031

Investigator's Signature Page

Study Title:	A prospective, multicentre observational study to evaluate the BioMimics 3D Self-Expanding Stent System in the treatment of peripheral arterial disease: MIMICS-3D
PROTOCOL NUMBER & ISSUE:	02, 03 August 2016
Study Centre:	

_____
(Print name of study centre)

I, the undersigned, have read and understand the Protocol specified above and agree with its content. 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. I will provide copies of this Protocol and all pertinent information to the Study personnel under my supervision and my hospital Ethics Committee/ Institutional Review Board. I will discuss this material with them and ensure they are fully informed regarding the conduct of the Study according to Declaration of Helsinki, and any local and national regulations.

_____
SITE PI – Print Name

_____
SITE PI – Signature

_____
DATE

TABLE OF CONTENTS

CONTENTS

[redacted]

PROTOCOL SUMMARY

Study Title:	A prospective, multicentre observational study to evaluate the BioMimics 3D Self-Expanding Stent System in the treatment of peripheral arterial disease: MIMICS-3D
Study Objective:	The MIMICS-3D Study will evaluate safety, effectiveness and device performance within a real-world clinical population of patients undergoing femoropopliteal intervention.
Study Device & intended use	BioMimics 3D Self-Expanding Stent System. Device will be used in accordance with CE Mark approved indication and all approved and commercially available stent sizes will be included in this study.
Study Design:	Prospective, multicentre, observational study (non-investigational)
Device Regulatory Status:	CE Mark was approved in November 2012.
Estimated Enrolment:	Minimum of 500 patients
Subject Population:	Patients who receive treatment with Veryan's BioMimics 3D Stent System in accordance with the current approved CE Mark indication for use as stated in the Instructions for Use (IFU).
Clinical Sites:	Up to 40 sites in any country where CE mark is recognised and device is legally marketed
Study Follow-Up:	After index procedure on Day 0, patients will be evaluated at 30 days then 12, 24, and 36 months.
Study Duration:	First patient enrolled August 2016 Last patient enrolled August 2018 Last patient, last visit August 2021
Primary Outcome Measures:	<u>Primary safety endpoint:</u> The primary outcome measure for safety will be a composite of major adverse events (MAE) comprising death, any major amputation performed on the index limb or clinically-driven target lesion revascularisation (CDTLR) through 30 days. <u>Primary effectiveness endpoint:</u> The primary outcome measure for effectiveness will be freedom from clinically-driven target lesion revascularisation (CDTLR) through 12 months.
Secondary Outcome Measures:	1. Acute technical success defined as the achievement of a final residual diameter stenosis ≤30% at the end of the procedure 2. Acute procedural success defined as both acute technical success and absence of the following adverse events: death, stroke, MI, acute onset of limb ischemia, index bypass graft or treated segment thrombosis, and/or need for urgent/emergent vascular surgery, within 72 h of the index procedure. 3. Incidence of individual components of MAE (death, any major amputation performed on the index limb or CDTLR) at 30 days, 12, 24and 36 months 4. Overall rate and incidence of adverse events from Day 0 through completion of study follow-up at Month 36. 5. Stent patency rate assessed by duplex ultrasound, as available, determined at Months 12, 24 and 36. This will be assessed using values of PSVR >2.0, >2.4; >2.5; and >3.5 each to indicate loss of patency on duplex ultrasound.

	6. Clinical outcome: comparison of Rutherford Clinical Category measured at Baseline, Day 30, Months 12 24 and 36. 7. Functional outcome: comparison of the ankle brachial index (ABI) measurement at Baseline, within 30 days after index procedure, then at Months 12, 24 and 36. 8. Incidence of reported stent fractures through 36 months. 9. Operator assessment of device use
Inclusion Criteria:	1. Patient is age ≥18 and ≤85 years at date of consent. 2. Patient has provided written informed consent for participation in the study prior to index procedure. 3. Patient has documented symptomatic peripheral arterial disease scheduled for treatment with the BioMimics 3D stent in accordance with the approved CE Mark indication and Instructions for Use (IFU)
Exclusion Criteria:	1. Patients whose lesions cannot be crossed with a wire and/or balloon catheter and cannot be dilated sufficiently to allow passage of the delivery system. 2. Patients with a history of intolerance or adverse reaction to antiplatelet and/or anticoagulation therapies, bleeding diathesis, severe hypertension or renal failure. 3. Patients with known hypersensitivity to nickel-titanium. 4. Patient has a comorbidity that in the Investigator's opinion would limit life expectancy to less than 12 months. 5. Patient is pregnant or breastfeeding. 6. Patient is unable or is unwilling to comply with site standard of care procedures and follow-up visit schedules for patients undergoing femoropopliteal intervention.
Sponsor	Veryan Medical Limited, Block 11, Galway Technology Park, Parkmore, Galway, Co. Galway, Ireland
Principal Investigators:	Dr Michael Lichtenberg (Arnsberg, Germany)
Study Management:	Veryan Medical Ltd., Galway, Ireland
Monitoring:	Veryan Medical Ltd., Galway, Ireland
Data Management:	Veryan Medical Ltd., Galway, Ireland

1.0 INTRODUCTION AND BACKGROUND

1.1 Introduction

The MIMICS-3D Study is a prospective, multicentre, observational study of the BioMimics 3D Stent System in patients undergoing endovascular intervention to relieve symptomatic peripheral arterial disease of the femoropopliteal artery. The Study is designed to enable the collection, analysis and reporting of data from "real-world" use of the BioMimics 3D Stent System used in accordance with the Instructions for Use (IFU) associated with the product's CE Mark approval.

Data collection will include that relating to safety, effectiveness and device performance and the period of observation during which data will be collected will extend from the index procedure through 3 years (36 months), according to the standard follow-up practice of the enrolling institution.

1.2 Literature Summary

Atherosclerosis is a chronic vascular disease that can manifest itself in the coronary, neurovascular and peripheral vascular beds with end organ and distal extremity vascular impact. Specifically, peripheral arterial disease (PAD) is a common manifestation of atherosclerosis and is a chronic occlusive arterial disease caused by plaque build-up in the arterial lumen that leads to diminished blood flow. The rising prevalence of PAD with increasing age, and within a population increasingly at risk from obesity and diabetes, is a major international health care issue with substantial economic ramifications. A recent estimate concluded that the global prevalence of PAD presently exceeds a quarter of a billion and that this number grew by more than 20% in the period 2000 to 2010 [1]. Patients with PAD have an increased risk of myocardial infarction, stroke, and death. Major risk factors for the development of PAD include family history, age, hypertension, cigarette smoking, diabetes, and dyslipidaemia; the greatest risk factors being diabetes and smoking. The treatment of PAD is initially directed at a combination of lifestyle or behavioural modification and medical management to hopefully slow the disease and symptom progression. When these methods fail to provide symptomatic relief, revascularisation may be achieved through endovascular or surgical approach.

1.3 Disease Process

Anatomically, 70% of PAD lesions are present in the femoropopliteal and tibial arteries with more than 50% of all PAD interventions involving the superficial femoral and popliteal arteries [2]. Femoropopliteal disease is characterised by long, diffuse obstructive or occlusive lesions that create a unique slow-flow and high resistance environment.

1.4 Alternative Treatments / Interventions

The treatment of the femoropopliteal arteries using endovascular treatments has gained popularity with patients and physicians alike due to these procedures being less invasive, and potentially with fewer complications, than the surgical options [2]. Percutaneous transluminal angioplasty (PTA) is one of the simplest endovascular methods to treat PAD, but the technical success and durability of this technique are often dependent on the lesion morphology [3].

Endovascular stenting with Nitinol stents has become an established and widely used treatment for femoropopliteal lesions, specifically the SFA and proximal popliteal arteries with reported patency rates above 80% at 12 months[4,5]. However, despite improvements in stent design, restenosis is a limiting factor as a result of intimal hyperplasia following stent placement [6]. The mechanism for the development of restenosis is multi-factorial but may include vessel injury during angioplasty, stent implantation, sub-optimal flow conditions and mechanical factors.

Given that the SFA and popliteal arteries are under continuous mobility during knee flexion the resultant mechanical forces on the vessel include compression, flexion, extension, torsion and pulsatile distension (see Figure 1). Stents deployed in these vessels are also subjected to these forces [7]. The suitability of a stent for the femoropopliteal artery may therefore depend on its ability to shorten in a controlled manner, without inducing strains which lead to fatigue fracture [8]. The inability of long and /or multiple straight stent segments to shorten or "take up the slack" during motion, leads to large strains, kinking and fatigue fractures [7,9]. In addition, if the stent is unable to shorten, it may create biomechanical incompatibilities leading to acute and chronic injury to adjacent vessel segments subjected to substantial deformation where knee flexion may induce acute vascular angulation (kinking) [9–11]. A stent which can shorten naturally in order to reduce focal deformation and provide longitudinal flexibility may therefore provide a favourable solution for recanalisation of the SFA and popliteal artery.

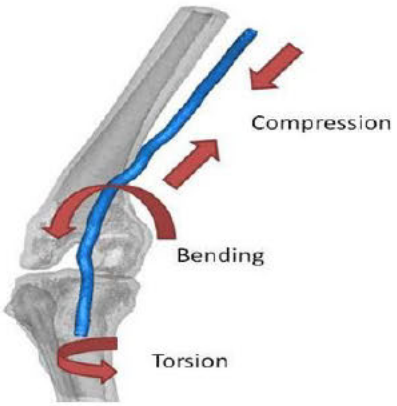

Figure 1: Forces on the femoropopliteal artery during lower limb movement

[redacted]

1.5.2 [redacted]

[redacted]

- [redacted]

[redacted]

1.6 Clinical experience with BioMimics 3D Stent System

Veryan has conducted a prospective, multicentre, randomised study (Mimics study) to evaluate the safety and effectiveness of BioMimics 3D Stent System in the superficial femoral and proximal popliteal arteries (Mimics study). Data from this study was used as a basis for Veryan's application for CE Mark approval, which was approved in November 2012. The device was made available commercially in 2015.

A further study in the superficial femoral and proximal popliteal arteries (MIMICS-2 study) is currently enrolling at sites in the US, Germany and Japan to provide data for regulatory approval in the US and other countries (https://clinicaltrials.gov/ct2/show/NCT02400905). The first patient was enrolled in June 2015. It is anticipated that enrolment will be completed by August 2016, and the study will therefore be complete after 3 years' follow-up in 2019.

1.7 BioMimics 3D Study Purpose

The BioMimics 3D Study is designed to enable the collection, analysis, reporting and presentation of data from use of the BioMimics 3D Stent System purchased by the hospital or clinic and used in accordance with the Instructions for Use associated with the product's CE Mark approval. The intent of this post-market observational study is to increase the understanding of the performance of the BioMimics 3D Stent System in a larger population of patients representative of a real-world situation. In addition, a broader cohort of interventionalists (i.e., angiologists, cardiologists, radiologists and vascular surgeons) will be included than that so far involved in Veryan's clinical evaluation.

There is an extensive body of literature supporting femoropopliteal stenting including in 'real-world' registries [12–14] The principles of evaluating safety at 30 days and effectiveness (patency of the stented segment) at 12 months are well-established clinical endpoints for such a real-world registry. However, the specific attributes of the BioMimics 3D stent (promotion of swirling blood flow and improved biomechanical compatibility within the femoropopliteal artery) have the potential for chronic outcome benefits supporting the longer term follow-up objective of this study.

2.0 STUDY DEVICE

2.1 Intended Use

The BioMimics 3D Self-Expanding Stent System will be used in accordance with the current approved CE Mark indication for use as stated in the Instructions for Use (IFU).

The current IFU is included in Appendix A.

2.2 CE Mark Status

CE Mark was approved in November 2012.

2.3 Device Preparation and Deployment Procedure

The BioMimics 3D Stent will be prepared and deployed as described in the IFU that accompanies each device.

Procedures for patient preparation and follow-up, including medication and vascular access, will be according to hospital / institutional standard of care.

2.4 BioMimics 3D stent and delivery system size matrix

All CE Mark approved and commercially available stent sizes will be included in this study. The current size matrix can be found in the IFU.

3.0 STUDY PLAN

3.1 Study Objective

The MIMICS-3D Study will evaluate safety, effectiveness and device performance within a real-world clinical population of patients undergoing femoropopliteal intervention.

3.2 Design

Prospective, multicentre, observational study (non-investigational) of patients who receive treatment with Veryan's BioMimics 3D Stent System.

3.3 Enrolment

A minimum of 500 patients will be enrolled in the study. The study will be conducted at up to 40 centres in any country where CE Mark is recognised and the device is legally marketed.

A minimum of 50 patients treated with drug coated balloon (DCB) will be enrolled (DCB cohort). All primary and secondary endpoints will be assessed separately for this cohort.

3.4 Study Duration and Follow-Up

It is anticipated that enrolment will commence in August 2016 and is expected to continue until August 2018. The last patient visit is expected in 2021.

Patient follow up will be in accordance with standard of care. Data will be collected according to the following schedule: baseline (medical history), index procedure through discharge, 30 days (± 7 days), 12 months (365 days ± 60 days), 24 months (730 days ± 60 days) and 36 months (1095 days ± 60 days). Follow-up may be conducted by clinic visit or telephone, according to site standard of care.

4.0 ENDPOINTS AND SUBJECT POPULATION

4.1 Primary Outcome Measures

4.1.1 Primary safety endpoint:

The primary outcome measure for safety will be a composite of major adverse events (MAE) comprising death, any major amputation performed on the index limb or clinically-driven target lesion revascularization (CDTLR) through 30 days.

4.1.2 Primary effectiveness endpoint:

The primary outcome measure for effectiveness will be freedom from clinically-driven target lesion revascularization (CDTLR) through 12 months.

4.2 Secondary Outcome Measures

- Acute technical success defined as the achievement of a final residual diameter stenosis $\leq$30% at the end of the procedure

- Acute procedural success defined as both acute technical success and absence of the following adverse events: death, stroke, MI, acute onset of limb ischemia, index bypass graft or treated segment thrombosis, and/or need for urgent/emergent vascular surgery, within 72 h of the index procedure.

- Incidence of individual components of MAE (death, any major amputation performed on the index limb or CDTLR) at 30 days, 12, 24 and 36 months

- Overall rate and incidence of adverse events from Day 0 through completion of study follow-up at Month 36.

- Stent patency rate assessed by duplex ultrasound, as available, determined at Months 12, 24 and 36. This will be assessed using values of PSVR >2.0, >2.4; >2.5; and >3.5 each to indicate loss of patency on duplex ultrasound.

- Clinical outcome: comparison of Rutherford Clinical Category measured at Baseline, Day 30, Months 12 24 and 36.

- Functional outcome: comparison of the ankle brachial index (ABI) measurement at Baseline, within 30 days after index procedure, then at Months 12, 24 and 36.

- Incidence of reported stent fractures through 36 months.

- Operator assessment of device use

4.3 Eligibility Criteria

Patients are required to meet ALL the following criteria in order to be included in this study:

4.3.1 Inclusion Criteria

1. Patient is age ≥18 and ≤85 years at date of consent.

2. Patient has provided written informed consent for participation in the study prior to index procedure.

3. Patient has documented symptomatic peripheral arterial disease scheduled for treatment with the BioMimics 3D stent in accordance with the approved CE indication and Instructions for Use (IFU)

4.3.2 Exclusion Criteria

1. Patients whose lesions cannot be crossed with a wire and/or balloon catheter and cannot be dilated sufficiently to allow passage of the delivery system.

2. Patients with a history of intolerance or adverse reaction to antiplatelet and/or anticoagulation therapies, bleeding diathesis, severe hypertension or renal failure.

3. Patients with known hypersensitivity to nickel-titanium.

4. Patient has a comorbidity that in the Investigator's opinion would limit life expectancy to less than 12 months.

5. Patient is pregnant or breastfeeding.

6. Patient is unable or is unwilling to comply with site standard of care procedures and follow-up visit schedules for patients undergoing femoropopliteal intervention.

5.0 SCREENING AND ENROLMENT

5.1 Screening

All consecutive patients who meet the eligibility criteria should be considered for enrolment in the study. Sites should maintain a cumulative log of all enrolled patients. The Investigator or designee should

determine potential eligibility according to Section 4.3. Patients who meet all criteria should be provided with further information on the study in accordance with the procedures in Section 5.2.

5.2 Informed Consent

Written Consent for Data Collection with the Ethics Committee (EC)/Institutional Review Board (IRB) approved consent form will be obtained for all patients prior to Study procedure and collection of any Study-specific information. There are no additional procedures or tests required in addition to routine standard of care.

The patient shall be given adequate time to read the Written Consent for Data Collection consent form and have the data collection and data transmission procedures explained prior to signing the Informed Consent form. All patients providing informed consent for data collection are to receive copies of their signed informed consent documentation. The consent process may be obtained up to 30 days prior to enrolment in the Study.

5.3 Enrolment

All patients who provide written informed consent for the Study, meet all eligibility criteria and are treated with BioMimics 3D stent system will be considered enrolled in the Study. If the BioMimics 3D Stent System is inserted into the vasculature and treatment is attempted, but the procedure is aborted without delivery of a stent, only device failure and malfunction information and/or device related adverse events should be collected, if applicable.

Patients who are consented but the BioMimics 3D Stent System is not inserted into the vasculature will be considered screen failures. No data will be collected on screen failures.

Patients who are enrolled and treated, but who are later discovered to not meet all of the eligibility criteria will remain in the Study for follow-up and a Protocol Deviation form will be completed.

Patients who are enrolled and undergo staged treatment using BioMimics 3D Stent System in both limbs will be considered a single enrolment. Procedural information for both limbs will be collected.

For the purpose of this study, the point of enrolment is time of index procedure.

5.4 Withdrawal

Patients may withdraw at any time from the Study without prejudice; participation is entirely voluntary. If a subject prematurely terminates from the Study, the reason for termination will be recorded in the eCRF.

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, the subject completes the Study follow-up, or the adverse event is otherwise explained.

All reasonable efforts will be made to obtain complete data for all subjects; however, missing observations will occur due to loss to follow-up, withdrawal, or variation in site standard of care assessments. Site shall make all reasonable efforts to contact subjects who do not respond to follow-up requests. In the event patient does not respond to a final contact attempt via certified letter, patient will be considered lost to follow-up. Patients who withdraw consent after treatment will have their data evaluated until the time of their withdrawal (unless consent for data retention is removed in accordance with local or national regulations). Patients who withdraw or are lost to follow-up will not be replaced.

6.0 DATA COLLECTION PROCEDURES

6.1 Visit Schedule

Study participation will last for a total of 36 months (± 60 days). Data collection will be completed at baseline index hospitalisation, 30 days (± 7 days), 12 months (365 days ± 30 days), 24 months (730 days ± 60 days) and 36-months (1095 days ± 60 days). Follow-up may be by clinic visit or telephone according to site standard of care.

A summary schedule of the data collection for tests and evaluations is in Table 1. Data should only be collected if tests and evaluations are completed per standard of care.

Table 1: Data Collection Schedule

Assessment	Baseline	Day 0 Index Procedure (Enrolment / Treatment)	Follow-up Visits 30 days (± 7 days), 12 months (365 days ± 30 days), 24 months (730 days ± 60 days), 36-months (1095 days ± 60 days)
Informed Consent	X		
Medical History	X		X
ABI/TBI	X		X
Rutherford Clinical Category (RCC)	X		X
Procedural data & technical success		X**	
Index procedure angiographic assessments		X	
Follow-up standard of care imaging assessments, as applicable: • Angiography • Duplex ultrasound • X-ray			X
Concomitant antiplatelet and anticoagulant medications	X	X	X
Adverse Event Assessment		X	X
Subsequent intervention (target limb)			X
Device use questionnaire (operator)		X	
Walking Impairment Questionnaire (WIQ)*	O		O

*WIQ is optional (O) and may be collected if standard of care at site.
** Females of childbearing potential should have a negative pregnancy test before procedure (according to site standard of care)

6.2 Baseline

The following baseline data will be collected:

- Demographic information (age at time of treatment/enrolment, sex, ethnicity)
- Relevant medical history including previous peripheral interventions and cardiovascular risk factors
- Physical examination (as available)
  - Height and weight
  - Ankle Brachial Index (ABI) or Toe Brachial Index (TBI) (if applicable)
  - Rutherford Clinical Category
- Concomitant antiplatelet and anticoagulant medication

6.3 Index Procedure

All procedures should be conducted in accordance with site standard of care and patient needs, there are no prohibited concomitant treatments. BioMimics 3D stent deployment shall be conducted in accordance with the IFU.

Data will only be collected on patients who have provided their consent and are treated, or treatment is attempted with BioMimics 3D stent system. All other patients will be considered screen failures and no data will be collected.

The following data will be collected at index procedure through to discharge:

- Lesion pre-treatment, e.g., PTA, drug-eluting balloon therapy, atherectomy, laser
- Baseline angiographic assessment, i.e., lesion size, inflow and outflow disease
- Stent placement: location, size and lot number/expiry of stent(s)
- Post-stenting treatment
- Assessment of final lumen patency via angiogram at the conclusion of the index procedure (percent angiographic stenosis)

- Procedure time
- Concomitant peripheral procedures
- Adverse events and device observations
- Device use questionnaire (completed by operator)
- Concomitant antiplatelet and anticoagulant medication

6.4 Follow-Up

The following data will be collected at **Day 30** (± 7 days), **Month 12** (365 days ± 30 days), **Month 24** (730 days ± 60 days) and **Month 36** (1095 days ± 60 days) post Index Procedure:

- Relevant medical history including peripheral interventions (target limb)
- Physical examination (as available)
    - Ankle Brachial Index (ABI, or TBI, if applicable)
    - Rutherford Clinical Category
- Concomitant antiplatelet and anticoagulant medication
- Imaging data including patency assessment, evidence of stent fracture
- Adverse events

6.5 Medications

Patients should be prescribed antiplatelet medication in accordance with site standard of care and the recommendations in the IFU.

Use of aspirin, clopidogrel and other antiplatelet and anticoagulant use will be recorded from baseline through 36 months.

7.0 ADVERSE EVENTS

For the purpose of this Study all potentially device-related and procedure-related adverse events, major adverse events, and all vascular adverse events in the target limb will be documented throughout the 36-month visit and reported to Sponsor via the eCRF.

The Sponsor shall review all adverse events for their relationship to the Study device(s) and/or procedures and comparative anticipated safety event rates. The Sponsor will conduct evaluations of any device-related event per standard operating procedures.

An independent Clinical Events Committee (CEC) will be responsible for systematic review and adjudication of all Major Adverse Events including death, and all potentially device- -related adverse events.

7.1 Adverse Event definitions

Adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in subjects, whether or not related to the investigational device or procedure. In addition, the definition of AE applies to any event with an onset during enrolment / index 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 enrolment is not reported as an AE, but any increase in the severity of the underlying disease is to be reported as an AE. This definition includes events occurring during the follow-up period.

Adverse Device Effect (ADE) / Device-Related Adverse Event*:* an adverse device effect (or device-related adverse event) is defined as any untoward adverse effect 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.

> NOTE 1: This definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
>
> NOTE 2: This definition includes any event resulting from user error or from intentional misuse of the investigational medical device.

***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 Study device (i.e., BioMimics 3D Stent System) used. Other products, surgical techniques, or medications required specifically for the procedure are likely to have contributed to the occurrence of the event.

A ***serious adverse event*** is defined as an adverse event that:

- Led to death,
- Led to a 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 hospitalisation or prolongation of existing hospitalisation
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function, or
- Led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalisation for a pre-existing condition or elective cosmetic procedures, or a procedure required by the investigational plan without serious deterioration in health, is not considered a serious adverse event.

Major Adverse Event (MAE)

For the purposes of this study, the definition of a major adverse event includes:

- Death
- Any major amputation performed on the target limb
- Clinically-driven target lesion revascularisation

7.2 Adverse Event Reporting Requirements

7.2.1 General Reporting Requirements

The following adverse events should be recorded on the eCRF through 36 months post-index procedure:

- All potentially device and/or procedure-related adverse events
- All major adverse events (MAE)
- All vascular adverse events in the target limb.

The report should include: description of event, severity, duration, action taken, treatment outcome and relationship of the adverse experience to the study device and/or procedure (i.e., unrelated, possibly related, related or relationship not assessable).

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.

All reportable events should be followed until resolution or the end of the study.

7.2.2 Reporting Requirements for Serious and Major Adverse Events

All serious and potentially device and/or procedure-related, MAE and vascular adverse events in the target limb must be reported to the Sponsor within 24 hours of knowledge of the event or by the end of the next working day. This may be done via phone, fax, email or eCRF.

Sponsor will review all reported events for potential reporting in accordance with MEDDEV 2.12.1, Rev 8 (2013) "Guidelines on a Medical Devices Vigilance System". Sponsor may request medical record documentation (e.g., procedure notes, operative notes, discharge summary, relevant progress notes, imaging, or lab studies) to facilitate this review.

The Sponsor will determine whether all of the local Investigators need to be informed immediately of an SAE or UADE, or whether this can be postponed until the next regularly scheduled study update.

The Investigator is responsible for reporting applicable serious adverse events to their EC/IRB as required by EC/IRB procedures and local/national regulations. A copy of each EC/IRB safety report will be provided to Sponsor.

7.2.3 Device Failures and Malfunctions

All device observations / performance issues, malfunctions or failures of the Veryan BioMimics 3D stent, whether or not associated with an adverse event must be reported via the eCRF within 24 hours of knowledge of the event or by the end of the next working day.

Sponsor will review all reported events for potential reporting in accordance with MEDDEV 2.12.1, Rev 8 (2013) "Guidelines on a Medical Devices Vigilance System". Sponsor may request medical record documentation (e.g., procedure notes, operative notes, discharge summary, relevant progress notes, imaging, or lab studies) to facilitate this review.

8.0 RISK/BENEFIT ASSESSMENT

8.1 Risks

The BioMimics 3D Stent System is being used in accordance with the approved CE Mark indication and Instructions for Use. As with all procedures that utilise techniques for introducing a catheter into a vessel, complications may occur. These complications as listed in the instructions for use include, but are not limited to:

- Allergic reaction to Nitinol
- Allergic/anaphylactoid reaction
- Amputation
- Aneurysm
- Angina/coronary ischemia
- Arrhythmia
- Arterial occlusion/restenosis of the treated lesion/vessel without reintervention
- Arterial occlusion/restenosis of the treated lesion/vessel with intervention
- Arterial occlusion/thrombus, near the puncture site
- Arteriovenous fistula
- By-pass surgery
- Death related to procedure
- Death unrelated to procedure
- Deployment failure
- Device failure
- Embolisation, arterial
- Embolisation, stent
- Fever
- Haematoma bleed at needle, device path: nonvascular procedure
- Haematoma bleed, puncture site: vascular procedure
- Haematoma bleed, remote site
- Haemorrhage/bleeding requiring a blood transfusion
- Hypersensitivity reactions
- Hypotension/hypertension
- Incorrect positioning of the stent requiring further stenting or surgery
- Infection/abscess formation at access site
- Intimal injury/dissection
- Ischemia requiring intervention
- Ischemia/infarction of tissue/organ
- Liver failure
- Local infection
- Myocardial infarction
- Open surgical repair

- Pain
- Pancreatitis
- Partial stent deployment leading to surgical repair
- Pneumothorax
- Pseudoaneurysm
- Pulmonary embolism
- Radiation injury
- Renal failure
- Respiratory arrest
- Septicaemia/bacteraemia
- Shock
- Spasm
- Stent fracture
- Stent kinking
- Stent malapposition
- Stent migration
- Stroke
- Thrombosis
- Tissue necrosis
- Venous occlusion/thrombosis, near the puncture site
- Worsened claudication/rest pain

8.2 Risk Minimization

As with any endovascular procedure, appropriate safety precautions will be followed. In addition, this Protocol provides additional steps to minimize risk to study subjects. These include the following:

- **Investigator Selection & Training**: All investigators are required to be appropriately qualified by education, training and expertise in peripheral interventional techniques and placement of intravascular stents.
- **Subject Screening**: Patient selection will be in accordance with the Protocol and the IFU. Patients with known contraindications e.g. history of intolerance or adverse reaction to antiplatelet and/or anticoagulation therapies, bleeding diathesis, severe hypertension or renal failure, known hypersensitivity to nickel-titanium will not be eligible for the Study.

8.3 Potential Benefits

Prior human clinical experience in a population of 60 subjects has validated that the BioMimics 3D Stent System can be used to safely and effectively stent the femoropopliteal arteries, resulting in acute and long term luminal patency. Clinical study populations are defined by eligibility criteria more restrictive than the device IFU which may limit the application of results to a broader population. The MIMICS-3D Study is intended to evaluate the safety and effectiveness of the BioMimics 3D Stent System in a larger "real-world" clinical population.

9.0 STATISTICAL ANALYSIS PLAN

The analysis of the data from this study will be primarily descriptive. Continuous endpoints will be summarized by N, mean, standard deviation, median, minimum, and maximum. Categorical or binary endpoints will be summarised by N and percentage with confidence intervals as appropriate. Kaplan Meier plots will be used to display and summarise time to event data.

The planned sample size for analysis is at least 500 patients which is believed to be adequate to provide an accurate characterisation of BioMimics 3D in a "real-world" clinical settings.

9.1 Analysis Population

- *Intention-to-Treat (ITT) Analysis Set*: includes all enrolled subjects.
- *Modified Intention-to-Treat (mITT) Analysis Set*: includes all enrolled subjects in whom the BioMimics 3D Stent System is implanted. Those subjects in whom the procedure is aborted without implantation of a stent will be excluded from this analysis set. This is the primary

analysis set for the primary safety and effectiveness endpoints, as well as secondary and exploratory endpoints.

- *Per-Protocol (PP) Analysis Set*: includes all enrolled subjects in whom the BioMimics 3D Stent System is implanted and who met all inclusion/exclusion criteria with no major protocol deviations. Those subjects in whom the procedure is aborted without implantation of a stent will be excluded from this analysis set. This is a secondary analysis set for the primary safety and effectiveness endpoints, as well as secondary endpoints.

While mITT is intended as the primary analysis set for all safety and effectiveness endpoints, the primary safety and effectiveness endpoints will additionally be evaluated in the ITT and PP analysis sets as supportive information. All subjects excluded from mITT analysis set will be described and the reasons for aborted procedures, if any, detailed.

A separate analysis will be conducted for the DCB cohort.

9.2 Population Demographics

The demographics and medical history will be presented in tabular form for all subjects enrolled in this study (ITT analysis set). Means, standard deviations, and sample size will be used to summarise continuous characteristics such as age. Frequencies and percentages will be used to summarise categorical characteristics such as gender. Demographic and medical history data will be additionally tabulated for the mITT and PP analysis sets.

9.3 Primary Endpoint Analysis

Endpoints will be analysed using the modified intention-to-treat analysis set. An additional supportive analysis will be conducted in the ITT and PP analysis sets for the primary safety and effectiveness endpoints. All available data will be used for each endpoint and no imputations will be done.

The primary safety endpoint of MAE at 30 days will be presented as frequency and percentage and the 2-sided 95% confidence interval will be calculated via Agresti-Coull.

Similarly, the primary outcome measure for effectiveness, clinically-driven target lesion revascularisation (TLR) through 12 months, will be presented as frequency and percentage and the 2-sided 95% confidence interval will be calculated via Agresti-Coull.

9.4 Secondary Endpoint Analysis

All secondary endpoints will be tabulated. Means, standard deviations and sample size will be used to summarise continuous characteristics. Distributions of continuous data will be examined and if non-normality is exhibited, medians and interquartile ranges will be presented. Frequencies and percentages will be used to summarise categorical characteristics. Measures collected serially over time (for example, Rutherford Clinical Category) will be presented at each time point, and the measure at each time point will be compared to the baseline measure as well as tested for trends. All available data will be used for each endpoint and no imputations will be done. The mITT analysis set will be used for these analyses. As a secondary analysis, the PP analysis set will be displayed.

9.5 Site Poolability

Poolability of study subjects across investigational sites will be explored by comparing the primary outcome measure across site. Testing of the primary outcomes will be conducted across site at a two-sided alpha=0.15 level using a chi-square test, unadjusted for covariates. If differences between sites exist at the alpha=0.15 level, summary statistics will be presented for each site. Any differences by study site will be discussed in the study report. If substantial differences emerge, a sensitivity analysis of the primary outcomes may be performed by excluding outlying sites from the analysis.

9.6 Sample Size

This study is not powered for formal statistical hypothesis testing and is intended to be descriptive in nature. Assuming an MAE rate of 90% to 99%, the corresponding width of the 95% confidence interval would range from 5.5% to 2%, respectively. Similarly, assuming an event rate of 75% for CDTLR at 12 months, the width of the 95% confidence interval would be approximately 8% allowing for up to 10% attrition. Thus, it is felt that enrolling 500 subjects provides adequate precision to estimate the primary endpoint event rates in this cohort.

9.7 Handling of Missing Data

No imputation of missing data is planned. Subjects who have ascertainment of status at a later out-of-window date (for example, subjects who are known to be free of MAE past 30 days but missed the 30 day visit) are not considered missing as their status is known and their data will be used.

9.8 Interim Analysis

There is no interim analysis planned with the purpose of altering the protocol or planned statistical analyses. Interim analyses may be undertaken for the purpose of presentations or publication.

10.0 ETHICAL, QUALITY ASSURANCE AND ADMINISTRATIVE ASPECTS

10.1 Sponsor Responsibilities

Veryan Medical Ltd., as Sponsor is responsible for the overall conduct and quality of the Study, including the assurance that the Study complies with Declaration of Helsinki, relevant Data Protection regulations and all relevant international standards and regulations applicable to medical device registries. Veryan will ensure that all applicable national regulatory and Data Protection approvals are in place prior to commencement of the Study at each site. Veryan will implement systems to select and train investigators, collect data, oversee the quality of the Study and monitor investigator compliance with their responsibilities as detailed in this Protocol.

10.2 Investigator Responsibilities

The Investigators are responsible for ensuring that this Study is conducted according to this Protocol, Declaration of Helsinki, relevant Data Protection regulations, and any other local, national or EC/IRB requirements that apply to registries at their site.

It is also the Investigator's responsibility to ensure that all sub-investigators and staff assisting with this Study have the appropriate qualifications and that they complete training on the Protocol procedures, and that patient confidentiality is respected. Other Investigator responsibilities are detailed throughout Section 10.0.

10.3 Selection of Clinical Sites & Investigators

Veryan is responsible for selection of sites for Study participation based upon review of the following criteria:

- Investigator(s) are appropriately qualified by education, training and expertise in peripheral interventional techniques and placement of intravascular stents.
- Investigator(s) are appropriately qualified for commercial supply of BioMimics3D stent in accordance with Veryan requirements. This includes completion of all relevant training and/or case support.
- Investigator(s) are willing to conduct the Study in accordance with this Protocol and all applicable local and national regulatory requirements, including Informed Consent requirements.
- Adequate staff to comply with Study data collection and reporting standards.
- Appropriate facilities, resources and equipment to conduct the Study including ability to support EDC requirements
- Willing to allow access to representatives of the Sponsor and/or regulatory authorities for data monitoring/audit.

10.4 Investigator Training

It is a prerequisite for site selection that investigators are appropriately qualified for commercial supply of BioMimics3D stent in accordance with Veryan requirements. This includes completion of all relevant training and/or case support. No additional device training or support is required for Study participation. Veryan will ensure that Investigators and site staff are trained in the Study Protocol, including consent requirements, and data collection procedures. Training may be completed by on-site visit, WebEx and/or web-based training modules.

10.5 EC/IRB Approvals

The Investigator at each site is responsible for obtaining EC/IRB approval for the Protocol and the Informed Consent documents **prior** to enrolment of the first Study patient at site. The Sponsor **must** also review and approve the final Informed Consent documents prior to their use. The Sponsor must receive a copy of EC/IRB final approval letter and the final approved Informed Consent.

The Investigator is responsible for ensuring that all applicable local, national, and Declaration of Helsinki requirements are met when completing the informed consent process. Written, Informed Consent is to be obtained for all patients **prior** to enrolment.

The Investigator or clinical site staff will not make amendments to this Protocol or the Informed Consent form without **PRIOR** written approval from the Sponsor. All approved amendments must then be submitted to the local EC/IRB, as appropriate for approval.

If the Investigator's IRB or EC withdraws their approval to conduct this study for any reason, the Investigator **must** notify the Sponsor as soon as possible, but in no event later than **five working days** after the withdrawal of the approval.

The Investigator must submit and, where necessary, obtain approval from the EC/IRB for all subsequent significant Protocol amendments and significant changes to the Informed Consent form. The Investigator should notify the EC/IRB of deviations from the Protocol and safety reports in accordance with local procedures.

The Investigator will be responsible for obtaining annual EC/IRB approval and renewal, where applicable, throughout the duration of the study. Copies of the Investigator's reports and the EC/IRB continuance of approval must be sent to Veryan.

10.6 Required Documentation

The Investigator will maintain all CRFs, source documents and all Study documents and correspondence as required by applicable regulatory requirements for the duration of the study.

The following documents should be provided to the Sponsor before Study starts:

- Copy of EC/IRB approval and membership list and any other relevant local approvals.
- Copy of the EC/IRB approved Informed Consent form and any other approved patient information.
- Financial disclosures for the Investigator and sub-Investigator(s), if applicable.
- Signed and dated Protocol Signature page.
- Current signed and dated curriculum vitae for each Investigator and sub-Investigator.
- Fully executed study agreement, including financial agreement.

10.7 Clinical Data Collection

Standardised electronic case report forms (eCRF) will be used to collect complete and accurate records of the clinical data. The Investigator and/or staff under his/her direction is responsible for accurately recording the clinical data for this Study and submitting it to the Sponsor in a timely manner. All data from the trial will be entered into eCRF via a secure, web-based system with password protection. All data should be entered completely and promptly. Data will be remotely reviewed and queried to identify inconsistent or missing data and any adverse events.

Investigators are required to maintain adequate source documents including laboratory results, supporting medical records, and signed Informed Consent forms. These will be used during on-site monitoring visits to verify data contained on the completed eCRF. For source documents, corrections should be made in a manner that does not obscure or eliminate the original error, by striking through the original data with one line, and initialling and dating the change, along with the reason for the change (if not obvious).

The investigator must ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs which are derived from source documents must be consistent with the source documents or the discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator, to be filed in the subject file.

Only authorised persons can complete an eCRF. An eCRF shall be signed by investigators as specified on the Delegated Tasks List included in the Investigator Site File.

The Electronic Data Capture (EDC) system maintains an audit trail on entries, changes or corrections in eCRFs. If a person only authorised to complete an eCRF makes changes to an already signed eCRF, the investigator shall re-sign this eCRF.

10.8 Device Accountability

Sites will use devices supplied according to standard hospital/clinic procedures for the supply of commercial products. Device size, lot number and expiry dates will be recorded in the eCRF. No other device accountability procedures will apply.

10.9 Subject Compensation

Study patients will not be reimbursed or compensated for their time in participating in the trial.

10.10 Confidentiality

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

10.11 Monitoring

Veryan will designate appropriately qualified monitors to review compliance with Protocol and data collection procedures, to assess the accuracy and completeness of eCRF data and record retention. These will be assessed by remote data review and periodic on-site visits. Frequency and timing of on-site monitoring will be determined by Veryan based on review of factors including, but not limited to enrolment rate, adverse event reporting and Protocol compliance.

The Investigator will make available all regulatory documents, completed eCRF, Informed Consent documents, source documentation and other relevant records for enrolled subjects at the site. It is important that the Investigator and other relevant site personnel are available for consultation with the clinical monitor during the monitoring visits and that sufficient time is devoted at the site to the monitoring process.

10.12 Audits and Inspections

The Investigator will allow representatives of the Sponsor, EC/IRB and applicable regulatory agencies to inspect all trial records, eCRF, and corresponding portions of the subject's office and/or hospital medical records at regular intervals throughout the trial. These inspections are for the purposes of verifying adherence to the Protocol, completeness and exactness of the data being transcribed into the eCRF, and compliance with regulatory agency regulations.

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

The Investigator and/or designees must be available to respond to reasonable requests by authorised Sponsor, CRO and regulatory agency representatives during the monitoring and inspection process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current study (i.e., Inspection Observations) or their qualification as an Investigator in clinical studies conducted by the Sponsor. The Sponsor will provide any needed assistance to the clinical site for regulatory audits, if any.

10.13 Protocol Compliance/ Deviations

The Investigators are responsible for ensuring that this Study is conducted according to this Protocol. All deviations from the Protocol must be reported to the Sponsor.

Investigators shall be required to obtain prior approval from the Sponsor before initiating deviations from the Protocol, except where necessary to protect the life or physical well-being of a subject in

an emergency. Such approval shall be documented in writing and maintained in Sponsor and Investigator files.

Investigators will also adhere to procedures for reporting Protocol deviations to their EC/IRB in accordance with their specific EC/IRB reporting policies and procedures.

For reporting purposes, the Sponsor classifies the following as major protocol deviations: Any deviation from subject inclusion and exclusion criteria, subject informed consent procedures, safety reporting, or unauthorised device use.

10.14 Investigational Site Termination

The Sponsor reserves the right to terminate an investigational site from the Study for any of the following reasons:

- Failure to obtain Informed Consent.
- Failure to comply with safety reporting requirements.
- Repeated Protocol violations or safety concerns.
- Repeated failure to complete electronic Case Report Forms.
- Failure to enrol an adequate number of patients.

10.15 Clinical Events Committee

An independent Clinical Events Committee (CEC) will be responsible for systematic review and adjudication of all Major Adverse Events including death, and all potentially device-related adverse events, at minimum.

At a minimum, the CEC shall consist of at least three (3) independent physicians, with experience in interventional peripheral endovascular procedures.

In order to enhance objectivity and reduce the potential for bias, the CEC members shall be independent of the Sponsor as well as the investigational sites and investigators. The methodology for performing these responsibilities shall be developed and outlined in the CEC Charter. Operational provisions shall be established to minimise potential bias.

11.0 RECORDS, REPORTS AND PUBLICATION

11.1 Record Retention

Sponsor and Investigators will maintain their Study records until two (2) years after the final report is completed, or longer if required by local, national or international regulatory agencies. The Sponsor will notify each site regarding the regulatory requirements for record retention at the time of Study close-out.

11.2 Reporting Timelines

The Investigator will report information and events according to the timelines in Table 2.

Table 2: MIMICS-3D investigator reporting timelines

Form/Report	Submission Timeframe
eCRF	Completion within 10 working days of visit/follow-up.
All serious and potentially device- and/or procedure-related, MAE and vascular adverse events in the target limb	Submit notification to Sponsor within 24 hours of the site becoming aware of the event, or by the end of the next working day; submit to the local EC/IRB as required according to local and national regulations.
All device observations / performance issues, malfunctions or failures	Submit notification to Sponsor within 24 hours of the site becoming aware of the event, or by the end of the next working day; submit to the local EC/IRB as required according to local and national regulations.
Study Progress Reports	As required by the local EC/IRB (minimum annually).

Final Report to the EC/IRB	Within 3 months of Study completion.

11.3 Study Reports

All information and data generated in association with the study will be held in strict confidence and remains the sole property of the Sponsor. The Investigator agrees to use this information for the sole purpose of completing the study and for no other purpose without prior approval of the Sponsor.

The Sponsor will submit all required reports to regulatory authorities throughout the study.

Upon receipt of the final Study data and the final reports from each centre, the Sponsor will complete a final Study report. Copies of the final report will be provided to each Investigator.

11.4 Publication Policies

Publications and presentations will be coordinated by Veryan to allow the use of all available data. The following publication policy will have to be adhered to by all participating investigation sites:

Authorship on any publication(s) will be assigned according to substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published. This is in accordance with the Vancouver principles (The Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, ICMJE, October 2008), as agreed upon by the editors of all major medical journals. The number of authors will be dependent on the regulations of the concerning journal with a maximum of 10 authors. Names of all participating investigators will appear in the Acknowledgment of the paper.

Based on the principle that Veryan owns the Study data, a single investigation site may access and use the data provided by itself for scientific publications following prior approval by Veryan.

Pooling data from several investigation sites for publication purposes, national projects and international projects all require prior approval by Veryan.

Veryan as the owner of the data can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research and development of devices or educational use.

Participating subjects will not be identified by name in any published reports about the Study. This Study will be registered with www.clinicaltrials.gov.

12.0 STUDY DEFINITIONS

Access Site Haemorrhage: Bleeding from the access site which requires transfusion, hospitalisation (either admission or extended stay), or further treatment for management. Haemorrhage needing ≥ 1 unit RBCs will be considered a serious adverse event.

Access Site Infection: Culture-proven wound infection or presumptive treatment with antibiotics for clinically diagnosed wound infection.

Acute procedural success: defined as both acute technical success and absence of the following adverse events: death, stroke, MI, acute onset of limb ischemia, index bypass graft or treated segment thrombosis, and/or need for urgent/emergent vascular surgery, within 72 h of the index procedure[15].

Acute technical success: defined as the achievement of a final residual diameter stenosis ≤30% at the end of the procedure)[15]

Allergic Reaction: An allergic reaction characterised by rash, upper respiratory congestion, urticaria, shortness-of-breath, or general collapse (anaphylaxis).

Amputation:

Major: any requirement for amputation of the target limb above the ankle.
Minor: any requirement for amputation of the of the target limb below the ankle.

Anaemia: Decrease from baseline in red blood cells, haemoglobin, or total blood volume that is associated with haemodynamic changes or requires transfusion, or a drop in haematocrit to below 26%. An anaemic event requiring ≥2 units packed red blood cells (PRBC) will be considered an SAE.

Angina, unstable: Angina that increases in frequency, intensity, or duration, which occurs at rest, or which is new in onset. Unstable angina is a syndrome that is intermediate between stable angina and myocardial infarction: it is characterised by an accelerating or "crescendo" pattern of chest pain that lasts longer than stable angina, occurs at rest or with less exertion than stable angina, or is less responsive to medication. Unstable angina and myocardial infarction are considered acute coronary syndromes.

Ankle Brachial Index (ABI): The ratio of systolic blood pressure measured at the ankle to systolic blood pressure measured at the brachial artery. It is used to predict the severity of peripheral arterial disease (PAD). ABIs >0.9-1.2 = normal, ≤ 0.9 = peripheral arterial disease, < 0.4 = severe peripheral arterial disease (ischemic pain and ulceration). ABI > 1.2 is likely due to incompressible arteries and is commonly observed in association with long-standing diabetes mellitus, extreme old age, or calcinosis.

Instructions for ABI Calculations:

1. Obtain systolic blood pressures (SBP) for both arms (brachials) and both ankles [posterior tibials (PT) & dorsalis pedals (DP)].
2. Divide the higher of the two SBPs for each leg (highest between the PT and DP) by the higher of the two arm pressures to get the right and left ABIs.

Arterial Occlusion / Thrombosis at Groin Puncture Site: Angiographic or ultrasonographic evidence of occlusion at the puncture site limiting antegrade flow to the distal limb.

Arterial Perforation/Rupture/Puncture of an Arterial Wall: Classified as follows:

Angiographic perforation: Perforation detected by the clinical site at any point during the procedure.
Clinical perforation: Perforation requiring additional treatment (including efforts to seal the perforation), or resulting in significant extravasation of blood from the site, abrupt closure, limb ischemia or death.

Arteriovenous Fistula (AVF): An abnormal passage or communication between an artery and a vein which may be due to the percutaneous introduction of ancillary devices (e.g., needles, catheters, guide wires) confirmed by imaging studies.

Bleeding Complication (Major): Bleeding resulting in ≥3 g/dl decrease in hemoglobin (if haemoglobin level not available, a decrease in haematocrit of ≥ 10%), or necessitating transfusion of >1 unit of PRBC's /whole blood, or necessitates surgery/endoscopic intervention.

Access site: Bleeding from the arteriotomy site which requires transfusion, hospitalisation (either admission or extended stay), or further treatment for management.

Cardiac Arrhythmia: Electrical disruption of the heart rhythm requiring specific medication, DC shock, or pacemaker insertion to address condition.

Cardiogenic Shock: Subject presents with SBP < 80 mm Hg for more than 30 minutes unresponsive to fluids or requiring intravenous vasopressor agent or an intra-aortic balloon pump (IABP).

Cerebral Vascular Accident (CVA): See Stroke.

Classification of Calcification: Intimal and medial vessel wall calcification at the target lesion site as assessed by high intensity fluoroscopy and digital subtraction angiography (DSA) assessed in the AP projection [16].

Peripheral Arterial Calcium Scoring System (PACSS):
Grade 0: No visible calcium at the target lesion site.
Grade 1: Unilateral calcification <5cm: a) intimal calcification; b) medial calcification; c) mixed type.
Grade 2: Unilateral calcification ≥5cm: a) intimal calcification; b) medial calcification; c) mixed type.
Grade 3: Bilateral calcification <5cm: a) intimal calcification; b) medial calcification; c) mixed type.
Grade 4: Bilateral calcification ≥5cm: a) intimal calcification; b) medial calcification; c) mixed type.

Closure, Abrupt: Occurrence of new (during the index procedure), persistent slow, reduced, or loss of flow within the target vessel that requires intervention other than the index or adjunct treatment. Abrupt closure may also be referred to as acute occlusion if there is a total loss of flow.

Closure, Late: Target lesion site occlusion that occurs greater than 30 days after the index procedure is completed.

Closure, Subacute: Target lesion site occlusion that occurs after the index procedure is completed (e.g., the subject has left the treatment area) and within 30 days of procedure.

Contrast-Induced Nephropathy: Associated with contrast agent resulting in > 25% increase in serum creatinine or an absolute value of > 0.5 mg/dl.

Contrast Media Reaction: An allergic reaction, immediate or delayed, associated with the intravascular administration of contrast media that results in symptoms (e.g. itching, hives) or physiologic changes requiring treatment (e.g. anaphylactic reaction) or death.

Critical Limb Ischemia (CLI): Clinical manifestation of peripheral arterial disease characterised by Rutherford Clinical Scale Category of 4-6.

Death: Death is divided into 2 categories:

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

1. Acute myocardial infarction.
2. Sudden cardiac death.
3. Death due to heart failure.
4. Death due to stroke.
5. Death due to other cardiovascular causes.
6. Death not attributable to any other cause (e.g., undetermined cause of death).

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

Deep Vein Thrombosis (DVT): Thrombosis of a deep vein, as confirmed by imaging study or direct visualization.

Femoropopliteal: DVT involvement limited to the superficial femoral or popliteal veins, with or without distal (e.g. toward foot) DVT involvement, based on duplex ultrasound exam.
Iliofemoral: DVT involvement of the common or external iliac veins or the common femoral vein, with or without distal (e.g. toward foot) DVT involvement, based on duplex ultrasound exam.

De Novo Lesion: An obstructive or occlusive lesion without previous endovascular or surgical intervention

Device Failure: A device that is used in accordance with the Instructions for Use, but does not perform according to the Instructions for Use and negatively impacts the treatment.

Device Malfunction: A malfunction or deterioration should be understood as a failure of a device to perform in accordance with its INTENDED PURPOSE when used in accordance with the MANUFACTURER's instructions.

Dissection: Disruption of an arterial wall resulting in separation of the intimal layer. May or may not be flow limiting.

Dissection Classifications (National Heart, Lung and Blood Institute – NHLBI)

Type A: Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.
Type B: Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles.
Type C: Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material.
Type D: Spiral shaped filling defect with our without delayed run-off of the contrast material in the antegrade flow.
Type E: Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen.
Type F: Filling defect accompanied by total coronary occlusion.

Embolisation, Distal: Any distal emboli confirmed by imaging.

Embolisation, Symptomatic: Clinical signs or symptoms of distal emboli detected in the treated limb distal to the treated lesion after the index procedure ***or*** noted angiographically and requiring mechanical or pharmacologic means to improve flow. This includes new abrupt occlusions or filling defects.

Enrolment: Subjects who are consented and meet all inclusion criteria and none of the exclusion criteria and are treated or treatment is attempted with the study device will be considered enrolled into the study.

Haematoma: Collection of blood (or its degradation products) which exceeds 5 cm in diameter, requires treatment, or prolongs hospitalisation.

Hypertension: Systolic BP >140 mmHg, or diastolic >90 mmHg requiring specific medical therapy.

Hypotension: Any prolonged systolic blood pressure <80 mmHg associated with symptoms and requiring intravenous vasopressor medications.

Infection, access site: Infection at the vascular access site, documented by lab culture or clinical evidence requiring medical treatment (irrigation, debridement, antibiotics, etc.) to resolve.

Infection, systemic: Systemic infection documented by positive lab culture or clinical evidence, requiring medical treatment to treat and resolve.

Intention to Treat (ITT): The principle of including outcomes of all subjects in the analysis who are enrolled and treated (attempted or completed) into the study, regardless of noncompliance, Protocol deviations, or withdrawal.

Limb Ischemia: Deficient supply of oxygenated blood to the tissues in the limbs that is due to obstruction of the inflow of arterial blood characterised by pain and/or discoloration of the limb and/or tissue loss.

Luminal Patency: Restenosis <50% as determined by angiography or duplex ultrasound.

Major Adverse Event (MAE): An MAE comprises all-cause death, any major amputation performed on the target limb or clinically-driven target lesion revascularisation.

Myocardial Infarction (MI): Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

Patency, Primary Stent: Patency is defined as the composite of (1) freedom from more than 50% restenosis within the stented segment and (2) freedom from clinically-driven target lesion revascularisation (TLR).

Patency, Tibioperoneal Run-Off: Subject has at least one patent tibioperoneal run-off vessel with <50% stenosis confirmed by angiography.

Perforation: Puncture of an arterial wall.

Pseudoaneurysm: Disruption of the arterial wall characterised by an out-pouching or pocket with swirling, flowing blood outside of the confines of the arterial lumen.

Recurrent Occlusion: Occlusion (i.e. total obstruction of vessel lumen) after a successful canalisation.

Recurrent Thrombosis: Thrombosis (i.e. sub-total obstruction of vessel lumen) following successful treatment.

Reference Vessel Diameter, Proximal (RVD_{prox}): Diameter of normal vessel immediately proximal to the treated segment.

Reference Vessel Diameter, Distal (RVD_{dist}): Diameter of normal vessel immediately distal to the treated segment.

Renal Failure (Acute): Acute post-operative renal insufficiency resulting in one or more of the following: (a) increase of > 1.0 mg/dl in serum creatinine from most recent prior measured level, and current measured absolute value is > 2.0 mg/dl; (b) a new requirement for dialysis.

Renal Insufficiency: An increase in serum creatinine of ≥ 1.0 mg/dl over previous value requiring medical treatment but which does not require dialysis to resolve.

Respiratory Failure: New onset of respiratory insufficiency that requires placement of endotracheal tube and/or pneumothorax with or without chest tube.

Respiratory Insufficiency: Deterioration of subject's respiratory efforts that require supportive or medical treatment.

Restenosis: Reoccurrence of narrowing or blockage or target lesion. Recurrence of ≥ 50% diameter stenosis within ± 5 mm proximal and/or distal to the target lesion as measured by duplex ultrasound or angiography

Retroperitoneal Bleed: Bleeding into the back of the abdomen from a vascular access or puncture site.

Rutherford Clinical Category Scale: Clinical scale identifying three grades of claudication and three grades of critical limb ischemia ranging from rest pain alone to minor and major tissue loss [17].

Category	Clinical Description
0	Asymptomatic
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Ischemic rest pain
5	Minor tissue loss
6	Ulceration or gangrene

Stent Fracture: Defined as clear interruption of stent strut observed in a minimum of two projections, determined by core lab examination of X-ray images.

Stent Strut Fracture Types: [18], [19]

Type 0: No strut fractures.
Type I: Single strut fracture only.
Type II: Multiple single strut fractures that can occur at different sites.
Type III: Multiple strut fractures resulting in complete transection of the stent, without displacement of the stent segments.
Type IV: Multiple strut fractures resulting in displacement of segments of the stent.
Type V: Spiral strut fracture.

Stroke: Any neurological deficit lasting 24 hours or longer, or lasting less than 24 hours with a brain imaging study showing infarction consistent with deficit. May be further categorized as:

- Ischemic Stroke: neurologic deficit meeting the study definition for Stroke that is attributed to thromboembolic event.

- Haemorrhagic Stroke: neurologic deficit meeting the study definition for Stroke that is attributed to bleeding into brain tissue, epidural, subdural, or subarachnoid space; or a combination of these sites.

Target Lesion Revascularisation, Clinically-driven (CDTLR): Revascularisation of the target lesion with objective evidence of recurrent symptoms associated with an angiographic determination of ≥50% stenosis and new distal ischemic signs (worsening ABI or worsening Rutherford Category associated with the index limb).

Target Limb: Any symptomatic limb that contains the target lesion and all vessels from aortic bifurcation to the foot.

Target Vessel Revascularisation, Clinically-driven (CDTVR): Revascularisation of the target vessel with objective evidence of recurrent symptoms associated with an angiographic determination of ≥50% stenosis and new distal ischemic signs (worsening ABI or worsening Rutherford Category associated with the index limb).

Thrombocytopenia: A persistent decrease in the number of blood platelets to subnormal levels.

Thrombus: Blood clot that obstructs a blood vessel.

Transient Ischemic Attack: A neurological event where symptoms last for less than 24 hours, with no evident permanent functional impairment.

Walking Impairment Questionnaire (WIQ): A measure of subject-perceived walking performance for patients with PAD and/or intermittent claudication. This questionnaire estimates walking distance, walking speed, and stair climbing. Improvement is defined as an increase of walking distance

13.0 REFERENCES

1. Fowkes, F. G. R. *et al.* Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *The Lancet* **382,** 1329–1340 (2013).
2. Zeller, T. Current state of endovascular treatment of femoro-popliteal artery disease. *Vasc. Med.* **12,** 223–234 (2007).
3. Krepel, V. M., van Andel, G. J., van Erp, W. F. & Breslau, P. J. Percutaneous transluminal angioplasty of the femoropopliteal artery: initial and long-term results. *Radiology* **156,** 325–328 (1985).
4. Mitra, A. K. & Agrawal, D. K. In stent restenosis: bane of the stent era. *J Clin Pathol* **59,** 232–239 (2006).
5. Davaine, J.-M. *et al.* One-year Clinical Outcome after primary stenting for TASC C and Dfemoropopliteal lesions (the STELLACohort). *Eur. J. Vasc. Endovasc. Surg.* **44,** 432–441 (2012).
6. Iida, O. Influence of stent fracture on the long term patency in the femoropopliteal artery; experience of 4 years. *JACC Cardiovasc. Interv.* **2,** 665–71 (2009).
7. Rits, J., van Herwaarden, J. A., Jahrome, A. K., Krievins, D. & Moll, F. L. The incidence of arterial stent fractures with exclusion of coronary, aortic, and non-arterial settings. *Eur. J. Vasc. Endovasc. Surg. Off. J. Eur. Soc. Vasc. Surg.* **36,** 339–345 (2008).
8. Ansel, G. Interim 1-year VIBRANT resultspresented for Gore Viabahn in SFA treatment. (2009).
9. Allie, D., Hebert, C. & Walker, C. M. Nitinol stent fractures in the SFA. *Endovasc Today* **3,** 22–34 (2004).
10. Scheinert, D. *et al.* Prevalence and clinical impact of stent fractures after femoropopliteal stenting. *J. Am. Coll. Cardiol.* **45,** 312–315 (2005).
11. Smouse, B. H., Nikanorov, A. & LaFlash, D. Biomechanical forces in the femoropopliteal arterial segment. *Endovasc. Today* **4,** 60–66 (2005).
12. Nikanorov, A. *et al.* Fracture of self-expanding nitinol stents stressed in vitro under simulated intravascular conditions. *J. Vasc. Surg.* **48,** 435–440 (2008).
13. Arena, F. J. Arterial kink and damage in normal segments of the superficial femoral and popliteal arteries abutting nitinol stents--a common cause of late occlusion and restenosis? A single-center experience. *J. Invasive Cardiol.* **17,** 482–486 (2005).
14. Zocholl, G., Zapf, S., Schild, H. & Thelen, M. Functional angiography of the arteries near the knee joint: consequences for stent implantation? [German translation]. *RöFo Fortschritte Auf Dem Geb. Röntgenstrahlen Nukl.* **153,** 658–662 (1990).

15. Jonker, F. H., Schlosser, F. J. V., Moll, F. L. & Muhs, B. E. Dynamic forces in the SFA and popliteal artery during knee flexion. *Endovasc Today* 53–8 (2008).
16. Werner, M. *et al.* Treatment of complex atherosclerotic femoropopliteal artery disease with a self-expanding interwoven nitinol stent: midterm results from the Leipzig SUPERA 500 registry. *EuroIntervention* **10,** 861–868 (2014).
17. Dake, M. D. *et al.* Sustained Safety and Effectiveness of Paclitaxel-Eluting Stents for Femoropopliteal Lesions. *J. Am. Coll. Cardiol.* **61,** 2417–2427 (2013).
18. Krankenberg, H. *et al.* German multicenter real-world registry of stenting for superficial femoral artery disease: clinical results and predictive factors for revascularization. *J. Endovasc. Ther. Off. J. Int. Soc. Endovasc. Spec.* **21,** 463–471 (2014).
19. Patel, M. R. *et al.* Evaluation and treatment of patients with lower extremity peripheral artery disease: consensus definitions from Peripheral Academic Research Consortium (PARC). *J. Am. Coll. Cardiol.* **65,** 931–941 (2015).
20. Rocha-Singh, K. J., Zeller, T. & Jaff, M. R. Peripheral arterial calcification: Prevalence, mechanism, detection and clinical implications: Peripheral Arterial Calcification. *Catheter. Cardiovasc. Interv.* n/a–n/a (2014). doi:10.1002/ccd.25387
21. ACC/AHA 2005 Guidelines for the Management of Patients With Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic): Executive Summary A Collaborative Report From the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Available at: http://www.sciencedirect.com/science/article/pii/S0735109705023624. (Accessed: 18th June 2014)
22. Jaff, M., Dake, M., Popma, J. & Ansel, G. Standardized Evaluation and Reporting of Stent Fractures in Clinical Trials of Noncoronary Devices. *Catheter. Cardiovasc. Interv. Off. J. Soc. Card. Angiogr. Interv.* **70,** 460–462 (2007).

APPENDIX A – INSTRUCTIONS FOR USE (IFU)

The Instructions for Use in this appendix are current at the time of protocol finalisation. In the event of an update to the approved IFU, this Appendix will be updated administratively.