BOLSTER
Clinical Study

CLINICAL STUDY PROTOCOL

Title:	**A Prospective, Multi-Center, Non-Randomized, Single-Arm Study of the BARD® LIFESTREAM™ Balloon Expandable Vascular Covered Stent in the Treatment of Iliac Artery Occlusive Disease (BOLSTER)**
Protocol Number:	**BPV-12-001**
Study Type:	**Investigational Device Exemption (IDE)**
IDE:	**G140138**
NCT:	**02228564**
Date:	**June 15, 2015**
Version:	**Version 3.0**
Study Device:	**LIFESTREAM™ Balloon Expandable Vascular Covered Stent**
Sponsor:	**Bard Peripheral Vascular, Inc. 1625 West 3rd Street Tempe, AZ 85281**

Sponsor – [redacted] Date

Lead Principal Investigator – [redacted] Date

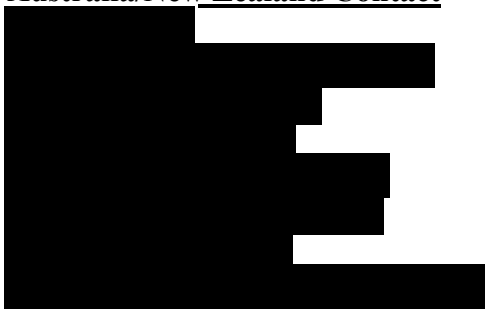
BARD | PERIPHERAL VASCULAR

Sponsor Contacts:

Global Project Manager / U.S. Contact

Europe (Germany) Contact

Australia/New Zealand Contact



Medical Monitor:

Revision History:

Protocol Version #	Description of Changes
1.0	Initial Protocol Version for IDE Submission
1.1	Minor modifications to statistical section (ITT definition, poolability definition, exploratory analysis) based on study design considerations from FDA. Other administrative changes.
2.0	Updated Sponsor contacts; section 3.2 minor clarifications on review of events; section 6.2 updated p-value; section 5.2.7 added exclusion for aspirin allergy; section 14 minor update to add reporting requirements; section 2.0 added interim analysis discussion; section 6.8 added entire section.
3.0	Updated interim analysis discussion in sections 2.0, 6.2, and 6.8. Clarified Blood Urea Nitrogen (BUN) lab requirements. Updated study document requirements in section 11.7

Principal Investigator's Responsibility

Prior to participation in the BARD® LIFESTREAM™ Balloon Expandable Vascular Covered Stent (BOLSTER) Study, the Investigator must sign the Clinical Study Agreement (CSA) and obtain written approval from his/her Institutional Review Board (IRB)/Ethics Committee (EC). This approval must be in the Investigator's name and a copy sent to Bard Peripheral Vascular, Inc. ("Bard") along with the IRB/EC-approved Informed Consent Form (ICF) and the signed CSA prior to first device shipment. The Principal Investigator (PI) must receive Bard-sponsored training prior to study initiation. The PI is responsible for training all Sub-Investigators to ensure adequate training is obtained prior to performing any data collection or study-related procedures.

The Investigator must also:

- Conduct the study in accordance with the study protocol, the signed CSA, the Declaration of Helsinki, applicable national privacy laws (e.g., Health Insurance Portability and Accountability Act (HIPAA) requirements in the U.S.), applicable Food and Drug Administration (FDA), European, and International Organization for Standardization (ISO) regulations (21 Code of Federal Regulations (CFR) Parts 812, 50, 54, 56; ISO 14155:2011(E)).

- Ensure that the study does not commence until FDA and IRB/EC approvals have been obtained.

- Ensure that written informed consent is obtained from each subject prior to the conduct of any study procedure, using the current IRB/EC-approved ICF.

- Provide all required data and reports and agree to source document verification of study data with subject's medical records.

- Allow Bard personnel or their designee(s), as well as FDA representatives and other applicable authorities, to inspect and copy any documents pertaining to the study.

- Provide appropriate resources to ensure compliance with all study-related procedures and prompt submission of all electronic case report forms (eCRFs).

- Use best efforts to communicate protocol requirements to referring physicians.

The PI may delegate one or more of the above functions to a Sub-Investigator provided that the Sub-Investigator first signs the Sub-Investigator Protocol Signature Page and receives appropriate training. However, the PI retains overall responsibility for IRB/EC approval and proper conduct of the study, including obtaining and documenting the Informed Consent process, compliance with the study protocol, signed CSA, the collection of all required data, and ensuring that all study personnel have been properly trained on the protocol and have received other necessary training (if applicable) prior to performing any data collection or study-related procedures.

Principal Investigator Protocol Signature Page

Site name: _____

I have read and understand the contents of the BARD® LIFESTREAM™ Balloon Expandable Vascular Covered Stent (BOLSTER) Study protocol. I agree to follow and abide by the requirements set forth in this document. I agree to conduct the study in accordance with the study protocol, the signed CSA, the Declaration of Helsinki, applicable national privacy laws (e.g., HIPAA requirements in the U.S.), and applicable FDA, European and ISO regulations (21 CFR Parts 812, 50, 54, 56; ISO 14155:2011(E)). I agree to participate in Bard-sponsored training prior to performing any data collection or study-related procedures.

_____
Principal Investigator Name (print)

_____ _____
Principal Investigator Signature Date

Sub-Investigator Protocol Signature Page

Site name: _____

I have read and understand the contents of the BARD® LIFESTREAM™ Balloon Expandable Vascular Covered Stent (BOLSTER) Study protocol. I agree to follow and abide by the requirements set forth in this document. I agree to conduct the study in accordance with the study protocol, the signed CSA, the Declaration of Helsinki, applicable national privacy laws (e.g., HIPAA requirements in the U.S.), and applicable FDA, European and ISO regulations (21 CFR Parts 812, 50, 54, 56; ISO 14155:2011(E)). I agree to receive training by the PI and/or Bard personnel prior to performing any data collection or study-related procedures.

_____
Sub-Investigator Name (print)

_____ _____
Sub-Investigator Signature Date

Clinical Protocol Summary

Title:	A Prospective, Multi-Center, Non-Randomized, Single-Arm Study of the BARD® LIFESTREAM™ Balloon Expandable Vascular Covered Stent in the Treatment of Iliac Artery Occlusive Disease (BOLSTER)
Sponsor:	Bard Peripheral Vascular, Inc. ("Bard") 1625 West 3rd Street Tempe, Arizona 85281 USA
Objectives:	The objective of this study is to assess the safety and effectiveness of the LIFESTREAM™ Balloon Expandable Vascular Covered Stent for the treatment of stenoses and occlusions in the common and/or external iliac arteries.
Design:	This is a prospective, multi-center, non-randomized, single-arm clinical study of the LIFESTREAM™ Balloon Expandable Vascular Covered Stent for the treatment of stenoses and occlusions in the common and/or external iliac arteries. A composite safety and effectiveness measure of subjects receiving the BARD® Balloon-Expandable Covered Stent will be compared to a Performance Goal (PG) derived from iliac stent published literature. The study will be conducted at a maximum of 35 investigational sites ("sites") in the United States, Europe, and Australia/New Zealand. Clinical follow-up for all treated subjects will be performed at hospital discharge, 30-days, and 9-, 12-, 24-, and 36-months post-index procedure. A telephone screen for all treated subjects will be performed at 6-months post-procedure.
Devices:	The LIFESTREAM™ Balloon Expandable Vascular Covered Stent is an electropolished stainless steel balloon expandable stent encapsulated by two layers of expanded polytetrafluoroethylene (ePTFE). Size Matrix:
Enrollment:	Enrollment will continue until one-hundred fifty-four (154) subjects are treated with the LIFESTREAM™ Balloon Expandable Vascular Covered Stent, which is an estimated three-hundred eight (308) consecutive subjects in a non-randomized fashion. Subjects will be considered enrolled in the study at the time the informed consent document is signed (an estimated 308 subjects). After the subject has met all eligibility criteria, undergone successful PTA of the target lesion(s), and the LIFESTREAM™ Balloon Expandable Vascular Covered Stent catheter is introduced (i.e. delivery system enters the subject's body), the subject will enter the primary analysis population (up to 154 subjects).

Balloon Diameter (mm)	Reference Implant Length (mm)			
5	16	26	37	
6	16	26	37	58
7	16	26	37	58
8	16	26	37	58
9			38	58
10			38	58
12			38	58

Investigational Sites:	Up to thirty-five (35) sites will be utilized for this study throughout the United States (U.S.), Europe, and Australia/New Zealand.
Study Population:	Subjects will be males or non-pregnant females, at least 21 years of age, with an expected lifespan sufficient to allow for completion of all study procedures. Eligible subjects will have intermittent claudication or ischemic rest pain and angiographic confirmation of either de novo or restenotic (non-stented) lesion(s) ≥ 50% in the common and/or external iliac arteries.
Eligibility Criteria:	**Inclusion Criteria** **Clinical Inclusion Criteria** 1. The subject provides written informed consent using an Informed Consent Form (ICF) that is reviewed and approved by the Ethics Committee (EC) / Institutional Review Board (IRB) for the site. 2. Subject agrees to comply with the protocol-mandated follow-up procedures and visits. 3. The subject is a male or non-pregnant female ≥ 21 years old with an expected lifespan sufficient to allow for completion of all study procedures. Female subjects of childbearing potential must have a negative pregnancy test (urine or blood) within 14 days prior to the index procedure. 4. The subject has intermittent claudication (Rutherford Category 2-3) or ischemic rest pain (Rutherford Category 4). 5. The subject is able and willing to comply with any required medication regimen. **Angiographic Inclusion Criteria** 6. The subject has evidence of single, bilateral, or multiple de novo and/or restenotic (non-stented) lesion(s) in the native common and/or external iliac artery that is (are) ≥ 50% stenosed (including total occlusions) as determined by the Investigator's visual estimate. 7. The target lesion(s) can be successfully crossed with a guide wire and pre-dilated with an appropriately sized PTA balloon. Devices such as chronic total occlusion (CTO) catheters or re-entry devices may be used to facilitate target lesion(s) crossing. 8. The reference vessel diameter(s) is (are) between 4.5 mm and 12.0 mm in diameter as determined by the Investigator's visual estimate. 9. The target lesion(s) is (are) ≤ 100 mm in combined length (per side) as determined by the Investigator's visual estimate. 10. The subject has angiographic evidence of a patent (< 50% stenosis) profunda and/or superficial femoral artery (SFA) in the target limb(s) as determined by the Investigator's visual estimate. Ipsilateral and contralateral SFA lesions may be treated before or after target lesion treatment, considering the following criteria are met: - ≥ 50% stenosis - Stenosis(es) ≤ 15cm in total length or a Total Occlusion ≤ 5cm in length - ≥ 1 vessel run-off

- No thrombus or severe calcification
- Use of on-label devices

Contralateral iliac lesions (not meeting study eligibility criteria) may be treated at the discretion of the investigator with on-label (non-investigational) devices at the time of the index procedure. Other planned interventions must take place 30 days before the index procedure or after 30 days post-index procedure.

Exclusion Criteria

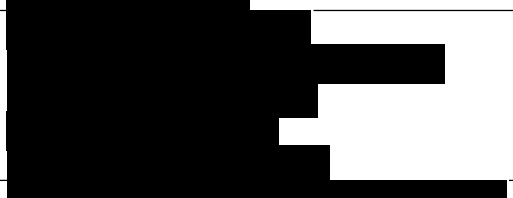
Clinical Exclusion Criteria

1. The subject is unable or unwilling to provide written informed consent, or is unable or unwilling to conform to the study protocol follow-up procedures and visits.
2. The subject is or plans to become pregnant during the study.
3. The subject is asymptomatic, has mild claudication or critical limb ischemia with tissue loss described as Rutherford Category 0 (asymptomatic), 1 (mild claudication), 5 (minor tissue loss), or 6 (major tissue loss).
4. The subject has a vascular graft previously implanted in the native iliac vessel.
5. The subject suffered a hemorrhagic stroke or transient ischemic attack (TIA) within 3 months prior to the index procedure.
6. The subject has a known uncorrectable bleeding diathesis or active coagulopathy (platelet count < 80,000/μL).
7. The subject has a serum creatinine ≥ 2.5 mg/dl or is currently on dialysis.
8. The subject has a known allergy or sensitivity to stainless steel (i.e., Nickel), ePTFE, or has intolerance to the antiplatelet, anticoagulant or thrombolytic medications required per the protocol.
9. The subject has a known allergy or sensitivity to contrast media, which cannot be adequately pre-medicated.
10. The subject had a prior vascular intervention(s) within 30 days before, or has an intervention planned for within 30 days after the index procedure. Refer to inclusion criterion #10 for exceptions on SFA lesions and contralateral iliac lesions.
11. The subject has another medical condition, which, in the opinion of the Investigator, may cause him/her to be non-compliant with the protocol, confound the data interpretation, or is associated with a life expectancy insufficient to allow for the completion of study procedures and follow-up.
12. The subject is currently participating in an investigational drug, biologic, or another device study. Studies requiring extended follow-up for products that are now commercially available are not considered investigational studies.

Angiographic Exclusion Criteria

13. The subject has extensive peripheral vascular disease, which in the opinion of the Investigator, would preclude safe insertion of an introducer sheath. The ipsilateral common femoral artery should be

	patent (< 50% stenosis) by the Investigator's visual estimate. 14. The target lesion(s) requires treatment other than angioplasty (e.g., atherectomy, cryoplasty, cutting/scoring balloons, etc.) to facilitate subject device delivery. Devices such as CTO catheters or re-entry devices may be used to facilitate target lesion(s) crossing. 15. The subject has severe calcification of the target lesion(s), which prevents inflation of a PTA balloon (pre-dilatation of the target lesion is required). 16. The target lesion(s) has been previously treated with a stent (bare or covered). A target vessel(s) with a previously placed stent is permitted as long as the subject device(s) will not come into contact with the previously placed stent during treatment of the target lesion(s). 17. The subject has angiographic evidence of acute thrombus at the target lesion(s). 18. The target lesion(s) involves the origin of the internal iliac artery such that successful treatment of the lesion(s) would require the subject device(s) to cross/occlude the side branch. Note, if the internal iliac artery is already occluded, the subject device(s) can be placed across the occluded vessel. 19. The target lesion(s) is (are) located in the distal external iliac artery such that successful treatment of the lesion(s) would require the subject device(s) to cross/occlude side branches (inferior epigastric artery and/or deep circumflex iliac artery) or be exposed to compressive forces associated with the close proximity to the common femoral artery. Note, if the side branch(es) is (are) already occluded, the subject device(s) can be placed across the occluded vessel(s) as long as the device is above the inguinal ligament. 20. The subject has an abdominal aortic aneurysm (AAA) contiguous to the iliac artery target lesion(s). The presence of AAA grafts and/or endografts are not permitted. 21. The subject has a pre-existing target iliac artery aneurysm or perforation or dissection of the target iliac artery prior to the initiation of the treatment for this study.
Procedures:	All subjects will undergo a clinical evaluation at baseline/screening (prior to index procedure); treated subjects will undergo additional evaluations prior to hospital discharge, 30-days and 9-, 12-, 24- and 36-months post-index procedure. A telephone screen for all treated subjects will be performed at 6-months post-index procedure.
Primary Endpoint:	A composite safety and effectiveness measure defined as device and/or procedure-related death or myocardial infarction (MI) through 30 days, or any TLR, target limb(s) major amputation, or restenosis (as determined by Duplex Ultrasonography) through 9-months post-index procedure. The primary endpoint will be evaluated against a PG of 19.5%, which was derived from iliac stent published literature.

Secondary Endpoints:	– The rate of **Major Adverse Events (MAE)** defined as device and/or procedure-related death or MI through 30 days, or any TLR or target limb(s) major amputation through 9-months post-index procedure. – **Acute Lesion Success** defined as attainment of < 30% residual stenosis of the target lesion after the index procedure using any percutaneous method and/or non-investigational device (i.e., post-dilatation). – **Acute Procedure Success** defined as lesion success and no peri-procedural complications (death, stroke, myocardial infarction (MI), emergent surgical revascularization, significant distal embolization in target limb, and thrombosis of target vessel) prior to hospital discharge. – **Acute Technical Success** defined as successful deployment of the LIFESTREAM™ Balloon Expandable Vascular Covered Stent at the intended location. – **Target Lesion Revascularization (TLR)** at 6-, 9-, 12-, 24-, and 36-months post-index procedure. – **Target Vessel Revascularization (TVR)** at 6-, 9-, 12-, 24-, and 36-months post-index procedure. – **Sustained Clinical Success** at 30-days and 9-, 12-, 24-, and 36-months post-index procedure. – **Primary Patency** at 9-, 12-, 24- and 36-months post-index procedure corresponding to PSVR ≤ 2.4. – **Primary Assisted Patency** at 9-, 12-, 24-, and 36-months post-index procedure corresponding to PSVR ≤ 2.4. – **Secondary Patency** at 9-, 12-, 24-, and 36-months post-index procedure corresponding to PSVR ≤ 2.4. – **Quality of Life** at baseline, 30-days and 9-, 12-, 24- and 36-months post-index procedure.
Lead Principal Investigator:	**John Laird, MD** 
Angiographic Core Lab:	
Duplex Ultrasound Core Lab:	

Please refer to Site Contacts List for all Sponsor, Investigator, and Vendor contact information.

Protocol Abbreviations/Acronyms

Abbreviation/Acronym	Definition
ABI	Ankle-Brachial Index
ACT	Activated Clotting Time
ADE	Adverse Device Effect
AE	Adverse Event
ASA	Aspirin
Bard	Bard Peripheral Vascular, Inc.
CBC	Complete Blood Count
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CIA	Common Iliac Artery
CLI	Critical Limb Ischemia
CSA	Clinical Study Agreement
CV	Curriculum Vitae
DFMEA	Design Failure Mode and Effects Analysis
DSMB	Data Safety Monitoring Board
DUS	Duplex Ultrasonography
(e)CRF	(electronic) Case Report Form
EDC	Electronic Data Capture
ePTFE	Expanded Polytetrafluoroethylene
EC	Ethics Committee
EIA	External Iliac Artery
FDA	Food and Drug Administration
HIPAA	The Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions for Use
INR	International Normalized Ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
IV	Intravenous
KM	Kaplan-Meier
LTF	Lost to Follow-up
MAE	Major Adverse Event
MI	Myocardial Infarction
MM	Medical Monitor
NDA	Non-Disclosure Agreement
OUS	Outside of the United States
PAD	Peripheral Arterial Disease
PG	Performance Goal

PI	Principal Investigator
PMA	Pre-Market Approval
PP	Per-Protocol
PSVR	Peak Systolic Velocity Ratio
PTA	Percutaneous Transluminal Angioplasty
RVD	Reference Vessel Diameter
SAE	Serious Adverse Event
SIV	Site Initiation Visit
SSED	Summary of Safety and Effectiveness Data
TASC	TransAtlantic Inter-Society Consensus
TIA	Transient Ischemic Attack
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
UADE	Unanticipated Adverse Device Effect
U.S.	United States
WIQ	Walking Impairment Questionnaire

TABLE OF CONTENTS

1. INTRODUCTION

The BARD® LIFESTREAM™ Balloon Expandable Vascular Covered Stent (BOLSTER) Study is a prospective, multi-center, non-randomized, single-arm clinical study intended to collect confirmatory evidence of the safety and effectiveness of the LIFESTREAM™ Balloon Expandable Vascular Covered Stent ("LIFESTREAM™ Covered Stent") for the treatment of stenoses and occlusions in the iliac arteries. This study will be conducted in conformance with the Declaration of Helsinki, applicable national privacy laws (e.g., Health Insurance Portability and Accountability Act (HIPAA) requirements in the U.S.), applicable Food and Drug Administration (FDA), European and International Organization for Standardization (ISO) regulations (21 Code of Federal Regulations (CFR) Parts 812, 50, 54, 56; ISO 14155:2011(E)).

1.1. Background and Rationale

1.1.1. Peripheral Arterial Disease

Peripheral Arterial Disease (PAD) is an atherosclerotic syndrome that affects approximately 10 Million people in the United States. Approximately 40% of these individuals have common PAD symptoms such as leg pain and claudication. Of patients between age 50 and 69, and more significantly over 70 years of age, with a history of smoking and diabetes, 29% will manifest PAD. The detection rate, today, is less than 20% of all PAD prevalent patients and the mortality and morbidity of patients with PAD is high.[1,2,3]

Approximately 25% of PAD patients suffer from claudication (discomfort, fatigue, numbness, cramping, and/or pain) due to flow limiting stenosis in their iliac, femoral, popliteal or tibial arteries. Usually claudication limits one's ability to perform their normal daily activities because the pain is aggravated by walking. In later stages, blood flow is so reduced that ischemic rest pain, ulceration, and gangrene can occur. This stage is known as critical limb ischemia (CLI) and approximately 5% - 10% of patients with intermittent claudication will progress to CLI. The presence of CLI is a significant risk factor for subsequent cardiovascular complications. By six months, 40% of affected patients will undergo amputation, and 20% will die.[4,5]

1.1.1.1. PAD in Iliac Arteries

The latest update of the Millennium Market Research Report 2011 demonstrates that in 2012, 31% of all interventions in peripheral (lower extremity) arteries are for the treatment of iliac artery occlusive disease.[6]

1.1.2. The Current Standard of Care

Conservative therapy, including medication, walking exercises, smoking cessation and change of diet can be highly effective in compliant patients with symptoms of claudication. Patients with a confirmed flow limiting stenosis often benefit from invasive treatment when conservative therapy fails.

The most recent treatment recommendations according to the TransAtlantic Inter-Society Consensus Work Group suggest endovascular treatment in all TASC A and B lesions and in

TASC C lesions in higher risk surgical candidates. In all patients with TASC B and C lesions, the recommendations state that the patient's co-morbidity, fully informed patient preference and the local operator long-term success rates must be considered.[5]

The guidelines from the European Society of Cardiology state that a primary endovascular approach may also be considered in TASC D lesions in patients with severe comorbidities and the availability of an experienced interventionist.[7]

1.1.3. Endovascular Therapy

Endovascular therapy most often involves the placement of a bare metal stent (balloon expandable or self expanding) as primary therapy for iliac occlusive disease. According to published clinical literature primary patency rates between 70% and 97% at 12 months have been shown with the treatment of iliac artery stenoses and occlusions with metal stents.[8-16]

Over the past several years, the safety and effectiveness of endovascular treatment of patients with extensive TASC C and D disease was evaluated in clinical studies and the long term clinical outcomes were found to be comparable to those historically achieved with surgery.[15-17] Not surprisingly, however, extensive TASC C and D lesions appear to have a slightly lower primary patency at 12 months compared to TASC A and B lesions.[10-12,15,16,18-20]

According to physicians' input and results from early studies, the use of an expanded polytetrafluoroethylene (ePTFE) covered stent in the iliac arteries may have the additional benefit of preventing in-stent restenosis and tissue prolapse through the stent interstices in patients with a highly calcified plaque burden and/or fresh thrombotic material. Furthermore, a covered stent may reduce showering and embolism of plaque particles into the outflow arteries.[21,22]

One published clinical study (single center, retrospective analysis) from Sabri et al. supports a benefit of balloon expandable covered stents over bare metal stents in lesions treated with kissing stents. In this study, covered stents demonstrated a 92% patency rate after two years, compared to 62% with bare stents.[21]

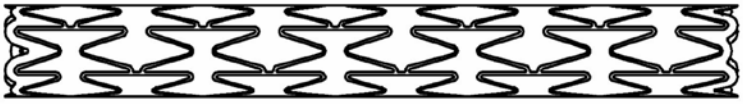
Additionally, a multicenter prospective randomized controlled study by Mwiapatyi et al. suggests that aortoiliac lesions treated with a covered stent were significantly more likely to remain free from binary restenosis than those that were treated with a bare metal stent. Subgroup analyses demonstrated a significant difference in freedom from binary restenosis for covered stents in TASC C and D lesions compared with bare stents.[22]

This study will provide clinical evidence to demonstrate reasonable assurance of safety and effectiveness of the LIFESTREAM™ Covered Stent. At the initiation of this protocol, no other clinical studies or clinical data are available for the LIFESTREAM™ Covered Stent.

1.2. Device Description

The LIFESTREAM™ Covered Stent is comprised of an electropolished stainless steel balloon-expandable stent, encapsulated by two layers of ePTFE. The implant will be pre-mounted on a balloon delivery system (see Figure 1).

Figure 1: LIFESTREAM™ Balloon Expandable Vascular Covered Stent



The LIFESTREAM™ Covered Stent is intended to treat atherosclerotic lesions found in the iliac arteries. The proposed size range offering is included in Table 1.

Table 1: LIFESTREAM™ Covered Stent Size Matrix

Balloon Diameter (mm)	Reference Implant Length (mm)			
5	16	26	37	
6	16	26	37	58
7	16	26	37	58
8	16	26	37	58
9			38	58
10			38	58
12			38	58

2. STUDY DESIGN

This is a prospective, multi-center, non-randomized, single-arm clinical study of the LIFESTREAM™ Covered Stent for the treatment of stenoses and occlusions in the common and/or external iliac arteries. A composite safety and effectiveness measure of subjects receiving the LIFESTREAM™ Covered Stent will be compared to a Performance Goal (PG) derived from iliac stent published literature (See Section 3.1).

The study will be conducted at a maximum of 35 active investigational sites ("sites") in the United States, Europe, and Australia/New Zealand. Enrollment will continue until one-hundred fifty-four (154) subjects are treated with the LIFESTREAM™ Covered Stent, which is an estimated three-hundred eight (308) consecutive subjects in a non-randomized fashion (See Section 5.2.2). Approximately 30-50% of the treated subjects will be U.S. subjects. An interim analysis will be conducted when one hundred three (103) subjects are followed for 9 months.

Clinical follow-up for all treated subjects will be performed at hospital discharge, 30-days, and 9-, 12-, 24-, and 36-months post-index procedure. A telephone screen for all treated subjects will be performed at 6-months post-index procedure.

3. STUDY ENDPOINTS

Reference Section 6 for Statistical Overview.

3.1. Primary Endpoint with Hypothesis Testing

The primary endpoint of the study is a composite safety and effectiveness measure defined as device and/or procedure-related death or myocardial infarction (MI) through 30 days, or any Target Lesion Revascularization (TLR), target limb(s) major amputation, or restenosis through 9-months post-index procedure.

Device and/or procedure-related death, MI, and target limb(s) major amputation will be adjudicated by a Clinical Events Committee (CEC). TLR is defined as the first revascularization procedure (e.g., PTA, atherectomy, etc.) of the target lesion(s) following the index procedure as determined by an Independent Angiographic Core Lab (or CEC, as necessary). Restenosis will be assessed by duplex ultrasonography (DUS), where the target lesion(s) is determined to have a peak systolic velocity ratio (PSVR) > 2.4 with post-stenotic turbulence, as determined by an Independent DUS Core Lab. In this study, a PSVR of > 2.4 suggests > 50% restenosis.

The primary endpoint will be evaluated against a PG of 19.5%, which was derived from iliac stent published literature (See Section 6).

3.2. Secondary Endpoints

The following secondary endpoints will be evaluated to provide further information related to the safety and effectiveness of the LIFESTREAM™ Covered Stent.

- The rate of **Major Adverse Events (MAEs)** defined as device and/or procedure-related death or MI through 30 days, or any TLR or target limb(s) major amputation through 9-months post-index procedure. Major amputation is defined as an amputation at or above the ankle. TLR will be verified by an Independent Angiographic Core Lab. All other MAEs will be verified by a CEC.

- **Acute Lesion Success** defined as attainment of < 30% residual stenosis of the target lesion after the index procedure using any percutaneous method and/or non-investigational device (i.e., post-dilatation), as determined by an Independent Angiographic Core Lab.

- **Acute Procedure Success** defined as lesion success and no peri-procedural complications (death, stroke, myocardial infarction (MI), emergent surgical revascularization, significant distal embolization in target limb, and thrombosis of target vessel) prior to hospital discharge. Lesion success is determined by an Independent Angiographic Core Lab and complications are adjudicated by a CEC.

- **Acute Technical Success** defined as successful deployment of the LIFESTREAM™ Covered Stent at the intended location, as determined by the Investigator.

- **Target Lesion Revascularization (TLR)** at 6-, 9-, 12-, 24-, and 36-months post-index procedure. TLR is defined as the first revascularization procedure (e.g., PTA, atherectomy, etc.) of the target lesion(s) following the index procedure, as determined by an Independent Angiographic Core Lab.

- **Target Vessel Revascularization (TVR)** at 6-, 9-, 12-, 24-, and 36-months post-index procedure. TVR is defined as the first revascularization procedure (e.g. PTA, stenting, surgical bypass, etc.) in the target vessel(s) following the index procedure, as determined by an Independent Angiographic Core Lab.

- **Sustained Clinical Success** defined as sustained cumulative improvement from baseline value of ≥ 1 Rutherford Category[23] at 30-days and 9-, 12-, 24-, and 36-months post-index procedure, as determined by the Investigator.

- **Primary Patency** at 9-, 12-, 24- and 36-months post-index procedure corresponding to PSVR ≤ 2.4. Primary Patency will be assessed by DUS, where the target lesion(s) is determined to be no longer patent at a PSVR > 2.4 with post-stenotic turbulence, as determined by an Independent DUS Core Lab. TLR is also considered a loss of primary patency.

- **Primary Assisted Patency** at 9-, 12-, 24-, and 36-months post-index procedure corresponding to PSVR ≤ 2.4, as determined by an Independent DUS Core Lab. Primary Assisted Patency is independent of whether or not patency is re-established via an endovascular procedure following restenosis.

- **Secondary Patency** at 9-, 12-, 24-, and 36-months post-index procedure corresponding to PSVR ≤ 2.4, as determined by an Independent DUS Core Lab. Secondary Patency is independent of whether or not patency is re-established via an endovascular procedure following restenosis or occlusion.

- **Quality of Life** as assessed by a Walking Impairment Questionnaire (WIQ) at baseline, 30-days and 9-, 12-, 24- and 36-months post-index procedure.

4. STUDY POPULATION

4.1. Subject Selection

Subjects will be males or non-pregnant females, at least 21 years of age, with an expected lifespan sufficient to allow for completion of all study procedures. Eligible subjects will have intermittent claudication or ischemic rest pain and angiographic confirmation of either de novo or restenotic (non-stented) lesion(s) ≥ 50% in the common and/or external iliac arteries.

4.2. Number of Subjects

Enrollment will continue until 154 subjects are treated with the LIFESTREAM™ Covered Stent, which is an estimated 308 consecutive subjects in a non-randomized fashion (See Section 5.2.2).

No more than 31 (~20%) treated subjects may be enrolled at any site. Each site is anticipated to enroll a minimum of 3 treated subjects; sites with fewer than 10 treated subjects will be pooled for analysis (see Section 6.3). It is anticipated that the required 154 treated subjects will be enrolled over a 12-month timeframe.

4.3. Eligibility Criteria

4.3.1. Inclusion Criteria

A subject must meet the following criteria to be enrolled and considered a treated subject in the study:

Clinical Inclusion Criteria

1. The subject provides written informed consent using an Informed Consent Form (ICF) that is reviewed and approved by the Ethics Committee (EC) / Institutional Review Board (IRB) for the site.

2. Subject agrees to comply with the protocol-mandated follow-up procedures and visits.

3. The subject is a male or non-pregnant female ≥ 21 years old with an expected lifespan sufficient to allow for completion of all study procedures. Female subjects of childbearing potential must have a negative pregnancy test (urine or blood) within 14 days prior to the index procedure.

4. The subject has intermittent claudication (Rutherford Category[23] 2-3) or ischemic rest pain (Rutherford Category 4).

5. The subject is able and willing to comply with any required medication regimen.

Angiographic Inclusion Criteria

6. The subject has evidence of single, bilateral, or multiple de novo and/or restenotic (non-stented) lesion(s) in the native common and/or external iliac artery that is (are) ≥ 50% stenosed (including total occlusions) as determined by the Investigator's visual estimate.

7. The target lesion(s) can be successfully crossed with a guide wire and pre-dilated with an appropriately sized PTA balloon. Devices such as chronic total occlusion (CTO) catheters or re-entry devices may be used to facilitate target lesion(s) crossing.

8. The reference vessel diameter(s) is (are) between 4.5 mm and 12.0 mm in diameter as determined by the Investigator's visual estimate.

9. The target lesion(s) is (are) ≤ 100 mm in combined length (per side) by visual estimate.

10. The subject has angiographic evidence of a patent (< 50% stenosis) profunda and/or superficial femoral artery (SFA) in the target limb(s) as determined by the Investigator's visual estimate.

    Ipsilateral and contralateral SFA lesions may be treated before or after target lesion treatment, considering the following criteria are met:
    - ≥ 50% stenosis
    - Stenosis(es) ≤ 15cm in total length or a Total Occlusion ≤ 5cm in length
    - ≥ 1 vessel run-off
    - No thrombus or severe calcification
    - Use of on-label devices

    Contralateral iliac lesions (not meeting study eligibility criteria) may be treated at the discretion of the investigator with on-label (non-investigational) devices at the time of the index procedure. Other planned interventions must take place 30 days before the index procedure or after 30 days post-index procedure.

4.3.2. Exclusion Criteria

A subject must be excluded if any of the following criteria are met:

Clinical Exclusion Criteria

1. The subject is unable or unwilling to provide written informed consent, or is unable or unwilling to conform to the study protocol follow-up procedures and visits.

2. The subject is or plans to become pregnant during the study.

3. The subject is asymptomatic, has mild claudication or critical limb ischemia with tissue loss described as Rutherford Category[23] 0 (asymptomatic), 1 (mild claudication), 5 (minor tissue loss), or 6 (major tissue loss).

4. The subject has a vascular graft previously implanted in the native iliac vessel.

5. The subject suffered a hemorrhagic stroke or transient ischemic attack (TIA) within 3 months prior to the index procedure.

6. The subject has a known uncorrectable bleeding diathesis or active coagulopathy (platelet count < 80,000/μL).

7. The subject has a serum creatinine ≥ 2.5 mg/dl or is currently on dialysis.

8. The subject has a known allergy or sensitivity to stainless steel (i.e., Nickel), ePTFE, or has intolerance to the antiplatelet, anticoagulant or thrombolytic medications required per the protocol.

9. The subject has a known allergy or sensitivity to contrast media, which cannot be adequately pre-medicated.

10. The subject had a prior vascular intervention(s) within 30 days before, or has an intervention planned for within 30 days after the index procedure. Refer to inclusion criterion #10 for exceptions on SFA lesions and contralateral iliac lesions.

11. The subject has another medical condition, which, in the opinion of the Investigator, may cause him/her to be non-compliant with the protocol, confound the data interpretation, or is associated with a life expectancy insufficient to allow for the completion of study procedures and follow-up.

12. The subject is currently participating in an investigational drug, biologic, or another device study. Studies requiring extended follow-up for products that are now commercially available are not considered investigational studies.

Angiographic Exclusion Criteria

13. The subject has extensive peripheral vascular disease, which in the opinion of the Investigator, would preclude safe insertion of an introducer sheath. The ipsilateral common femoral artery should be patent (< 50% stenosis) by the Investigator's visual estimate.

14. The target lesion(s) requires treatment other than angioplasty (e.g., atherectomy, cryoplasty, cutting/scoring balloons, etc.) to facilitate subject device delivery. Devices such as CTO catheters or re-entry devices may be used to facilitate target lesion(s) crossing.

15. The subject has severe calcification of the target lesion(s), which prevents inflation of a PTA balloon (pre-dilatation of the target lesion is required).

16. The target lesion(s) has been previously treated with a stent (bare or covered). A target vessel(s) with a previously placed stent is permitted as long as the subject device(s) will not come into contact with the previously placed stent during treatment of the target lesion(s).

17. The subject has angiographic evidence of acute thrombus at the target lesion(s).

18. The target lesion(s) involves the origin of the internal iliac artery such that successful treatment of the lesion(s) would require the subject device(s) to cross/occlude the side branch. Note, if the internal iliac artery is already occluded, the subject device(s) can be placed across the occluded vessel.

19. The target lesion(s) is (are) located in the distal external iliac artery such that successful treatment of the lesion(s) would require the subject device(s) to cross/occlude side branches (inferior epigastric artery and/or deep circumflex iliac artery) or be exposed to compressive forces associated with the close proximity to the common femoral artery. Note, if the side branch(es) is (are) already occluded, the subject device(s) can be placed across the occluded vessel(s) as long as the device is above the inguinal ligament.

20. The subject has an abdominal aortic aneurysm (AAA) contiguous to the iliac artery target lesion(s). The presence of AAA grafts and/or endografts are not permitted.

21. The subject has a pre-existing target iliac artery aneurysm or perforation or dissection of the target iliac artery prior to the initiation of the treatment for this study.

5. STUDY PROCEDURES

Prior to the conduct of any study procedures, the subject must voluntarily provide consent and comply with applicable national and state privacy laws (e.g., HIPAA requirements in the U.S.). All study procedures will be documented in the medical record and/or source document and on study electronic case report forms (eCRFs).

See Appendix 1 for the Time and Events Schedule of study procedures.

5.1. Subject Screening and Baseline Evaluation

During the screening, the investigator (or authorized designee) will be responsible for describing the nature of the study, verifying that the eligibility criteria have been met, and obtaining informed consent. Prior to the conduct of any study procedures, the subject must voluntarily provide consent and comply with applicable national and state privacy laws (e.g., HIPAA requirements in the U.S.). All study procedures will be documented in the medical record and/or source document and on study eCRFs.

The following specific procedures will be conducted and documented:

5.1.1. Informed Consent

All subjects will provide written informed consent for the study prior to collection of study data or performance of study-related procedures (See Section 11.4). The ICF templates are stand-alone documents to facilitate revision(s), as necessary, without requiring a protocol amendment. Documentation of the Informed Consent process must be present in the medical record and/or source document.

5.1.2. Eligibility

The subject's eligibility for study enrollment will be reviewed and documented, and a related progress note should indicate that the subject met all study (eligibility) criteria at the time of screening and enrollment.

5.1.3. Demographics and Medical History

The subject's demographic information will be obtained, including:
- Date of Birth (minimum year of birth)
- Sex
- Cardiovascular History

- History of risk factors
- Previous interventions (e.g., interventional and/or surgical; coronary and/or peripheral)

5.1.4. Baseline Examinations

Each subject will have the following baseline examinations performed prior to the index procedure:

- Review of concomitant medications (antiplatelets, anticoagulants, direct thrombin inhibitors, and factor Xa inhibitors) taken within 72 hours prior to index procedure
- Comprehensive physical examination of the subject's overall health status conducted within 30 days prior to index procedure, including Height and Weight
- Urine or blood pregnancy test for women of childbearing potential within 14 days prior to index procedure (to confirm eligibility criteria only)
- Laboratory testing including Blood Urea Nitrogen (BUN) or Creatinine and Complete Blood Count (CBC), including Platelets, within 30 days prior to index procedure (to confirm eligibility criteria only)
- Comprehensive physical examination of the subject's vascular status conducted within 30 days prior to index procedure, including:
    - Resting bilateral ABIs
    - Target Limb Assessment
    - Rutherford Category & Grade Assignment
- Quality of Life Assessment
    - WIQ to be completed within 30 days prior to index procedure

5.1.5. Clinical Evaluations

Please refer to the site regulatory binder for detailed information on the standard guidelines/instructions for clinical evaluations such as ABI, DUS, and completion of the WIQ.

5.1.6. Procedural Medications

During the index procedure, it is recommended that subjects receive intravenous (IV) heparin or bivalirudin, as per the institutional standard of care. If the subject is not currently taking clopidogrel, a loading dose of 300 mg – 600 mg (oral) should be administered at the time of the index procedure, or immediately following successful intervention. Ticlopidine may be administered if the subject has an allergy or contraindication to clopidogrel. Clopidogrel is not required if a subject is taking warfarin, prasugrel, ticagrelor, and/or approved direct thrombin inhibitors (e.g., dabigatran) or factor Xa inhibitors (e.g., rivaroxaban, apixaban). The total amount of heparin (bivalirudin) or clopidogrel (ticlopidine) that is administered during the index procedure should be documented.

If the subject is diabetic, it should be documented whether the subject is on insulin, oral agents, or a dietary regiment for treatment.

5.1.7. Diagnostic Angiogram

Prior to any study intervention, subjects meeting the clinical eligibility criteria for the study will undergo diagnostic angiography to better characterize the degree of atherosclerosis and ensure that the subject meets all angiographic inclusion and exclusion criteria.

Access should be gained per the institution's standard technique. The procedure begins at the time that arterial access is obtained.

All angiography shall be performed using the identical angles, magnification and angiographic technique as described in the "Angiography Guidelines" supplied by the Angiographic Core Lab. **It is important to use the specified calibrated measurement catheter so that the Angiographic Core Lab may properly assess the target lesion characteristics** (e.g., reference vessel diameter, lesion diameter and length). **Properly labeled angiographic-recorded media are to be uploaded or sent to the Angiographic Core Lab for evaluation.**

5.2. Index Procedure

Preparation should be conducted adhering to the site's standard of care for procedures and monitoring, including the use of standard sterile operative techniques.

5.2.1. Target Lesion(s) PTA

All subjects will undergo conventional PTA pre-dilatation at the target lesion site(s) previously identified by angiography. Prior to PTA, the Investigator shall identify (by visual estimation) the beginning and end of each target lesion(s). The target lesion(s) should have a combined (single or multiple lesions) **lesion length of less than or equal to 100 mm per side** (unilateral or bilateral disease). PTA shall be limited to predetermined treatment segment(s).

It is required that angiographic image(s) of the inflated PTA balloon be captured.
Choice of specific balloon catheters and inflation pressure should be determined by the Investigator based on his/her standard of care practices, and should be recorded. It is **not** acceptable for the Investigator to use additional commercially-approved treatment modalities (e.g., atherectomy, cryotherapy, cutting/scoring balloon) during the study procedure. Subjects who require treatment with any of these alternative modalities should not be enrolled in the study. It is acceptable for the Investigator to use CTO catheters or re-entry devices to facilitate target lesion(s) crossing.

In certain instances, a dissection may occur following PTA of the target lesion(s).

Target Lesion including Dissection: Less than or equal to 100 mm

- If a flow-limiting dissection occurs, and extends beyond the target lesion(s), but the total length of the target lesion(s) plus the dissected segment is less than or equal to 100 mm in length, the LIFESTREAM™ Covered Stent(s) may be used to properly treat the dissected segment.

Target Lesion including Dissection: Greater than 100 mm

- If the total length of the target lesion(s) plus the dissected segment extends greater than 100 mm, the Investigator should **not** place the LIFESTREAM™ Covered Stent(s) to treat the dissected segment. The Investigator should use standard of care practices to treat the dissected segment. As the study device will **not** be introduced, these subjects requiring treatment of dissected segments extending greater than 100 mm will be treated as an intra-procedure screen failure and will not be included in the ITT analysis.

Dissection including the internal iliac (hypogastric) artery or other important collaterals

- If a dissection occurs at the origin of the hypogastric artery (or other important collateral), the Investigator should **not** place the LIFESTREAM™ Covered Stent(s) to treat the dissected segment. The Investigator should use standard of care practices to treat the dissected segment, which may include placing an approved iliac bare metal stent in order to treat the dissection without occluding the hypogastric (or collateral) artery. As the study device will **not** be introduced, these subjects will be treated as an intra-procedure screen failure and will not be included in the ITT analysis. However, if the hypogastric (or collateral) artery is already occluded and the lesion (including dissection) is less than or equal to 100 mm in length, the LIFESTREAM™ Covered Stent(s) may be used to properly treat the dissected segment as long as the device is above the inguinal ligament.

5.2.2. Enrollment

Enrollment

A subject is considered enrolled in the study once he/she has agreed to study participation and has provided consent (an estimated 308 subjects assuming a 50% screen failure rate). Subjects who fail to meet eligibility criteria should be treated according to the Investigator's standard of care practices. Such subjects' study participation will end at the time of eligibility failure.

Treated Subject

After the subject has met all eligibility criteria, undergone successful PTA of the target lesion(s), and the LIFESTREAM™ Covered Stent catheter is introduced (i.e., delivery system enters the subject's body), the subject will be considered to be a treated subject in the study. Treated subjects will continue study participation through the study's 36-month follow-up period. Subjects that do not receive the LIFESTREAM™ Covered Stent implant (but the LIFESTREAM™ Covered Stent catheter was introduced) will be followed through the 30-day follow-up visit to assess any safety events and will be included in the ITT and PP analyses (see Section 6).

5.2.3. Placement of the LIFESTREAM™ Covered Stent

The use of up to two (2) LIFESTREAM™ Covered Stents (placed in an overlapping fashion) is acceptable in this study (per side in bilateral disease). The recommended overlap distance between the two (2) LIFESTREAM™ Covered Stents is approximately 10 mm.

In the case of a geographic miss (or dissection) which necessitates placement of more than two (2) LIFESTREAM™ Covered Stents, one more LIFESTREAM™ Covered Stent may be placed (three total subject devices). However, if a dissection extends down to or includes the internal iliac artery, standard of care should be applied, including the placement of a commercially-available stent, which does not include the LIFESTREAM™ Covered Stent (unless the internal iliac was already occluded). In this case, the subject will be included in the ITT analysis.

Kissing stents may be placed at CIA ostial lesions. In the case of unilateral ostial disease, a LIFESTREAM™ Covered Stent may be placed in the healthy contralateral vessel (i.e., bilateral treatment using kissing stents), as this is standard of care when placing covered stents. In such a case, the healthy vessel would also become a treatment vessel (i.e., unilateral disease, but bilateral treatment due to ostial disease). No crossover procedures are allowed for treatment of outflow disease once kissing stents are placed.

It is required that a pre-deployment angiographic image(s) of the LIFESTREAM™ Covered Stent(s) be captured.

It is required that angiographic image(s) of the fully-inflated LIFESTREAM™ Covered Stent balloon(s) be captured.

It is required that a post-deployment angiographic image(s) of the LIFESTREAM™ Covered Stent(s) be captured.

Post-dilatation of each LIFESTREAM™ Covered Stent can be performed to ensure proper expansion of the LIFESTREAM™ Covered Stent. If post-dilated, the Investigator should select a balloon size of the same approximate diameter as the native vessel. **Balloon dilation of the healthy vessel beyond the proximal or distal edges of the LIFESTREAM™ Covered Stent should be avoided.**

If post-dilated, it is required that the post-dilatation angiographic image(s) of the LIFESTREAM™ Covered Stent be captured.

All angiography shall be performed using the identical angles, magnification and angiographic technique as described in the "Angiography Guidelines" supplied by the Angiographic Core Lab.

5.2.4. Intra-Procedure – Other Treatment Modalities

If the entirety of the lesion(s) cannot be treated to an angiographically acceptable result, consideration should be given to other medically-appropriate treatment modalities, in each case, as dictated by clinical circumstances, institutional standard of care, and Investigator preference. All subjects that receive a LIFESTREAM™ Covered Stent and undergo other treatment modalities will be followed per protocol specifications, will be documented, and included in the ITT analysis. If a subject is converted to bypass surgery and the LIFESTREAM™ Covered Stent is explanted, then the subject will be followed through the 30-day follow-up visit to assess any safety events and will also be included in the ITT. An emergent intervention of any kind is allowed at any time at the discretion of the Investigator, and should be documented in the medical record/source documents.

5.2.5. Final Angiogram

Completion angiography of the distal infrapopliteal vessels should be performed to rule-out the possibility of distal embolization. **Properly-labeled angiographic-recorded media are to be uploaded or sent to the Angiographic Core Lab for evaluation.**

5.2.6. Guide Catheter/Sheath Removal Guidelines

Immediately following the procedure, in accordance with the institution's standard of care practices, heparin should be discontinued. An on-label vascular closure device may be used at the discretion of the Investigator, in accordance with the manufacturer's directions. The index procedure ends at the time that the last guidewire is removed.

5.2.7. Post-Procedure Medications

Treated subjects are to receive a minimum of 75 mg of ASA orally per day for a minimum of 6 months, and a minimum of 75 mg of clopidogrel orally per day for a minimum of 3 months. Subjects should be excluded if they have an allergy to aspirin at baseline. Ticlopidine may be prescribed if the subject has an allergy or contraindication to Clopidogrel. Clopidogrel is not required if a subject is taking warfarin, prasugrel, ticagrelor, and/or approved direct thrombin inhibitors (e.g., dabigatran) or factor Xa inhibitors (e.g., rivaroxaban, apixaban); however the subject should receive a minimum of 75 mg of ASA orally per day for a minimum of 6 months. Investigators may elect to use additional anticoagulants, for example, low molecular weight heparin as they deem medically appropriate. If the treated subject requires subsequent surgery that necessitates the discontinuation of these medications, then the subject is to resume protocol required medications as soon as possible after the medical procedure.

5.3. Hospital Discharge Procedures

Prior to hospital discharge, each treated subject should have the following examinations/assessments performed:

- Comprehensive physical examination of the subject's overall health status, including:
  - Target Limb Assessment
  - Concomitant Medication(s): antiplatelets, anticoagulants, direct thrombin inhibitors, and factor Xa inhibitors (e.g., ASA, clopidogrel, ticlopidine, prasugrel, ticagrelor, warfarin, dabigatran, rivaroxaban, apixaban)
- Documentation of occurrence of Adverse Events (AEs) or serious adverse events (SAEs) since index procedure.

5.4. Subject Follow-Up

All treated subjects who receive a LIFESTREAM™ Covered Stent will be followed at 30-days and 6-, 9-, 12-, 24-, and 36-months post-index procedure.

5.4.1. 30-Day Follow-Up Visit (30 Days ± 7 Days)

- Comprehensive physical examination of the subject's overall health status, including:
  - Target Limb Assessment
  - Concomitant Medication(s): antiplatelets, anticoagulants, direct thrombin inhibitors, and factor Xa inhibitors (e.g., ASA, clopidogrel, ticlopidine, prasugrel, ticagrelor, warfarin, dabigatran, rivaroxaban, apixaban)
- Comprehensive physical examination of the subject's vascular status, including:
  - Resting bilateral ABIs
  - DUS of Target Limb employing "Ultrasound Guidelines"
    - DUS images shall be uploaded or sent to the Ultrasound Core Laboratory for evaluation.
  - Rutherford Category & Grade Assignment
- Documentation of occurrence of AEs or SAEs since discharge.
- Documentation of occurrence of TLR/TVR since discharge. If TLR/TVR was performed, properly labeled angiographic-recorded media shall be uploaded or sent to the Angiographic Core Laboratory for evaluation.
- Quality of Life Assessment (WIQ)

5.4.2. 6-Month Telephone Screening (180 Days ± 30 Days)

- Documentation of Concomitant Medication(s): antiplatelets, anticoagulants, direct thrombin inhibitors, and factor Xa inhibitors (e.g., ASA, clopidogrel, ticlopidine, prasugrel, ticagrelor, warfarin, dabigatran, rivaroxaban, apixaban)
- Documentation of occurrence of AEs or SAEs since last visit.
- Documentation of occurrence of TLR/TVR since last visit. If TLR/TVR was performed, properly labeled angiographic-recorded media shall be uploaded or sent to the Angiographic Core Laboratory for evaluation.

  Note, this information may also be collected at an office visit (instead of a telephone screen), as long as the visit occurs within the above mentioned follow-up window.

5.4.3. 9-Month Follow-Up Visit (270 Days ± 30 Days)

- Comprehensive physical examination of the subject's overall health status, including:
  - Target Limb Assessment
  - Concomitant Medication(s): antiplatelets, anticoagulants, direct thrombin inhibitors, and factor Xa inhibitors (e.g., ASA, clopidogrel, ticlopidine, prasugrel, ticagrelor, warfarin, dabigatran, rivaroxaban, apixaban)
- Comprehensive physical examination of the subject's vascular status, including:
  - Resting bilateral ABIs
  - DUS of Target Limb employing "Ultrasound Guidelines"
    - DUS images shall be uploaded or sent to the Ultrasound Core Laboratory for evaluation.
  - Rutherford Category & Grade Assignment
- Documentation of occurrence of AEs or SAEs since last visit.

- Documentation of occurrence of TLR/TVR since last visit. If TLR/TVR was performed, properly labeled angiographic-recorded media shall be uploaded or sent to the Angiographic Core Laboratory for evaluation.
- Quality of Life Assessment (WIQ)

5.4.4. 12-Month (1 Year) Follow-Up Visit (365 Days ± 30 Days)

- Comprehensive physical examination of the subject's overall health status, including:
    - Target Limb Assessment
    - Concomitant Medication(s): antiplatelets, anticoagulants, direct thrombin inhibitors, and factor Xa inhibitors (e.g., ASA, clopidogrel, ticlopidine, prasugrel, ticagrelor, warfarin, dabigatran, rivaroxaban, apixaban)
- Comprehensive physical examination of the subject's vascular status, including:
    - Resting bilateral ABIs
    - DUS of Target Limb employing "Ultrasound Guidelines"
        - DUS images shall be uploaded or sent to the Ultrasound Core Laboratory for evaluation.
    - Rutherford Category & Grade Assignment
- Documentation of occurrence of AEs or SAEs since last visit.
- Documentation of occurrence of TLR/TVR since last visit. If TLR/TVR was performed, properly-labeled, angiographic-recorded media shall be uploaded or sent to the Angiographic Core Laboratory for evaluation.
- Quality of Life Assessment (WIQ)

5.4.5. 24-Month (2 Year) Follow-Up Visit (730 Days ± 30 Days)

- Comprehensive physical examination of the subject's overall health status, including:
    - Target Limb Assessment
    - Concomitant Medication(s): antiplatelets, anticoagulants, direct thrombin inhibitors, and factor Xa inhibitors (e.g., ASA, clopidogrel, ticlopidine, prasugrel, ticagrelor, warfarin, dabigatran, rivaroxaban, apixaban)
- Comprehensive physical examination of the subject's vascular status, including:
    - Resting bilateral ABIs
    - DUS of Target Limb employing "Ultrasound Guidelines"
        - DUS images shall be uploaded or sent to the Ultrasound Core Laboratory for evaluation.
    - Rutherford Category & Grade Assignment
- Documentation of occurrence of AEs or SAEs since last visit.
- Documentation of occurrence of TLR/TVR since last visit. If TLR/TVR was performed, properly-labeled, angiographic-recorded media shall be uploaded or sent to the Angiographic Core Laboratory for evaluation.
- Quality of Life Assessment (WIQ)

5.4.6. 36-Month (3 Year) Follow-Up Visit (1095 Days ± 30 Days)

- Comprehensive physical examination of the subject's overall health status, including:

  - Target Limb Assessment
  - Concomitant Medication(s): antiplatelets, anticoagulants, direct thrombin inhibitors, and factor Xa inhibitors (e.g., ASA, clopidogrel, ticlopidine, prasugrel, ticagrelor, warfarin, dabigatran, rivaroxaban, apixaban)
- Comprehensive physical examination of the subject's vascular status, including:
  - Resting bilateral ABIs
  - DUS of Target Limb employing "Ultrasound Guidelines"
    - DUS images shall be uploaded or sent to the Ultrasound Core Laboratory for evaluation.
  - Rutherford Category & Grade Assignment
- Documentation of occurrence of AEs or SAEs since last visit.
- Documentation of occurrence of TLR/TVR since last visit. If TLR/TVR was performed, properly-labeled, angiographic-recorded media shall be uploaded or sent to the Angiographic Core Laboratory for evaluation.
- Quality of Life Assessment (WIQ)

5.5. Subject Discontinuation

The follow-up period for this study is 36 months (1095 Days ± 30 Days). Subjects may be discontinued for the following reasons:

- Lost to Follow-Up (LTF): A subject may be considered LTF if the site personnel are unable to locate the subject despite two documented attempts to notify the subject via telephone and a third attempt by certified mail. Before the site considers a subject LTF, written agreement should be obtained from Bard.
- Withdrawn Consent: The subject requests to terminate his/her participation in the study (the Investigator, or authorized designee, must attempt to identify and document the reasons for termination).
- Death: The subject becomes deceased. If known, the cause of death should be documented.
- Withdrawal by Investigator: Participation may be immediately terminated by the Investigator if, in the opinion of the Investigator, the subject would be exposed to inappropriate risk by continuing in the study. Additionally, the Investigator may terminate a subject's participation with prior written approval from Bard if the subject is repeatedly noncompliant with study procedures.
- Study Termination: The study is terminated by Bard. (See Section 16)

Additional subjects will not be enrolled to replace those who withdraw from the study.

6. STATISTICAL ANALYSIS PLAN

6.1. Analysis Populations

The ITT population consists of those subjects who have signed the Informed Consent Form and had the LIFESTREAM™ Covered Stent catheter introduced (i.e., delivery system enters the subject's body).

Subjects who do not receive the study implant (section 5.2.2), but the LIFESTREAM™ Covered Stent catheter was introduced will be included in the ITT population. Subjects who need more than two (2) LIFESTREAM™ Covered Stents (section 5.2.3) or undergo other treatment modalities (section 5.2.4) will be included in the ITT population.

A per-protocol (PP) population may be created if there are subjects who have any major protocol deviations. Major Protocol Deviations are defined as those that occur to protect the life or physical well-being of a subject in an emergency, or those that may affect the scientific soundness of the study, or the rights, safety or welfare of human subjects. The PP population will consist of any subjects in the ITT population who do not have any major protocol deviations, including deviations of study eligibility criteria. Subjects who do not receive the study implant (section 5.2.2), but the LIFESTREAM™ Covered Stent catheter was introduced will be included in the PP population. Subjects who need more than two (2) LIFESTREAM™ Covered Stents and require placement of a commercially-available stent (section 5.2.3), or undergo other treatment modalities (section 5.2.4) will be excluded from the PP population.

All effectiveness and safety analyses including the primary analysis will be primarily based on the ITT population. A PP analysis may also be performed for the primary endpoint. It will only serve as a sensitivity analysis for the primary analysis which is based on the ITT population.

6.2. Primary Endpoint: Study Hypothesis

The primary endpoint of the study is a composite safety and effectiveness measure defined as device and/or procedure-related death or MI through 30 days or any TLR, target limb(s) major amputation, or restenosis through 9 months post-index procedure.

The BOLSTER study is a single-arm study of treated subjects receiving the LIFESTREAM™ Covered Stent compared to a PG derived from published literature of stents for the treatment of iliac artery stenosis/occlusion. Specifically, the PG rate was derived as 19.5%.

The primary endpoint will be evaluated by the following hypothesis:

H_0: The proportion of subjects in the LIFESTREAM™ Covered Stent group (P_{BBX}) with events in the primary endpoint is greater than or equal to that of the PG of 19.5%.

H_1: The proportion of subjects in the LIFESTREAM™ Covered Stent group (P_{BBX}) with events in the primary endpoint is less than that of the PG of 19.5%.

$$\mathbf{H_0: P_{BBX} \geq 19.5\% \quad vs. \quad H_1: P_{BBX} < 19.5\%}$$

A one-sided p-value will be derived based on an exact binomial test. The study device will be considered to have achieved the primary objective if the one-sided p-value is less than0.0335 at interim analysis or 0.0325 at final analysis (see section 6.8).

6.3. Assessment of Poolability of Sites

The sites will be tested for potential differences in the primary endpoint. Sites with fewer than 10 treated subjects will be combined for this purpose. The pooling will be restricted within country. The sites with less than 10 treated subjects will be sorted by site number within each country and pooled by order to form one or more combined site(s) with at least 10 treated subjects. A logistic regression analysis will be performed with sites as a fixed effect. If the p-value associated with the sites effect is < 0.15, it will be considered as evidence of statistical significance.

If there are any site effects, the sites that have similar and dissimilar results will be grouped and exploratory analyses will be performed to investigate the potential reason for the differences among sites.

An analysis will be performed to examine the potential difference in the primary endpoint between the two geographic regions (US vs. OUS). A logistic regression model will be fit that includes fixed effect for geography. If the p-value of the geography effect is <0.15, it will be considered evidence of a statistically significant difference between the geographic regions, and additional analyses will be performed to explore the differences between geographies to assess their potential causes and whether or not they are clinically meaningful.

Additionally, an analysis will be performed to explore the potential difference in the primary endpoint between males and females. If the p-value of the gender effect is <0.15, it will be considered evidence of a statistically significant difference between the males and females.

6.4. Evaluation of Secondary Endpoints

The following secondary endpoints are intended to be reported in the device's labeling and will be summarized using descriptive statistics. Kaplan-Meier survival analysis of the time to events will also be performed. The details of the definition of the secondary endpoints are described in Section 3.2.

- MAE
- Acute Lesion Success
- Acute Procedure Success
- Acute Technical Success
- TLR at 6-, 9-, 12-, 24-, and 36-months post-index procedure
- TVR at 6-, 9-, 12-, 24-, and 36-months post-index procedure
- Sustained Clinical Success at 30-days and 9-, 12-, 24-, and 36-months post-index procedure.
- Primary Patency at 9-, 12-, 24- and 36-months post-index procedure

- Primary Assisted Patency at 9-, 12-, 24-, and 36-months post-index procedure
- Secondary Patency at 9-, 12-, 24-, and 36-months post-index procedure
- Quality of Life at baseline, 30-days, and 9-, 12-, 24- and 36-months post-index procedure.

6.5. Exploratory Analyses

The primary endpoint and Primary Patency secondary endpoint will be explored in the following subgroups:

- Common iliac artery vs. external iliac artery
- Stenosis vs. occlusion
- TASC categories
- Unilateral vs. bilateral disease
- Gender

This information is intended to be reported in the device's labeling and will be summarized using descriptive statistics.

6.6. Handling of Missing Data

Study endpoints may be missing due to withdrawal of consent, investigator's decision, lost to follow-up and death. As long as the missing data is unrelated to the study intervention and the observed and unobserved data, limiting the analysis to those subjects who contribute endpoints produces unbiased estimates of the event rates.

Additionally, Kaplan-Meier survival analyses will be performed to estimate the event rates at various time-points. In survival analyses, unobserved endpoints are a standard part of the analysis. They are known as censored observations.

The reason for missing data for all subjects will be reported. If there is any indication that missing data is related to the study intervention, a worst-case analysis may be performed in addition to the standard analysis. In a worst-case analysis, a failure of effectiveness or safety will be assumed to have occurred at the time the subject was censored.

In addition, regardless of whether missing data are related to the study intervention, a tipping-point analysis will be performed, in which assumptions about missing data are varied from worst-case to best-case to examine at what point the missing data would alter the results of the analysis.

6.7. Sample Size Determinations

The sample size calculation assumes the following:

1. The LIFESTREAM™ Covered Stent composite event rate is estimated at 10.5%

2. The PG is set at 19.5%

3. The Type 1 error, $\alpha = 0.05$ (one-sided).

4. The Type 2 error, $\beta = 0.10$ (Power = 1 - β = 90%).

The calculated sample size is 139 subjects to be followed through the 9-month follow-up visit (using nQuery 7.0). To accommodate 10% censoring, the sample size is increased to 154.

Note, Bard estimates that 50% of consented subjects will not meet the eligibility criteria (e.g., Screen Failures), and therefore will not enter the analysis population. The estimated consented population will therefore be 308 [154 * 2 = 308].

6.8. Interim Analysis

An interim analysis will be performed when all of the first 103 enrolled subjects (at two thirds of the originally planned sample size) either complete the 9-month visits or discontinued from the study. The primary analysis at interim will be based on the first 103 enrolled subjects and no others whether or not there are additional subjects who may have completed their 9-month visits or discontinued at the time.

The linear alpha spending function will be used to control for the overall study-wise type I error rate of 0.05 (Proschan et al, 2006, Chapter 5 and 14)[24]. The null hypothesis will be rejected at interim based on n=103 (93 evaluable) if the one-sided p-value is less than 0.0335 (calculated by R package ldbounds). If unsuccessful at interim, the null hypothesis will be rejected based on n=154 (139 evaluable) if the one-sided p-value is less than 0.0325 (calculated by R package ldbounds).

A simulation study (Table 2) was performed to evaluate the operating characteristics of the procedure described above. Based on 100,000 simulations, the probability of achieving success at the interim analysis, the overall power of study (i.e., the probability of achieving success either at interim or at final analysis), and the probability of achieving success at interim but failing the final analysis were estimated with various assumptions of the composite event rate, including under the null hypothesis. Additionally, study power without an interim analysis was estimated as well for each of the scenarios.

Table 2: Simulation results

True Event Rate	Interim Analysis (IA) success	Overall study power with IA	Reject at IA but fail at Final	Study power without IA
19.5%	1.8%	3.8%	0.8%	4.9%
12.5%	37.9%	64.7%	2.1%	71.7%
11.5%	49.1%	77.0%	1.6%	82.8%

10.5%	61.3%	87.1%	1.0%	91.1%
9.5%	73.3%	93.7%	0.5%	95.9%
8.5%	83.5%	97.5%	0.2%	98.6%
7.5%	91.1%	99.3%	0.1%	99.6%
6.5%	96.0%	99.9%	<0.1%	99.9%

When data were simulated under the null hypothesis, i.e., the composite event rate is 19.5%, there is a risk of 1.8% that the null hypothesis will be rejected falsely at interim and an overall false positive risk of 3.8%, which is below the study-wise type I error rate of 0.05.

When data were simulated under the alternative hypothesis, e.g., if the true composite event rate is 10.5% as originally assumed in the sample size calculation, there is a 61.3% chance the study will meet its primary objective at interim with two thirds of the planned sample size and a risk of 1.0% of failing the final analysis after declaring success at interim. By adding the interim analysis, the overall power of the study decreases slightly to 87.1% from the original designed 90% power. However, if the true composite event rate is a few percentage points better than originally assumed, for example at 8.5%, there is a 83.5% chance the study will declare success at interim and the overall power of the study is 97.5% with very little risk of achieving success at interim but failing at final analysis.

The simulation results show that the proposed interim analysis can potentially achieve study success faster with two thirds of the planned sample size, particularly if the true composite event rate is lower than originally assumed. It is unlikely that a final analysis would fail after success is achieved at interim. The added interim analysis may cause some loss of overall study power, but the amount of loss is small.

7. CLINICAL EVENT REPORTING

The Principal Investigator (PI), or authorized designee, is responsible for the detection and documentation of events meeting the criteria and definitions set forth in Section 7.1. Collection of these events will begin immediately following subject enrollment (events occurring prior to becoming a treated subject as defined in 5.2.2 will be documented as medical history), during the index procedure through final subject follow-up visit or early termination.

7.1. Definitions of Events

7.1.1. Adverse Events

An AE is defined as 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 study device [ISO14155:2011(E)]. A list of possible complications and/or risks of the study device is outlined in Section 9.

7.1.2. Adverse Device Effect

An Adverse Device Effect (ADE) is an AE related to the use of the LIFESTREAM™ Covered Stent. This includes AEs resulting from insufficient or inadequate IFU, deployment, implantation, installation, or operation, or any malfunction of the LIFESTREAM™ Covered Stent. Additionally, this definition includes any event resulting from use error or from intentional misuse of the LIFESTREAM™ Covered Stent.

7.1.3. Serious Adverse Events

Each AE will be assessed to determine whether it is serious or non-serious. (NOTE: The term serious is not synonymous with severity, which may be used to describe the intensity of an event experienced by the subject.).

An SAE is an AE that:

1) led to a death
2) led to a serious deterioration in the health of the subject, that either resulted in:
    a) a life-threatening illness or injury, or
    b) a permanent impairment of a body structure or a body function, or
    c) in-patient or prolonged hospitalization, or
    d) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
3) led to fetal distress, fetal death or a congenital abnormality or birth defect

Note: Planned hospitalization for a pre-existing condition, or a procedure required by this study (including subsequent TLR/TVRs assessed in the study endpoints), without serious deterioration in health, is not considered an SAE [ISO14155:2011(E)].

7.1.4. Serious Adverse Device Effect or Unanticipated (Serious) Adverse Device Effect

A Serious Adverse Device Effect (SADE) is an ADE that has resulted in any of the consequences characteristic of an SAE.

An Unanticipated (Serious) Adverse Device Effect (UADE/USADE) is any (serious) adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with, a study device, in which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

UADEs/USADEs will be reported to FDA as required by 21 CFR Part 812, and to the appropriate governing body per ISO 14155:2011(E).

7.2. Severity of Adverse Events

Each AE should be assessed for its severity, or the intensity of an event, experienced by the subject.

- **Mild:** Awareness of a sign or symptom that does not interfere with the subject's activity or is transient and is resolved without treatment or sequelae.
- **Moderate:** May interfere with the subject's activity and require additional intervention and/or treatment, and may have additional sequelae.
- **Severe:** Significant discomfort to the subject and/or interferes with the subject's activity. Additional intervention and or treatment are necessary. Additional sequelae occur.

7.3. Relationship of Adverse Event to Device(s)/Procedure

Investigators will assess each AE/SAE for its relationship to the study device (LIFESTREAM™ Covered Stent) or procedure as follows.

1) Assess each AE for its relationship to the device or procedure as follows:

- **Device(s) Related:** This category should be restricted to AEs directly attributable to the study device(s) used as part of the index procedure.
- **Procedure Related**: A procedure includes any activity performed during the index procedure.

2) The following categories should be used for assigning the certainty of the relatedness:

- **Definitely Related**: An AE is definitely related if it is obvious, certain or there is little doubt regarding the relationship.
- **Possibly Related**: An AE is possibly related if it is capable of being related but relatively unlikely or there insufficient information to determine if the AE is related to the device or procedure.
- **Not Related**: An AE is not related if it is determined that there is no plausible association.

7.4. Reporting of Events

All AEs determined to be unrelated to the device/procedure, or non-serious, should be recorded on the appropriate eCRF.

The procedure for reporting device/procedure-related AEs/SAEs or UADEs/USADEs is as follows.

- All sections of the appropriate eCRF must be completed.
- Device/procedure-related AEs/SAEs, SADEs, or UADEs/USADEs must be reported to Bard within one (1) business day of the site becoming aware of the event(s).
    - De-identified copies of all relevant documentation (i.e., procedure reports, physician/nurses notes, discharge summary, etc.) should be submitted to Bard, as appropriate.

It is the responsibility of the Investigator to notify the IRB/EC of events in accordance with the governing IRB/EC's requirements.

7.4.1. Subject Death

Subject death, for any reason during the study, must be reported to Bard within one (1) business day of the site becoming aware of the event.

Notification of subject death may include email, phone, or fax to Bard. All available medical records related to the subject's death must be maintained.

7.5. Safety Committees

7.5.1. Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will be comprised of at least 4 members (biostatistician, interventional radiologist, interventional cardiologist, and vascular surgeon) who are not directly involved in the conduct of the study. The DSMB is responsible for independently overseeing interim safety and effectiveness analyses as described in the clinical protocol, or as recommended by the FDA or other regulatory authority. The DSMB will independently conduct evaluations of subject safety during the trial and make recommendations that the trial be continued, amended, or terminated to prevent new or additional SAEs to study subjects.

7.5.2. Clinical Events Committee and Medical Monitor

The CEC will be comprised of at least 2 members (interventional radiologists, interventional cardiologists, or vascular surgeons) who are not directly involved in the conduct of the study. The CEC is responsible for the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study, as determined by the CEC charter.

The Medical Monitor (MM) will be responsible for reviewing adjudicated events for AE trends.

7.5.3. Safety Committee Procedures

The CEC will review all complications and AEs during the study. The CEC will have access to the eCRFs associated with reported AEs for each subject. Bard will forward all associated relevant documents (e.g., cath lab reports, physician notes, operative reports, etc.) to the CEC upon request.

The committees will meet at time intervals specified in their respective charter. The CEC will forward an adjudication report of AEs to Bard in a timely fashion. The DSMB will forward a "report of recommendations" following each DSMB meeting to Bard in a timely fashion.

When appropriate, conference calls between Bard and members of the committees will commence to discuss reported complications and AE details, and to determine whether the study

should be terminated due to safety issues. Minutes of all conference calls and meetings will be recorded and distributed as appropriate.

Bard will ensure that appropriate information is provided to the FDA, the Investigators, and all reviewing IRB/EC's.

8. DEVICE DEFICIENCY

The Investigator will record any device deficiencies on the appropriate eCRF. A device deficiency has occurred if a study device used in the study procedure failed to meet its performance specifications whether due to mechanical failure, malfunction, or defects. Device deficiencies also include errors and inadequate labeling.

This applies to:

- Study devices used in the subject; or
- Study devices in which the catheter package was opened, but the device was not used for catheterizing the subject; or
- Study devices with which insertion attempts were made, but the study device did not remain (was not used) in the subject.

All mechanical failures, malfunctions, and defects of the study devices will be recorded on the appropriate eCRF page and will be promptly reported to Bard. The device(s) should be returned to Bard as outlined in the site regulatory binder.

If the device deficiency was associated with an AE, the reporting provisions for AEs, ADEs, SAEs, SADEs and UADEs/USADEs as outlined in Section 7 above apply.

Any device deficiency that did not lead to an AE but could have led to an SADE, if suitable action had not been taken, if intervention had not been made, or if circumstances had been less fortunate, must be reported to Bard within one (1) business day of the event per Section 7.4.

It is the responsibility of the Investigator to notify the IRB/EC of such device deficiencies in accordance with the IRB/EC and/or the Competent Authority's local regulations.

9. RISK/BENEFIT ANALYSIS

The potential benefits that may result from treatment with the LIFESTREAM™ Covered Stent may include:

- A low incidence of device and/or procedure-related death or MI through 30 days or any TLR, target limb(s) major amputation, or restenosis through 9 months post-index procedure.

The risks associated with the use of the LIFESTREAM™ Covered Stent have been identified by performing a Design Failure Mode and Effects Analysis (DFMEA) on the system. At the completion of the DFMEA, a Risk Analysis was generated to summarize the risk analysis process and provide documented evidence that the risks associated with the study device are

acceptable. Prior to study participation, the Investigator must explain to each subject the risks and benefits of this study.

The known possible risks associated with the use of the LIFESTREAM™ Covered Stent are listed below, and have been made available to the Investigator(s) in the study device IFU. Additionally, Bard conducted verification testing to confirm that the LIFESTREAM™ Covered Stent has element safety and efficacy to treat the iliac arteries. Detailed information regarding pre-clinical testing can be found in the Investigator's Brochure (IB).

Potential patient/device adverse effects associated with peripheral vascular stenting/covered stenting that may occur include, but are not limited to, the following:

- Abscess
- Allergic/anaphylactoid reaction
- Amputation
- Aneurysm/pseudoaneurysm
- Angina/coronary ischemia
- Arterial occlusion/thrombus, near the puncture site
- Arterial occlusion/thrombus, remote from puncture site
- Arterial occlusion/restenosis of the treated vessel
- Arteriovenous fistula
- Arrhythmia
- Balloon rupture
- Blockage of major collateral artery or arterial branch
- Bypass surgery
- Covered stent slippage from balloon during tracking procedure
- Covered stent misplacement during placement procedure
- Covered stent migration post placement procedure
- Covered stent insufficient wall apposition
- Covered stent deformation/kink/fracture
- Death
- Distal embolization
- Drug reaction or allergic reaction to medication, substances or materials used for the procedure (e.g., anticoagulation or antiplatelet agent, contrast medium, stent or catheter materials)
- Edema
- Fever
- Hemorrhage/bleeding
- Hematoma and/or bleeding at puncture (access) site
- Hypotension/hypertension
- Inability to introduce/withdraw endovascular system
- Inability to track endovascular system to the target lesion
- Inability to inflate the balloon/deploy covered stent
- Infection at access site
- Infection at or around implant
- Inflammation
- Ischemia/infarction of tissue/organ

- Myocardial infarction
- Pain
- Radiation Injuries
- Renal insufficiency/failure/toxicity
- Respiratory arrest
- Restenosis in the treatment area/covered stent edge
- Sepsis
- Shock
- Stroke/Transient Ischemic Attack (TIA)
- Thromboembolic event/thrombosis
- Vasospasm
- Vessel wall trauma, perforation/dissection/rupture

Treatment associated with use of the LIFESTREAM™ Covered Stent may involve additional risks, the specific natures of which are currently unknown.

It is the responsibility of the Investigator to inform his/her IRB/EC of deaths (whether or not device and/or procedure related), and of any AEs in accordance with the governing IRB/EC's requirements.

10. DATA COLLECTION AND RECORD MAINTENANCE

The Investigator is responsible for completely and accurately recording study data in the appropriate sections of the eCRFs provided. The eCRFs must be signed by the Investigator or by his/her documented designee.

The monitor will ensure the accuracy of data recording at each site by comparing recorded data to supporting source documents during periodic site visits. Adherence to proper recording of information as well as ensuring that corrections are being made will also be addressed during these periodic visits.

10.1. Electronic Data Capture

The Investigator is responsible for ensuring the accuracy and completeness of all study documentation. All clinical study data will be recorded in the eCRFs provided to the site.

10.2. Independent Core Lab Analysis

The Investigator is responsible for ensuring that angiographic and DUS images are properly recorded, labeled, and shipped to the respective independent core labs for review and analysis as outlined in the site regulatory binder.

11. ADMINISTRATIVE REQUIREMENTS

11.1. Publication Policy

At the conclusion of the BOLSTER Study, an article may be prepared for publication in a reputable scientific journal. The publication of the principal results from any single-center experience within the study is not allowed until the preparation and publication of the multi-center results. Exceptions to this rule require the prior approval of Bard. The analysis of other pre-specified and non pre-specified endpoints will be performed by Bard or its designee. Such analyses, as well as other proposed investigations or manuscripts will require the approval of the Bard. A description of this clinical study will be available on http://www.clinicaltrials.gov, as required by U.S. law.

11.2. Investigator Selection

The Investigator must be of good standing as an Investigator and knowledgeable in relevant areas of clinical research to ensure adherence to the requirements of this protocol, including the protection of human subjects. Other site personnel must have appropriate research experience and infrastructure to ensure adherence to this protocol and enrollment of sufficient numbers of evaluable subjects. The curriculum vitae (CV) of the Investigator(s) and Study Coordinator(s) will be maintained in Bard's files as documentation of qualification by training and experience. Federal databases will be searched to ensure that the Investigator(s) and/or the site are not prohibited from engaging in federally-sponsored clinical research. The PI and Sub-Investigator(s) will sign the signature page of this protocol, agreeing to comply with all applicable government regulations and the requirements of this study as per the Clinical Study Agreement (CSA).

11.3. Ethical and Regulatory Considerations

Bard will obtain approval to conduct the study from the FDA in accordance with any applicable specific IRB/EC requirements prior to a site initiating the study. Before commencement of the study, the Investigator must provide Bard with written documentation of IRB/EC approval. The IRB/EC must give written renewal of the original approval at least annually to continue the study. A copy of the written renewal must be provided to Bard. No study devices will be shipped to the Investigator until the IRB/EC approval has been supplied to Bard, all relevant agreements have been executed, and approvals from applicable authorities have been issued. Additionally, Bard will provide Investigators with an Investigator Brochure, including any applicable literature searches and results of prior investigations.

11.4. Informed Consent and National Privacy Laws

Prior to any study procedure, the Investigator (or designee) must explain to each subject in layman's terms, the nature of the study, its purpose, expected duration, and the risks and benefits of study participation. Also, subjects will be informed of uses and disclosures of their medical information for research purposes, and their rights to access information about them. All applicable national privacy laws (e.g., HIPAA requirements in the U.S.) will be followed in this study. The subjects must be informed of their right to withdraw from the study at any time and

for any reason without sanction, penalty, or loss of benefits to which they are otherwise entitled, and that withdrawal from the study will not jeopardize their future medical care. Subjects will be informed of their right to new information and/or findings relating to the clinical study, and the process by which this information is made available. After this explanation and before any study procedure is conducted, and before entering the study, the subject must provide consent in accordance with 21 CFR Parts 50 and 56, and ISO 14155:2011(E). The subject will receive a copy of his/her ICF.

11.4.1. Confidentiality

All information and data sent to Bard or Bard designees concerning subjects or their participation in this study will be considered confidential. All data used in the analysis and reporting of this study will be used in a manner without identifiable reference to the subject. The Investigator consents to visits by personnel of Bard and its affiliates or designees, as well as, FDA representatives.

11.5. Deviations from Protocol and Medical Emergencies

The study will be conducted as described in this protocol. Any deviations from this protocol must be documented by the Investigator. If an emergency situation arises in which the safety and welfare of a subject may require immediate alternative intervention, the Investigator should act in the best interest of the subject. Bard and the site's IRB/EC must be notified immediately if this occurs; followed by written confirmation that describes the emergency action and outcomes, to Bard and the IRB/EC, within 10 business days from the date of the emergency action in accordance with the governing IRB/EC's requirements.

11.6. Device Accountability

The study device may only be used for treated subjects in this study under the supervision of the Investigator and under the terms of this protocol. The Investigator may not provide the devices to any unauthorized person. The Investigator will also ensure that the device components are stored under the conditions outlined in the IFU and maintained under secure storage. Device accountability records will be maintained and will include:

- Product code
- Lot number
- Serial number
- Receipt dates
- Dates and quantities dispensed including subject number and initials, if applicable
- Return date to Bard (if any). Any study devices that have failed or malfunctioned should be returned to Bard. Any used study devices that have malfunctioned should be placed in a biohazard bag, labeled "Biohazard", and returned to Bard. Please refer to the site regulatory binder for return instructions.

Bard will supply the Investigator with an adequate number of study devices for completion of the study. Study devices may not be re-sterilized or reused. Device Accountability shall be

completed in accordance with 21 CFR Parts 812.3, 812.100, 812.110, and 812.140, and ISO 14155:2011(E).

11.7. Required Documents

An Investigator may not screen or enroll subjects until authorized to do so by Bard. At a minimum, the following documentation must be received by Bard prior to the commencement of study activities:

- Signed and executed Non-disclosure Agreement (NDA) by PI and appropriate party at Bard;
- CV signed and dated within 2 years of study start for the PI ;
-
- Signed CSA by PI (or designee);
- Signed "Protocol Signature Page" by PISigned "Investigator Brochure Signature Page" by PI;
- Signed "Financial Disclosure Statement" by PI;
- Signed "Device Training Log" by PI;
- Study Personnel Identification list;
- Written approval from the IRB/EC of both the protocol and ICF, and any other applicable protocol specific material; and,
- IRB/EC Membership List, Assurance of Compliance Form, or equivalent.

12. MONITORING AND AUDITING

The study monitors are designated as agents of Bard and are assigned to oversee the conduct and progress of the study and to be the principal communication link between Bard and the Investigator. The study monitors may assist in pre-qualifying potential sites. The study monitors will periodically conduct on-site inspection and monitoring of sites and records, to ensure continued compliance with this protocol and adequacy of the Investigator and the site to conduct the study. In addition, the monitor will verify that the study device is being used in accordance with the protocol instructions. The monitor will perform several types of site visits during the course of the study.

The sites may also be subject to a quality assurance audit by personnel of Bard (and its affiliates), as well as FDA representatives and other applicable authorities.

It is important that the Investigator(s) and the relevant site personnel are available during the monitoring visits, and possible audits, and that sufficient time is devoted to the process.

12.1. Site Initiation Visits

Before the study begins, the study monitors conduct a Site Initiation Visit (SIV). The purpose of this visit is to review with the Investigator(s) and staff, the provisions and proper conduct of this study. This visit will include a detailed review of this protocol, verification that all necessary documents are on file at the site, and confirmation of IRB/EC approvals.

12.2. Ongoing Monitoring Visits

The study monitor will maintain personal contact with the Investigator and staff throughout the study by telephone, e-mail, fax, mail, and on-site visits. On-site monitoring will begin at each site after the first subject is enrolled and will continue until the study is completed. The study monitor will confirm that the ICF used is the version approved by the IRB/EC, confirm the applicable national privacy laws have been followed (e.g., confirm the presence of a signed HIPAA release in the U.S.), verify that all necessary documents are on file at the site, and confirm that there are provisions to continue and maintain all documents and records throughout the study as required by FDA regulations. These monitoring visits will assess continued protocol compliance, adequate subject enrollment, accurate data reporting (including the comparison and 100% verification of eCRFs with subject records for critical fields), monitoring of subject safety through identification and/or review of any device-related AEs, UADEs, or SAEs, device accountability, continued maintenance and calibration of study-specific equipment (if applicable), and continued IRB/EC acceptance of the study. The study monitor will evaluate and summarize the results of each visit in written reports, identifying any ongoing data or compliance problems with any site and specifying recommendations for resolution of noted deficiencies.

12.3. Final Monitoring Visit

At the completion of the study, the study monitor will conduct a final on-site visit. The purpose of this visit is to collect all outstanding study documents, confirm that the Investigator's files are accurate and complete, review the record retention requirements with the Investigator, provide for the return of unused devices to Bard, review records which account for device shipments, and ensure that all applicable requirements for closure of the study are met. The actions and observations made at this visit will be recorded and filed.

13. TRAINING

In addition to each Investigator and appropriate site personnel being trained on this protocol and study procedures during the SIV, device training will be provided by Bard and is required for each Investigator. Sub-Investigator(s) will also require device training provided from Bard, or proctored by the PI. The Investigator (or designee) may also train additional site personnel, as required and agreed upon by Bard. All training will be documented and filed at the site and with Bard. The Investigators participating in this study will have had substantial experience previously performing PTA and stent placement procedures for the treatment of iliac occlusive disease. The delivery and deployment of the LIFESTREAM™ Covered Stent is not vastly different than other commercially-available balloon-expandable stent and covered stent systems; therefore, roll-in subjects will not be required for this study.

14. REPORTING REQUIREMENTS

The Investigator must comply with 21 CRF Part 812.150 (a) and ISO 14155:2011(E), and must promptly report to Bard all progress, annual, and final reports and any withdrawal of IRB/EC approval at the site. At a minimum, the Investigator shall inform Bard of the following events according to the notification timelines below:

Event:	Notification to:	Time to Notification:
Device/procedure-related AEs/SAEs, SADEs, UADEs/USADEs, or death	Bard and IRB/EC (if applicable)	As soon as possible, but no later than one (1) business day after investigator awareness (see Sections 7.4 and 8.0)
Protocol Deviations (Major*)	Bard, IRB/EC, and FDA (by Bard, as applicable)	Within 5 business days
Device deficiencies	Bard and IRB/EC	As soon as possible, but no later than one (1) business day after investigator awareness (see Section 8.0)
Withdrawal of IRB Approval	Bard	Within 5 business days
Study Progress	Bard and IRB/EC	At least yearly
Final Report	Bard and IRB/EC	Within 3 months of study completion

**Major Protocol Deviations are defined as those that occur to protect the life or physical well-being of a subject in an emergency, or those that may affect the scientific soundness of the study, or the rights, safety or welfare of human subjects.*

15. RECORD RETENTION

The Investigator shall retain all study records for a period of 2 years after the later of the following two dates: the date on which the study is terminated or completed, or the date that the records are no longer required for purposes of supporting a Pre-Market Approval (PMA) application or a notice of completion of a product development protocol. The Investigator may withdraw from the responsibility to maintain records for the period required by transferring custody of the records to any other person who will accept responsibility for retaining them. Notice of a transfer shall be given to Bard and FDA not later than 10 business days after the transfer occurs [21 CFR Part 812.140 (d)].

16. TERMINATION OF STUDY

Bard reserves the right to suspend enrollment or terminate the study at any time as set forth in the CSA. Written notice will be submitted to the Investigator in advance of such termination. Bard may suspend enrollment or terminate the study at a specific site for reasons including, but not limited to, inadequate data collection, low subject enrollment rate, achievement of the total enrollment, or non-compliance with this protocol or other clinical research requirements. In the event of study termination, treated subjects must be followed through the 3-year study follow-up period.

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APPENDIX 1: Time and Events Schedule

Observation	Baseline/ Screening	Index Procedure	Hospital Discharge[1]	30 d[1] (± 7d)	6 mo[2] (± 30d)	9 mo (± 30d)	12, 24, & 36 mo (± 30d)
Eligibility Criteria	✓	✓					
Informed Consent	✓						
Demographics	✓						
Medical History	✓						
Pregnancy test	✓[3]						
Labs (BUN or Creatinine, CBC including Platelets)	✓						
Concomitant Medications	✓	✓	✓	✓	✓	✓	✓
Comprehensive Physical Exam	✓		✓	✓		✓	✓
Angiogram	✓[4]	✓[4]					
Resting ABI	✓			✓		✓	✓
Rutherford (Category & Grade)	✓			✓		✓	✓
Adverse Event Assessment		✓	✓	✓	✓	✓	✓
TLR/TVR Assessment				✓[4]	✓[4]	✓[4]	✓[4]
Color Flow Duplex Ultrasound				✓[5]		✓[5]	✓[5]
WIQ	✓[6]			✓		✓	✓

[1]Subjects meeting the criteria for deployment failure will be evaluated at hospital discharge and the 30-day follow-up visit to assess and document any AEs or SAEs that may have occurred since the index procedure.
[2]Telephone Screen
[3]Perform pregnancy test (urine or blood) for women who are of childbearing potential ≤ 14 days prior to the index procedure.
[4]Send images to Angiographic Core Laboratory
[5]Send images to Ultrasound Core Laboratory
[6]Complete WIQ ≤ 30 days prior to the index procedure