



CLINICAL PATIENT REGISTRY PROTOCOL

Title: A Prospective, Multicenter, Single Arm, Real-World Registry
Assessing the Clinical Use of the Lutonix® 035 Drug Coated Balloon
Catheter in Arteries of the Superficial Femoral Artery (SFA) and
Popliteal Artery (PA) (SAFE-DCB U.S. Registry)

Protocol Number: BPV-14-006

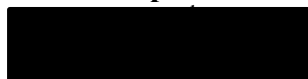
Protocol Type: Registry

Date: August 19, 2015

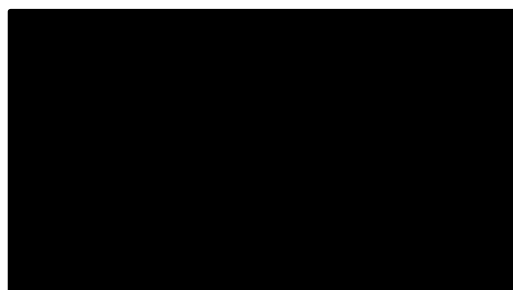
Version: 2

Registry Device: Lutonix® 035 Drug Coated Balloon

Sponsor: Bard Peripheral Vascular, Inc.



Sponsor Contact:



NCT Number: 02424383 (Number added post-approval per CT.gov requirement)

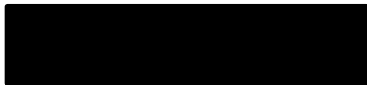
CONFIDENTIAL

This document contains information that is the confidential and proprietary property of Bard Peripheral Vascular, Inc. or its affiliates. Neither this document nor the information herein may be reproduced, used, or disclosed to or for the benefit of any third party without the prior consent of Bard Peripheral Vascular, Inc. Shred to dispose of document.

Revision History:

Protocol Version #	Description of Changes
2	Protocol Amendment to include additional device sizes and features, include additional sites, and increase number of subjects.

1. PROTOCOL SUMMARY

Title:	A Prospective, Multicenter, Single Arm, Real-World Registry Assessing the Clinical Use of the Lutonix® 035 Drug Coated Balloon (DCB) Catheter in Arteries of the Superficial Femoral Artery (SFA) and Popliteal Artery (PA) (SAFE-DCB U.S. Registry)
Sponsor:	Bard Peripheral Vascular, Inc. 
Objectives:	The objective of this patient registry is to assess the clinical use of the Lutonix® 035 DCB PTA Catheter in a heterogeneous patient population in a real world and on-label clinical application.
Design:	The registry is a prospective, multicenter, single arm post-market real-world registry in the U.S. assessing the clinical use, safety and outcomes of the Lutonix® 035 DCB Catheter in the Superficial Femoral Artery (SFA) and Popliteal Arteries (PA). Registry subjects will be followed for up to three year's post-index procedure.
Devices:	Commercial inventory will be utilized for this patient registry. The devices used in this registry will be ordered and purchased by each investigational site according to their standard device ordering process.
Enrollment:	Up to 2,000 registry subjects
Investigational Sites:	Up to 100 investigational sites in the United States (U.S.)
Patient Registry Population:	Male or non-pregnant female ≥ 21 years of age with an expected lifespan sufficient to allow for completion of all patient registry procedures. Eligible registry subjects will have stenotic or obstructive vascular lesions in the SFA/PA.
Eligibility Criteria	Inclusion Criteria <ol style="list-style-type: none">1. The subject provides written informed consent using an Informed Consent Form (ICF) that is reviewed and approved by the Institutional Review Board (IRB) for the site.2. The subject agrees to comply with the protocol-mandated follow-up procedures and visits.3. The subject is ≥ 21 years old.

	<p>4. The subject must have a lesion(s) that can be treated with available Lutonix® 035 DCB Catheter according to the Instructions For Use (IFU).</p> <p>Exclusion Criteria</p> <ol style="list-style-type: none"> 1. The subject is unable or unwilling to provide informed consent. 2. The subject is unable or unwilling to comply with the patient registry protocol follow-up procedures and visits. 3. The subject has another medical condition or is currently participating in an investigational drug or an investigational device study that, which, in the opinion of the Investigator, may cause him/her to be non-compliant with the protocol, confounds the data interpretation, or is associated with a life expectancy insufficient to allow for the completion of patient registry procedures and follow-up.
Procedures:	<p>All registry subjects will undergo a clinical evaluation at screening (prior to index procedure); after consent is voluntarily obtained registry subjects will be treated with the Lutonix® 035 DCB per the investigational site's standard of care and adhering to the IFU.</p> <p>As this is a patient registry examinations, evaluations, procedural preparation, angiography, treatment, and hospital discharge procedures will be conducted per the investigational site's standard of care.</p> <p>A clinical evaluation with a Duplex Ultrasound (DUS) will be performed at 12 months post index-procedure.</p>
Primary Endpoints:	<p>Primary Effectiveness:</p> <p>Freedom from Target Lesion Revascularization (TLR) at 12 months. TLR is defined as the first revascularization procedure (e.g. PTA, stenting, etc.) of the target lesion after the index procedure.</p> <p>Primary Safety:</p>

	<ul style="list-style-type: none"> Freedom from composite of device and/or procedure related perioperative (≤ 30 day) death, target limb major amputation (above the ankle), and target vessel revascularization.
Secondary Endpoints:	<p>The following secondary endpoints will be also be reported:</p> <ul style="list-style-type: none"> Target Vessel Revascularization (TVR) at -, 6-, 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 after the index procedure. TLR at 6 months, 24-, and 36-months post-index procedure. Acute Device and Procedural success defined as 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) and no peri-procedural complications (death, stroke, MI, emergent surgical revascularization, significant distal embolization in target limb, and thrombosis of target vessel) prior to hospital discharge. Primary Patency at 12 months post index-procedure. Primary Patency is defined as the absence of target lesion restenosis (defined by DUS peak systolic velocity ratio (PSVR) ≥ 2.5) and freedom from TLR. Freedom from composite of all-cause perioperative (≤ 30 day) death and from the following: index limb amputation, index limb reintervention, and index-limb-related death at -, 6-, 12-, 24-, and 36-months post-index procedure. Freedom from major amputation of the target limb defined as above the ankle amputation at -, 6-, 12-, 24-, and 36-months post-index procedure.
Lead Principal Investigators:	
Medical Monitor:	
Duplex Ultrasound Core Lab:	

Principal Investigator's Responsibility

Prior to participation in the SAFE-DCB U.S. Patient Registry, the Principal Investigator (PI) must sign the Clinical Study Agreement (CSA) and obtain written approval from his/her Institutional Review Board (IRB). This approval must be in the Investigator's name and a copy sent to Bard along with the IRB approved Informed Consent Form (ICF) and the signed CSA, prior to Site Initiation. The PI is responsible for training all Sub-Investigators to ensure adequate training is obtained prior to performing any data collection or patient registry-related procedures.

The PI must also:

- Conduct the patient registry in accordance with the patient registry protocol, the signed CSA, the Declaration of Helsinki, Health Insurance Portability and Accountability Act (HIPAA) requirements, and Good Clinical Practice (GCP) including 21 CFR Parts 50, 54, and 56.
- Ensure that the patient registry does not commence until IRB approvals have been obtained.
- Ensure that written informed consent is obtained from each subject prior to the conduct of any patient registry procedure; using the current IRB approved ICF.
- Provide all required data and reports and agree to source document verification of patient registry data with subject's medical records.
- Allow Bard personnel or their designee(s), to inspect and copy any documents pertaining to the patient registry.
- Provide appropriate resources to ensure compliance with all patient registry-related procedures and prompt submission of all case report forms.
- 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 Principal Investigator retains overall responsibility for IRB approval and proper conduct of the patient registry, including obtaining and documenting the Informed Consent process, compliance with the patient registry protocol, obtaining a signed CSA, the collection of all required data, and ensuring that all patient registry personnel have been properly trained on the protocol and have received other necessary training (if applicable) prior to performing any data collection or patient registry-related procedures.

Principal Investigator Protocol Signature Page

Site name: _____

I have read and understand the contents of the SAFE-DCB U.S. Patient Registry protocol. I agree to follow and abide by the requirements set forth in this document. I agree to conduct the patient registry in accordance with the patient registry protocol, the signed CSA, the Declaration of Helsinki, HIPAA requirements, and GCP including 21 CFR Parts 50, 54, and 56.

I agree to participate in the Bard-sponsored training prior to performing any data collection or patient registry-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 SAFE-DCB U.S. Patient Registry protocol. I agree to follow and abide by the requirements set forth in this document. I agree to conduct the patient registry in accordance with the patient registry protocol, the signed CSA, the Declaration of Helsinki, HIPAA requirements, and GCP including 21 CFR Parts 50, 54, and 56.

I agree to participate in the Bard-sponsored training prior to performing any data collection or patient registry-related procedures.

Sub-Investigator Name (print)

Sub-Investigator Signature

Date

Protocol Abbreviations/Acronyms

Abbreviation/Acronym	Definition
AE	Adverse Event
Bard	Bard Peripheral Vascular, Inc.
CFR	Code of Federal Regulations
CSA	Clinical Study Agreement
CV	Curriculum Vitae
DCB	Drug Coated Balloon
DUS	Duplex Ultrasound
(e)CRF	(electronic) Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
M.D.	Medical Doctor
MDR	Medical Device Report
NDA	Non-Disclosure Agreement
OTW	Over-the-Wire
PA	Popliteal Artery
PAD	Peripheral Arterial Disease
PI	Principal Investigator
PSVR	Peak Systolic Velocity Ratio
PTA	Percutaneous Transluminal Angioplasty
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFA	Superficial Femoral Artery
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
U.S.	United States

TABLE OF CONTENTS

1. PROTOCOL SUMMARY	3
2. INTRODUCTION.....	11
2.1. Background.....	11
2.2. Registry Objective.....	11
3. DEVICE DESCRIPTION	11
4. PATIENT REGISTRY DESIGN	12
5. PATIENT REGISTRY ENDPOINTS.....	13
5.1. Primary Endpoints.....	13
5.2. Secondary Endpoints.....	13
6. INCLUSION AND EXCLUSION CRITERIA.....	14
6.1. Inclusion Criteria.....	14
6.2. Exclusion Criteria	14
7. PATIENT REGISTRY PROCEDURES.....	14
7.1. Pre-Treatment Evaluations:.....	14
7.2. Treatment Procedures	15
7.3. Follow-Up Visits.....	15
8. ADVERSE EVENTS	15
8.1. Definition of Adverse Event	16
8.2. Adverse Events Classification	16
8.3. Definition of Serious Adverse Event	16
8.4. Relationship of Adverse Event to Device(s)/Procedure.....	17
8.5. Subject Death	18
9. STATISTICAL PLAN	18
9.1. Patient Registry Hypothesis	18
9.2. Data Analysis.....	19
10. DATA COLLECTION AND RECORD MAINTENANCE.....	19
10.1. Electronic Data Capture (EDC)	19
11. ADMINISTRATIVE REQUIREMENTS	19
11.1. Investigator Selection.....	19
11.2. Ethical and Regulatory Considerations.....	20
11.3. Informed Consent and National Privacy Laws	20
11.3.1. Confidentiality.....	20
11.4. Deviations from Protocol and Medical Emergencies.....	20
11.5. Required Documents.....	21
12. MONITORING AND AUDITING	21
12.1. Site Initiation Visits	21
12.2. Ongoing Monitoring Visits	22
12.3. Final Monitoring Visit	22
13. TRAINING.....	22
14. REPORTING REQUIREMENTS.....	22
15. RECORD RETENTION	23
16. TERMINATION OF PATIENT REGISTRY	23
17. REFERENCES.....	24

APPENDIX A: Table of Assessments

2. INTRODUCTION

This Patient Registry is a prospective, multi-center, single-arm, patient registry which is intended to assess the clinical use in a heterogeneous patient population in a real world clinical application. The Lutonix® 035 Drug Coated Balloon (DCB) PTA Catheter was approved by FDA on October 9, 2014 (PMA P130024) for the indication of percutaneous transluminal angioplasty (PTA), after pre-dilatation, of de novo or restenotic lesions up to 150 mm in length in native superficial femoral artery (SFA) or popliteal arteries (PA) with reference vessel diameters of 4-6 mm. This is the first approved DCB used to treat stenoses in the SFA and in the PA as a result of peripheral arterial diseases (PAD).

This patient registry will be conducted in conformance with the Declaration of Helsinki, Health Insurance Portability and Accountability Act (HIPAA) requirements and Good Clinical Practice (GCP) including 21 CFR Parts 50, 54, and 56.

2.1. Background

PAD occurs when a narrowing, or blockage, develops in the arteries; PAD most commonly affects the legs¹. The primary cause of lower extremity PAD is atherosclerosis. Atherosclerosis of the lower extremity arteries results in symptoms ranging from intermittent claudication (pain in the buttocks, thighs, or calf which occurs with exercise, and relieves with rest) to pain at rest, and can ultimately progress to ulceration and gangrene. A number of risk factors can be directly correlated with the onset of progressive PAD, including cigarette smoking, diabetes mellitus, dyslipidemia, hypertension, hyperhomocysteinemia, and advanced age.^{1,2}

2.2. Registry Objective

The objective of this registry is to assess the clinical use of the Lutonix® 035 DCB PTA Catheter in a heterogeneous patient population in a real world, on-label clinical application per the Instructions For Use (IFU).

3. DEVICE DESCRIPTION

The LUTONIX® 035 DCB PTA Catheter is a standard PTA catheter with a drug coating on the balloon portion of the catheter. The LUTONIX® Catheter 035 model is an over-the-wire (OTW) with working lengths of 75 and 130 cm and is compatible with 0.035" guidewire. Marker bands are located at the proximal and distal ends of the balloons to assist in delivery and placement. The balloon surface between the marker bands is coated with a specialized immediate release non-polymer based coating formulation that includes the anti-proliferative drug – paclitaxel - at a surface concentration of 2µg/mm². Please refer to the IFU for complete instructions, preparation and procedural use of the device.

Commercial inventory will be utilized for this registry. The devices used in this registry will be ordered and purchased by each investigational site according to their standard device ordering process.

Figure 1: Lutonix® 035 Drug Coated Balloon Catheter

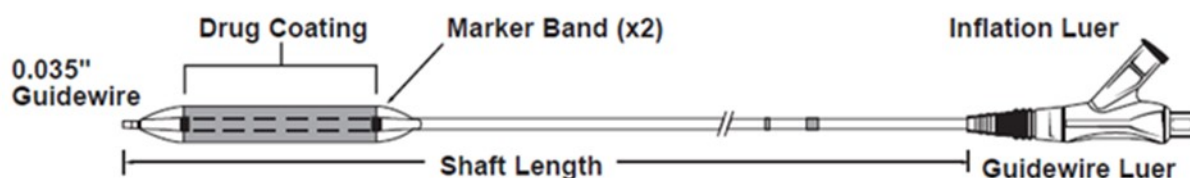
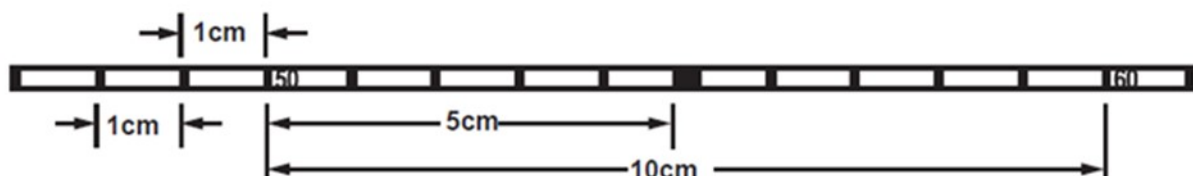


Figure 1. LUTONIX® 035 Drug Coated Balloon PTA Catheter, Model 9004



4. PATIENT REGISTRY DESIGN

The patient registry is a prospective, multicenter, single arm, post-market real-world registry in the U.S. assessing the clinical use, safety and outcomes of the LUTONIX® DCB Catheter in the SFA and PA. Registry subjects will be enrolled at up to 100 investigational sites and up to 2,000 registry subjects followed for up to three years post-index procedure. This registry will be performed with marketed devices within the indications for use. There are no additional treatments or exams that are required to take place within this registry. There will be minimal patient registry activities that will be conducted for data collection for the purpose of this registry in addition to routine standard of care procedures; including:

- The subject (or legally authorized representative) signing an informed consent form (ICF);
- The possibility of performing follow-up visits via the telephone, if these are not routinely performed as on-site visits at the requested times, so that the data as detailed in Appendix 1 can be obtained.
- The collection and descriptive analysis of collected subject data.

5. PATIENT REGISTRY ENDPOINTS

5.1. Primary Endpoints

The following primary endpoints will be reported:

Primary Effectiveness:

- Freedom from Target Lesion Revascularization (TLR) through 12 months. TLR is defined as the first revascularization procedure (e.g. PTA, stenting, etc.) of the target lesion after the index procedure.

Primary Safety:

- Freedom from composite of device and/or procedure related perioperative (≤ 30 day) death, target limb major amputation (above the ankle), and target vessel revascularization.

5.2. Secondary Endpoints

The following secondary endpoints will be reported through 3 years at these timepoints; 30 days, 6 months, 12 months (1 year), 24 months (2 years), and 36 months (3 years).

- Target Vessel Revascularization (TVR) at -, 6-, 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 after the index procedure.
- TLR at 6-, 24-, and 36-months post-index procedure.
- Acute Device and Procedural success defined as 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) and no peri-procedural complications (death, stroke, MI, emergent surgical revascularization, significant distal embolization in target limb, and thrombosis of target vessel) prior to hospital discharge.
- Primary Patency at 12 months post index-procedure. Primary Patency is defined as the absence of target lesion restenosis (defined by DUS peak systolic velocity ratio (PSVR) ≥ 2.5) and freedom from TLR.
- Freedom from composite of all-cause perioperative (≤ 30 day) death and from the following: index limb amputation, index limb reintervention, and index-limb-related death at -, 6-, 12-, 24-, and 36-months post-index procedure.
- Freedom from major amputation of the target limb defined as above the ankle amputation at -, 6-, 12-, 24-, and 36-months post-index procedure.

6. INCLUSION AND EXCLUSION CRITERIA

All registry subjects consented must meet the inclusion and exclusion criteria.

6.1. Inclusion Criteria

1. The subject provides written informed consent using an Informed Consent Form (ICF) that is reviewed and approved by the Institutional Review Board (IRB) for the site.
2. The subject agrees to comply with the protocol-mandated follow-up procedures and visits.
3. The subject is ≥ 21 years old.
4. The subject must have a lesion(s) that can be treated with available Lutonix® 035 DCB Catheter according to IFU.

6.2. Exclusion Criteria

1. The subject is unable or unwilling to provide informed consent.
2. The subject is unable or unwilling to comply with the patient registry protocol follow-up procedures and visits.
3. The subject has another medical condition or is currently participating in an investigational drug or an investigational device study that, which, in the opinion of the Investigator, may cause him/her to be non-compliant with the protocol, confounds the data interpretation, or is associated with a life expectancy insufficient to allow for the completion of patient registry procedures and follow-up.

7. PATIENT REGISTRY PROCEDURES

During the screening, the investigator (or designee) will be responsible for describing the nature of the patient registry, verifying that the eligibility criteria have been met, and obtaining informed consent. Prior to the conduct of any patient registry procedures, the subject must voluntarily sign and date the ICF and HIPAA Authorization. All patient registry procedures will be documented in the medical record and/or source document and on patient registry electronic case report forms (eCRF). After consent is obtained the subject must meet all other eligibility criteria.

7.1. Pre-Treatment Evaluations:

After the subject voluntarily signs the ICF and HIPAA Authorization all patient registry procedures will be documented in the medical record and/or source document and on patient registry eCRF. The subject's eligibility for patient registry enrollment will be reviewed, and the following pre-treatment data points for those registry subjects that are treated will be collected:

- The subject's demographic information (e.g., Date of Birth, Sex, etc.)
- The subject's medical history
- The subject's risk factors (e.g., diabetes, HTN, dyslipidemia, etc.)

7.2. Treatment Procedures

As this is a registry all examinations, evaluations, procedural preparation, angiography, treatment, and hospital discharge procedures will be conducted per the investigational site's standard of care. Treatment with the Lutonix® 035 DCB will be per the investigational site's standard of care and adhering to the IFU. For detailed information on device use and procedural and medication recommendations reference the IFU. The treatment characteristics that will be collected for this patient registry are:

- Procedural information (e.g., lesion type, treated lesion length and location, CTO, calcification, adjunctive treatment, number of run-off vessels, etc.)
- Device characteristics (adjunctive treatment used to treat the lesion during the procedure)

7.3. Follow-Up Visits

Registry subjects are to be followed according to the investigational site's standard of care practices. The only difference from routine clinical practice and this registry is data collection and reporting of all AEs to be collected within each follow-up window through 3 years: 30 days (± 7 days), 6 months (± 1 month), 12 months-1 year (± 1 month), 24 months-2 year (± 1 month), and 36 months-3 year (± 1 month). Contact may be made either by telephone or by a clinical visit for each visit other than the 12 month follow-up visit (clinical visit is not required per protocol). A clinical evaluation with a Duplex Ultrasound (DUS) will be performed at 12 months post index-procedure.

The following information to be collected is:

- Occurrence of device and/or procedure related AEs or SAEs since discharge
- TLR/TVR evaluation

At the 12 month follow-up visit, the DUS of Target Limb images will be submitted to DUS Core Laboratory for evaluation. Reference the "Ultrasound Guidelines" for Imaging and upload/submission guidelines which is found external from this protocol.

8. ADVERSE EVENTS

The Principal Investigator (PI) is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. Collection and

reporting of AEs/SAEs will be limited to those events that are device and/or procedure related and reporting will begin immediately following subject enrollment, during the index procedure.

8.1. Definition of Adverse Event

Collection of AEs will be limited to those that are associated with a localized or systemic clinical manifestation that reasonably suggests the involvement of the patient registry device(s) and/or procedure.

- **Device(s)-Related:** This category should be restricted to AEs directly attributable to the Lutonix® DCB Catheter device(s) used as part of the procedure.
- **Procedure-Related:** A procedure includes any activity performed during a patient registry-related procedure.

8.2. Adverse Events Classification

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.

8.3. Definition of Serious Adverse Event

Each device and/or procedure related 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:
 - a. resulted in a life-threatening illness or injury
 - b. resulted in a permanent impairment of a body structure or a body function
 - c. required in-patient hospitalization or prolongation of existing hospitalization
 - d. resulted in medical or surgical intervention to prevent impairment to body structure or a body function
3. led to fetal distress, fetal death, or a congenital abnormality or birth defect

Note: Planned hospitalization for pre-existing conditions or procedures (including subsequent TLR/TVRs- assessed in the patient registry endpoints), without serious deterioration in health are not considered SAEs.

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

Each AE/SAE should be assessed for its relationship to the device or procedure as follows:

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.
- **Not Related:** An AE is not related if it is determined that there is no plausible association.

Potential adverse events which may be associated with a peripheral balloon dilatation procedure include:

- Additional intervention
- Allergic reaction to drugs, excipients or contrast medium
- Amputation/loss of limb
- Aneurysm or pseudoaneurysm
- Arrhythmias
- Embolization
- Hematoma
- Hemorrhage, including bleeding at the puncture site
- Hypotension/hypertension
- Inflammation
- Occlusion
- Pain or tenderness
- Pneumothorax or hemothorax
- Sepsis/infection
- Shock
- Stroke
- Thrombosis
- Vessel dissection, perforation, rupture, or spasm

Although systemic effects are not anticipated, refer to the Physicians' Desk Reference for more information on the potential adverse events observed with paclitaxel.

Potential adverse events, not described above, which may be unique to the paclitaxel drug coating include:

- Allergic/immunologic reaction to the drug coating (paclitaxel)

- Alopecia
- Anemia
- Blood product transfusion
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage, or necrosis
- Myalgia/Arthralgia
- Myelosuppression
- Peripheral neuropathy

Any AE report that may be considered a potential Medical Device Report (MDR) (21 CFR 803(e)) should be handled according to the Bard MDR Reporting Procedure, which complies with 21 CFR 803(e).

8.5. Subject Death

Subject death, for any reason during the patient registry from time of consent through discharge, must be reported to Bard within 1 business day of the investigational site becoming aware of the event.

Notification of death must include a brief statement of the pertinent details. All available medical records related to the subject's death must be maintained.

9. STATISTICAL PLAN

This section describes the planned statistical analyses for this patient registry. A detailed Statistical Analysis Plan (SAP) will be completed and placed on file prior to database lock. The SAP will contain a comprehensive explanation of the methodology used in the statistical analyses described below.

9.1. Patient Registry Hypothesis

There is no formal statistical hypothesis for this patient registry.

Sample Size Considerations

This patient registry is projected to enroll up to 2000 registry subjects at approximately 100 sites. The sample size is based on potential adequacy of data to meet the patient registry objectives. It is not based on any statistical consideration.

9.2. Data Analysis

The analysis population consists of all enrolled registry subjects who have signed the Informed Consent Form and have been treated with the patient registry device.

The patient registry endpoints will be summarized using descriptive statistics. Summary statistics for categorical variables will include frequency counts and percentages and for continuous variables mean, standard deviation, minimum, median and maximum.

The key patient registry endpoints of freedom from TLR and TVR rates as well as primary patency rate will be reported by time point along with their 95% confidence intervals. The calculation of rates at each time point will be based on available data at the time point. Missing data will not be imputed. Additionally, a Kaplan-Meier curve across the whole duration of the patient registry for TLR and TVR and Patency may be created. The rates at each time point derived from the Kaplan-Meier curve take into account of information from registry subjects who discontinue from the registry prematurely and cause missing data.

10. DATA COLLECTION AND RECORD MAINTENANCE

The Investigator is responsible for ensuring the complete and accurate recording of patient registry data in the appropriate sections of the source documentation and eCRFs are provided. The monitor will ensure the accuracy of data recording at each investigational 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 (EDC)

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

11. ADMINISTRATIVE REQUIREMENTS

11.1. 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 registry subjects. Other site personnel must have appropriate research experience and infrastructure to ensure adherence to this protocol and enrollment of sufficient numbers of evaluable registry 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 investigational site are not prohibited from engaging in federally-sponsored clinical research. The Principal Investigator and Sub-Investigator(s) will sign the signature pages of this protocol, agreeing to comply with all applicable government regulations and the requirements of this patient registry as per the Clinical Study Agreement (CSA).

11.2. Ethical and Regulatory Considerations

The Investigator must provide Bard with written documentation of IRB approval prior to the patient registry being initiated. The IRB must give written renewal of the original approval at least annually to continue the patient registry. A copy of each written renewal must be provided to Bard.

11.3. Informed Consent and National Privacy Laws

Prior to any patient registry procedure, the Investigator (or designee) must explain to each subject in layman's terms, the nature of the patient registry, its purpose, expected duration, and the risks and benefits of patient registry participation. Also, registry 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) will be followed in this patient registry. The registry subjects must be informed of their right to withdraw from the patient registry 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 patient registry will not jeopardize their future medical care. After this explanation and before any patient registry procedure is conducted, and before entering the patient registry, the subject must voluntarily provide consent. The subject will receive a copy of his/her signed ICF.

11.3.1. Confidentiality

All information and data sent to Bard or Bard designees concerning registry subjects or their participation in this patient registry will be considered confidential. All data used in the analysis and reporting of this patient registry 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.

11.4. Deviations from Protocol and Medical Emergencies

The patient registry 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 interests of the subject. Bard and the investigational site's IRB must be

notified immediately if this occurs followed by written confirmation that describes the emergency action and outcomes.

11.5. Required Documents

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

- Signed and executed Non-disclosure Agreement (NDA) by PI and appropriate party at Bard;
- Signed CSA by PI (or designee);
- CVs, signed within 2 years of patient registry start, and for the PI;
- CVs for Study Coordinator(s);
- Signed Protocol Signature Page by PI;
- Signed Financial Disclosure Statement by PI;
- Written approval from the IRB of both the protocol and ICF

12. MONITORING AND AUDITING

The patient registry monitor(s) are designated as agents of Bard and are assigned to oversee the conduct and progress of the patient registry and to be the principal communication link between Bard and the Investigator. The patient registry monitor(s) will assist in pre-qualifying potential investigational sites. The patient registry monitor(s) will periodically conduct on-site inspection and monitoring of investigational sites and records, to ensure continued compliance with this protocol and adequacy of the Investigator and the investigational site to carry out the patient registry.

The investigational sites may also be subject to quality assurance audit by personnel of Bard (and its affiliates). It is important that the Investigator(s) and the relevant investigational 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 patient registry begins, the patient registry monitor(s) may visit the investigational site or conduct an online meeting (e.g., WebEx) to review with the Investigator(s) and staff the provisions and proper conduct of this patient registry. This visit will include a detailed review of this protocol, verification that all necessary documents are on file at the investigational site and confirmation of IRB approvals.

12.2. Ongoing Monitoring Visits

The patient registry monitor will conduct limited and periodic on-site inspection and monitoring of the investigational site and records, to ensure compliance with this protocol.

The patient registry monitor will maintain personal contact with the Investigator and staff throughout the patient registry by telephone, e-mail, fax, mail and on-site visits. The patient registry monitor will confirm that the ICF to be used is the version approved by the IRB, verify that all necessary documents are on file at the investigational site. This monitoring will oversee IRB acceptance of the patient registry.

12.3. Final Monitoring Visit

At the completion of the patient registry, the patient registry monitor will conduct a final on-site visit. The purpose of this visit is to collect all outstanding patient registry data documents, confirm that the Investigator's files are accurate and complete, review the record retention requirements with the Investigator, and ensure that all applicable requirements for closure of the patient registry are met. The actions and observations made at this visit will be recorded and filed.

13. TRAINING

Each Investigator and appropriate site personnel being trained on this protocol and patient registry procedures. All training will be documented and filed at the investigational site and with Bard. The Investigators participating in this patient registry will have had substantial experience previously performing endovascular procedures with DCB PTA, standard PTA, and other adjunctive endovascular procedures (e.g., stent and stent graft procedures) and therefore device training is not required.

14. REPORTING REQUIREMENTS

The Investigator must promptly report to Bard all progress and final reports and any withdrawal of IRB approval at the investigational 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-related AEs, SAEs, or death	Bard and IRB (if applicable)	As soon as possible, but no later than one (1) business day after investigator awareness (see Section 7)
Withdrawal of IRB Approval	Bard	Within 5 business days

Patient Registry Progress	Bard and IRB	At least yearly
---------------------------	--------------	-----------------

15. RECORD RETENTION

The Investigator shall retain all patient registry records for a period of two years after the later of the following two dates: the date on which the patient registry is terminated or is completed.

16. TERMINATION OF PATIENT REGISTRY

Bard reserves the right to suspend enrollment or terminate the patient registry at any time as set forth in the Clinical Study Agreement. Written notice will be provided in advance of such termination. Bard may suspend enrollment or terminate the patient registry at a specific investigational 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.

17. REFERENCES

- 1 Weitz, J.I., Byrne, J., Clagett, G.P., Farkouh, M.E., Porter, J.M., Sackett, D.L., Strandness, D.E., & Taylor, L.M. (1996). Diagnosis and Treatment of Chronic Arterial Insufficiency of the Lower Extremities: A Critical Review. *Circulation*, 94, 3026-3049.
- 2 Hirsch AT, et al. (2006). ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): A collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation*, 113(11): e463–e654.

Appendix 1: Time and Events Schedule

Procedure	Screening	Index Procedure	Hospital Discharge	30 days (± 7d)	6 months (±1 month)	12 months-1 year (±1 month)	24 months-2 year (±1 month)	36 months-3 year (±1 month)
Informed Consent	✓							
Eligibility Criteria	✓	✓						
Demographics	✓							
Medical History / Risk factors	✓							
Treatment Procedural Information		✓						
Adverse Event Assessment		✓	✓	✓	✓	✓	✓	✓
TLR/TVR Assessment		✓	✓	✓	✓	✓	✓	✓
DUS Evaluation / DUS image submission to Core Lab						✓		