ULTRASCORE™
Focused Force PTA Balloon

CLINICAL PROTOCOL

Title:	**A Prospective, Multi-Center, Single-Arm, Real-World Study Assessing the Clinical Use of the Bard® UltraScore™ Focused Force PTA Balloon**
Protocol Number:	**BPV-16-001**
Study Type:	**Post-Market**
Date:	**May 2, 2017**
Version:	**1.0**
Study Device:	**ULTRASCORE™ Focused Force PTA Balloon**
Sponsor:	**Bard Peripheral Vascular, Inc.** 1625 West 3rd Street Tempe, AZ 85281

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Revision History:

Protocol Version	Description of Changes
1.0	Initial Protocol Version

1 PROTOCOL SUMMARY

Title:	A Prospective, Multi-Center, Single-Arm, Real-World Study Assessing the Clinical Use of the Bard® UltraScore™ Focused Force PTA Balloon
Sponsor:	Bard Peripheral Vascular, Inc. 1625 West 3rd Street Tempe, AZ 85281
Objectives:	The objective of this study is to assess the clinical use of the Bard® UltraScore™ Focused Force PTA balloon in a heterogeneous patient population in a real world, on-label clinical application.
Design & Overview:	This is a prospective, multi-center, single-arm, real-world study to assess the clinical use of the Bard® UltraScore™ Focused Force PTA balloon for the treatment of stenotic lesions of the superficial femoral artery (SFA), popliteal artery, and infra-popliteal arteries (posterior tibial, anterior tibial and peroneal arteries). Follow-up for all treated subjects will be performed at hospital discharge, 30 days, and 6 and 12 months post-index procedure.
Study Device:	The UltraScore™ Focused Force PTA balloon is a flexible, over the wire (OTW) catheter shaft with a semi-compliant balloon fixed at the distal end. There are radiopaque markers to aid in visualization of the working length of the balloon during fluoroscopy. Two scoring wires, oriented 180° apart provide focused force upon dilatation. The UltraScore™ Focused Force PTA balloon is compatible with .014" or .035" guidewires. Shaft sizes are either 130cm (.035") or 150cm (.014") and include the GeoAlign® Marking System.
Enrollment:	A maximum of 350 subjects will be treated in the study. This will allow for approximately 175 subjects in an above the knee (ATK) cohort and 175 subjects in a below the knee (BTK) cohort. Endpoint analysis will occur when all subjects have completed the 12 month follow up. All subjects will be followed for 12 months post index-procedure.
Study Sites:	Up to 35 investigational sites in the United States (US) will participate.
Study Population:	Male or non-pregnant female ≥ 21 years of age with an expected lifespan sufficient to allow for completion of all study procedures. Eligible subjects will have a stenotic lesion of the SFA, popliteal, or infra-popliteal arteries. ATK subjects will be those that have a lesion of the SFA or popliteal artery. BTK subjects will be those that have a lesion in the infra-popliteal arteries (posterior tibial, anterior tibial or peroneal arteries).

Inclusion Criteria	**Inclusion Criteria** 1. Subject must voluntarily sign and date the Informed Consent Form (ICF) prior to collection of study data or performance of study procedures. 2. Subject must be either a male or non-pregnant female ≥ 21 years of age with an expected lifespan sufficient to allow for completion of all study procedures. 3. Subject must be willing to comply with the protocol requirements, including the follow-up procedures. 4. Subject must have a target lesion (de novo lesion or prior failed treatment) that can be treated with the UltraScore™ Focused Force PTA balloon according to the Instructions for Use (IFU). Only a target lesion in the SFA, popliteal, or infra-popliteal arteries (posterior tibial, anterior tibial, or peroneal arteries) may be treated for this study. 5. Subject must have an ATK or BTK target lesion with at least one vessel run-off. 6. The target lesion must be able to be crossed using a guidewire (use of chronic total occlusion (CTO) or atherectomy is allowed).

Exclusion Criteria	**Exclusion Criteria** 1. Subjects that are to receive one or more stents as adjunctive therapy at the target lesion (bail out stenting is allowed). 2. The subject has a single target lesion that involves both ATK and BTK arteries. 3. The subject has a target lesion in a previously placed stent or stent graft (in-stent restenosis). 4. The subject has a lesion, which in the opinion of the Investigator, would preclude safe use of the UltraScore™ Focused Force PTA balloon. 5. The subject has a flow limiting dissection at the target lesion prior to use of the UltraScore™ Focused Force PTA balloon. 6. The subject has acute limb ischemia. 7. The subject has been assessed Rutherford category 6. 8. The subject has a known allergy or sensitivity to contrast media, which cannot be adequately pre-medicated. 9. The subject has another medical condition or is currently participating in an investigational drug or another device study that, 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.
Procedures:	All subjects will undergo a clinical evaluation at screening (prior to index procedure); after consent is voluntarily obtained study subjects will be treated with the UltraScore™ Focused Force PTA balloon per the site's standard of care and adhering to the IFU. Examinations, evaluations, procedural preparation, angiography, treatment and hospital discharge procedures will be conducted per the study site's standard of care. Investigators are able to treat 1 (one) lesion per patient in this study. If a subject has multiple eligible lesions, the investigator may use his or her medical judgment as to which becomes the study target lesion. Standard of care treatment of non-target lesions is allowed. Subjects with treated ATK lesions will undergo clinical evaluations with a Duplex Ultrasound (DUS) performed at 30 days and 6 and 12 months post-index procedure. Subjects with treated BTK lesions will undergo clinical evaluations performed at 30 days and 6 and 12 months post-index procedure. DUS is not required for subjects with a treated BTK lesion for this study.

Primary Endpoints	**Primary Endpoints** • Achieve optimal PTA results (≤30% residual stenosis, without major flow limiting dissection). • Achieve technical success of use where the UltraScore™ Focused Force PTA balloon is delivered to the target lesion and inflated without movement.
Secondary Endpoints:	**Secondary Endpoint** After UltraScore™ Focused Force PTA balloon: • Rate of bail-out stenting due to dissection Through follow-up (at 30 days and 6 and 12 months): • Freedom from Target Lesion Revascularization (TLR) • Freedom from major amputation (above the ankle) • Improved clinical measures from baseline (ABI, Rutherford) • Primary patency for ATK subjects only (as measured by DUS core lab; a PSVR ≥2.5 suggests 50% restenosis)
Other Analyses:	Other Analyses • Target lesion characteristics (e.g. location, type) • Procedure details (e.g. duration, inflation times, inflation pressures, number of inflations to efface/dilate the target lesion) • Adjunctive therapies before and after UltraScore use Subgroup Analyses • Comparison of primary and secondary endpoints between above the knee (ATK) and below the knee (BTK) subjects • Outcomes based on adjunctive treatments

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DUS Core Laboratory	**DUS Core Lab** Ido Weinberg, M.D. VasCore 62 Staniford Street Boston, MA 02114 Telephone: (617) 726-2256

Principal Investigator's Responsibility

Prior to participation in the UltraScore™ Focused Force PTA Balloon Study (the UltraScore study), 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 beginning enrollment. The PI must receive Bard-sponsored training prior to beginning enrollment. The PI (or designee) is responsible for training all Sub-Investigators prior to performing any data collection or study-related procedures.

The PI must also:

- Conduct the study in accordance with the study protocol, the signed CSA, the Declaration of Helsinki, Health Insurance Portability and Accountability Act (HIPAA) requirements, Good Clinical Practice (GCP) including 21 CFR Parts 50, 54, and 56.
- Ensure that the study 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 study procedure; using the current IRB 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, 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 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 study, including obtaining and documenting the Informed Consent process, compliance with the study protocol, obtaining a 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 UltraScore 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, HIPAA requirements, GCP including 21 CFR Parts 50, 54, and 56.

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 UltraScore 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, HIPAA requirements, GCP including 21 CFR Parts 50, 54, and 56.

I agree to complete training prior to performing any data collection or study-related procedures.

_____
Sub-Investigator Name (print)

_____ _____
Sub-Investigator Signature Date

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2 INTRODUCTION

The Bard® UltraScore Study is a prospective, multi-center, single-arm, real-world study assessing the clinical use of the Bard® UltraScore™ Focused Force PTA balloon for the treatment of stenotic lesions of the superficial femoral artery (SFA), popliteal artery, and infra-popliteal arteries.

This study 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 and Rationale

Peripheral arterial disease (PAD) occurs when a narrowing, or blockage, develops in the arteries; PAD most commonly affects the legs. 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, gangrene and amputation. Percutaneous transluminal angioplasty (PTA) has long been the first step of treating a stenosed artery. Other treatments available include atherectomy and other vessel preparation, and more recently, treatment with a drug coated balloon with or without stenting.

2.2 Study Rationale

This study is being done to provide physicians with real world data on the outcomes of use of the UltraScore™ Focused Force PTA balloon, including optimal PTA results and long-term freedom from clinical target lesion revascularization (TLR), major amputation, and patency. For this study, optimal PTA results are those where ≤30% residual stenosis remains after use of the UltraScore™ Focused Force PTA balloon.

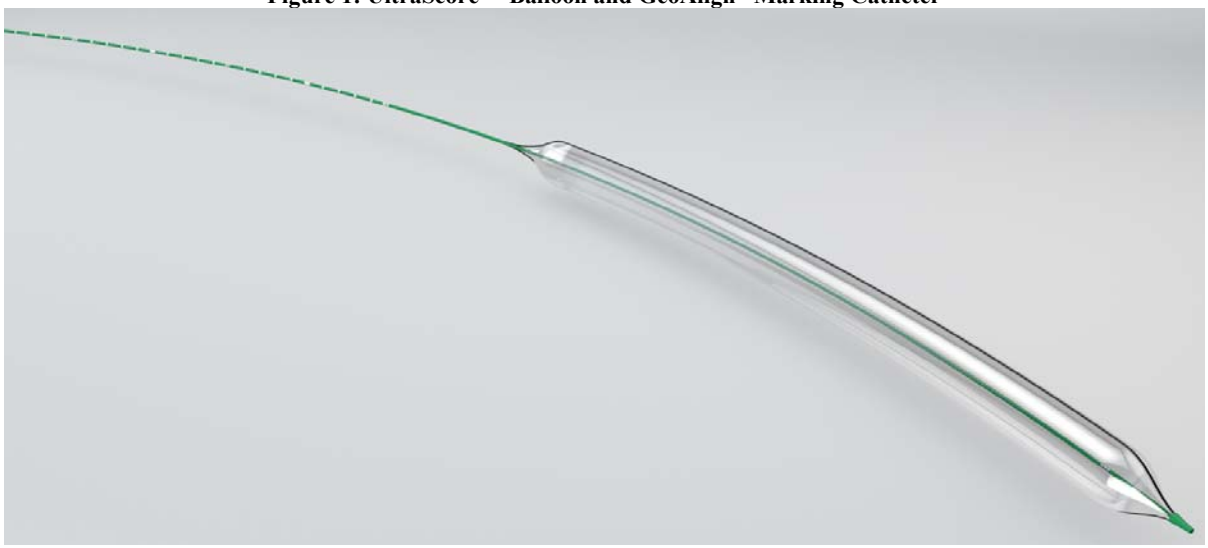
2.3 Device Description

2.3.1 UltraScore™ Focused Force PTA Balloon

The UltraScore™ Focused Force PTA balloon is a flexible, over the wire (OTW) catheter shaft with a semi-compliant balloon fixed at the distal end. There are radiopaque markers to aid in visualization of the working length of the balloon during fluoroscopy. Two scoring wires, oriented 180° apart provide focused force upon dilatation.

The UltraScore™ Focused Force PTA balloon is compatible with .014” or .035” guidewires. Shaft sizes are either 130cm (.035”) or 150cm (.014”) and include the GeoAlign® Marking System.

Figure 1: UltraScore™ Balloon and GeoAlign® Marking Catheter



3 STUDY DESIGN

This study is a prospective, multi-center, single-arm, real-world study in the United States assessing the clinical use of the UltraScore™ Focused Force PTA balloon.

A maximum of 350 subjects will be treated in the study. This will allow for approximately 175 subjects in an above the knee (ATK) cohort and 175 subjects in a below the knee (BTK) cohort. ATK subjects will be those that have a target lesion of the SFA or popliteal artery. BTK subjects will be those that have a target lesion in infra-popliteal arteries (posterior tibial, anterior tibial, and peroneal arteries). For this study, ATK arteries (SFA and popliteal) will end at the takeoff of the first tibial artery.

Treated subjects will be followed for 12 months post-index procedure. Endpoint analysis will occur when all subjects have completed the 12 month follow up. No site will be allowed to enroll more than 20% of the overall number of subjects to ensure the study be reasonably well–balanced.

The UltraScore device has been cleared for use by the F.D.A. The use of UltraScore will be done within the indications for use found in the product IFU. A duplex ultrasound (DUS) will be done at 30 days and 6 and 12 months post-index procedure for ATK subjects. Otherwise, there are no additional treatments or exams that are required to take place within this study. There will be minimal patient activities that will be conducted for data collection purposes for this study in addition to routine standard of care procedures, including:

- The subjects (or legally authorized representative) signing an informed consent form (ICF);

- Subjects with a treated ATK target lesion will undergo clinical evaluations with a Duplex Ultrasound (DUS) performed at 30 days and 6 and 12 months post-index procedure;
- Subjects with a treated BTK target lesion will undergo clinical evaluations performed at 30 days and 6 and 12 months post-index procedure. DUS is not required for subjects with a treated BTK lesion for this study;

4 STUDY ENDPOINTS

4.1 Primary Endpoint

4.1.1 Primary Endpoints

See section 7.4 for primary endpoint analysis discussion.

- Achieve optimal PTA results (≤30% residual stenosis, without major flow limiting dissection)
- Achieve technical success of use where the UltraScore™ Focused Force PTA balloon is delivered to the target lesion and inflated without movement

4.2 Secondary Endpoints

Several secondary endpoints will be analyzed as part of this study. See section 7.5.

After UltraScore™ Focused Force PTA balloon:

- Rate of bail-out stenting due to dissection

Through 12 months follow-up:

- Freedom from TLR
- Freedom from major amputation (above the ankle)
- Improved clinical measures from baseline (ABI, Rutherford)
- Primary patency for ATK subjects only (as measured by DUS core lab; a PSVR ≥2.5 suggests 50% restenosis)

5 STUDY POPULATION

This study will include a maximum of 350 subjects at up to 35 U.S. sites. The following describe the clinical eligibility (inclusion and exclusion) criteria for this study.

5.1 Inclusion Criteria

1. Subject must voluntarily sign and date the Informed Consent Form (ICF) prior to collection of study data or performance of study procedures.

2. Subject must be either a male or non-pregnant female ≥ 21 years of age with an expected lifespan sufficient to allow for completion of all study procedures.
3. Subject must be willing to comply with the protocol requirements, including the follow-up procedures.
4. Subject must have a target lesion (de novo lesion or prior failed treatment) that can be treated with the UltraScore™ Focused Force PTA balloon according to the Instructions for Use (IFU). Only a target lesion in the SFA, popliteal, or infra-popliteal arteries (posterior tibial, anterior tibial, or peroneal arteries) may be treated for this study.
5. Subject must have an ATK or BTK target lesion with at least one vessel run-off.
6. The target lesion must be able to be crossed using a guidewire (use of chronic total occlusion (CTO) or atherectomy is allowed).

5.2 Exclusion Criteria

1. Subjects that are to receive one or more stents as adjunctive therapy at the target lesion (bail out stenting is allowed).
2. The subject has a single target lesion that involves both ATK and BTK arteries.
3. The subject has a target lesion in a previously placed stent or stent graft (in-stent restenosis).
4. The subject has a lesion, which in the opinion of the Investigator, would preclude safe use of the UltraScore™ Focused Force PTA balloon.
5. The subject has a flow limiting dissection at the target lesion prior to use of the UltraScore™ Focused Force PTA balloon.
6. The subject has acute limb ischemia.
7. The subject has been assessed Rutherford category 6.
8. The subject has a known allergy or sensitivity to contrast media, which cannot be adequately pre-medicated.
9. The subject has another medical condition or is currently participating in an investigational drug or another device study that, 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.

6 STUDY / TREATMENT PROCEDURES

Appendix B displays the required schedule for subject treatment and evaluation.

6.1 Subject Screening and Baseline Evaluations

During the screening and recruitment process, 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. All study procedures will be documented in the medical record and/or source document and on study electronic Case

Report Forms (eCRFs). The following specific procedures will be conducted and documented.

6.1.1 Informed Consent

The background and purpose of the study, participation requirements, as well as the potential benefits and risks of the procedure(s) must be explained to the subject. Prior to the conduct of any protocol-specific procedures (including any procedure performed to determine subject eligibility); the subject must voluntarily provide consent and comply with applicable national and state privacy laws (e.g., HIPAA requirements). The ICF templates are standalone documents to facilitate revision(s), as necessary, without requiring a protocol amendment.

6.1.2 Eligibility

The subject's eligibility for study enrollment will be reviewed and documented. The documentation should indicate that the subject met all study (eligibility) criteria at the time of screening and enrollment (see Sections 5.1 and 5.2).

6.1.3 Baseline Examinations

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

- The subject's demographic information (e.g., date of birth, sex, etc.)
- The subject's medical history, including antiplatelet/anticoagulation medications
- The subject's risk factors (e.g., diabetes, hypertension, dyslipidemia, etc.)
- Rutherford Classification
- Ankle Brachial Index (ABI) for treated limb only

6.2 Index Procedure

This study is collecting data on an F.D.A. cleared medical device, consistent with the product IFU. Examinations, evaluations, procedural preparation, angiography, treatment, and hospital discharge procedures will be conducted per the investigational site's standard of care. Treatment with the UltraScore™ Focused Force PTA balloon will be per the investigational site's standard of care and adhere to the IFU. For detailed information on device use and procedural and medication recommendations, reference the IFU. Data collected for this study include:

- Demographics and procedural information (e.g., target lesion type, TASC classification, location and length, degree of calcification, adjunctive treatment(s), baseline stenosis, etc.)

- Procedural outcomes (e.g., residual stenosis, flow limiting dissections, target lesion adjunctive treatments, etc.)

Investigators are able to treat one (1) target lesion as the study lesion, per patient in this study. The investigator may use his or her medical judgment as to which lesion becomes the study target lesion if a subject has multiple eligible lesions.

ATK subjects will be those that have a target lesion of the SFA or the popliteal artery. BTK subjects will be those that have a target lesion in the infra-popliteal arteries (posterior tibial, anterior tibial, and peroneal arteries). For this study, ATK arteries (SFA and popliteal) will end at the takeoff of the first tibial artery.

Lesions that cross from ATK to BTK may not be treated as the study target lesion.

Diffuse lesions will be considered separate lesions if there is 2 cm of healthy tissue between lesions.

Standard of care treatment of non-target lesions is allowed.

See the Instructions for Use for inflation and hold time recommendations.

Subjects are considered enrolled in the study when the UltraScore balloon is introduced into the subject.

If an angiographically acceptable result cannot be obtained after two inflations of the UltraScore™ balloon (>30% residual stenosis), the subject should be considered a treatment failure. Subjects will continue to be seen at the protocol specified follow-up time points.

6.2.1 Adjunctive Treatment of the Target Lesion

Adjunctive treatment of the target lesion before or after use of the UltraScore™ balloon as part of standard of care procedures is allowed. All adjunctive treatments of the target lesion will be documented on the appropriate eCRF. Care should be taken to limit stent usage in the study lesion. Bail out stenting and stenting of non-study lesions is acceptable at any time.

6.2.2 Angiographic Imaging

Angiographic imaging is required as part of this study. Below is a list of angiographic requirements to be completed for each procedure.

It is required that the following angiographic images of the target lesion are captured:

- **Baseline target lesion (diagnostic);**
- **During UltraScore™ Focused Force PTA balloon inflation(s);**
- **Post UltraScore™ Focused Force PTA balloon inflation(s);**
- **Final run (after adjunctive treatment), with 1 vessel run-off**

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 a calibrated measurement ruler so that the Angiographic Core Lab may properly assess the target lesion characteristics (e.g., location, 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.

6.2.3 Flow Limiting Dissections

Major flow limiting dissections are being collected for this study and reporting is restricted to grades D, E, and F per the National Heart, Lung, and Blood Institute (NHLBI)[1]. See below.

Defined as:

- Type A: Radiolucent areas within the artery lumen during contrast injection with minimal or no persistence of contrast after the dye has cleared.
- Type B: Parallel tracts, intimal flaps or double lumens separated by a radiolucent area during contrast injection with minimal or no persistence of contrast after the dye has cleared.
- Type C: Contrast appears angiographically outside the artery lumen with persistence of contrast in the area after clearance of dye from the artery lumen.
- Type D: Spiral luminal filling defects.
- Type E: Appearance of new and persistent filling defects with reduced flow.
- Type F: Total occlusion without distal flow.

6.3 Post-Index Procedure and Discharge

Medication therapy and medical treatment will be conducted at the discretion of the Investigator per the investigational site's standard of care. Subjects will be treated and discharged according to the site's standard of care.

- *Documentation of Adverse Events (AEs):* Documentation of occurrence of AEs since the index procedure (see Section 8).

6.4 Subject Follow-Up

All study subjects are to be followed according to the investigational site's standard of care practices. In addition to the standard of care visits, study participants will either return to the site or be reached by telephone at the following intervals:

- *Follow-up Contact 1:* 30 ± 7 days post-procedure;
- *Follow-up Contact 2:* 6 months ± 30 days post-procedure;
- *Follow-up Contact 3:* 12 months ± 30 days post-procedure.

Subjects with a treated ATK target lesion will return to the site to undergo a Duplex Ultrasound (DUS) performed at 30 days and 6 and 12 months post-index procedure. DUS imaging of the target lesion employing the "Ultrasound Guidelines" shall be uploaded or sent to the core laboratory for analysis.

Subjects with a treated BTK target lesion will return to the site for a standard of care clinical evaluation at 30 days and 6 and 12 months post-index procedure. DUS is not required for BTK subjects.

The following will be collected during follow-up and documented in the subject's medical record at the site:

- *Documentation of Status:* Determine and document whether the subject has undergone a TLR or target vessel revascularization (TVR), amputation procedure since last contact, and antiplatelet/anticoagulation medications. Angiographic imaging of any TLR/TVR must be sent to the angiographic core lab for analysis. Measurement of target limb ABI and Rutherford Classification.
- *Documentation of AEs:* Documentation of occurrence of AEs since last follow-up (see Section 8).

6.5 Subject Discontinuation

Following the index procedure, subjects should remain in the study until completion of required follow-up. The follow-up period for this study is 12 months (365 ± 30 days).

However, a subject's participation may be discontinued. Potential reasons for discontinuation may include, but are not limited to the following:

- *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. This does not apply to missed visits, where the subject misses one of the follow up contact time points, but completed a subsequent one (when a subject misses two consecutive follow-ups with failure of contact attempt, the subject may be considered LTF and withdrawn from the study). Before the site considers a subject LTF, written agreement should be obtained from the Sponsor.

- *Withdrawn Consent:* The subject requests to terminate his/her participation in the study (the Investigator must attempt to identify and document the reasons for termination).

- *Death:* The subject becomes deceased. If known, the cause of death must be documented (see Section 8.5).

- *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 the Sponsor if the subject is repeatedly noncompliant with study procedures.

- *Study Termination:* The study is terminated by the Sponsor (see Section 11.9).

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

7 STATISTICAL ANALYSIS PLAN

This section describes the planned statistical analyses for this study. 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.

7.1 Study Hypothesis

There is no formal statistical hypothesis for this study.

7.2 Sample Size Considerations

This study will enroll up to a maximum 350 subjects at approximately 35 sites. The sample size is based on potential adequacy of data to meet the study objectives; it is not based on any statistical consideration.

7.3 Data Analysis

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

Study 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.

Primary endpoints will be reported by rate and with a 95% confidence interval. The calculation of rates will be based on available data. Missing data will not be imputed.

7.4 Evaluation of Primary Endpoints

Primary endpoints are:

- Achieve optimal PTA results (≤30% residual stenosis, without flow limiting dissection)
- Achieve technical success of use where the UltraScore™ Focused Force PTA balloon is delivered to the target lesion and inflated without movement

7.5 Evaluation of Secondary Endpoints

The following secondary endpoints will be reported at the index procedure or through 12 months at these time points: 30 days, 6 months, and 12 months.

After UltraScore™ Focused Force PTA balloon:

- Rate of bail-out stenting due to dissection

Through follow-up (30 days, 6 and 12 months):

- Freedom from TLR
- Freedom from major amputation (above the ankle)
- Improved clinical measures from baseline (ABI, Rutherford)
- Primary patency for ATK subjects only (as measured by DUS core lab; a PSVR ≥2.5 suggests 50% restenosis)

7.6 Other Analyses

- Target lesion characteristics (e.g. location, type)
- Procedure details (e.g. duration, inflation times, inflation pressures, number of inflations to efface/dilate the target lesion)
- Adjunctive therapies before and after UltraScore use

7.7 Subgroup Analyses

- Primary and secondary endpoints will be explored between above the knee (ATK) and below the knee (BTK) subjects
- Primary and secondary endpoints will be explored between different adjunctive treatments

8 ADVERSE EVENTS AND DEVICE DEFICIENCIES

The PI is responsible for the detection, documentation and reporting to the Sponsor of events meeting the criteria and definitions set forth in this Section. Collection and reporting of AEs/SAEs will be limited to those events that are device and/or procedure related as outlined below and reporting will begin immediately following subject enrollment, during the index procedure.

8.1 Definitions of Events

8.1.1 Definition of Adverse Events (AEs)

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 UltraScore device and/or procedure.

- Device-Related: This category should be restricted to AEs directly attributable to the UltraScore™ Focused Force PTA balloon device used as part of the procedure.

- Procedure-Related: This category should be restricted to AEs directly attributable to the portion of the procedure when the UltraScore™ Focused Force PTA balloon is used, including insertion, inflation, deflation and removal of the balloon. AEs that arise from arterial access and adjunctive therapies (pre- and post-UltraScore use) should not be reported in this study.

8.1.2 Serious Adverse Events (SAEs)

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). A SAE is an AE that:

1) Led to a death; or

2) Led to serious deterioration in the health of the subject, that either resulted in:

   a) A life-threatening illness or injury;

   b) A permanent impairment of a body structure or a body function;

   c) In-patient or prolonged existing 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 conditions or procedures required by this study (including subsequent re-interventions assessed in study endpoints), without serious deterioration in health, are not considered SAEs.

To report an SAE, an event must first meet the protocol definition of an AE as described in section 8.1.

8.2 Severity of Adverse Events

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

- *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 additional sequelae.

- *Moderate:* Interferes with the subject's usual activity and/or requires additional intervention and/or treatment, and may have additional sequelae.

- *Severe:* Symptom(s) causing severe discomfort to the subject and/or significant impact on the subject's usual activity. Additional intervention and or treatment are necessary. Additional sequelae occur.

8.3 Relationship of Adverse Event to Device(s)/Procedure

Investigators will assess each AE for its relationship to the device or procedure. 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 peripheral balloon dilatation with the UltraScore balloon are found in the IFU.

8.4 Reporting of Events

All AEs determined to be related to the device/procedure, should be recorded on the appropriate eCRF.

It is the responsibility of the Investigator to notify the IRB of applicable AEs in accordance with the governing IRB requirements.

See section 11.7 for all study reporting requirements.

8.5 Subject Death

Subject death, for any reason during the study, must be reported to the Sponsor within one (1) working day of the investigational site becoming aware of the event. Notification of a subject death should be done by email, telephone call, or fax.

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.

8.6 Device Deficiencies

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 defect. 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 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 the Sponsor. **The device(s) should be returned to the Sponsor as outlined in the sites regulatory binder.**

If the device deficiency was associated with an AE, the reporting provisions for AEs apply.

Any device deficiency that did not lead to an AE but could have led to one, if suitable action had not been taken, if intervention had not been made or if circumstances had been less fortunate must be reported to the Sponsor within one (1) working day of the event per Section 8.4.

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

9 DATA COLLECTION AND RECORD MAINTENANCE

The Investigator is responsible for ensuring the complete and accurate recording of patient study data in the appropriate sections of the source documentation and eCRFs 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.

9.1 Electronic Data Capture (EDC)

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

9.2 Record Retention

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

10 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 investigational 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.

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.

10.1 Site Initiation Visits

Before the study begins, the study monitors 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 study. 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.

10.2 Ongoing Monitoring Visits

The study monitor will conduct periodic on-site or remote inspection and monitoring of the investigational site and records to ensure compliance with this protocol.

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. The study monitor will confirm that the ICF to be used is the version approved by the IRB and verify that all necessary documents are on file at the investigational site.

10.3 Final Monitoring Visit

At the completion of the study, the study monitor will conduct a final visit. The purpose of this visit is to collect all outstanding study 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 study are met. The actions and observations made at this visit will be recorded and filed.

11 ADMINISTRATIVE REQUIREMENTS

11.1 Investigator and Site 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 study subjects. The curriculum vitae (CV) of the Investigator(s), Sub-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 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 study as per the Clinical Study Agreement (CSA).

11.2 Training

Each investigator and appropriate site personnel will be trained on this protocol and study procedures. All training will be documented and filed at the investigational site and with Bard. The Investigators participating in this study will have had substantial experience previously performing endovascular procedures with scoring balloons (including VascuTrak), standard PTA, and other adjunctive endovascular procedures (e.g., DCB PTA, atherectomy, stent and stent graft procedures). Specific training on the UltraScore™ Focused Force PTA balloon will be completed during the initiation visit.

11.3 Ethical and Regulatory Considerations

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

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 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) will be followed. 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.

After this explanation and before any study procedure is conducted, and before entering the study, the subject must voluntarily provide consent. The subject will receive a copy of his/her signed ICF.

11.4.1 Confidentiality

All information and data sent to the Sponsor or its designees that constitutes protected health information of study subjects 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.

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

11.6 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;
- CVs, signed and dated within 2 years of study start for the PI;
- CVs for Study Coordinator(s);
- Signed Clinical Study Agreement (CSA) by PI (or designee);
- Signed "Protocol Signature Page" by PI;
- Signed "Financial Disclosure Statement" by PI;
- Written approval from the IRB of both the protocol and ICF.

11.7 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:

Table 3: Reports and Notifications Required from Clinical Investigators

Event/Report Type:	Notification to:	Time to Notification:
Device-related AEs/SAEs	Bard and IRB (as applicable)	As soon as possible, but no later than one (1) working day after investigator awareness and per local IRB requirements.
Procedure-related AEs / SAEs	Bard and IRB (as applicable)	As soon as possible and per local IRB requirements.
Subject Death	Bard and IRB	As soon as possible, but no later than one (1) working day after investigator awareness and per local IRB requirements. Relevant documentation to be submitted to the Sponsor no later than three (3) working days (See Section 8.5).
Device Deficiencies	Bard and IRB (as applicable)	As soon as possible. **The device(s) should be returned to Bard.** 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 the Sponsor within one (1) working day of the event.
Protocol deviations (major*)	Bard and IRB	As soon as possible, but in no event later than five (5) working days after emergency occurs (see Section 11.5).
Withdrawal of IRB approval	Bard	Immediately by telephone followed by a copy of the notification within five (5) working days.
Study progress report	Bard and IRB	At regular intervals or annually
Failure to obtain ICF	Bard	Within five (5) working days.
Final report	Bard	Within three (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.

11.8 Publication Policy

At the conclusion of this 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

multicenter results. A description of this study will be available on http://www.clinicaltrials.gov, as required by U.S. law.

11.9 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 provided in advance of such termination. Bard may suspend enrollment or terminate the patient study 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.

12 REFERENCES

1 Coronary Artery angiographic changes after PTCA: Manual of Operations NHBLI PTCA Registry 1985; 6:9.

13 APPENDICES

13.1 Appendix A – Abbreviations and Acronyms

Abbreviation/Acronym	Definition
AE	Adverse Event
ASA	Aspirin
CFR	Code of Federal Regulations
CSA	Clinical Study Agreement
CTO	Chronic Total Occlusion
CV	Curriculum Vitae
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HIPAA	The Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
LTF	Lost to Follow-up
MM	Medical Monitor
NDA	Non-Disclosure Agreement
PI	Principal Investigator
PTA	Percutaneous Transluminal Angioplasty
SAE	Serious Adverse Event
US	United States

13.2 Appendix B – Time and Events Schedule

	Screening / Index Procedure / Discharge	30 Days (±7 days)	6 Months (±30 days)	12 Months (±30 days)
Informed Consent	✓			
Demographics / Medical History	✓			
Physical Examination	✓			
Rutherford (Category and Grade)	✓	✓	✓	✓
Resting ABI (Treated Limb only)	✓	✓	✓	✓
Anticoagulation/Anti-platelets	✓	✓	✓	✓
Eligibility Criteria	✓			
Angiographic Image Collection	✓			
Duplex Ultrasound§		✓	✓	✓
TLR Assessment		✓	✓	✓
Adverse Event Assessment	✓	✓	✓	✓

§ATK subjects only