PRISTINE POST-MARKET STUDY

Clinical Investigational Protocol

Protocol Title:	**A Prospective, Multi-Center, Single-Arm Clinical Study of the Pristine™ Long-Term Hemodialysis Catheter**
Short Title:	**Pristine Post-Market Study**
Protocol Number:	**BDPI-21-001**
Version Date:	**19 January 2022**
Version Number:	**1.0**
Study Device:	**Pristine™ Long-Term Hemodialysis Catheter**
Study Type:	**Post-Market**
Sponsor Name:	**Becton, Dickinson and Company (BD)**
Legal Registered Address:	**Bard Peripheral Vascular, Inc. 1625 West 3rd Street Tempe, AZ 85281, USA**
Sponsor Contact:	**Joshua Black Associate Clinical Project Manager 520-599-6124 Joshua.black@bd.com**

Regulatory Agency Identifier Number(s)
N/A. Clinicaltrials.gov NCT ID # will be added before study start.

Approval Date: 02/04/2022

National Principal Investigator:
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Docusign NPI

Medical Monitor:
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Docusign Medical Monitor

Version History

Version Number	Date	Type
1.0	01/19/2022	Original

SPONSOR PROTOCOL APPROVAL

Signature below indicates approval of the protocol as written.			
Individual or function	**Name**	**Signature**	**Date**
Medical Affairs Team Representative	Anna Lovas	*This document is signed electronically in the eTMF system*	
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PRINCIPAL INVESTIGATOR AGREEMENT PAGE

Investigator Responsibilities

1. Prior to participation in this study, the Investigator or Institution must sign the Clinical Study Agreement (CSA) and obtain written approval from the appropriate Institutional Review Board (IRB)/Ethics Committee (EC).
2. The Investigator must receive BD-sponsored training prior to site activation. The Investigator is responsible for ensuring that all Sub-Investigators and clinical staff are adequately trained prior to performing any data collection or study-related procedures.
3. The Principal Investigator shall ensure that the study is conducted in accordance with the study protocol, any modifications as requested by the IRB/EC, the signed CSA, the ethical principles of the Declaration of Helsinki, Good Clinical Practice (ICH E6) / ISO 14155:2020), and applicable national/regional regulations and laws.
4. If applicable, ensure that written informed consent is obtained from each participant prior to the conduct of any study procedure, using the current IRB/EC approved Informed Consent Form.

I have read and understand the contents of this study protocol. I agree to follow and abide by the requirements set forth in this document. I agree to conduct the trial in accordance with the study protocol, the signed Clinical Study Agreement, and Good Clinical Practice (GCP) as well as applicable FDA and ISO regulations (e.g., 21 CFR Parts 50, 54, 56, and 812; ISO 14155:2020). I agree to participate in BD-Sponsored training prior to performing any data collection or study-related procedures.

Agreed to by (Investigator):

_____
Printed Name – Investigator

_____
Signature – Investigator

_____
Site Number

_____
Date

Table of Contents

Abbreviations

ADE	Adverse device effect
AE	Adverse event
Bard	C. R. Bard, Inc.
BD	Becton Dickinson and Company
BMI	Body Mass Index
CFR	Code of Federal Regulations
CI	Confidence Interval
CIP	Clinical Investigation Protocol
CRBSI	Catheter-related Blood Stream Infection
CRF	Case Report/Record Form
CRO	Contract Research Organization
CVC	Central Venous Catheter
DFMEA	Design failure mode and effect analysis
DOPPS	Dialysis Outcomes and Practice Patterns Study
eCRF	Electronic Case Report Form
ESRD	End-Stage Renal Disease
EtO	Ethylene Oxide
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IFU	Instructions for Use
IRB/EC	Institutional or Independent Review Board/Ethics Committee
KDOQI	Kidney Disease Outcomes Quality Initiative
LTF	Lost-to follow-up
NKF	National Kidney Foundation
SADE	Serious adverse device effect
SAE	Serious Adverse Event
SD	Standard Deviation
SoA	Schedule of Activities
SOC	Standard of Care
UADE	Unexpected Adverse device effect
UFMEA	User Failure Mode Effects Analysis

1 PROTOCOL SUMMARY

1.1 Synopsis

STUDY SYNOPSIS	
Version/Date:	1.00, 19/Jan/2022
Study Number:	BDPI-21-001
Study Title:	A Prospective, Multi-Center, Single-Arm Clinical Study of the Pristine™ Long-Term Hemodialysis Catheter
Sponsor:	Becton Dickinson Peripheral Intervention
Development Phase:	Post-Market
Study Product(s):	Test product(s): Pristine™ Long-Term Hemodialysis Catheter Reference/Comparator product(s): Not Applicable Ancillary Product(s): As per the Device Instructions for Use (IFU)
Product Intended Use:	The Pristine™ Long-Term Hemodialysis Catheters are indicated for use in attaining short-term or long-term vascular access for hemodialysis, apheresis, and infusion. Access is attained via the jugular vein, subclavian vein, or femoral vein. Catheters longer than 40 cm are intended for femoral vein insertion. Catheters may be inserted percutaneously.
Rationale:	The purpose of this clinical investigation is to provide clinical evidence to further demonstrate reasonable assurance of safety and performance of the Pristine™ Long-Term Hemodialysis Catheter to provide short- and long-term hemodialysis access.
Planned Study Period:	Q2 FY2022 through Q3 FY2024
Planned Sample Size:	A total of approximately 142 enrolled participants will be included in this investigation at up to a maximum of 15 investigational sites in the United States.

<table>
<tr><td>Objectives and Endpoints:</td><td>
<table>
<tr><th>Objective(s)</th><th>Endpoint(s)</th></tr>
<tr><td>Primary</td><td></td></tr>
<tr><td>• Assess the overall complication rate of the Pristine™ Catheter against an overall hemodialysis catheter complication rate derived from clinical literature.</td><td>• The combined Primary Endpoint is the overall rate of infectious complications and non-infectious complications requiring revision to maintain patency and improve access performance at 3 months, evaluated against a performance goal (PG) derived from the Dialysis Outcomes and Practice Patterns Study (DOPPS) data.</td></tr>
<tr><td>Secondary</td><td></td></tr>
<tr><td>• Assess the short- and long-term safety and performance of the Pristine™ Catheter.</td><td>At 1-month, 3-months, 6-months, and 12 months post-index procedure:
• Rate of freedom from catheter-related bloodstream infection (CRBSI)
• Rate of freedom from Device and/or Procedure-related adverse events
• Rate of Technical Success
• Overall Participant Survival Rate
• Overall Catheter Survival Rate
• Overall Patency Rate</td></tr>
<tr><td>Exploratory</td><td></td></tr>
<tr><td>• Determine and characterize the short- and long-term safety and performance of the device and ancillary kit components.</td><td>• Kit Component Safety and Performance</td></tr>
</table>
</td></tr>
<tr><td>Study Design and Overview:</td><td>This is a prospective, multi-center, single-arm study designed to assess the safety and performance of the Pristine™ Long-Term Hemodialysis Catheter.

Follow-up for all enrolled participants will be performed at 1-month, 3-months, 6-months, and 12-months post-Index Procedure.</td></tr>
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Study Population:	Approximately 142 male or non-pregnant female participants in the US, ≥18 years of age who meet indications for use of the Pristine™ Catheter will be enrolled and have the Pristine™ Catheter placed in the United States (US).
Eligibility Criteria:	**Clinical Inclusion Criteria** A participant must meet ALL the following criteria to be enrolled in the study: 1) The participant or legally designated representative must voluntarily sign and date the approved Informed Consent Form (ICF) prior to collection of study-specific data or performance of study-specific procedures. 2) The participant must be willing and able to comply with protocol requirements, including all study visits and procedures. 3) The participant must be either a male or non-pregnant female ≥18 years of age. 4) The participant must have a diagnosis of End Stage Renal Disease with indication for a tunneled dialysis catheter creation. 5) Participant must require chronic hemodialysis treatments 3 times per week with intended use of the Pristine™ Long-Term Hemodialysis Catheter. 6) The participant meets the indications for hemodialysis use and does not meet any of the contraindications per the Pristine Instructions for Use (IFU). 7) The participant must have a patent jugular vein or subclavian vein. **Clinical Exclusion Criteria** A participant must NOT meet ANY of the following criteria to be enrolled in the study: 1) The participant has known central venous stenosis 2) Based on the local primary investigator's discretion, the patient would not be an appropriate study candidate.

	3) The participant has already undergone an AVF or AVG procedure and is awaiting maturation. 4) The participant has an active infection at the time of study enrollment. 5) The participant has a presence of bacteremia or infection within 7 days prior to enrollment. 6) The participant has a history neutropenia or a history of severe immunodeficiency disease. 7) The participant has uncontrolled abnormal coagulation parameters and are at additional risk for clotting or excessive bleeding at time of enrollment per physicians opinion. 8) The participant has a known allergy, intolerance or sensitivity to heparin, or previous incidence of heparin-induced thrombocytopenia. 9) The participant has a known allergy or hypersensitivity to any of the device materials or Ethylene oxide (EtO). 10) The participant has another medical condition or treatment, which in the opinion of the investigator, the participant may be non-compliant with the protocol, confound the data interpretation, or is associated with a life expectancy insufficient to allow for completion of study procedures and follow-up. 11) The participant is currently participating in an investigational drug or another device study that has not completed the study treatment or that clinically interferes with the study endpoints. Note: Studies requiring extended follow-up visits for products that were investigational but have since become commercially available, are not considered investigational studies.
Study Methodology:	All participants will undergo a clinical evaluation at the Screening Visit (prior to Index Procedure). Participants that meet Eligibility Criteria will be consented, have the Pristine™ Long-Term Hemodialysis Catheter placed,

and will undergo additional follow-ups. Follow-up for all enrolled participants will be performed via in-person or telephone visit to the participant and dialysis center at 1-month, 3-months, 6-months, and 12-months post-Index Procedure.

	Screening	Index Procedure	Participant Follow-up				Unscheduled
			1-month (±7-days)	3-months (±15-days)	6-months (±15-days)	12-months (±30-days)	
In-Clinic Visit or Telephone Visit (Screening must be in-clinic visit)	x	x	x	x	x	x	
Informed Consent	x						
Eligibility	x						
Demographics	x						
Physical Examination	x						
Medical History	x						
Dialysis History	x						
Procedure Overview		x					
Study Device Details		x					
Hemodialysis Catheter Assessment			x	x	x	x	
Dialysis Session Logs			x	x	x	x	
Device Deficiencies / Malfunctions		x	x	x	x	x	x
Re-Intervention Assessment		x	x	x	x	x	x
Adverse Event Assessment		x	x	x	x	x	x
Protocol Deviations	x	x	x	x	x	x	x

Statistical Methods:	**Primary Endpoint:** The combined primary endpoint is the overall rate of infectious complications and non-infectious complications requiring revision to maintain patency and improve access performance at 3 months. Based on the DOPPS study data, competitor control devices had an average incidence rate of 31.5 complications per 1000 patient days. To show non-inferiority of the Pristine™ Catheter, a 5 complications per 1000 patient days non-inferiority margin is used to establish a performance goal (PG) of 36.5 events per 1000 patient days. The analysis of the primary endpoint will be based on the following test of Poisson rate: **H_0**: The complication rate through 3 month is greater than or equal to 36.5 events per 1000 patients days at 3 months. **H_1**: The complication rate through 3 month is less than 36.5 events per 1000 patient days at 3 months. That is: **H_0**: $\lambda \geq \lambda_0$ **H_1**: $\lambda < \lambda_0$ Where λ_0 is the PG of 36.5 events per 1000 patient days. A one-sided p-value will be derived based on an Poisson distribution. The Pristine™ Catheter will be considered to have achieved the primary endpoint objective if the one-sided p-value is less than 0.025. Conditioned on the success of the above test, a superiority test will be conducted to show that the Pristine™ Catheter is superior to the performance goal. The above test will be repeated with a PG of 31.5 events per 1000 patient days. The analyses of the primary endpoint will be based on the ITT population and repeated with per-protocol population as sensitivity analyses. **Sample Size:** **Based on hypothesis test of Non-inferiority** • Assumptions: o The complication rate of our PG is estimated at 31.5 events per 1000 patient days with a 90 days follow-up based on

	DOPPS study data. The complication rate for Pristine is expected to be similar. ○ The PG is set at 36.5 events per 1000 days using a 5 events per 1000 days non-inferiority margin; ○ The attrition through 90 days is assumed to be 15% ○ The Type 1 error is 0.025 (one-sided). ○ The Type 2 error is 0.2. • Sample Size: ○ Total required exposure is 12765 patient days which translates to 142 subjects with average exposure of 90 days (PASS 2019). **<u>Based on hypothesis test of Superiority</u>** • Assumptions: ○ The complication rate of our PG is estimated at 31.5 events per 1000 patient days with a 90 days follow-up based on literature review, which is set as the PG. ○ The complication rate for the Pristine™ Catheter is assumed to be 26.5 events per 1000 patient days. ○ The attrition through 90 days is assumed to be 15% ○ The Type 1 error is 0.025 (one-sided). • Sample Size: ○ Total exposure of 12765 patient days (which translates to 142 subjects with average exposure of 90 days) will provide 85% power of the test (PASS 2019).
Principal Investigator and Study Location(S):	<u>National Principal Investigator:</u> • Jeffrey Hoggard, MD <u>Site Locations:</u> • All, up to 15, sites will be located in the United States.
Regulatory Status:	The BD Pristine™ Long-Term Hemodialysis Catheter has been cleared by the Food and Drug Administration (FDA) on 02 April 2021. The BD Pristine™ Long-Term Hemodialysis Catheter is not anticipated to receive CE Mark (European Conformity) before initiation of the clinical trial. The Pristine study will be a Post-Market evaluation in accordance with the study protocol, any modifications as requested by the IRB/EC, the ethical principles of the Declaration of Helsinki, Good Clinical Practice (ICH E6) / ISO 14155:2020), and all applicable national/regional regulations and laws.

1.2 Schedule of Activities

Procedure	Screening		Study Visits				
		Index Procedure Day 1	Follow-Up Visit 1 1 month (±7-days)	Follow-Up Visit 2 3-months (±15-days)	Follow-Up Visit 3 6-months (±15-days)	Follow-Up Visit 4 12-months (±30-days)	Unscheduled
In-Clinic Visit or Telephone Visit (Screening must be in-clinic visit)	x	x	x	x	x	x	x
Informed Consent	x						
Eligibility	x						
Demographics	x						
Physical Examination	x						
Medical History	x						
Dialysis History	x						
Procedure Overview		x					
Study Device Details		x					
Hemodialysis Catheter Assessment			x	x	x	x	x
Dialysis Session Logs			x	x	x	x	x
Device Deficiencies / Malfunctions		←	—	—	—	—	→
Re-Intervention Assessment		←	—	—	—	—	→
Adverse Event Assessment		←	—	—	—	—	→
Protocol Deviations	←	—	—	—	—	—	→

2 INTRODUCTION

The Pristine™ Post-Market study is a prospective, multi-Center, single-arm clinical study to evaluate the safety and performance of the BD Pristine™ Long-Term Hemodialysis Catheter. 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) regulations (21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 812), Institutional Review Board (IRB) requirements, and International Organization for Standardization (ISO) 14155:2020 standards.

2.1 Background

With introduction of hemodialysis as a feasible and effective treatment in the early 1940s, the grim outlook of death evolved to a prospect of survival for patients with advancing kidney failure. By reducing the time and effort required by the patient and caregivers, technological advancements have gradually transformed hemodialysis from an intensive bedside therapy to a more streamlined treatment, sometimes even self-administered in the comfort of patient's home. Standards have been established and guidelines were put in place to efficiently care for large numbers of patients with a balance of resources and patient time.

According to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative, (2015 NKF KDOQI) over 400,000 patients are currently treated with hemodialysis in the United States, with Medicare spending reportedly approaching $90,000 per patient per year of care in 2012. In 2012, the European Renal Association - European Dialysis and Transplant Association reported a prevalence of 372 patients per million in the United Kingdom.[1, 2]

Appropriate care of hemodialysis patients requires constant maintenance of vascular access patency and function, to accommodate for a flow rate to the dialyzer that is adequate for the dialysis prescription. The failure of access is a major cause of morbidity for patients on hemodialysis therapy, with a number of reports indicating that a high percentage of hospitalizations for patients with chronic kidney disease were caused by vascular access complications. The United States Renal Data System (USRDS) reported that hemodialysis access failure was the most frequent cause of hospitalization for patients with stage 5 chronic kidney disease and, in some centers, it accounted for the largest number of hospital days. Ideally, vascular access has a long use-life, and has a low rate of complications. The surgically created arteriovenous fistula has shown the best 4- to 5-year patency rates and has required the fewest interventions compared with other access types. However, use of grafts and cuffed central venous catheters (CVCs) for permanent hemodialysis access is common, accompanied by an increased rate of access related complications.

Despite the burden of catheter-associated conditions and risks for patients, the use of cuffed tunneled central venous catheters is frequently vital as a standalone treatment modality of acute and chronic renal failure and serves as a bridge until recovery of renal function, maturation of fistula, or finding a donor organ. The need for better performing hemodialysis catheters still exists.

Catheter design can impact performance. Some hemodialysis catheters have side holes in their distal lumens. These side holes, which were intended to increase inflow and reduce risk of blockage, have been shown to be prone to clot formation. Under electron microscopy side holes have been shown to have rough edges where thrombi can attach. Due to the side holes flow, anticoagulant given at the end of dialysis may not be able to reach the tip of the catheter.

The Pristine™ Long-Term Hemodialysis Catheter, is an innovative split, symmetrical, side-hole–free tip. The Pristine™ Catheter's side-hole free tip is designed to help minimize thrombus adhesion that can be associated with hemodialysis catheters that have side holes.

In a previous feasibility study, the primary objective was to observe the performance of the Pristine™ Long-Term Hemodialysis Catheter in participants with End-Stage Renal Disease or Acute Renal Failure. The study was performed at a single investigation site in the Dominican Republic. Forty-five (45) participants (males or non-pregnant females with ESRD or ARF requiring hemodialysis treatment) received the current 15.5F Pristine™ catheter. The primary endpoint was primary patency, prespecified for evaluation at 30 days post-catheter implantation and was defined as a catheter that provided adequate hemodialysis (flow >300mL/min) without the need for additional interventions (i.e., TPA infusions or fibrin sheath stripping or catheter exchange) to maintain flow or correct device failure.[3]

Participants were followed for 6 months post-catheter implantation at four sites that were affiliated with the placement institution. All catheters (n=44) were patent at 30 days post implantation. Primary patency at 60- and 180- days post procedure was 100.0% and 90.9%, respectively. The following adverse events (AE) were reported in accordance with MedDRA v. 22.1. There were 9 infections, 6 of which were reported as device-related and 3 (2 pneumonia and 1 abdominal abscess) were reported as not related to the study device. There were 2 cardiac disorders and 2 vascular disorders, none of which were reported as device related. There were 6 general disorder and access site conditions, 2 of which were reported as device related. There were 9 deaths reported in the study, none of which were reported as related to the device or procedure.[3]

2.2 Rationale

The purpose of this clinical investigation is to provide clinical evidence to further demonstrate reasonable assurance of safety and performance of the Pristine™ Long-Term

Hemodialysis Catheter to provide immediate hemodialysis access. The Pristine™ Catheter has already been cleared by the FDA and is currently on the market in the United States.

2.3 Risk/Benefit Assessment

The risks associated with the use of Pristine™ Long-Term Hemodialysis Catheters have been identified by performing a Design Failure Mode and Effects Analysis (DFMEA) and a Use Failure Mode and Effects Analysis (UFMEA). At the completion of the DFMEA and UFMEA, a Risk Management Report was generated to summarize the risk analysis process and provide documented evidence that the risks associated with the study device are acceptable. Prior to any study procedure, the Investigator (or designee) must explain to each participant in layman's terms, the nature of the study, its purpose, expected duration, and the risks and benefits of study participation.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of Pristine™ Long-Term Hemodialysis Catheters may be found in the Instructions for Use (IFU).

2.3.1 Risk Assessment

The known possible risks associated with the use of the BD Pristine™ Long-Term Hemodialysis Catheter are listed below. The study involves only the collection of data, the only risk of taking part is the possible loss of confidentiality of your information collected in the study. None of the procedures or devices in this study are considered experimental.

Potential complications and Adverse Events (AEs) associated with the use of the Pristine™ Long-Term Hemodialysis Catheter may include the usual complications associated with central venous catheter procedures. These complications can occur singularly or collectively, and may include the following:

- Air Embolism
- Arterial Puncture
- Brachial Plexus Injury
- Cardiac Arrhythmia
- Cardiac Tamponade
- Catheter Erosion or Extrusion Through Skin
- Catheter Infection
- Catheter Occlusion or Breakage
- Catheter Thrombosis
- Catheter Tip Migration or Malposition
- Deep Vein Thrombosis – Lower Extremity
- Endocarditis
- Hemothorax
- Hydrothorax
- Inferior Vena Cava Injury
- Intolerance Reaction to Implanted Device
- Lower Extremity Ischemia
- Mediastinal Widening
- Pneumothorax
- Pulmonary Emboli
- Pulmonary Embolism
- Retroperitoneal Bleed
- Right Atrial Puncture
- Sepsis

- Exit Site Infection
- Exsanguination
- Extravasation
- Femoral Artery Damage
- Femoral Artery Dissection
- Femoral Nerve Damage
- Fibrin Sheath Formation
- Hematoma
- Hemorrhage
- Subclavian Artery Puncture
- Subcutaneous Tunnel Infection
- Superior Vena Cava Puncture
- Thoracic Duct Injury
- Thoracic Duct Laceration
- Thrombosis of Vein
- Trauma to major vessel or Right Atrium
- Tunnel Infection
- Venous stenosis

Table 1: Associated / Concomitant Procedures

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Associated / Concomitant Procedures		
Risks associated with sedation and / or anesthesia	These risks can include: • Nausea • Vomiting • Hematoma at injection site • Sore throat / hoarse voice • Chills • Brain damage • Death	• As delineated in Section 12 the PI as well as any additional operators (as applicable) must be experienced in the field of application. • Clinical Eligibility Criteria must be met and documented using prior to treatment including assessment of the participants eligibility to receive sedation and / or anesthesia (Section 5.1). • The CIP required follow-up ensures close participant monitoring for AEs throughout the course of the study participation (Section 9).
Risks associated with catheter placement, if completed.	These risks can include: • Air Embolism • Allergic reaction • Hemolysis	• As delineated in Section 12 the PI as well as any additional operators

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	• Hemothorax • Infection • Migration • Pneumothorax • Venous injury	(as applicable) must be experienced in the field of application. • The CIP required follow-up ensures close participant monitoring for AEs throughout the course of the investigation (Section 9).

There are minimal additional risks for enrolled participants due to the study being post-market. All procedures will be performed per standard of care treatment in the US with an FDA cleared device.

2.3.2 Benefit Assessment

You will not receive any direct benefit from being in the study. However, the information gained from your taking part in this study may help others in the future. Potential benefits that may result from the Pristine™ Catheter and procedure may include:

- Reduce the risk of infection and reduced chance of thrombi formation.
- Higher likelihood of a lasting usable catheter for hemodialysis.
- Vascular access for hemodialysis treatment.

2.3.3 Overall Benefit: Risk Conclusion

This protocol is specifically designed to manage and minimize risks through careful participant selection, training of Investigators, adherence to the pre-determined time points to assess participant clinical status and regular clinical monitoring visits by Sponsor-appointed monitoring personnel.

The Risk Management Report and the results of non-clinical (e.g. bench testing, biocompatibility, etc.) and pre-clinical testing did not reveal any unacceptable residual risks.

Taking into consideration the measures to minimize risk to participants in this study, the potential risks identified in association with treatment using the BD Pristine™ Long-Term

Hemodialysis Catheter are justified by the anticipated benefits that may be afforded to participants with End-Stage Renal Disease.

3 OBJECTIVES AND ENDPOINT

The objective of this study is to assess the safety and performance of the BD Pristine™ Long-Term Hemodialysis Catheter for attaining vascular access for hemodialysis. The information obtained from the study is intended to be reported in the device's labeling.

3.1 Primary Endpoint

Primary Safety and Performance Endpoint

This study has a combined Safety and Performance endpoint derived from the Dialysis Outcomes and Practice Patterns Study (DOPPS) data. The combined Primary Endpoint will be overall complications including infectious and non-infectious complications at 3 months.

Infectious Complications are defined as:
Complications due to any documented diagnosis of access infection requiring medical intervention (managed in an outpatient or inpatient setting) or sepsis as diagnosis in the hospitalization file whether access related or not.[4]

Non-infectious complications are defined as:
Complication due to any noninfectious cause (thrombosis of the access, fibrin material within or around a catheter, catheter migration, central vein stenosis or thrombosis) requiring a revision procedure to maintain patency or improve access performance (i.e., thrombolysis, angioplasty, or surgical correction) in an inpatient or outpatient setting or removal or abandonment with creation of a new access that was not due to an access-related infection).[4]

3.2 Secondary Endpoints

The following secondary endpoints will be evaluated using descriptive statistics to provide further information related to the safety and performance of the Pristine™ Long-Term Hemodialysis Catheter. All secondary endpoints will be summarized with descriptive statistics.

- *Rate of freedom from catheter-related bloodstream infection (CRBSI),* defined by 2019 KDOQI Guidelines for CRBSI through 1-month, 3-months, 6-months, and 12 months post-index procedure.

- *Rate of freedom from Device and/or Procedure-related adverse events,* at 1-month, 3-months, 6-months, and 12 months post-index procedure.
- *Rate of Technical Success,* defined as the successful placement of the Pristine™ Long-Term Hemodialysis Catheter, as assessed by the Investigator during the Index Procedure.
- *Overall Participant Survival Rate* at 1-month, 3-months, 6-months, and 12 months post-index procedure, defined as the proportion of participants that have not died from any catheter related complication.
- *Overall Catheter Survival Rate* at 1-month, 3-months, 6-months, and 12 months post-index procedure, defined as the proportion of Pristine™ Catheters that have not been removed for any cause.
- *Overall Patency Rate,* at 1-month, 3-month, 6-months, and 12-months post-index procedure, defined as the Pristine™ catheter having the ability to achieve a mean dialysis blood flow of ≥300mL/min without need for additional interventions. [5,6]

3.3 Exploratory Endpoints

The following endpoints may be evaluated in an exploratory fashion. Data will be collected throughout the course of the investigation in support of this endpoint.

- *Kit Component Safety and Performance, defined as the overall rate of the catheter's procedure kit component complications from time of procedure to discharge.*

4 STUDY DESIGN

4.1 Overall Design

This is a prospective, multi-center, post market, single-arm study designed to assess the safety and performance of the Pristine™ Long-Term Hemodialysis Catheter. The primary objective of this study is to assess the overall complication rate of the Pristine™ Catheter against an overall hemodialysis catheter complication rate derived from clinical literature.

A total of 142 patients will be enrolled and have the Pristine™ Long-Term Hemodialysis Catheter placed. Under the current enrollment assumptions, up to 15 investigational sites in the United States (US) will participate. The study will be enrolling male or non-pregnant female participants ≥18 years of age meeting study inclusion/exclusion and labeled indication for hemodialysis for adequate completion of study procedures and collection of data. Eligible participants will have End Stage Renal Disease requiring hemodialysis through a tunneled dialysis catheter. Follow-up for all enrolled participants will be performed at 1-month, 3-months, 6-months, and 12-months post-Index Procedure. No site will be allowed to enroll more than 20% of the overall number of participants to ensure a reasonably well-balanced, multi-center study.

For this study, we have a combined Safety and Performance endpoint derived from the Dialysis Outcomes and Practice Patterns Study (DOPPS) data.[4] Our combined Primary Endpoint will be overall complications including non-infectious and infectious at 3 months.

4.2 Scientific Rationale for Study Design

The combined safety and performance primary endpoint is compared to a performance goal of 31.5 complications per 1000 catheter days derived from the Dialysis Outcomes and Practice Patterns Study (DOPPS).[5] The DOPPS data was chosen due to it's significant sample size of tunneled catheters (n=4207) and it's clear definition of non-infectious and infectious complications. DOPPS I-III enrolled 27, 129 participants that provided access data. DOPPS I enrolled within France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States. DOPPS II and DOPPS III enrolled in Australia, Belgium, Canada, New Zealand, and Sweden.[5] There have been few hemodialysis catheter studies performed in the last 10 years with many lacking sufficient sample size for statistically powered endpoints. The hemodialysis catheter studies that report 'complication' rates or infection rates have a significant variance in definitions. The KDOQI guidelines have stated a need for consistent definitions and outcomes between tunneled catheter studies.[6] DOPPS is a globally renowned study providing clinically meaningful definitions with a significant sample size not seen in other studies.

The primary endpoint for this study is a combined complication rate of non-infectious and infectious complications. Non-infectious complications are defined as, complications due to any noninfectious cause (thrombosis of the access, fibrin material within or around a catheter, catheter migration, central vein stenosis or thrombosis) requiring a revision procedure to maintain patency or improve access performance (i.e., thrombolysis, angioplasty, or surgical correction) in an inpatient or outpatient setting or removal or abandonment with creation of a new access that was not due to an access-related infection). This definition of non-infectious provides the clinically relevant point of re-intervention. Thrombosis, fibrin material, and catheter migration are all common events for tunneled catheters. When these events start to disrupt dialysis treatment, they require re-intervention thus putting more burden on the patient and healthcare system. The other part is infectious complications defined as, complications due to any documented diagnosis of access infection requiring medical intervention (managed in an outpatient or inpatient setting) or sepsis as diagnosis in the hospitalization file whether access related or not. Infection rate for catheters is arguably the most crucial reported value being the main cause of catheter related deaths. The infectious complications defined include exit site infections and all blood stream infections causing sepsis.

Showing a statistically significant difference by our powered primary endpoint against the performance goal will attest to the performance, safety, and clinical benefits of the Pristine™ Catheter.

4.3 Potential Influencing or Confounding Factors and Bias

Another potential foreseeable factor pertains to the global nature of this investigation and the varying practice patterns across the regions that may participate. These differences could stem for example from differing surveillance programs, differing criteria for initiating CVC hemodialysis, among others. This factor is mitigated through CIP stipulated training requirements, as well as maximum enrollment limitations on any single site, and standardization for follow-up interval timing and pertinent requirements. Subgroup analyses between regions may be conducted to explore regional differences for standard of care differences. This could also be expanded to inter-region subgroup analyses should there be differences in institution types (e.g. public versus private) that participate within a region.

In addition to region and institution type, the training and level of experience with the Pristine™ Long-Term Hemodialysis Catheter as well as the specialty of the operator could also be a foreseeable factor that could impact the study outcomes. As a mitigation of this factor the training and operator approval requirements delineated in Section 13.2 are implemented. Subgroup analyses looking at the experience level and / or specialty of the operator may also be performed to investigate the impact on results.

4.4 End of Study Definition

A participant is considered to have completed the study upon conclusion of the 12-Month (±1 month) follow-up visit. The end of the study is defined as the date of the last visit of the last participant in the study.

5 STUDY POPULATION

Study population includes participants with end stage renal disease requiring hemodialysis through a tunneled dialysis catheter. All participants must meet all inclusion and exclusion criteria.

Participants will be recruited for enrollment in the study from each site's existing pool of patients. Enrollment of participants will continue until a total of 142 patients at up to 15 sites have been enrolled and undergo the placement procedure successfully of the BD Pristine™ Long-Term Hemodialysis Catheter. It is anticipated that enrollment will be approximately 12 months in duration. The following describes the clinical eligibility (inclusion and exclusion) criteria for this study:

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. The participant or legally designated representative must voluntarily sign and date the approved Informed Consent Form (ICF) prior to collection of study-specific data or performance of study-specific procedures.

2. The participant must be willing and able to comply with protocol requirements, including all study visits and procedures.

3. The participant must be either a male or non-pregnant female ≥18 years of age.

4. The participant must have a diagnosis of End Stage Renal Disease with indication for a tunneled dialysis catheter creation.

5. Participant must require chronic hemodialysis treatments 3 times per week with intended use of the Pristine™ Long-Term Hemodialysis Catheter.

6. The participant meets the indications for hemodialysis use and does not meet any of the contraindications per the Pristine Instructions for Use (IFU).

7. The participant must have a patent jugular vein or subclavian vein.

5.2 Exclusion Criteria

A participant must NOT meet ANY of the following criteria to be enrolled in the study:

1. The participant has known central venous stenosis

2. Based on the local primary investigator's discretion, the patient would not be an appropriate study candidate.

3. The participant has already undergone an AVF or AVG procedure and is awaiting maturation.

4. The participant has an active infection at the time of study enrollment.

5. The participant has a presence of bacteremia or infection within 7 days prior to enrollment.

6. The participant has a history neutropenia or a history of severe immunodeficiency disease.

7. The participant has uncontrolled abnormal coagulation parameters and are at additional risk for clotting or excessive bleeding at time of enrollment per physicians' opinion.

8. The participant has a known allergy, intolerance or sensitivity to heparin, or previous incidence of heparin-induced thrombocytopenia.

9. The participant has a known allergy or hypersensitivity to any of the device materials or Ethylene oxide (EtO).

10. The participant has another medical condition or treatment, which in the opinion of the investigator, the participant may be non-compliant with the protocol, confound the data interpretation, or is associated with a life expectancy insufficient to allow for completion of study procedures and follow-up.

11. The participant is currently participating in an investigational drug or another device study that has not completed the study treatment or that clinically interferes with the study endpoints. Note: Studies requiring extended follow-up visits for products that were investigational but have since become commercially available, are not considered investigational studies.

5.3 Lifestyle Considerations

No lifestyle restrictions are required for this study.

5.4 Screen Failures

Individuals that consent to participate in the study but subsequently fail to meet eligibility criteria and do not undergo treatment with the study device at the Index Procedure will be considered SCREEN FAILURES. Study participation for screen failures will end at the time of

eligibility failure and these individuals may not be rescreened. Documentation of the reason(s) for screen failure should be present in the participant's medical record and/or source documents.

6 STUDY TREATMENT

All participants will undergo a clinical evaluation at the Screening Visit (prior to Index Procedure). Participants that meet Eligibility Criteria will have the BD Pristine™ Long-Term Hemodialysis Catheter placed and will undergo additional follow-ups. Follow-up for all enrolled participants will be performed via in-person or telephone screen to the participant and dialysis center at 1-month, 3-months, 6-months, and 12-months post-Index Procedure.

6.1 Pristine™ Long-Term Hemodialysis Catheter

The Pristine™ Long-Term Hemodialysis Catheter is a chronic hemodialysis catheter consisting of a dual lumen radiopaque shaft with a pre-formed split tip, which enables long-term vascular access for hemodialysis, apheresis, and infusion. The proximal end of the catheter features two color coded luer adapters. The luer adapters are connected to clear extension tubes. Each extension tube contains a clamp and is connected to the catheter bifurcation and suture wings (hub). The distal end of the catheter hub is connected to the dual lumen catheter shaft. The shaft contains a cuff and extends to a symmetrical split tip. The design of the catheter's distal tip includes a split, symmetric Y-Tip™ with notches and without side-holes or slots. The symmetric Y-Tip™ design allows a spatial separation between the distal ends of the two lumens. The Pristine™ Long-Term Hemodialysis Catheter is provided as a sterile, single use device, and is sterilized using a validated ethylene oxide process.

The Pristine™ Long-Term Hemodialysis Catheter is FDA cleared and will be evaluated in a post-market fashion for its approved indication in the USA. Sites are to use the product off-the-shelf. The product shall be used in accordance with its IFU. The device will be identified using its product code and lot number for traceability. Please refer to the standard medical device reporting for any failed or malfunctioned Pristine™ Catheters.

7 STUDY PROCEDURES AND ASSESSMENTS

Study procedures, assessments, and their timing are summarized in the Schedule of Activities (SoA) in Section 1.2. Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. All study procedures must be documented in the participant's medical record and/or source documents as well as in the electronic Case Report Forms (eCRFs).

Prior to the collection of any study-specific data, the participant must voluntarily sign and date the IRB approved ICF. All participants will undergo an in-office clinical evaluation at the Screening Visit (prior to Index Procedure). Participants that meet Eligibility Criteria will be treated with the Pristine™ Long-Term Hemodialysis Catheter and will undergo additional follow-ups. Follow-up for all enrolled participants will be performed via in-person or telephone screen to the participant and dialysis center at 1-month, 3-months, 6-months, and 12-months post-Index Procedure.

7.1 Screening and Enrollment

During the recruitment and screening process, the Investigator (or authorized designee) will be responsible for describing the nature of the study to the participant, verifying that initial eligibility criteria have been met, obtaining Informed Consent, collecting participant information, and performing relevant screening procedures. The following procedures will be conducted and documented during the screening process:

7.1.1 Informed Consent

The background and purpose of the study, participation requirements, and the potential benefits and risks of the procedure(s) must be explained to the participant in layman's terms. Prior to the collection of any study-specific data or the conduct of any protocol-specific assessments, the participant or the legally designated representative must voluntarily provide Informed Consent and comply with applicable federal and state privacy laws (e.g. HIPAA requirements in the US). Documentation of the Informed Consent process along with the signed Informed Consent Form should be present with the participant's source documents and dated prior to initiation of study-specific assessments. Procedures conducted as part of the participant's routine clinical management (e.g. imaging, labs, etc.) and obtained before signing of the ICF may be utilized for Screening purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA. Please refer to Section 14.2 for additional details on informed consent.

7.1.2 Enrolled Participants

Individuals that consent to participate in the study will be considered **ENROLLED**. Participants that fail to meet eligibility criteria post-consent and prior to undergoing device placement with the study device will be considered **SCREEN FAILURES** per Section 5.4.

7.1.3 Demographics and Medical History

The following demographic and medical history information must be collected and documented during the Screening Visit:

- Demographics

- Age, Sex, Race, and Ethnicity
- Relevant Medical History and Risk Factors including, but not limited to:
  - Renal disease Diagnosis
  - Etiology of End-Stage Renal disease
  - History of kidney-related medical conditions, treatments, and procedures.
  - History of other relevant medical conditions, treatments, and procedures.

7.1.4 Physical Exam

A physical examination must be conducted or documented within 30 days prior to Index Procedure in accordance with each investigational site's standard of care and must include:

- Height and Weight

7.1.5 Lab Tests

No lab tests are required for study participation.

7.1.6 Eligibility Assessment

The participant's eligibility for treatment with Pristine™ Long-Term Hemodialysis Catheter will be reviewed and source documentation should indicate that the participant met all study eligibility criteria prior to the Index Procedure treatment. Refer to Section 5.4 if eligibility criteria are not met.

7.2 Index Procedure Visit

The Index Procedure should be conducted per the investigational site's standard practices for hemodialysis catheter procedures, medication therapy, patient monitoring, sterile operative techniques, and within the bounds and requirements of the Pristine™ Long-Term Hemodialysis Catheter IFU. The following must be documented at the Index Procedure Visit:

7.2.1 Clinical Procedure

After the PI, or authorized designee(s), has determined that the participant is eligible for participation based on the criteria listed in Section 5.1 and 5.2, the participant may be enrolled and undergo the Pristine™ Catheter placement procedure. Examinations, evaluations, procedural preparation, angiography, treatment, and hospital / facility discharge procedures will be conducted per the investigational site's SOC.

The placement of the Pristine™ Catheter, will be per the investigational site's SOC and must adhere to the device IFU. Operators of the Pristine™ Catheter must be approved by the Sponsor as an operator in writing before conducting an index procedure on enrolled participants (refer also to Section 13.3). For detailed information on device use and procedural medication recommendations, reference the IFU.

Enrolled participants will continue clinical participation through the 12-month follow-up period. Participants into whom the Pristine™ Catheter was not introduced should be treated per SOC and the reason documented on the appropriate eCRF. Participation for these participants will end at time of the index procedure.

7.2.2 Adjunctive Procedures

Adjunctive procedures during the index procedure, as part of SOC is allowed. All adjunctive procedures will be documented on the appropriate eCRF.

7.3 Post-Index Procedure and Discharge

Medication therapy and medical treatment will be conducted at the discretion of the PI per the investigational site's SOC. Participants will be treated and discharged according to the site's SOC. Prior to discharge, the following data will be collected and documented on the appropriate eCRF for participants into whom the Pristine™ Catheter was placed:

- Documentation of Adverse Events (AEs): Documentation of AEs (refer to Section 9) that have occurred since the start of the index procedure (defined to begin at the time of the initial skin puncture to gain vessel access).
- Documentation of Re-Interventions: Any additional interventions the participant has undergone since the completion of the index procedure (defined to end at the time of leaving the operating room).

7.4 Participant Follow-Up

7.4.1 Follow-Up Intervals and Methods

Enrolled participants will have follow-up visits at 1-month, 3 months, 6-months, and 12-months via either in person visit or telephone call. For participants into whom the Pristine™ Catheter was introduced during the index procedure, but procedure success was not achieved, only the procedure eCRF will be collected and limited to the collection of safety events and interventions for up to 30 days.

Follow-up windows will be calculated from the index procedure date. Refer to Section 1.2 for an overview of follow-up window time frames and requirements for each visit. The

following data will be collected and documented on the appropriate eCRF for each follow-up unless otherwise specified for treated participants:

- Hemodialysis Catheter Assessment:
  - Document how the participant has been receiving hemodialysis and document the date of the participant's last HD session.
- Dialysis Session Blood Flow Rate:
  - If dialyzing through the Pristine™ Catheter, document the reported dialysis sessions and details such as date of dialysis session, average blood flow rate, number of line reversals, and length of dialysis session.
- **If Needed:**
  - Documentation of any protocol deviations that have occurred since the last follow-up.
  - Documentation of occurrence and / or status of AEs since the last follow up (refer to Section 9).
  - Any catheter reinterventions the participant has undergone since the prior follow-up.

7.4.2 Unscheduled Follow-up

An unscheduled visit eCRF should also be completed for participants who return for additional unscheduled examination(s) pertaining to their HD vascular access. The participant will be required to complete the next scheduled follow-up visit if the unscheduled visit is out of the CIP allotted follow-up window or if the required elements of the respective follow-up were not completed as part of the unscheduled visit.

If the participant is treated by a health-care professional other than the PI for treatment related complications during the course of the follow-up period, the PI or authorized designee should request copies of the medical records and, if necessary, complete the appropriate eCRFs.

7.5 Participant Investigation Completion and Premature Discontinuation

Following the index procedure, every participant into whom the Pristine™ Catheter was placed should remain in the study until completion of the required follow-up period or until day of remove of the Pristine™ Catheter. The follow-up period for this clinical investigation is 12 months (365 ± 30 days) for participants who had the Pristine™ Catheter successfully placed. An enrolled participant is considered to have completed the study if the participant has completed the formal follow-up period associated with this clinical investigation through the 12-Month follow-up as described in the Schedule of Activities (Section 1.3).

Upon investigation completion or premature discontinuation (in the situations where applicable), the participant's continued care should be administered per SOC at the discretion of the PI and / or their primary care physician.

8 PARTICIPANT DISCONTINUATION/WITHDRAWAL

8.1 Discontinuation/Withdrawal

- A participant may withdraw from the study at any time at his/her own request (Withdrawal of Consent) or may be withdrawn at any time at the discretion of the investigator (Investigator's Decision) or sponsor (Sponsor's Decision) for safety, behavioral, compliance, or administrative reasons.
- Once a participant discontinues from the study, no further data will be collected.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the reason for withdrawal must be documented.

8.1.1 Lost to Follow-Up

A participant will be considered Lost to Follow-Up (LTFU) if he/she repeatedly fails to return for/complete scheduled visits and is unable to be contacted by the investigational site. This does not apply to missed visits, where the participant misses one (1) follow-up visit but completes a subsequent one.

The following actions must be taken if a participant fails to return for/complete a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed LTFU, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record and source documents.
- Should the participant continue to be unreachable, he/she will be considered LTFU effective the date of the final failed contact attempt.

9 ADVERSE EVENTS AND DEVICE DEFICIENCIES

9.1 Definitions of Events

9.1.1 Adverse Events (AEs)

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to study device [ISO14155:2020(E)].

Pre-existing conditions should be considered as part of the participant's medical history and should not be reported as an AE unless there is a substantial increase in severity or frequency of the condition. Likewise, planned hospital visits and/or hospital stays should not be considered as adverse events. Exacerbation of an existing condition should be reported as an AE if the event meets the protocol definition of an AE.

The clinical course of the event will be followed according to accepted standards of medical practice until the event resolves, stabilizes, or in the opinion of the Investigator, is no longer considered clinically significant. The Investigator must supply the Sponsor with information concerning the follow up and/or resolution of the AE.

9.1.2 Serious Adverse Events (SAEs)

A serious adverse event (SAE) is defined by ISO 14155:2020 and/or 21 CFR 803.3 as an adverse event that:

a. Led to death;
b. Led to serious deterioration in health that resulted in life-threatening illness or injury, resulted in permanent impairment;
c. Required inpatient hospitalization/prolonged hospitalization, or resulted in medical/surgical intervention to prevent life-threatening illness/injury or permanent impairment; or
d. Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

9.1.3 Adverse Device Effect (ADE) / Serious Adverse Device Effect (SADE)

An adverse device effect (ADE) is defined as any adverse event that is considered to be related to the use of an medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use, deployment, implantation, or

operation or any malfunction of the investigational device (study device) and includes any event that is a result of a user error.

A serious adverse device effect (SADE) is defined as an ADE that has resulted in any of the consequences characteristic of an SAE.

9.1.4 Unanticipated (Serious) Adverse Device Effect (UADE/USADE)

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, which by its nature, incidence, severity, or outcome has not been identified in the current instructions for use and/or 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 participants.

UADEs/USADEs will be reported to FDA as required by 21 CFR Part 822 and to the appropriate governing body per ISO 14155:2020.

9.1.5 Device Deficiencies

The Investigator will record a device deficiency if a device used in the study procedure failed to meet its performance specifications whether due to mechanical failure, malfunction, or defect. Device deficiencies also include use errors and inadequate labeling. This applies to: devices used to treat the participant, or devices in which the package was opened, but the device was not used for treatment, or devices with which treatment was attempted, but the device did not remain through the entire study procedure/period.

All mechanical failures, malfunctions, missing components, and defects of the study devices will be recorded on the appropriate Case Report Form and will be promptly reported to the Sponsor. The device(s) should be returned to the Sponsor as outlined in the site's regulatory binder.

If the device deficiency was associated with an AE, the reporting provisions for AEs, ADEs, SAEs, SADEs and UADEs/USADEs apply.

Reported deficiencies will be investigated and reported under 21 CFR part 803 Medical Device Reporting by the Sponsor if necessary. The site may be contacted to provide additional information to allow the Sponsor to conduct a thorough investigation.

It is the responsibility of the Investigator to notify the IRB of such device deficiencies in accordance with the local IRB's requirements.

9.2 Severity of Adverse Events

Each AE shall be assessed for its severity, by the Primary Investigator according to the criteria below.

Table 2: Severity of Adverse Event

Severity Rating	Description
Mild	Event, signs, or symptoms that do not interfere with the participant's daily activity, are usually considered self-limiting, can be treated with non-prescription type medications, and do not require medical intervention
Moderate	Event may interfere or cause low level inconvenience with the participant's daily activity. Requires medical intervention and/or treatment; however, unlikely to require hospitalization or be considered potentially life-threatening in nature
Severe	Event may cause significant discomfort to the participant and/or interferes with the participant's daily activity. Requires medical intervention and/or treatment to preclude a permanent impairment; may be life threatening and/or require hospitalization

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

Each AE will be assessed for its relationship to the study device or procedure according to the following guidelines.

A. Assess each AE for its relationship to the device or procedure.

- Device Related: This category should be restricted to AEs directly attributable to the study device used from the placement procedure of the Pristine™ Catheter to completion of all follow-up for that patient.

- Procedure Related: A procedure includes any study-related activity performed during the index procedure of the Pristine™ Catheter.

B. The following categories shall be used for assigning the certainty of the relatedness.

Table 3: Relationship of Adverse Events

Relatedness	Description
Not Related	Event is independent of study intervention and/or evidence exists that the event is related to another etiology. There must be an alternative etiology documented by the clinician.
Unlikely Related	Event in which the temporal relationship to study intervention makes a causal relationship improbable (e.g., the event did not occur within a reasonable time of the study device use) and in which underlying disease provides plausible explanations (e.g., the participant's clinical condition other concomitant treatments).
Likely Related	Event in which there is evidence to suggest a causal relationship and the influence of other factors is less likely. The event occurs within a reasonable time after use of the study device and is less likely to be attributed to concurrent disease.
Related	Event in which there is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. The event occurs in a plausible time relationship to use of the study device and cannot be explained by concurrent disease.

9.4 Reporting of Events

For all adverse events, all sections of the appropriate Case Report Form (CRF) must be completed.

- All AEs, SAEs, SADEs, and/or UADEs/USADEs must be reported on the appropriate eCRF.
- Any device related AEs, must be reported to the Sponsor within one (1) working day of the site/investigator becoming aware of the event.
    - De-identified copies of all relevant documentation (i.e., procedure reports, physician / nurses' notes, discharge summary, etc.) should be submitted to the Sponsor within 72 hours of knowledge of a UADE or death, as appropriate.
    - UADEs / USADEs will be evaluated and assessed / escalated by the Sponsor per ISO 14155:2020 and as per local regulations.

Table 4: Reports and Notifications Required from Clinical Investigators

Safety Event Type	Notification to:	Reporting Timeline
Device/procedure related AEs / SAEs, ADEs / SADEs, or UADEs / USADEs	Sponsor and IRB (if applicable)	No > than 1 business day of becoming aware of event
Death(s) (All-Cause)	Sponsor and IRB (if applicable)	No > than 1 business day of becoming aware of event
Device Deficiencies	Sponsor and IRB (if applicable)	As soon as possible, but no later than one (1) working day after site awareness and per local IRB / EC requirements. The device(s) should be returned to Sponsor. Any device deficiency that did not lead to an AE but could have led to a 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.
Requests for or Reports of Significant Deviations	Sponsor and IRB (if applicable)	As soon as possible, but no later than five (5) working days after emergency / deviation occurs
Failure to Obtain ICF	Sponsor and IRB (if applicable)	Within five (5) working days after index procedure.
Withdrawal of IRB	Sponsor and IRB (if applicable)	Immediately by telephone followed by a copy of the notification within five (5) working days.
Investigation Suspension / Premature Termination	IRB	The PI must notify the IRB of all terminations / suspensions. The PI must notify the IRB in writing as soon as possible but no later than within ten (10) working days (or sooner as required by the IRB) if the premature termination is related to safety or compliance issues.

Notice of Inspection or Audit by the Health Authorities	Sponsor	As soon as possible after becoming aware of the impending inspection / audit.

It is the responsibility of the Investigator to report adverse events to individual Institutional Review Boards (IRBs) according to the local governing IRB's requirements.

9.5 Safety Committees

9.5.1 Medical Monitor

The Medical Monitor (MM) will be responsible for AE trending review as well as for the identification of signals that could indicate a serious health threat as specified in the Safety Management Plan.

10 STATISTICAL METHODS

10.1 Overview of Study Design

This is a prospective, multi-center, single-arm study designed to assess the safety and performance of the Pristine™ Long-Term Hemodialysis Catheter for Attaining Vascular Access for Hemodialysis by comparison to a performance goal derived from the Dialysis Outcomes and Practice Patterns Study data.

10.2 Sample Size Considerations

The primary objective of the study is to show the overall complication rate for Pristine is non-inferior to the performance goal at 3 months. If successful, the next step is to show superiority of Pristine at 3 months.

Based on hypothesis test of Non-inferiority

- Assumptions:
  - The complication rate of our performance goal is estimated at 31.5 events per 1000 patient days with a 90 days follow-up based on DOPPS study data. The complication rate for Pristine is expected to be similar.
  - The performance goal is set at 36.5 events per 1000 days using a 5 events per 1000 days non-inferiority margin;
  - The attrition through 90 days is assumed to be 15%
  - The Type 1 error is 0.025 (one-sided).

- The Type 2 error is 0.2.

- Sample Size:
  - Total required exposure is 12765 patient days which translates to 142 participants with average exposure of 90 days (PASS 2019).

Based on hypothesis test of Superiority

- Assumptions:
  - The complication rate of our performance goal is estimated at 31.5 events per 1000 patient days with a 90 days follow-up based on literature review, which is set as the performance goal.
  - The complication rate for the Pristine™ Catheter is assumed to be 26.5 events per 1000 patient days.
  - The attrition through 90 days is assumed to be 15%
  - The Type 1 error is 0.025 (one-sided).
- Sample Size:
  - Total exposure of 12765 patient days (which translates to 142 participants with average exposure of 90 days) will provide 85% power of the test (PASS 2019).

10.3 Analysis Population

Sites will be limited to enrolling 20% (28) of the total sample size. The following populations are defined:

Table 5: Analysis Population List

Population	Description
Enrolled	All participants who sign the ICF will be classified as enrolled.
Intent-to-Treat (ITT)	The intent-to-treat population will consist of all participants into whom has signed the ICF, met all inclusion/exclusion criteria, and the Pristine™ Catheter was placed.
Per-Protocol	A Per-Protocol (PP) population may be created if there are participants who have any major deviations. The PP population will consist of any participants in the ITT population who do not have any major deviations. The deviations that are considered to have a “major” grade will be defined a priori in the SAP.

10.4 General Considerations

10.4.1 Handling of Missing Data

Study endpoints may have missing data due to a participant's withdrawal of consent, the withdrawal of a participant by the PI, a participant loss to follow-up and the death of a participant. Data may also be missing from investigation endpoints due to deviations and / or missing data collection. It is important to minimize missing data by all means and to always record the reason for omission.

10.5 Primary Endpoint

The combined primary endpoint is the overall rate of infectious complications and non-infectious complications requiring revision to maintain patency and improve access performance at 3 months. Based on the DOPPS study data, competitor control devices had an average incidence rate of 31.5 complications per 1000 patient days. To show non-inferiority of the Pristine™ Catheter, a 5 complications per 1000 patient days non-inferiority margin is used to establish a performance goal (PG) of 36.5 events per 1000 patient days.

The analysis of the primary endpoint will be based on the following test of Poisson rate:
H_0: The complication rate through 3 month is greater than or equal to 36.5 events per 1000 patients days at 3 months.

H_1: The complication rate through 3 month is less than 36.5 events per 1000 patient days at 3 months.

That is:

H_0: $\lambda \geq \lambda_0$

H_1: $\lambda < \lambda_0$

Where λ_0 is the PG of 36.5 events per 1000 patient days.

A one-sided p-value will be derived based on an Poisson distribution. The Pristine™ Catheter will be considered to have achieved the primary endpoint objective if the one-sided p-value is less than 0.025.

Conditioned on the success of the above test, a superiority test will be conducted to show that the Pristine™ Catheter is superior to the performance goal. The above test will be repeated with a PG of 31.5 events per 1000 patient days.

The analyses of the primary endpoint will be based on the ITT population and repeated with per-protocol population as sensitivity analyses.

10.6 Secondary Endpoint(s)

The secondary endpoints will be summarized with descriptive statistics (without formal statistical hypothesis testing) using the ITT population. For categorical variables, summary statistics will include frequency counts and percentages. For continuous variables, summary statistics will include mean, standard deviation, minimum, median, and maximum. CIs (95%) will also be provided.

10.7 Tertiary/Exploratory Endpoint(s)

The exploratory endpoints may or may not be presented in the clinical investigation report. If reported, the descriptive statistics will be presented.

10.8 Interim Analysis

An interim analysis will be conducted after all eligible patients have completed their 3-month follow-up visit. The Primary endpoint of combined complications will be analyzed and reported. Secondary endpoints will be reported with descriptive statistics.

11 DATA COLLECTION AND RECORD MAINTENANCE

11.1 Case Report Forms

The Investigator is responsible for ensuring the completeness and accuracy of all study documentation.

All required clinical data will be collected/documented in sponsor-provided electronic Case Report Forms (CRFs). Corrections should be made using the principles of Good Documentation Practice. FDA 21 CFR 11 is followed as well as other applicable legislation on the handling of electronic data. Modification of the CRFs will only be made if deemed necessary by the Sponsor and/or the appropriate regulatory body.

All required clinical data for this trial will be collected in web-based standardized eCRFs. The eCRFs are designed to accommodate the specific elements of this clinical investigation and it is the responsibility of the PI to confirm that the data is completely and accurately entered in the appropriate sections of the eCRF. Data reported on these eCRFs shall be derived from, and be consistent with, source documents and will be approved by the PI. An audit trail of changes or corrections to eCRFs will be maintained. Discrepancies between the source documents and the eCRFs shall be explained in writing. Modification of the eCRF will only be made if deemed necessary by the Sponsor and / or the appropriate regulatory body.

ISO 14155:2020(E) shall be followed as well as other applicable legislation on the handling of electronic data.

Participant personal information will be pseudonymized. Site numbers and participant numbers will be used to track participant information throughout the clinical investigation. The link between the participant number and each participant shall be retained by the PI in a secure location.

11.2 Source Documentation

Original or certified copies of all relevant clinical findings, observations, and other activities throughout the clinical investigation must be recorded and maintained in the study file of each enrolled participant. Where there is no prior written or electronic record of data, such as for subjective data (questionnaires), these data may be recorded directly on the CRF(s) and the CRF is then considered to be the source.

The PI will permit clinical investigation related monitoring, audits, IRB review and authority inspections by allowing direct access to the source data. In case of electronic source data, access must be allowed, or certified printouts should be available prior to the monitoring or audit visits. Printouts will not be limited to the index AVF only but will include all available data related to the identified participant(s).

11.3 Data Management

Data management is the responsibility of the Sponsor. Data from completed CRFs will be managed in a secured, controlled database. A Data Management Plan (DMP) will be developed that outlines the procedures used for data review, database cleaning and issuing/resolving data queries. Procedures for validations and data storage will also be contained within the DMP.

11.4 Record Retention

The Investigator shall retain all study records for a minimum of two (2) years after the later of the following two dates: the date on which the study is terminated/completed or the date that the records are no longer required for purposes of supporting a pre-market approval application or a notice of completion of a product development protocol (21 CFR Part 812.140). The data for some of these records may be available in computerized form but the final responsibility for maintaining study records remains with the Investigator. All PIs must contact the Sponsor prior to destroying or archiving off site any records or reports pertaining to the clinical investigation to ensure they are no longer needed to be maintained on-site.

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 the Sponsor and FDA, if applicable, not later than ten (10) working days after the transfer occurs.

12 QUALITY CONTROL AND ASSURANCE

12.1 Control of Investigational Device

The Pristine™ Catheter has been cleared by the FDA and will be evaluated in a post-market fashion in accordance with its labeled indication in the United States (US). Sites are to use the product off-the-shelf. The product shall be used according to the supplied IFU. The device will be identified using its product code and lot number for traceability.

Any Pristine™ Catheters that have failed or malfunctioned should be returned to the Sponsor. If the malfunctioned Pristine™ Catheter has been used (examples including, but not limited to, the sterile barrier opened and exposed to the participant) should be placed in a biohazard bag, labeled “Biohazard”, and returned to the Sponsor. Please refer to the investigational site regulatory binder for return instructions.

12.2 Monitoring

The Sponsor will designate trained and qualified personnel to monitor the progress of this clinical study in accordance with established standard operating procedures and the study-specific Monitoring Plan.

Prior to study start, a study initiation visit (SIV) will be conducted 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/EC approvals.

During the study, routine monitoring visits (RMVs) will be conducted to assure the site continues to adhere to the protocol, the investigator agreement, and regulations regarding conduct of clinical studies. The Sponsor-Monitor will confirm that the ICF to be used is the version approved by the IRB/EC, confirm the applicable national privacy laws have been followed, verify that all necessary documents are on file at the investigational site and confirm that there are provisions to continue and maintain all documents and records throughout the study as required by applicable regulations. These monitoring visits will assess continued protocol compliance, adequate participant enrollment, accurate data reporting, monitoring of participant 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.

At the completion of the study, the Sponsor-Monitor will conduct a final close-out visit or COV. The purpose of this visit may include but is not limited to collecting all outstanding study data documents, confirming that the Investigator's files are accurate and complete, reviewing the record retention requirements with the Investigator, providing for the return of unused devices to the Sponsor, reviewing records which account for device shipments and ensuring that all applicable requirements for closure of the study are met.

12.3 Audits and Inspections

If the study is selected for audit by the Sponsor or if there is an inspection by the appropriate Health Authorities, the Investigator and his team will make themselves available during the visit. The Investigator must agree to the inspection of all study related records and give the auditor/inspector direct access to source documents for verification of data on CRFs. The participant's anonymity must be ensured, and data checked during the audit must remain confidential.

As soon as the Investigator is aware of an upcoming inspection/audit by the Health Authorities, he/she will promptly inform the Sponsor. As agreed with the Investigator, Sponsor personnel may be present at the site during the inspection.

12.4 Protocol Deviations

A protocol deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the protocol.

Except when necessary to protect the life or physical well-being of a participant, protocol deviations are not permitted. The Sponsor and the investigational site's IRB/EC must be notified immediately if an emergency situation arises in which the safety of a participant may require immediate intervention different than that defined in the protocol. This must be followed by written confirmation that describes the emergency action and outcomes, within five (5) working days from the date of the emergency action in accordance with the governing IRB/EC's requirement.

It is the Investigator's responsibility to ensure that there are no deviations from the Protocol. Except in an emergency, when a protocol deviation is planned or anticipated, the Sponsor should be contacted for approval. Any and all deviations must be recorded on the appropriate CRF regardless of whether medically justifiable or sponsor approved. Upon evaluation by the Sponsor, actions may be required to prevent additional deviations, such as retraining of the site, implementation of additional site procedures, and more frequent

monitoring. If these steps fail, more serious measures, up to and including termination of enrollment at the site.

13 ADMINISTRATIVE REQUIREMENTS

13.1 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 participants. Other site personnel must have appropriate research experience and infrastructure to ensure adherence to this protocol and enrollment of sufficient numbers of evaluable participants. The curriculum vitae (CV) of the Investigator(s), Sub-Investigator(s) and Study Coordinator(s) will be maintained in the Sponsor's files as documentation of qualification by training and experience.

The Principal Investigator will sign the Investigator Agreement pages of this protocol, agreeing to comply with all applicable regulations and the requirements of this study as per the clinical study agreement. 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.

Any site that is deactivated prior to initial enrollment, either by the Sponsor or by the individual site itself, may be replaced.

13.2 Training

In addition to each Investigator and appropriate site personnel being trained on this protocol and study procedures during the Site Initiation Visit, product training will be provided by the Sponsor or designee and is required for each Investigator. Additional study staff (e.g., Sub-Investigator(s)) will also require device training provided from the Sponsor or proctoring by the PI. All training will be documented and filed at the investigational site and with the Sponsor.

13.3 Required Documents

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

- Fully executed Non-disclosure Agreement (NDA) between PI/site and Sponsor;
- CVs, signed and dated within 2 years of study start for the PI and Sub-Investigator(s);

- CVs for Study Coordinator(s);
- Signed CSA by PI/site (or designee);
- Signed Investigator Agreement Page by PI and Sub-Investigator(s);
- Signed Financial Disclosure Statement by PI and Sub-Investigator(s);
- Completed and Signed Training Log by PI and Sub-Investigator(s);
- 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.
- Statement of completing at least two prior Pristine Catheter placements.

13.4 Publication Policy

The sponsor believes that results of applicable clinical studies should be published in peer-reviewed literature in a timely, accurate, complete and balanced manner, regardless of study outcomes, whenever possible. As such, at the conclusion of this study, an article may be prepared for publication in a reputable scientific journal. Formal presentation(s) or publication(s) of data collected from this study will be considered as a joint publication by the investigator(s) and the appropriate personnel of the Sponsor. Authorship will be based on generally accepted criteria of the ICMJE (International Committee of Medical Journal Editors) and determined by mutual agreement.

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. Exceptions to this rule require the prior approval of the Sponsor. The analysis of other pre-specified and non-pre-specified endpoints will be performed by the Sponsor or its designee. Such analyses, as well as other proposed investigations or manuscripts will require the approval of the Sponsor.

13.5 Study Registration

In compliance with Title VIII of Public Law 110-85, known as FDA Amendments Act of 2007 (FDAAA), the Sponsor will register this study studies and disclose study results in a publicly accessible database (i.e., ClinicalTrials.gov). This study will be registered no later than 21 days after commencing enrollment. Study results will be posted to the website within 12 months of the last participant visit for collection of primary endpoint data.

13.6 Termination of Study

The Sponsor reserves the right to suspend enrollment or terminate the study at any time for any reason. The Sponsor may suspend enrollment or terminate the study at a

specific investigational site for reasons including, but not limited to, inadequate data collection, low participant enrollment rate, achievement of the total enrollment, conditions imposed by the reviewing IRB/EC and/or non-compliance with this protocol or other clinical research requirements. Written notice will be submitted to the Investigator in advance of such termination.

In the event of study suspension or termination, the Sponsor will send a report outlining the circumstances to the IRB/EC, and all Investigators and Regulatory Authorities as required by regulation.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 IRB Approval

Investigators or designees must submit the study protocol, Informed Consent Form (if applicable), and all other locally required documentation to an appropriate IRB and obtain study-specific written approval (favorable opinion) before being allowed to participate in the study. Before commencement of the study, the Investigator or designee must provide the Sponsor with written documentation of such approval. The IRB 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 the Sponsor.

The IRB will be notified of any amendments to the protocol, as well as possible associated information and consent form changes, where applicable, and written approval (favorable opinion) will be obtained prior to implementation, as applicable.

The Investigator or designee is responsible for fulfilling any conditions of approval imposed by the IRB, such as regular safety reporting, study timing, etc. The Investigator or designee will provide the Sponsor with copies of such reports.

14.2 Informed Consent and Confidentiality

Prior to any study procedure, the Investigator (or designee) must explain to each participant in layman's terms, the nature of the study, its purpose, expected duration, and the risks and benefits of study participation. Also, participant 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 participants 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. Participants 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, given sufficient time to decide whether to participate, before any study procedure is conducted, and before entering the study, the participant must voluntarily provide consent in accordance with 21 CFR Parts 50 and 56 and ISO 14155:2020.

14.2.1 Confidentiality

Participant confidentiality must be strictly held in trust by the Investigator, study staff, and the Sponsor. Participant confidentiality and anonymity will be maintained by removal of identifiers from any data, documentation, or clinical samples submitted to the Sponsor.

Any data collected meeting the definition of protected/confidential health information or personal identifying information will be collected and maintained using the designated authorizations and following privacy procedures as specified in the applicable health authority regulations.

The Sponsor-Monitor, authorized representatives of the sponsor, and/or applicable Health Authorities may inspect all documents and records required to be maintained by the Investigator. The Investigator/Site will permit access to such records.

14.3 Regulatory Status

The Pristine™ Long-Term Hemodialysis Catheter is FDA approved and will be evaluated in a post-market fashion for its approved indication in the US. Sites in these regions are to use the product off-the-shelf. The product shall be used according to the supplied IFU.

14.4 Statement of Compliance

This clinical investigation will be conducted in compliance with the protocol and following regulatory requirements:

- 21 CFR 50, 54, 56 and 822;
- ISO 14155:2020 and/or 21 CFR 812.28(a)(1) (Good Clinical Practice);
- Ethical principles of the Declaration of Helsinki, in its current revision; and
- Applicable sections of the national laws and regulations.

The clinical investigation will not commence at a clinical site until approval (favorable opinion) from the respective IRB/EC has been received. All additional requirements imposed by the IRB/EC(s) will be followed. Involvement of the national competent authorities (e.g. by notification, seeking authorization) will be accomplished as required by national laws and regulations.

15 REFERENCES

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3. Tal MG, Yevzlin AS. Catheter-related blood stream infection in hemodialysis patients with symmetric tunneled non-side-hole hemodialysis catheters. The Journal of Vascular Access. July 2021. doi:10.1177/11297298211027058
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5. Lok CE, Huber TS, Lee T, et al. KDOQI Clinical Practice Guideline for Vascular Access: 2019 Update [published correction appears in Am J Kidney Dis. 2021 Apr;77(4):551]. *Am J Kidney Dis*. 2020;75(4 Suppl 2):S1-S164. doi:10.1053/j.ajkd.2019.12.001
6. Allon M, Brouwer-Maier DJ, Abreo K, et al. Recommended Clinical Trial End Points for Dialysis Catheters. Clin J Am Soc Nephrol. 2018;13(3):495-500. doi:10.2215/CJN.12011116

16 APPENDICES

Appendix A - Study Definitions
Appendix B - IFU

16.1 Appendix A - Definitions

Term	Definition
Access Censoring Events	Include participant transfer to Peripheral dialysis, kidney transplantation, AVF, AVG, or the event of a participants premature discontinuation in the investigation due to withdrawn consent, withdrawal by PI, LTF, or participant death (refer to abbreviations for definitions).
Active Participant	An investigation participant who has not completed all required investigation follow-up and who has not prematurely discontinued participation in this clinical investigation (refer to Section 6.5) at the timepoint of reference.
Adjunctive Procedure	Procedure(s) completed during the index procedure (prior to leaving the procedure room) as part of SOC procedures. Procedures to ensure HD continuity, as well as procedures to address AEs.
Adverse Device Effect (ADE)	An ADE is an AE that is considered to be related to the use of the Pristine™ Catheter. This includes AEs resulting from insufficient or inadequate IFU, operation, or any malfunction of the Pristine™ Catheter. Additionally, this definition includes any event resulting from use error or from intentional misuse of the Pristine™ Catheter.
Adverse event (AE)	An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users, or other persons, whether or not related to the Pristine™ Catheter and whether anticipated or unanticipated. For users or other persons, this definition is restricted to events related to the use of the Pristine™ Catheter. **Note:** Pre-existing conditions should be considered as part of the participant's medical history and should not be reported as an AE unless there is a substantial increase in severity or frequency of the condition, which has not been attributed to natural history. Exacerbation of an existing condition should be reported as an AE if the event meets the CIP definition of an AE.
All Interventions [Post Creation / After First Use]	The number of interventions [post creation / after first use] inclusive of all interventions (facilitation, maintenance, and HD continuity interventions).

Term	Definition
Audit	Systematic examination of activities and documents related to a clinical investigation performed by (an) independent person(s) to determine whether these activities were conducted, and the data recorded, analyzed, and accurately reported, according to this CIP, standard operating procedures, applicable standards, and applicable regulatory requirements.
Audit trail	Documentation that allows reconstruction of the course of events.
(electronic) Case Report Forms (eCRFs)	Electronic documents for each participant on which information to be reported to the Sponsor is recorded, as required by this CIP.
Certified Copy / Printout	Copy (irrespective of the type of media used) of the original record that has been verified, (i.e. by a dated signature or by generation through a validated process), to have the same information including data that describe the context, content, and structure, as the original.
Chronic Kidney Disease	A term that includes stages such as mild, moderate, and severe loss of kidney function based on the patient's level of glomerular filtration rate (GFR).
Complications[4]	Non-infectious complications are defined as: Complication due to any noninfectious cause (thrombosis of the access, fibrin material within or around a catheter, catheter migration, central vein stenosis or thrombosis) requiring a revision procedure to maintain patency or improve access performance (i.e., thrombolysis, angioplasty, or surgical correction) in an inpatient or outpatient setting or removal or abandonment with creation of a new access that was not due to an access-related infection).[3] Infectious Complications are defined as: Complications due to any documented diagnosis of access infection requiring medical intervention (managed in an outpatient or inpatient setting) or sepsis as diagnosis in the hospitalization file whether access related or not.[3]

Term	Definition
Definitely Related AE	An AE is definitely related if it is obvious, certain or there is little doubt regarding the relationship.
Deviation	Instance(s) of failure to follow, intentionally or unintentionally, the requirements of this CIP.
Device Deficiency	Any inadequacy of a medical device with respects to its identity, quality, durability, reliability, usability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling. A device malfunction is defined as a failure of a medical device to perform in accordance with its intended purpose when used in accordance with the IFU or CIP. Device deficiencies are only applicable to the Pristine™ Catheter.
End Stage Renal Disease (ESRD)	Last stage of Chronic Kidney Disease. When the kidneys stop working well enough to meet the needs of daily life.
Enrolled Participant	A participant who has signed the ICF for this investigation.
Independent	Not involved in the development of the investigation device or the conduct of a clinical investigation, except for their specifically assigned responsibilities, in order to avoid bias or a conflict of interest.
Index Procedure	The initial procedure intended to place the Pristine™ Catheter for dialysis access.
Informed Consent	Process by which an individual voluntarily confirms willingness to participate in a particular clinical investigation, after having been informed of all aspects of the investigation that are relevant for the decision to participate.
Investigational Site	Institution or site where the clinical investigation is carried out.
KDOQI VA-2019 CVC-related infection definition	"Clinical manifestations and at least 1 positive BC from a peripheral source (dialysis circuit or vein) and no other apparent source, with either positive semiquantitative (>15 CFU/ catheter segment, hub or tip) or quantitative (>102 CFU/catheter segment, eg, hub or tip) culture, whereby the same organism (species and antibiogram) is isolated from the catheter segment (eg, hub or tip) and a peripheral source (dialysis circuit or vein) blood sample. If available, the following would be supportive: Simultaneous quantitative cultures

Term	Definition
	of blood samples with a ratio of ≥3:1 (catheter hub/tip vs peripheral [dialysis circuit/vein]); differential period of catheter culture versus peripheral BC positivity of 2 hours."
Legally Authorized Representative (LAR)	Individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective participant, to the participant's participation in the clinical investigation. "Legally designated representative" or "legally acceptable representative" are other terminologies used under national regulations for "legally designated representative".
Line Reversals	Reversal of lumens of the catheter to allow for completion of HD treatment.
Lost to Follow-Up (LTF)	A participant may be considered LTF if the investigation site team members are unable to locate the participant despite three documented attempts to notify the participant via telephone and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods. This does not apply to missed visits, where the participant misses one of the follow up contact time points but completed a subsequent one (when participant misses two consecutive follow-ups and is unable to be contacted with the documented attempts outlined before, the participant may be considered LTF and withdrawn from the clinical investigation). The site should also contact the HD center to ascertain the participant's status. Before the site considers a participant LTF, written agreement should be obtained from the Sponsor.
Malfunction	Defined as a failure of a medical device to perform in accordance with its intended purpose when used in accordance with the IFU or CIP.
Mild AE	Awareness of a sign or symptom that does not interfere with the participant's activity or is transient and is resolved without treatment or additional sequelae.
Moderate AE	Interferes with the participant's usual activity and / or requires additional intervention and / or treatment and may have additional sequelae.
Monitoring	Act of overseeing the progress of a clinical investigation and to ensure that it is conducted, recorded, and reported in accordance

Term	Definition
	with this CIP, written procedures, applicable standards, and the applicable regulatory requirements.
Not Related AE	An AE is not related if it is determined that there is no plausible association.
Operator	Primary individual responsible for conducting the index procedure.
Point of Enrollment	Time at which, following recruitment and before any clinical investigation-related procedures are undertaken, a participant signs and dates the ICF.
Possibly Related AE	An AE is possibly related if it is capable of being related but relatively unlikely or there is insufficient information to determine if the AE is related to the device or procedure.
Post Procedure Event	AE that occurred after the index procedure.
Principal Investigator	Qualified person responsible for conducting the clinical investigation at an investigation site. If a clinical investigation is conducted by a team of individuals at an investigation site, the PI is responsible for leading the team.
Procedure access Site	A site of incision access during index procedure.
Procedural Event	AE that occurred during the index procedure.
Procedure Duration	The duration of the index procedure as defined in this CIP.
Procedure Related AE	AEs directly attributable to the index procedure.
Procedure Success	Successful catheter creation using the Pristine™ Long-Term Hemodialysis Catheter with flow confirmed through the catheter.
Recruitment	Active efforts to identify participants who can be suitable for enrolment into the clinical investigation.
Re-interventions	Any additional procedures with the initial catheter after the index procedure.
Screen Failure	A participant who is excluded from this clinical investigation as based on the eligibility criteria.
Serious Adverse Device Effect (SADE)	ADE that has resulted in any of the consequences characteristic of a SAE.

Term	Definition
Serious Adverse Event	An AE that led to any of the following: • Death; or • Serious deterioration in the health of the participant, users or other persons as defined by one or more of the following: - A life-threatening illness or injury; or - A permanent impairment of a body structure or a body function including chronic diseases; or - In-patient or prolonged existing hospitalization; or - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; or • Fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment. **Note:** Planned hospital visits and / or hospital stays, or procedures required by this CIP (including subsequent interventions assessed in the clinical investigation endpoints), without serious deterioration in health should not be considered SAEs.
Serious Health Threat	Signal from any AE or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in participants, users, or other persons, and that requires prompt remedial action for other participants, users, or other persons. This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Severe AE	Symptom(s) causing severe discomfort to the participant and / or significant impact on the participant's usual activity. Additional intervention and / or treatment is necessary. Additional sequelae occur.
Severity (of AE)	The intensity of the AE as experienced by the participant or user.
Significant Deviation	A deviation that occur to protect the life or physical well-being of a participant in an emergency, or a deviation that may affect the

Term	Definition
	scientific soundness of the clinical investigation, or a deviation pertaining to the rights, safety or welfare of human participants.
Source Data	All information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation. This includes electronic source data initially recorded in an electronic format.
Source Document	Original or certified copy of printed, optical, or electronic document containing source data.
Sub-Investigator	Individual member of the investigation site team designated and supervised by the PI at an investigation site to perform clinical investigation-related procedures or to make important clinical investigation-related and medical treatment decisions.
Thrombosis	The formation or presence of a blood clot resulting in catheter occlusion.
Treated Participant	Defined as a participant that has met all eligibility criteria, into whom the Pristine™ Long-Term Hemodialysis Catheter was introduced and in whom procedure success was achieved.
Unanticipated (Serious) Adverse Device Effect (U(S)ADE)	A UADE / USADE is any (serious) ADE on health or safety or any life-threatening problem or death caused by, or associated with, the WavelinQTM EndoAVF System, which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment., or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of participants.
Use Error	User action or lack of user action while using the medical device that leads to a different result than intended by the manufacturer or expected by the user. User error includes the inability of the user to complete a task. User errors can result from a mismatch between the characteristics of the user, user interface, task or use environment. Users might be aware or unaware that a use error has occurred. An unexpected physiological response of the participant is not by itself considered a use error. A malfunction of a medical device that causes an unexpected result is not considered a use error.

16.1 Appendix B – IFU
Will attach as PDF.