# WAVE GLOBAL

# CLINICAL INVESTIGATION PLAN

| | |
|---|---|
| **Title:** | **The WavelinQ™ Arterio-Venous Endovascular Fistula: A Global, Multi-Center, Prospective, Post-Market, Confirmatory, Interventional, Investigation** |
| **Acronym:** | **WAVE Global** |
| **CIP Number:** | **BDPI-19-005** |
| **Investigation Type:** | **Post-Market Confirmatory Interventional** |
| **Version Date:** | **23 September 2020** |
| **Version:** | **1.0** |
| **Investigation Device:** | **WavelinQ™ EndoAVF System** |
| **Sponsor:** | **Bard Peripheral Vascular, Inc.**<br>**(BD Peripheral Intervention)**<br>1625 West 3rd Street<br>Tempe, AZ 85281 |

Anna Lovas — 23sept 2020

Sponsor – Anna Lovas, Director, Clinical Affairs — Date

Chlok — Sept. 25 2020

Lead Co-Principal Investigator – Charmaine Lok, MD, MSc, FRCPC — Date

N — 26/Sept 2020

Lead Co-Principal Investigator – Nicholas Inston, PhD, FRCS — Date

Panagiotis M. Kitrou — September 26th, 2020

Lead Co-Principal Investigator – Panagiotis Kitrou, MD, MSc, PhD, EBIR — Date

BD BARD has joined BD

## Sponsor Contacts:

Simon Lubek
Clinical Project Manager
+33 6 07 56 66 08
simon.lubek@bd.com

## Safety Contacts:

*Medical Monitor*
Prof. Dr. Hans-Peter Stoll
Internist & Cardiologist
[redacted]

*Safety Coordinator*
Dana L. Stegmeier
Sr. Clinical Safety Specialist
[redacted]

## Coordinating Investigators:

Nicholas Inston,
PhD, FRCS
Specialty: Transplant Surgery
Queen Elizabeth Hospital
Birmingham, United Kingdom
[redacted]

Panagiotis Kitrou,
MD, MSc, PhD, EBIR
Specialty: Interventional Radiology
Patras University Hospital
Patras, Greece
[redacted]

Charmaine Lok,
MD, MSc, FRCPC
Specialty: Nephrology
University Health Network
Toronto, Canada
[redacted]

## Imaging Transfer and Core Labs:

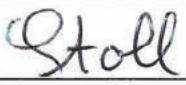
Syntactx
4 World Trade Center
150 Greenwich Street
44th Floor
New York, New York 10007
[redacted]

## Version History:

| CIP Version | Description of Changes |
|---|---|
| 1.0 | Initial Release |

## SPONSOR CLINICAL INVESTIGATON PLAN (CIP) 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* | |
| Investigation Statistician | Aimin Feng | *This document is signed electronically in the eTMF system* | |
| Regulatory Affairs | Kulveen Dhatt |  | 23 Sept 2020 |
| Project Manager | Simon Lubek | *This document is signed electronically in the eTMF system* | |
| Medical Monitor | Prof. Dr. Hans-Peter Stoll |  | 23-Sept 2020 |
| Legal Team Representative | Gregg Grunstra | *This document is signed electronically in the eTMF system* | |

**Responsibilities of the Principal Investigator**

The role of the Principal Investigator (PI) is to implement, oversee the management of the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects (referred to as participants in this clinical investigation plan [CIP]) involved in this clinical investigation. Prior to participation in this clinical investigation, the PI or authorized designee must indicate acceptance of this CIP by signing the signature page, sign the Clinical Study Agreement (CSA) and obtain written approval from the governing Institutional Review Board or Ethics Committee (IRB / EC). This approval must be dated, in the Investigator's name and a copy provided to the Sponsor along with the IRB / EC approved Informed Consent Form (ICF) and the signed CIP signature page as well as CSA, prior to beginning enrollment. Prior to implementation of any amendments to applicable investigation documents, written and dated approval from the governing IRB / EC must be obtained, if required. The PI and operating Sub-Investigator(s) must receive training prior to participant screening and enrollment. Operators must also complete BD-Sponsored training prior to operation of the WavelinQ™ EndoAVF System on any enrolled participant and only after approval by the Sponsor.

**The PI must also:**

- Conduct the clinical investigation in accordance and compliance with this CIP, all written recommendations and instructions received from the Sponsor and / or IRB / EC, the CSA, the Declaration of Helsinki, Good Clinical Practice (GCP), applicable national privacy laws (e.g. General Data Protection Regulation (GDPR) in the European Union (EU)), applicable International Organization for Standardization (ISO) regulations (ISO 14155:2020(E)) as well as any applicable regulatory requirements.
- Ensure full disclosure of all potential conflicts of interest, including financial, that can interfere with the conduct of the clinical investigation or interpretation of results.
- IRB / EC Compliance and Communications:
    - Ensure prompt reporting to the IRB / EC of applicable events as required by this CIP and / or the requirements of the governing IRB / EC (e.g. reporting of applicable safety events, of applicable deviations, of suspensions, etc.) is documented, completed in a timely manner and documentation thereof is provided to the Sponsor.
    - Provide the Sponsor with copies of any clinical investigation-related communications between the investigational site and the IRB / EC.
- Informed Consent:
    - Ensure that written informed consent is obtained from each participant prior to the conduct of any clinical investigation procedure; using the current IRB / EC approved ICF.

- Ensure compliance with the applicable regulatory requirements and ethical principles for the process of obtaining informed consent.
- Ensure and document appropriate training if an authorized designee is appointed to conduct the informed consent process.

- Source Documentation and Data Collection:
  - Create and maintain source documents throughout the clinical investigation and maintain documentation of the type and location of these source documents.
  - Ensure the accuracy, completeness, legibility (where applicable) and timeliness of the data reported to the Sponsor on the electronic case report forms (eCRFs) and in all required reports.
  - Provide all required data and reports and agree to source document verification of clinical investigation data with participant's medical records during monitoring visits or audits.
  - Ensure the retention of all investigation-related records as specified in this CIP.
- Deviations:
  - Propose to the Sponsor any appropriate modification(s) of the CIP or WavelinQ™ EndoAVF System or of the use of the WavelinQ™ EndoAVF System.
  - Refrain from implementing any modifications to the CIP without prior agreement from the Sponsor, EC and if required, the regulatory authorities.
  - Document and explain any deviation from the approved CIP that occurred during the course of the clinical investigation.
  - Determine the cause of and implement appropriate corrective and preventive actions to address significant noncompliance.
- Investigational Site Team Members and Resources:
  - Provide appropriate resources to ensure compliance with all clinical investigation-related procedures and prompt submission of all CRFs.
  - Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
  - Ensure adequate training and qualification of the investigation site team members and maintain oversight of their activities or delegated responsibilities.
  - Ensure that maintenance and calibration of the equipment relevant for the clinical investigation is appropriately performed and documented, where applicable.

- Investigation Device Handling:
    - Ensure that the investigation device is used according to its instructions for use (IFU).
    - Ensure the safe return of potentially biohazardous investigation devices to the Sponsor where possible in case of reported device deficiencies and collaborate with the Sponsor to provide the necessary information allowing an accurate analysis where appropriate.
- Safety Reporting and Handling:
    - Ensuring complete and timely safety event and / or device deficiency recording, assessment, and reporting per the requirements of this CIP and / or the IRB / EC to the required parties and supplying the Sponsor upon request any additional documentation / information pertaining to these events.
    - Inform the participant of the nature and possible cause of any adverse event (AE) experienced. Provide adequate medical care to a participant during and after a participant's participation in a clinical investigation in the case of AEs, as described in the informed consent.
- Monitoring and Auditing:
    - Allow and support the Sponsor personnel or their designee(s), IRB / EC representatives as well as regulatory representatives to perform monitoring and / or auditing activities and to inspect and copy any investigation related documents.
    - Be accessible to the monitor during monitoring visits.
- Participant Medical Care:
    - With the support of the Sponsor as necessary, inform the participants of any new significant findings occurring during this clinical investigation, including the need for additional medical care that may be required.
    - Provide the participant with well-defined procedures for possible emergency situations related to this clinical investigation and make necessary arrangements for emergency treatment as appropriate and per standard practices of the treating facilities.
    - Ensure that clinical records are clearly marked to indicate that the participant is enrolled in this clinical investigation as allowable by local IRB / EC and within local privacy guidelines.
    - If appropriate, provide participants enrolled in the clinical investigation with some means of showing their participation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).

- Inform, with the participant's approval or when required by national regulations, the participant's personal physician about the participant's participation in this clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a participant's premature withdrawal from the clinical investigation while fully respecting the participant's rights per IRB / EC requirements.

The PI may delegate one or more of the above functions to a Sub-Investigator provided that the Sub-Investigator first signs the Sub-Investigator CIP Signature Page and receives appropriate training as specified in this CIP. The PI may also delegate specific tasks to qualified members of the investigation site team. However, the PI retains overall responsibility for IRB / EC approval and proper conduct of the clinical investigation. This also applies to activities that are outsourced to external organizations on the PI's behalf in which case the PI shall implement procedures to ensure the integrity of all tasks performed and any data generated by this external organization.

## PRINCIPAL INVESTIGATOR AGREEMENT PAGE

I have read and understand the contents of the WAVE Global Clinical Investigation Plan (CIP). I agree to follow and abide by the requirements set forth in this and any supporting documents. I also agree to conduct the clinical investigation in accordance with the Clinical Study Agreement, Good Clinical Practice (GCP), applicable ISO regulations (ISO 14155:2020(E)) as well as any applicable EC / IRB and / or applicable regulatory requirements.

I agree to participate in BD-Sponsored training prior to performing any data collection or clinical investigation-related procedures. I also agree to participate in BD-Sponsored device training prior to operation of the WavelinQ™ EndoAVF System on any enrolled participant and not until being approved by the Sponsor in writing to do so.

Agreed to by:

| Printed Name - Investigator | Date |
|---|---|

| Signature |
|---|

| Site Name | Site Number |
|---|---|

## SUB-INVESTIGATOR AGREEMENT PAGE

I have read and understand the contents of the WAVE Global Clinical Investigation Plan (CIP). I agree to follow and abide by the requirements set forth in this and any supporting documents. I also agree to conduct the clinical investigation in accordance with the Clinical Study Agreement, Good Clinical Practice (GCP) as well as applicable ISO regulations (ISO 14155:2020(E)) as well as any applicable EC / IRB and / or applicable regulatory requirements.

I agree to receive training by the principal investigator and / or Sponsor personnel prior to performing any data collection or clinical investigation-related procedures. I also agree to participate in BD-sponsored device training prior to operation of the WavelinQ™ EndoAVF System on any enrolled participant and not until being approved by the Sponsor in writing to do so.

Agreed to by:

| Printed Name – Sub-Investigator | Date |
|---|---|

Signature

| Site Name | Site Number |
|---|---|

**TABLE OF CONTENTS**

# 1 CLINICAL INVESTIGATION PLAN (CIP) SUMMARY

## 1.1 Synopsis

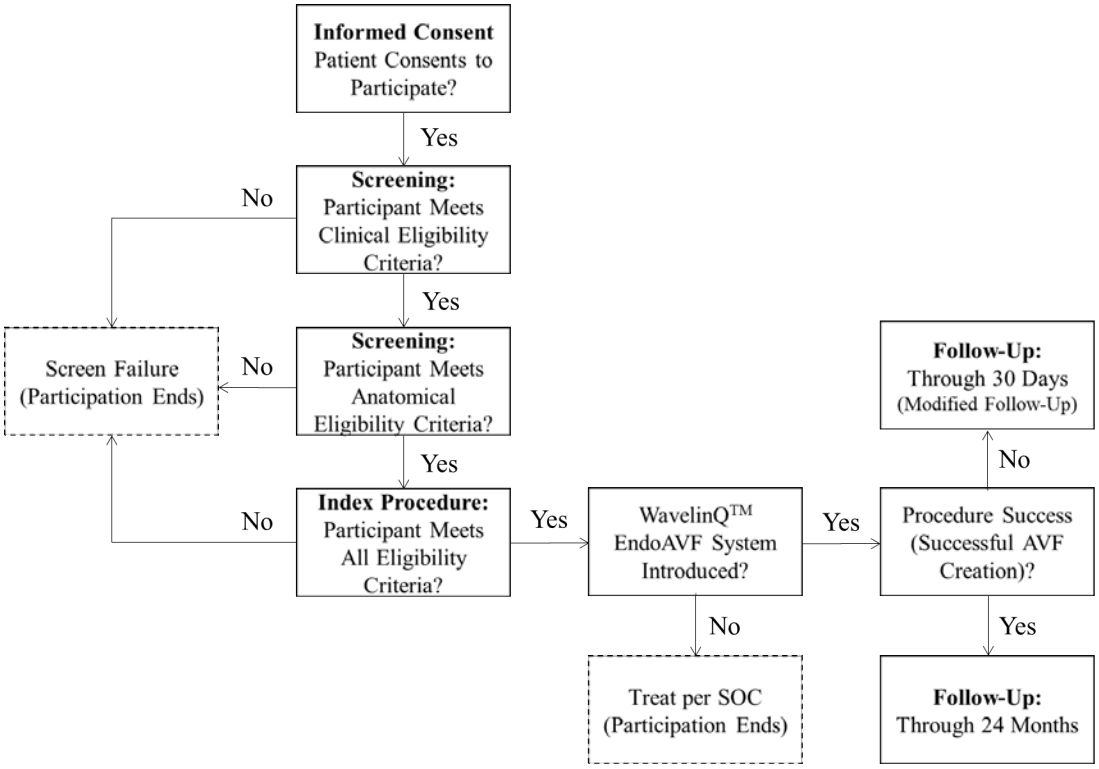
| | |
|---|---|
| **Title:** | The WavelinQ™ Arterio-Venous Endovascular Fistula: A Global, Multi-Center, Prospective, Post-Market, Confirmatory, Interventional, Investigation (WAVE Global) |
| **Sponsor:** | Bard Peripheral Vascular, Inc. (BD Peripheral Intervention) |
| **Development Phase:** | Post-Market, Confirmatory, Interventional |
| **Investigation Product(s):** | Test Product: The WavelinQ™ EndoAVF System<br>Reference / Comparator Product(s): Not Applicable<br>Ancillary Product(s): As per the Device Instructions for Use (IFU) |
| **Investigation Device Intended Use:** | Used as per the IFU. The WavelinQ™ EndoAVF System is intended for the cutting and coagulation of blood vessel tissue in the peripheral vasculature for the creation of an arteriovenous fistula (AVF) used for hemodialysis. |
| **Investigation Design & Overview:** | This is a global, multi-center, prospective, post-market, confirmatory, interventional, non-randomized, single-arm clinical investigation evaluating AVF creation by means of the WavelinQ™ EndoAVF System in patients who require a vascular access for hemodialysis (HD). |
| **Rationale:** | The purpose of this clinical investigation is to provide clinical evidence to further demonstrate reasonable assurance of safety and effectiveness of the WavelinQ™ EndoAVF System for endovascular fistula (endoAVF) creations in a post-market confirmatory interventional fashion. |
| **Investigational Sites:** | A target of approximately 15 investigational sites (up to a maximum of 30 investigational sites) will be included in this investigation and distributed globally outside the US. |
| **Investigation Target Population:** | A total of approximately up to one-hundred and fifty (150) treated participants will be included in this investigation. A treated participant is defined as a participant that has met all eligibility criteria, into whom the WavelinQ™ EndoAVF System was introduced, and in whom procedure success was achieved. Note that for the purposes of this CIP participant is synonymous with subject.<br>This investigation will enroll participants determined to be in need of an HD vascular access who are either already receiving HD at the time of screening (prevalent participants), regardless of access type (central venous catheter [CVC)] AVF, arteriovenous graft [AVG]), or those who are not yet receiving HD but are in need of a vascular access as determined by the referring clinician (incident participants). |
| **Inclusion Criteria:** | *Clinical Inclusion Criteria:*<br>The participant must:<br>1. Be able to comprehend, voluntarily sign and date the ICF prior to collection of clinical investigation data or performance of clinical investigation procedures (or where allowable the participant's legally authorized representative (LAR) on behalf of the participant).<br>2. Be able to and willing to comply with the CIP requirements, including clinical follow-up.<br>3. Be male or non-pregnant female ≥ 18 years of age with an expected lifespan sufficient (≥ 24 months) to allow for completion of all clinical investigation procedures.<br>4. Have established, non-reversible kidney failure, who are currently on HD at screening or are in need of a vascular access for HD as determined by the referring clinician. |

| | |
|---|---|
| **Inclusion Criteria (continued):** | *Anatomical Inclusion Criteria:*<br>The participant must have:<br>5. Target treatment vein diameter(s) for AVF creation ≥ 2.0 mm as measured via DUS or angiography.<br>6. A target treatment artery diameter ≥ 2.0 mm as measured via DUS or angiography.<br>7. Adequate collateral circulation to the hand, in the opinion of the Principal Investigator (PI) (or authorized designee).<br>*8.* At least one superficial outflow vein diameter ≥ 2.5 mm as measured via DUS or angiography that is in communication with the target creation site via a proximal forearm perforating vein. |
| **Exclusion Criteria** | *Clinical Exclusion Criteria:*<br>The participant must not have:<br>1. Active or nontreated hypercoagulable state.<br>2. Known bleeding diathesis.<br>3. Insufficient cardiac output to support the maturation and use of an AVF in the opinion of the PI (or authorized designee).<br>4. Known history of or current active intravenous drug abuse.<br>5. A "planned" major surgical procedure within 6 months following index procedure or major surgery, in the opinion of the PI (or authorized designee), within 30 days prior to index procedure.<br>6. Known allergy or hypersensitivity to contrast media which cannot be adequately treated with pre-medication.<br>7. Known adverse effects to sedation and / or anesthesia which cannot be adequately treated with pre-medication.<br>8. Evidence of active infection on the day of the index procedure (temperature of ≥ 38.0° Celsius and / or White Blood Cell (WBC) Count of ≥ 12,000 cells / μL, if collected).<br>9. Another medical condition, which, in the opinion of the PI (or authorized designee), may cause him / her to be non-compliant with the CIP, confound the data interpretation, or is associated with a life expectancy insufficient to allow for the completion of clinical investigation procedures and follow-up.<br>10. Current participation in an investigational drug or device clinical investigation that has not completed the clinical investigation treatment or that clinically interferes with the clinical investigation endpoints. *Note: Investigations requiring extended follow-up visits for products that were investigational, but have since become commercially available, are not considered investigational*.<br>*Anatomical Exclusion Criteria:*<br>The participant must not have:<br>11. Central venous stenosis or central vein narrowing ≥ 50% based on imaging, or any degree of central venous stenosis with accompanying signs or symptoms, on the same side as the planned AVF creation.<br>12. The absence of a proximal forearm perforating vein feeding the target cannulation vein(s) from the target creation site via DUS or angiography.<br>13. Occlusion or stenosis ≥ 50%, or any degree of stenosis with accompanying signs or symptoms of target cannulation vein(s) such as cephalic, median cubital, basilic, etc. assessed via DUS or angiography and as clinically determined by PI (or authorized designee).<br>14. Significantly compromised venous or arterial architecture (e.g. severe vessel calcification) or flow in the treatment arm as determined by the PI (or authorized designee) and DUS or angiography.<br>15. Presence of significant calcification at the target endoAVF location that could potentially impact the effectiveness of endoAVF creation as determined by the PI (or authorized designee). |

<table>
<tr><td>Primary Endpoints:</td><td colspan="2">
<ul>
<li>Safety<br><br>Objective: Assess that the device continues to maintain its safety profile.<br><br>Endpoint: The primary safety endpoint is the proportion of participants with freedom from Clinical Events Committee (CEC) adjudicated device- or procedure-related serious adverse events (SAEs) through 30 days.<br><br>The primary safety endpoint will be evaluated against a performance goal (PG) of 82.6%, which was set with a 10% non-inferiority margin of the estimated 92.6% through 30 days derived from pre-market data from the prior clinical investigations evaluating the WavelinQ™ EndoAVF System.</li>
<li>Effectiveness<br><br>Objective: Assess that the device yields an AVF that can be used for HD effectively and performs within clinical guideline expectations.<br><br>Endpoint: The primary effectiveness endpoint will evaluate the impact of endoAVF creations using the WavelinQ™ EndoAVF System on the number of interventions post creation to facilitate and / or maintain AVF use (facilitation interventions and / or maintenance interventions as defined in this CIP). This endpoint will be evaluated including all data collected for all participants up until the timepoint of the 6-month follow-up of the last active treated participant (i.e. including any and all data exceeding the 6-month follow-up visit up to this timepoint).<br><br>The number of facilitation and / or maintenance interventions per PY will be compared to a PG, that is composed of the combined targets for interventions to facilitate and maintain AVF use recommended by the 2019 update of the KDOQI Clinical Practice Guideline for Vascular Access.[8]</li>
</ul>
</td></tr>
<tr><td>Secondary Endpoints:</td><td colspan="2">Safety<br>• Device and Procedure Related SAEs evaluated through 6- and 24-months<br><br>Effectiveness<br>• Physiological Maturation evaluated through 6-weeks<br>• Cannulation Success evaluated through 6-months<br>• Cumulative Functional Patency evaluated through 12-months</td></tr>
<tr><td>Exploratory Endpoints:</td><td>
• Procedure Success<br>
• Adjunctive Procedures<br>
• Vascular Access at HD Initiation<br>
• Physiological Maturation*<br>
• Cannulation Success*<br>
• Functional Maturation<br>
• Functional HD Usability<br>
• Facilitation Interventions Post Creation<br>
• Maintenance Interventions Post Creation<br>
• All Interventions Post Creation<br>
• All Interventions Post First Use<br>
• Primary Patency
</td><td>
• Cumulative Patency<br>
• Primary Functional Patency<br>
• Cumulative Functional Patency*<br>
• CVC Exposure / Use<br>
• DUS Juxta- & Peri-Anastomotic as well as Perforator Vein Patency<br>
• Wrist Arterial Procedure Access Considerations<br>
• Participant Satisfaction / Quality of Life<br>
• HD arteriovenous (AV) Access Continuity<br><br>
*Evaluated through additional intervals
</td></tr>
</table>

| | |
|---|---|
| **Procedures:** | All participants will undergo a clinical evaluation at screening (prior to the index procedure). All participants that have met all eligibility criteria and into whom the WavelinQ™ EndoAVF System was introduced will undergo a clinical evaluation prior to discharge from the procedure facility<br>Follow-up visits for all treated participants will be conducted through in-person clinic visits at 30-days, 6-weeks as well as 6- and 12-months as well as through phone calls and remote record collection (e.g. from the participants HD center) at 3-, 18- and 24-months. Refer to section 1.3 for the Schedule of Activities.<br>Participants into whom the WavelinQ™ EndoAVF System was introduced but procedure success was not achieved will be followed through the 30-day follow-up to assess for any safety events and interventions. This follow-up can be conducted by phone for these participants at which time their participation in the investigation will end.<br>Participants into whom the WavelinQ™ EndoAVF System is not introduced should be treated per SOC and the reason documented on the appropriate eCRF. Participation for these participants will end at the time of the index procedure. |
| **Safety Committees:** | A CEC will be used to adjudicate AEs throughout the course of the clinical investigation and a Medical Monitor (MM) will be responsible for AE trending reviews as well as for the identification of signals that could indicate a serious health threat. |
| **Regulatory Status:** | The WavelinQ™ EndoAVF System is Conformité Européene (CE) marked and will be evaluated in a post-market fashion for its approved indication in the European Union (EU) and the United Kingdom (UK). Appropriate regulatory approvals will be obtained in other regions prior to initiating the clinical investigation in those regions, if applicable. |

## 1.2 Schema



## 1.3 Schedule of Activities

| | Screening (Section 6.1) | Screening / Index Procedure (Section 6.2) | Post-Index Procedure / Discharge (Section 6.3) | Participant Follow-Up (Section 6.4) | | | | | | | Unscheduled (Section 6.4.2) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 30-Day (± 5 days) | 6-Week (± 7 days) | 3-Month (± 30 days) | 6-Month (± 30 days) | 12-Month (± 30 days) | 18-Month (± 30 days) | 24-Month (± 30 days) | |
| In-Clinic Visit | ✓ | ✓ | ✓ | ✓† | ✓ | | ✓ | ✓ | | | ✓ |
| Phone Call | | | | † | | ✓ | | | ✓ | ✓ | ✓ |
| Informed Consent | ✓ | | | | | | | | | | |
| Eligibility | ✓ | ✓ | | | | | | | | | |
| Demographics / Medical History | ✓ | | | | | | | | | | |
| Angiography (Procedural & Final) | | ✓ | | | | | | | | | |
| DUS | ✓ | ✓ | | ✓ | ✓ | | ✓* | ✓* | | | # |
| Clinical Exam | ✓ | | ✓ | ✓ | ✓ | | ✓ | ✓ | | | ✓ |
| Medication Assessment | | ✓ | | | | | | | | | |
| QOL - EQ-5D Questionnaire | ✓ | | | | ✓ | | ✓ | ✓ | | ✓ | # |
| QOL - SF-VAQ | ✓ | | | | ✓ | | ✓ | ✓ | | ✓ | # |
| HD History and Status** | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Intervention Assessment | | | ✓ | ✓† | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Adverse Event Assessment | | ✓ | ✓ | ✓† | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Deviations | | ✓ | ✓ | ✓† | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

* DUS required at these visits only if participant is not successfully dialyzing with the AVF created as part of this clinical investigation using 2-needle cannulation and / or if the participant's wrist artery was used for procedure access during the index procedure.

**Determine and document if and how the participant has been and / or is receiving HD (AVF, CVC, etc.) and document the date of the participant's last HD session. Once HD (1- or 2-needle cannulation) is initiated via the AVF created as part of this investigation, HD details must be documented and detailed HD access data (e.g., cannulation logs) will be provided to the Sponsor or designee for review and analysis as per Section 6.4.1.

# These items are required for those unscheduled visits that fall within an allotted investigation schedule follow-up window if the visit is used in place of an investigation scheduled follow-up for which these items are required.

† For participants into whom the WavelinQ™ EndoAVF system was introduced but procedure success was not achieved, only the follow up at 30 days is required to collect adverse events and interventions. The visit for these participants may be completed by phone. Investigation participation for these participants ends after completion of this follow-up.

# 2 INTRODUCTION

This is a global, multi-center, prospective, post-market, confirmatory, interventional, non-randomized, single-arm clinical investigation evaluating arteriovenous fistula (AVF) creations by means of the WavelinQ™ EndoAVF System in patients who require vascular access for hemodialysis (HD). This clinical investigation will be conducted in conformance with the Declaration of Helsinki, applicable national privacy laws (e.g., General Data Protection Regulation (GDPR) in the European Union (EU)), and applicable ISO regulations (ISO 14155;2020(E)).

## 2.1 Background

End Stage Kidney Disease (ESKD) currently affects over 3.5 million people worldwide.[1] It is projected that the worldwide incidence of ESKD will increase dramatically over the next 10 years, due to the increasing incidence of an aging population, diabetes, hypertension, and obesity.[2] Currently, Kidney Replacement Therapy (KRT) for patients with ESKD consists of either dialysis (HD or peritoneal dialysis [PD]) or kidney transplantation. The number of people receiving KRT currently exceeds 2.5 million world-wide and this is projected to double to 5.4 million by 2030.[3] Dialysis is the predominant form of KRT; but the relative proportions of patients on HD or PD vary widely both locally (i.e. by facility) and internationally (e.g. by country). According to the United States Renal Data System (USRDS), in 2015 around 87.3% of U.S. patients requiring KRT received HD, 9.6% were treated with peritoneal dialysis, and the remainder had a kidney transplant.[2] Similarly in Europe, according to the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry Annual Report 2016, the majority of patients started KRT with HD (84%), while 12% of patients started with PD and 4% received a pre-emptive kidney transplant.[4]

Vascular access is a critical component in the care of patients undergoing HD. The three types of vascular access are: an autogenous AVF, a prosthetic arteriovenous graft (AVG) or a central venous catheter (CVC).[5] The AVF has been associated with superior outcomes compared to AVG and CVC access in terms of both mortality and morbidity.[6,7] This association has led to numerous initiatives worldwide to increase the creation and use of AVF as the preferred form of vascular access in patients requiring HD. The new National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines continue to support the AVF as the preferred vascular access in eligible patients according to their ESKD Life-Plan.[8] These and other guidelines have stressed the importance of proactive identification of patients requiring HD and have described procedures and quality initiatives to maximize vascular access longevity. The Society of Vascular Surgery (SVS) has also approved and sponsored initiatives around the development and publication of reporting standards for HD access and the development of practice guidelines for HD access.[9] Subsequently, a special issue published by the Clinical Journal of the American Society of Nephrology highlighted standardized definitions which could be used for clinical trials specifically designed for the development and assessment of innovations in

vascular access.[10] Authors of these papers included multidisciplinary clinicians (academic and community practice), patients, industry partners and regulatory partners (FDA). Clearly, the multi-faceted vascular access community recognizes the importance of the AVF and the need for clinical trials to support technology, innovation, and progress to improve AVF outcomes.

An AVF is traditionally created during a surgical procedure under general anesthesia. A surgical incision is made in the forearm or upper arm, followed by identification of target arteries and veins for surgical connection. Frequently, prior to the procedure, the vessels are mapped using duplex ultrasound (DUS) imaging, allowing for pre-operative vessel diameter measurement and vessel selection. Typically, the radial artery or brachial artery and the cephalic vein or basilic vein are selected. The target vessels are carefully dissected and mobilized, and the vein is transected. An arteriotomy is created, and an anastomosis is sewn between the vein and the artery. After completion, the flow is verified using palpation and DUS, and the incision is closed. Over the course of the following–1 – 3 months, the vein dilates due to the increased flow, maturing to allow for sufficient 2-needle cannulation and the acceptance of blood flow rates required to provide HD.

Though the AVF is the preferred vascular access, 28 – 60% of AVFs do not successfully mature and are rendered unusable for HD.[11,12] This has unintended consequences for patients who need HD, since a tunneled CVC must then be inserted to provide HD. CVCs are associated with higher morbidity, mortality, and costs compared to other forms of vascular access and are therefore considered a last resort.[13]

The WavelinQ™ EndoAVF System was developed to decrease the invasiveness of the AVF creation procedure by creating an endovascular AVF (endoAVF). Prior clinical investigations on both a 6F and 4F version have demonstrated that endoAVFs created using the WavelinQ™ EndoAVF Systems have high technical success rates, high patency, low complication rates, and low intervention rates.[14,15] These investigations are further supported by a global analysis including pooled data from three additional clinical investigations of the 4F device through 6-months for a total of 91 additional participants. These results are summarized subsequently.

### 2.1.1 Safety Results

In total, 22.0% (20/91) of participants experienced a significant event, defined as device- or procedure-related AEs that either could be limb-threatening if not promptly identified or treated, or required additional therapy to reestablish patency of the endoAVF access circuit, irrespective of whether they met the criteria for an SAE. These significant events included stenosis, occlusion, thrombosis, and pseudoaneurysm of the access circuit and / or endoAVF, as well as one participant with abandonment of the endoAVF after a cannulation induced brachial artery injury.

SAEs were reported in 26.4% (24/91) of the population. Of these events, 18/24 (75.0%) were unrelated to the device and unrelated to the procedure. There were 3 device-related SAEs reported in the investigations (3/91, 3.3%) and included 1 thrombosis of the endoAVF, 1 stenosis of the endoAVF, and 1 access circuit false aneurysm. There were 5 procedure related SAEs reported in 5.5% (5/91) of the population. None of the SAEs were related to the method of arterial access for the procedure. There were no reports of Unanticipated Adverse Device Effects (UADEs). There were no closure device-related SAE's or coil related SAE's reported.

#### 2.1.2 Effectiveness Results

Procedural success, defined as the successful creation of an endoAVF with blood flow confirmed intraoperatively by fistulography or postoperative duplex ultrasonography, was achieved in 96.7% (88/91) of the population. Using Kaplan-Meier (KM) point estimates at month 6, the cannulation success rate was 84.9% ± 5.3% for participants in the HD subset. The mean time to cannulation was 2.0 ± 1.6 months.

Primary patency and cumulative patency were determined using the KM point estimates at month 6. Primary patency was 72.4% ± 5.2% and cumulative patency was 77.3% ± 5.0%. Functional patency was 100% through 6 months in the population who used their endoAVF for HD.

## 2.2 Clinical Investigation General Rationale

The purpose of this clinical investigation is to provide clinical evidence to further demonstrate reasonable assurance of safety and effectiveness of the WavelinQ™ EndoAVF System for endovascular fistula (endoAVF) creations in a post-market confirmatory interventional fashion. See Section 3 for specific objectives and Section 4.5 for endpoint rationales.

## 2.3 Investigation Device Description

The WavelinQ™ EndoAVF System, manufactured by the Sponsor, is indicated for the cutting and coagulation of blood vessel tissue in the peripheral vasculature for the creation of an AVF used for HD. The device is intended to be used in patients suffering from chronic kidney disease requiring HD by physicians trained and experienced in endovascular techniques (Refer to Section 12.2 for training requirements). The WavelinQ™ EndoAVF System will be used for these intended purposes as part of this clinical investigation according to its IFU.

The WavelinQ™ EndoAVF System consists of two 4 Fr, single-use, disposable, magnetic, hydrophilic coated catheters: (1) a venous catheter powered by an Electrosurgical Unit (ESU) and (2) an arterial catheter. The system has been developed for use with commercially available accessories including the ESU, an electrosurgical pencil, grounding pads, an arm board, fixation straps, and a remote hand switch.

The venous catheter is a flexible magnetic catheter that contains a radiofrequency (RF) electrode, a hemostasis valve crosser for interfacing with the introducer sheath on the distal end and features a cable and plug for the delivery of RF energy on the proximal end. RF energy is delivered by connecting the venous catheter to the ESU via the electrosurgical pencil and is used with standard grounding pads.

The arterial catheter is a flexible magnetic catheter which contains the backstop for receiving the electrode from the venous catheter.

When placed in proximity, the magnets contained in each catheter attract each other, while aligning the electrode with the backstop. Rotational indicators are present in each catheter for use to accurately position the catheters. Once correctly aligned, RF energy can then be delivered through the electrode for cutting and / or coagulating tissue to create the endoAVF. The full procedural steps and associated information are detailed in the device IFU.

NOTE: If the participant has more than one brachial vein, embolization of one of the brachial veins is recommended to divert flow to the superficial veins to facilitate maturation of the endoAVF.

# 3 CLINICAL INVESTIGATION DESIGN

This is a global, multi-center, prospective, post-market, confirmatory, interventional, non-randomized, single-arm, clinical investigation to further demonstrate the safety and effectiveness of the WavelinQ™ EndoAVF System for endovascular fistula creations in the ulnar and radial vessels when accessed from the wrist (and / or upper arm) arteries and concomitant veins in the parallel or anti-parallel configuration.

*Safety objective:* The safety outcome of participants receiving treatment with the WavelinQ™ EndoAVF System will be compared to a Performance Goal (PG) derived from the prior clinical investigations evaluating the WavelinQ™ EndoAVF System to confirm that the safety profile of the device is maintained.

*Effectiveness objectives:* The effectiveness measure evaluated through the primary effectiveness endpoint will be used to assess the performance of the WavelinQ™ EndoAVF System when used in the creation of AVFs in a post-market fashion. The clinical investigation will aim to evaluate the number of interventions per patient year (PY) to facilitate (facilitation interventions) and maintain (maintenance interventions) use of the AVF and compare this to clinical guideline recommendations. Non-hypothesis tested secondary endpoints will evaluate the performance of the endovascularly created AVFs with respects to short-term (maturation / cannulation) and long-term (functional cumulative patency) performance characteristics.

A total of approximately one-hundred and fifty (150) treated participants will be included. Note that as per the definition of treated participant (refer to Section 6.2), this number does not include the participants into whom the WavelinQ™ EndoAVF System was introduced but in whom procedure success (as defined in Section 4.3) was not achieved (estimated to total approximately ten [10] participants).

Under the current enrollment assumptions, a target of approximately 15 investigational sites (up to a maximum of 30 investigational sites) may participate globally. This investigation will enroll participants who are either already receiving HD at the time of screening (prevalent participants), regardless of access type (CVC, AVF, and / or AVG), or those who are not yet receiving HD but are in need of a vascular access as determined by the referring clinician (incident participants).

Treated participants will be followed for 24-months post index procedure. The enrollment period is estimated to last about 18 months and the total clinical investigation duration is estimated to last 3.5 years from the enrollment of the first participant to the last follow-up visit of the last active treated participant. The primary endpoints will be analyzed when the last active treated participant has completed their 6-month follow-up. A final analysis will be completed when all participants have completed, or prematurely discontinued before, their 24-month follow-up.

# 4 CLINICAL INVESTIGATION ENDPOINTS

## 4.1 Primary Endpoints

There are two co-primary endpoints for this clinical investigation: An endpoint to evaluate safety and another to evaluate effectiveness. These endpoints are defined in this section.

### 4.1.1 Primary Safety Endpoint

*Safety through 30 Days*

The primary safety endpoint is the proportion of participants with freedom from Clinical Events Committee (CEC) adjudicated device- or procedure-related serious adverse events (SAEs) through 30 days.

The primary safety endpoint will be evaluated against a PG of 82.6%, which was set with a 10% non-inferiority margin of the estimated 92.6% through 30 days derived from premarket data from the prior clinical investigations evaluating the WavelinQ™ EndoAVF System.

### 4.1.2 Primary Effectiveness Endpoint

*Interventions Post Creation to Facilitate AVF Use and / or Maintain AVF Use (Facilitation and / or Maintenance Interventions) through the Timepoint of the 6-Month Follow-Up of the Last Active Treated Participant*

The primary effectiveness endpoint is the number of interventions post creation to facilitate and / or maintain AVF use (facilitation interventions and / or maintenance interventions as defined in Section 4.4). The procedures that will be evaluated as part of this endpoint are indicated in Table 1 in Section 4.4 and exclude adjunctive and second stage procedures.

The number of facilitation and / or maintenance interventions per PY will be compared to a PG that is composed of the combined targets for interventions to facilitate and maintain AVF use recommended by the 2019 update of the KDOQI Clinical Practice Guideline for Vascular Access.[8] This endpoint will be evaluated including all data collected for all participants up until the timepoint of the 6-month follow-up of the last active treated participant (i.e. including any and all data exceeding the 6-month follow-up visit up to this timepoint).

## 4.2 Secondary Endpoints

The secondary endpoints will be evaluated in a descriptive fashion and will be analyzed through the timepoints specified for each endpoint below. These endpoints will be reported at the timepoints specified in Section 7.9.

4.2.1 Safety

- *Device and Procedure Related SAEs*

  The proportion of participants with freedom from CEC adjudicated device-related or procedure-related SAEs (refer to Section 8 for definitions). This endpoint will be assessed through 6- and 24-months post creation.

4.2.2 Effectiveness

- *Physiological Maturation*

  The proportion of participants with AVFs that meet the definition of physiological maturation. Physiological maturation is defined as an AVF having at least 500 mL / min of flow in the brachial artery and an outflow vein diameter of ≥ 4 mm as measured by DUS.[16,17] Participants with AVFs that meet the definition of functional maturation (Refer to Section 4.3) will automatically meet physiological maturation. This endpoint will be assessed through 6-weeks post creation.

- *Cannulation Success*

  The interval of time between HD arteriovenous (AV) access creation to first successful use for HD using 2-needle cannulation and proportion of participants with successful first use for HD using 2-needle cannulation. This endpoint will be assessed through 6-months post creation.

- *Cumulative Functional Patency*

  The time from first successful HD AV access use for HD using 2-needle cannulation to access abandonment, when the access reaches an access censoring event as specified a priori in this CIP, or analysis timepoint / clinical investigation end. This endpoint will be assessed through 12-months post creation.

## 4.3 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 these endpoints.

- *Procedure Success*

  The proportion of participants with successful endoAVF creation using the WavelinQ™ EndoAVF System as confirmed via intraprocedural angiography and / or verified via DUS.

- *Adjunctive Procedures*

  The number of adjunctive procedures performed (see Section 4.4 for definition).

- *Vascular Access at HD Initiation*

  The vascular access HD modality used at the initiation of HD following the index procedure (CVC, AVG, clinical investigation AVF, or alternate AVF). Use of the clinical investigation AVF at initiation includes both one- and two-needle cannulation and may be presented as a combined total as well as by type of needle access. This endpoint applies to the incident participant population only.

- *Physiological Maturation*

  As defined for the secondary endpoint (see Section 4.2.2) evaluated through additional time intervals.

- *Cannulation Success*

  As defined for the secondary endpoint (see Section 4.2.2) evaluated through additional time intervals.

- *Functional Maturation*

  The proportion of participants with successful prescribed HD with 2-needle cannulation of the AVF for three (3) continuous weeks. Additionally, the time from HD AV access creation to the first day of the 3-week period.

- *Functional HD Usability*

  The proportion of participants dialyzed using successful 2-needle access of the AVF created as part of this clinical investigation for ≥ 75% of HD sessions over a continuous 28-day period. Additionally, the time from HD AV access creation to the first day of the 28-day period.

- *Interventions*

  Intervention related endpoints are categorized as follows:

  - *Interventions Post Creation to Facilitate AVF Use (Facilitation Interventions)*

    As defined for the primary effectiveness endpoint (see Section 4.1.2) evaluated separately.

  - *Interventions Post Creation to Maintain AVF Use (Maintenance Interventions)*

    As defined for the primary effectiveness endpoint (see Section 4.1.2) evaluated separately.

  - *All Interventions Post Creation (Facilitation, Maintenance and HD Continuity Interventions)*

    For this endpoint, the number of interventions post creation will include all interventions (facilitation, maintenance, and HD continuity interventions) in Table 1 of Section 4.4 but exclude adjunctive and second stage procedures.

- *All Interventions After First Use (Facilitation, Maintenance and HD Continuity Interventions)*

  As defined for the exploratory endpoint directly above with duration of evaluation adjusted to start from first successful HD AV access use.

- *Primary Patency*

  The time from HD AV access creation to the first one of the following events: access thrombosis; any facilitation or maintenance intervention intended to support maturation or cannulation, as well as those to maintain, or re-establish functionality*; access abandonment (as defined in Section 4.4); the access reaches an access censoring event as specified a priori in this CIP; or analysis timepoint / clinical investigation end.[18] *Excludes adjunctive and second stage procedures.

- *Cumulative Patency*

  The time from HD AV access creation to access abandonment, when the access reaches an access censoring event as specified a priori in this CIP, or analysis timepoint / clinical investigation end.[18]

- *Primary Functional Patency*

  The time from first successful HD AV access use for HD using 2-needle cannulation to the first one of the following events: access thrombosis; any facilitation or maintenance intervention intended to support maturation or cannulation as well as those to maintain or re-establish functionality*; access abandonment (as defined in Section 4.4); the access reaches an access censoring event as specified a priori in this CIP; or analysis timepoint / clinical investigation end. *Excludes second stage procedures.

- *Cumulative Functional Patency*

  As defined for the secondary endpoint (see Section 4.2.2.2) evaluated through additional time intervals.

- *CVC Exposure / Use*

  Data will be collected regarding CVC exposure and use.

  - For participants with a CVC in place at the index procedure, data will be collected after HD AV access creation to investigate the duration of CVC use.
  - For all participants, data will be collected to determine frequency of CVC placements, time to CVC removal, total days of CVC exposure, and total days of CVC use.

- *DUS Juxta/Peri-Anastomotic Area and Perforator Vein Patency*

  Data will be gathered using DUS examinations to evaluate the presence and characteristics of thrombosis and stenosis within the juxta-anastomotic area (defined as the arterial area extending 5cm before and the venous area extending 5cm after the anastomosis) and peri-anastomotic area (defined as the venous area extending from the juxta-anastomosis area to the start of the perforating vein) as well as within the perforator vein for all participants through 6 weeks.

- *Wrist Arterial Procedure Access Considerations*

  Data will be gathered using DUS examinations to evaluate the presence and characteristics of thrombosis and stenosis in arteries at the wrist used for procedure access during the index procedure. Images from these DUS examinations will be submitted to the Core Lab for review and assessment. Additionally, data will be captured for these participants on procedure-related AEs that are attributable to arterial access at the wrist as adjudicated by the CEC.

- *Participant Satisfaction and Quality of Life (QOL):*

  The Short Form-Vascular Access Questionnaire (SF-VAQ) and the European Quality of Life-5 Dimensions (EQ-5D) will be used to gather data on the participants QOL at the time points specified in Section 1.3 and Section 6.

- *HD AV Access Continuity*

  HD AV access continuity is defined as the ability for a participant to receive an alternate HD AV access in the same arm as the index AVF. This endpoint applies to participants for whom their index AVF is abandoned. The alternate type(s) of HD AV access(es) placed in these participants will be collected.

## 4.4 Applicable Endpoint Definitions

***Access Abandonment*** (permanent abandonment) is defined as the point at which the access can no longer be used for one or two needle prescribed HD as it may be unable to provide adequate flows and / or is deemed unsafe for the participant, and the associated problem cannot be corrected by any further intervention, including medical, surgical, or endovascular interventions or rest.[8,19] Participants with an abandoned index AVF will continue with follow-up through 24-months and data will be collected on safety and interventions.

A HD AV access is <u>not</u> considered abandoned:

- If the participant discontinues use of the AV access due to kidney transplant, initiation of PD, or participant preference.
- During the maturation period or while waiting for a second stage procedure unless the principal investigator (PI) determines the participant requires and they then receive an alternative HD vascular access.

- During planned interventions, including transposition.
- If all reasonable efforts have not been attempted (and documented) to improve the condition of the access for it to be used.

A discontinuation of use of the clinical investigation AVF for any reason that does not meet this definition of access abandonment will be considered a temporary interruption.

***Access Circuit Censoring Events*** include participant transfer to PD, kidney transplantation or the event of a participants premature discontinuation in the investigation due to withdrawn consent, withdrawal by PI, Lost to Follow-Up (LTF), or participant death (refer to Section 6.5 for definitions).

***Adjunctive Procedure(s)***: Procedure(s) completed during the index procedure (prior to leaving the procedure room) as part of Standard-of-Care (SOC) procedures. These may include procedures to facilitate maturation and / or cannulation of the AVF, procedures to maintain use of the AVF, procedures to ensure HD continuity, as well as procedures to address AEs.

***Second Stage Procedure(s)***: Facilitation Interventions (as defined below) intended to support the cannulation of arterialized vein segments that are determined to be needed a priori to or at the time of the index procedure (i.e. pre-planned facilitation interventions intended to support cannulation). Second stage procedures will not count against the intervention or patency endpoints and will require completion of the Second Stage Procedures eCRF.

***Intervention(s)***: Clinical investigation participants may require procedures that are not pre-determined or planned that are performed *after* the index procedure (adjunctive procedures are those performed *during* the index procedure and second stage procedures are expected procedures that are determined a priori or at the time of the index procedure). Interventions require the completion of the Intervention eCRF. For this clinical investigation, interventions are further classified as follows and delineated by endpoint in Table 1:

- *Facilitation Intervention(s):* Defined as those procedures that are intended to facilitate functionality of the index AVF (i.e. those intended to support the maturation or cannulation of arterialized vein segments) and / or a procedure to address an AE related to the facilitation of index AVF functionality.

- *Maintenance Intervention(s):* Defined as those procedures that are intended to maintain / re-establish functionality of the index AVF and / or a procedure to address an AE related to the maintenance of index AVF functionality.

- *HD Continuity Intervention(s)*: Defined as those procedures that are intended to ensure the continuity of HD (not including diagnostic studies) other than those related to the facilitation or maintenance of index AVF functionality and / or a

procedure to address an access related AE other than those related to the facilitation or maintenance of index AVF functionality. HD continuity interventions include all CVC related interventions up until the placement of a subsequent AV access following abandonment of the index AVF. HD continuity interventions exclude any intervention performed on a non-index AV access other than the placement of the non-index AV access itself.

**Table 1: Eligible Interventions and Classification by Intervention Endpoint**

| | **Facilitation Interventions** | | **Maintenance Interventions** | **HD Continuity Interventions** |
|---|---|---|---|---|
| **Applicable to Endpoint:** | **Support of AVF Maturation** | **Support of AVF Cannulation** | | |
| | •Angioplasty / Balloon-Assisted-Maturation<br>•Embolization of collaterals (coiling, plugging, or ligation)<br>•Stent / stent graft<br>•Surgical revision | •Superficialization / elevation<br>•Transposition | •Angioplasty**<br>•Banding<br>•Embolization of collaterals (coiling, plugging, or ligation)#<br>•Stent / stent graft<br>•Surgical revision<br>•Thrombectomy / thrombolysis<br>•Treatment of aneurysm / pseudoaneurysm<br>•Treatment of AV access infection | •Access ligation<br>•AVF placement<br>•AVG placement<br>•CVC placement<br>•Fibrin sheath removal<br>•Treatment of infection |
| **Primary Effectiveness:** Maintenance and / or Facilitation | Yes | Yes* | Yes | No |
| **Exploratory:** Facilitation | Yes | Yes* | No | No |
| **Exploratory:** Maintenance | No | No | Yes | No |
| **Exploratory:** All Interventions | Yes | Yes* | Yes | Yes |

* Excludes second stage procedures.
** Inclusive of use of specialty balloons (cryoplasty, cutting, drug-coated, scoring, etc.).
# Embolizations performed after successful use of the index AVF to maintain its use.

## 4.5 Scientific Rationale for Clinical Investigation Design

### 4.5.1 Endpoint Rationale

The primary safety endpoint was selected to evaluate the maintenance of the safety profile of the WavelinQ™ EndoAVF System. The safety of the WavelinQ™ EndoAVF System was previously demonstrated in prior clinical investigations and as such a performance goal was derived therefrom for comparison through 30 days. As a

non-hypothesis tested secondary endpoint the safety of the device will be investigated over the long-term.

The primary effectiveness endpoint and the non-hypothesis tested secondary endpoints provide a means to describe the performance of AVF created using the WavelinQ™ EndoAVF System throughout its life cycle. When combined, these endpoints follow the performance of the endoAVF in all phases of development and use.

The primary effectiveness endpoint which assesses the number of interventions per PY to facilitate and maintain AVF use provides a means to understand the performance of the AVF compared to guideline recommendations. The number of interventions per PY give an indication of the burden on both the patient and the healthcare system in facilitating and maintaining a functional vascular access. Examples of patient burden include direct pain and discomfort associated with the intervention, inconvenience, reduced satisfaction with their vascular access or reduced QOL. Interventions are associated with resource and time related burdens to the healthcare system. Demonstrating that the number of post creation interventions per PY required to attain and / or maintain functionality for the endoAVFs created using the WavelinQ™ Endovascular System are less than the target recommended by the KDOQI guidelines as evaluated through this endpoints would indicate that the endoAVF is able to provide a reliable access modality to patients with a level of burden that is considered acceptable by these society guidelines and recommendations. The guideline recommendations were selected as the effectiveness target as a means to evaluate the performance of the AVF against clinical expectations in absence of a direct comparator due to the novel nature of the AVF creation technique and unique resultant anatomical location. The endpoint is inclusive of the incident as well as prevalent populations allowing this investigation to examine the impact in a representative patient cohort. The 2019 update of the KDOQI Clinical Practice Guideline for Vascular Access use the number of interventions as the single critical target or measuring AVF utility and thereby this endpoint would be the most aligned to the latest update.[8]

The remaining descriptive secondary endpoints evaluated as part of this investigation will provide additional data to complete the picture of the safety and performance of endoAVFs created using the WavelinQ™ EndoAVF System from creation through abandonment and are in line with those previously assessed in prior clinical investigations pertaining to the device.

### 4.5.2 Potential Influencing or Confounding Factors and Bias

Known foreseeable factors that could potentially compromise the outcome of the investigation or interpretation of the results or introduce bias into the study are delineated in this section.

One such factor pertains to the participant population that could be enrolled in this investigation. Given the fact that the device could provide an option to receive an AV access for patients who are not candidates for AVF created using traditional surgical methods, could potentially entail a bias towards a population that could be subject to worse outcomes (e.g. an older population, one with more comorbidities, etc.). This potential factor has been mitigated so far as possible with the existing eligibility criteria. This factor could also be counterbalanced by the enrollment of incident participants which are not yet on HD but are in imminent need. These participants may be earlier in their disease progression and may present with comparatively fewer comorbidities than their contemporaries already on HD. Subgroup analyses on endpoints pertaining to participant demographics (e.g. by age group, comorbidities, etc.) may be conducted on any of the pertinent endpoints to explore any differences within the enrolled population.

An additional foreseeable factor pertaining to the patient population would be the potential differences between incident and prevalent participants. Furthermore, within these groups there are potential subgroups that may lend themselves to differences in outcomes. These seven (7) potential subgroups are categorized and defined as detailed in Table 2. To explore any differences in outcomes subgroup analyses may be conducted on the endpoints to explore the characteristics for each group.

**Table 2: Participant Status at Time of Index Procedure**

| Participant Status at Index Procedure | Sub-Classification | | History of Prior Failed AV Access(es) |
|---|---|---|---|
| Incident<br>Definition: Participants who have not previously and who were not actively receiving HD prior to or at the time of the index procedure but are in need of a vascular access as determined by the referring clinician | Pre-KRT | Definition: Participants who have not previously and who were not actively receiving any form of KRT prior to the index procedure | No |
| | | | Yes |
| | Pre-HD | Definition: Incident participants who have not previously and who were not actively receiving HD prior to the index procedure | No |
| | | | Yes |
| Prevalent<br>Definition: Participants who have previously and / or who were actively receiving HD prior to the index procedure | CVC Only | Definition: Prevalent participants who have only received HD using a CVC prior to the index procedure | No |
| | | | Yes |
| | AV HD Access | Definition: Prevalent participants who have received HD using any form of AV HD access (i e AVG / AVF) prior to the index procedure | Yes |

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 AVF cannulation, 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 WavelinQ™ EndoAVF system 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 12.2 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.

A factor that could impact the timeliness of endoAVF cannulation may be due to participant preference. Participants may be apprehensive towards cannulation of their access whether due to fear of needles, prior bad experiences (e.g. infiltration injury), among other reasons. This factor could be particularly prominent in those participants that initiate dialysis with a CVC or those that have switched to CVCs in the interim and become accustomed to a comparatively more comfortable HD experience. As a result, this may delay or prevent cannulation of the AVF upon attainment of maturity. This factor is difficult to proactively mitigate. A good relationship between the participant and their nephrologist is essential to provide the necessary education about the benefits of using an AV access for HD versus a CVC.

# 5 CLINICAL INVESTIGATION POPULATION

The WavelinQ™ EndoAVF System is indicated for the creation of an AVF in patients with chronic kidney disease that are in need of receiving HD. Specifically, adult patients with established, non-reversible kidney failure who are on HD (prevalent participants) or not yet on HD but are in need of a vascular access as determined by the referring clinician (incident participants) may be screened for enrollment in this clinical investigation. This clinical investigation is designed to include patients that are representative of the target patient population. Enrollment will continue until approximately 150 treated participants at a target of approximately 15 investigational sites (up to a maximum of 30 investigational sites) are included in this clinical investigation. No site will be allowed to treat more than 30% of the overall number of participants to ensure the clinical investigation is reasonably well balanced. The following describe the clinical eligibility (inclusion and exclusion) criteria for the clinical investigation.

## 5.1 Eligibility Criteria

Only participants that meet all the inclusion criteria, that cannot be precluded from participation based on any of the exclusion criteria, and that have signed the ICF may be considered for participation.

### 5.1.1 Inclusion Criteria

A participant must meet the following criteria to be enrolled in this clinical investigation:

*Clinical Inclusion Criteria:*

The participant must:

1. Be able to comprehend, voluntarily sign and date the ICF prior to collection of clinical investigation data or performance of clinical investigation procedures (or where allowable the participant's legally authorized representative (LAR) on behalf of the participant).

2. Be able to and willing to comply with the CIP requirements, including clinical follow-up.

3. Be male or non-pregnant female ≥ 18 years of age with an expected lifespan sufficient (≥ 24 months) to allow for completion of all clinical investigation procedures.

4. Have established, non-reversible kidney failure, who are currently on HD at screening or are in need of a vascular access for HD as determined by the referring clinician.

*Anatomical Inclusion Criteria:*

The participant must have:

5. Target treatment vein diameter(s) for AVF creation ≥ 2.0 mm as measured via DUS or angiography.

6. A target treatment artery diameter ≥ 2.0 mm as measured via DUS or angiography.

7. Adequate collateral circulation to the hand, in the opinion of the PI (or authorized designee).

8. At least one superficial outflow vein diameter ≥ 2.5 mm as measured via DUS or angiography that is in communication with the target creation site via a proximal forearm perforating vein.

5.1.2 Exclusion Criteria

A participant must not be able to be precluded by any of the following criteria to be enrolled in this clinical investigation:

*Clinical Exclusion Criteria:*

The participant must not have:

1. Active or nontreated hypercoagulable state.

2. Known bleeding diathesis.

3. Insufficient cardiac output to support the maturation and use of an AVF in the opinion of the PI (or authorized designee).

4. Known history of or current active intravenous drug abuse.

5. A "planned" major surgical procedure within 6 months following index procedure or major surgery, in the opinion of the PI (or authorized designee), within 30 days prior to index procedure.

6. Known allergy or hypersensitivity to contrast media which cannot be adequately treated with pre-medication.

7. Known adverse effects to sedation and / or anesthesia which cannot be adequately treated with pre-medication.

8. Evidence of active infection on the day of the index procedure (temperature of ≥ 38.0° Celsius and / or White Blood Cell (WBC) Count of ≥ 12,000 cells / µL, if collected).

9. Another medical condition, which, in the opinion of the PI (or authorized designee), may cause him / her to be non-compliant with the CIP, confound the data interpretation, or is associated with a life expectancy insufficient to allow for the completion of clinical investigation procedures and follow-up.

10. Current participation in an investigational drug or device clinical investigation that has not completed the clinical investigation treatment or that clinically interferes with the clinical investigation endpoints. *Note: Investigations requiring extended follow-up visits for products that were investigational, but have since become commercially available, are not considered investigational.*

*Anatomical Exclusion Criteria:*

The participant must not have:

11. Central venous stenosis or central vein narrowing ≥ 50% based on imaging, or any degree of central venous stenosis with accompanying signs or symptoms, on the same side as the planned AVF creation.

12. The absence of a proximal forearm perforating vein feeding the target cannulation vein(s) from the target creation site via DUS or angiography.

13. Occlusion or stenosis ≥ 50%, or any degree of stenosis with accompanying signs or symptoms of target cannulation vein(s) such as cephalic, median cubital, basilic, etc. assessed via DUS or angiography and as clinically determined by PI (or authorized designee).

14. Significantly compromised venous or arterial architecture (e.g. severe vessel calcification) or flow in the treatment arm as determined by the PI (or authorized designee) and DUS or angiography.

15. Presence of significant calcification at the target endoAVF location that could potentially impact the effectiveness of endoAVF creation as determined by the PI (or authorized designee).

## 5.2 Lifestyle Considerations

There are no investigation specific lifestyle considerations or modifications for participants outside of those required by the investigational sites SOC.

## 5.3 Screen Failures

A screen failure is defined as a participant who has enrolled in this investigation (consented to participate) but is excluded due to one or more of the eligibility criteria. Such participants' clinical investigation participation will end at the time of eligibility failure. These participants should be treated according to the investigational site's SOC practices. Screen failures will not be considered in the intent to treat (ITT) group of the clinical investigation. Data collected for screen failures will be limited to the participant's demographics and the reason for eligibility failure.

# 6 CLINICAL INVESTIGATION PROCEDURES AND ASSESSMENTS

The Schedule of Activities Table (Section 1.3) displays the required schedule for participant screening, treatment, and follow-up. This schedule is consistent with standard clinical care pre- and post-interventional procedures. Note that sponsor representatives may be present at the investigational site to offer case support during the screening and / or index procedure as well as for support during the cannulation of the endoAVF.

## 6.1 Participant Screening, Baseline Evaluations and Enrollment

The site may begin screening and perform baseline evaluations only after the Site Initiation Visit (SIV) has been completed and authorization to enroll from the Sponsor has been received. During the screening and recruitment process, the PI (or authorized designee) will be responsible for describing the nature of the clinical investigation to the patient, obtaining informed consent, verifying that the eligibility criteria have been met, as well as obtaining and documenting the necessary baseline data. All clinical investigation procedures will be documented in the participant's medical record and / or source document(s) as well as on clinical investigation eCRFs. The following procedures will be conducted and documented.

### 6.1.1 Informed Consent and Enrollment

After completion of SOC evaluations and prior to the initiation non-SOC, CIP-specific activities and evaluations (including any non-SOC procedure performed to determine participant eligibility); the background and purpose of the clinical investigation, participation requirements, as well as the potential benefits and risks of the procedure(s) must be disclosed to the participant. The process of obtaining informed consent shall be documented by the site and the completed, voluntarily signed and dated ICF retained in the participant's records. For a detailed summary of the informed consent requirements, refer to Section 12.3. The point at which the ICF is signed and dated is considered the point of enrollment for that participant in this clinical investigation and all participants who have signed an ICF will be considered ***enrolled*** participants.

### 6.1.2 Eligibility

The participant's eligibility for clinical investigation enrollment must be determined and documented. The documentation must indicate that the participant met all the clinical investigation inclusion criteria and could not be precluded from participation based on any of the exclusion criteria prior to the point of treatment with the WavelinQ™ EndoAVF System.

Enrolled participants who are excluded from this clinical investigation, based on eligibility criteria listed in Section 5.1, are considered ***screen failures*** and will be handled as described in Section 5.3.

### 6.1.3 Demographic Information and Medical History

The participant's demographic information must be collected and documented (i.e., gender, age, race, etc.). Additionally, the participant's applicable medical history, including but not limited to pre-existing medical conditions, and treatments received up to the time of the index procedure must be collected and documented.

### 6.1.4 Baseline Assessments

Each participant will have the following baseline assessments performed prior to the index procedure:

- *DUS:* A DUS assessment per the Ultrasound Guidelines must be performed. At minimum, images including the following characteristics are required and must be submitted to the Sponsor / Core Lab as per the details specified in the investigational site's regulatory binder:

    - Arteries and veins of the AVF target vessels: Patency (including characterization of each stenosis, if present), calcification, and inner diameters. Brachial artery volume flow.
    - Cannulation veins: Patency (including characterization of each stenosis, if present), calcification and inner diameters of the cannulation veins.
    - Perforator vein: Patency (including characterization of each stenosis, if present), calcification, and shape as well as inner diameter (with and without tourniquet) and length.
    - Procedure access wrist artery / arteries: Patency (including characterization of each stenosis, if present), confirmation of flow, and inner diameter.

- *Clinical Exam:* Overall health and assessment of target vessels must be evaluated and documented with a physical exam conducted by the PI or authorized designee in accordance with each investigational site's SOC.

- *HD History and Status:* Current HD access status as well as CVC, AVF, and AVG history must be collected and documented.

- *SF-VAQ and EQ-5D Surveys*: All participants will complete a participant satisfaction and health status survey. Surveys will be completed by the participant or verbally read and documented by an authorized delegated investigation site team member for completion.

## 6.2 Index Procedure

If the participant presents for the index procedure with any medical condition that precludes treatment, the procedure should be delayed until the medical condition is treated and resolved. The participant must be re-consented if the index procedure cannot occur within 60 days of consent.

### 6.2.1 Clinical Investigation Treatment

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, has completed all of the required baseline procedures, the participant may be treated using the WavelinQ™ EndoAVF System. It is recommended that eligibility for all participants (including DUS and determination of any central venous lesions) be verified at the time of the index procedure prior to the point of treatment with the WavelinQ™ EndoAVF System if anatomical eligibility verification was originally completed prior to the index procedure.

Examinations, evaluations, procedural preparation, angiography, treatment, and hospital / facility discharge procedures will be conducted per the investigational site's SOC.

The treatment using the WavelinQ™ EndoAVF System, will be per the investigational site's SOC and must adhere to the device IFU. Operators of the WavelinQ™ EndoAVF System must complete BD-Sponsored device training and must be approved by the Sponsor as an operator in writing before conducting a clinical investigation index procedure on enrolled participants (refer also to Section 12.2). For detailed information on device use and procedural medication recommendations, reference the IFU.

> NOTE: If the participant has more than one brachial vein, embolization of one of the brachial veins is recommended to divert flow to the superficial veins to facilitate maturation of the endoAVF.
>
> NOTE: Angiographic images collected during the index procedure including documentation of the final result must be submitted to the Sponsor. Refer to the investigational site's regulatory binder for guidelines on the collection of all DUS and angiographic images captured during the index procedure and details on submission of these images to the Sponsor / Core Lab.

A ***treated participant*** in this clinical investigation is defined as a participant that has met all eligibility criteria (as listed in Section 5.1), into whom the WavelinQ™ EndoAVF system was introduced, and in whom procedure success was achieved (as defined in Section 4.3). Treated participants will continue clinical investigation participation through the clinical investigation's 24-month follow-up period.

Participants into whom the WavelinQ™ EndoAVF System was introduced but procedure success was not achieved will be followed through the 30-day follow-up to assess for any safety events and interventions.

Participants into whom the WavelinQ™ EndoAVF System 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.

#### 6.2.2 Adjunctive Procedures

Adjunctive procedures to the index access circuit after creation of the AVF, but prior to leaving the procedure room, as part of SOC procedures are allowed. All adjunctive procedures (i.e. embolization, new CVC placement) will be documented on the appropriate eCRF.

> NOTE: If the participant has more than one brachial vein, embolization of one of the brachial veins is recommended to divert flow to the superficial veins to facilitate maturation of the endoAVF.

### 6.3 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 WavelinQ™ EndoAVF system was introduced:

- *Clinical Exam:* Overall health and assessment of AV access function must be evaluated and documented with a physical exam conducted by the PI or authorized designee in accordance with each investigational site's SOC.

- *Documentation of Adverse Events (AEs):* Documentation of AEs (refer to Section 8) 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 Interventions:* Any access circuit interventions the participant has undergone since the completion of the index procedure (defined to end at the time of last sheath removal – start of access site closure).

Note that for participants into whom the WavelinQ™ EndoAVF System was introduced but procedure success was not achieved, the clinical exam at discharge will review the health and assessment of the vessels interacted with during the index procedure. These vessels should also be imaged prior to discharge to confirm the absence of any AEs.

## 6.4 Participant Follow-Up

### 6.4.1 Follow-Up Intervals and Methods

All participants are to be followed according to the investigational site's SOC practices. In addition to the SOC visits, treated participants will have an investigation follow-up visit at 30-days and 6-weeks as well as 6- and 12-months post index procedure and will have a phone call follow-up at 3-, 18- and 24-months. For participants into whom the WavelinQ™ EndoAVF System was introduced during the index procedure but procedure success was not achieved, only the follow up at 30-days will be completed and limited to the collection of safety events and interventions. This follow-up may be conducted by phone for these participants and investigation participation for these participants will end upon completion of this follow-up.

All follow-up must be performed by authorized delegated clinical investigation site team members. Follow-up windows will be calculated from the index procedure date. Refer to Section 1.3 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:

- *DUS:* A DUS assessment per the Ultrasound Guidelines must be performed at the follow-up visits at 30-days and 6-weeks for all treated participants and again at 6- and 12-months for participants not yet successfully dialyzing with the AVF created as part of this clinical investigation using 2-needle cannulation. The 6- and 12-month DUS are also required for participants that are using the AVF created as part of this clinical investigation but for whom procedure access was obtained at the wrist artery during the index procedure. The DUS for these participants will be limited to the examinations of the artery that was accessed during the index procedure. At minimum, images including the following characteristics are required and must be submitted to the Sponsor / Core Lab as per the details specified in the investigational site's regulatory binder:

    - Arteries and veins of the AVF: Patency (including characterization of each stenosis, if present), and inner diameters. Brachial artery volume flow.
    - AV-anastomosis & juxta-anastomotic area: Patency (including characterization of each stenosis, if present).
    - Cannulation veins: Patency (including characterization of each stenosis, if present) and inner diameters.
    - Perforator vein: Patency (including characterization of each stenosis, if present), as well as inner diameter and length.
    - Procedure access wrist artery (if used during index procedure): Patency (including characterization of each stenosis, if present), confirmation of flow, and inner diameter.

- *Clinical Exam:* Overall health and assessment of AV access function must be evaluated and documented with a physical exam conducted by the PI or authorized designee in accordance with each investigational site's SOC.

- *HD History and Status*: Determine and document if and how the participant has been and / or is receiving HD (AVF, CVC, etc.), and document the date of the participant's last HD session. Once HD (1- or 2-needle cannulation) is initiated via the AVF created as part of this investigation, HD details must be documented and detailed HD access data (e.g., cannulation logs) will be provided to the Sponsor or designee for review and analysis as follows:

    - Detailed HD access data will be collected to indicate whether the participant successfully dialyzes with 2-needle AVF cannulation for at least 75% of HD sessions for three (3) continuous weeks and / or within 28 consecutive days. For the functional maturation and functional HD usability assessments, source documentation indicating HD success and vascular access used will be documented and collected until the endpoints are met (Sponsor verification is required before the clinical investigational site may stop collecting this HD access information).

    - Thereafter determine and document if and how the participant has been and / or is receiving HD and whether the participant continues to be successfully dialyzed through the index AVF (the AVF created as part of the index procedure of this investigation) and document the date of the participant's last HD session.

- *SF-VAQ and EQ-5D Surveys:* Surveys will be completed by the participant or verbally read and documented by an authorized delegated investigation site team member for completion during the 6-week as well as 6-, 12- and 24-month follow-ups.

- *Documentation of AEs:* Documentation of occurrence and / or status of AEs since the last follow up (refer to Section 8).

- *Documentation of Interventions:* Any access circuit interventions the participant has undergone since the index procedure and / or prior follow-up.

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 must request copies of the medical records and, if necessary, complete the appropriate eCRFs.

### 6.4.2 Unscheduled Follow-Up

An unscheduled visit follow-up eCRF should also be completed for participants who return for additional non-investigation scheduled follow-up examinations pertaining to their HD vascular access. The participant will be required to return for 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 (e.g. DUS, SF-VAQ and EQ-5D Surveys, etc.). Assessments completed and information obtained during an unscheduled visit may include:

- *Clinical Exam:* Overall health and assessment of AV access function should be evaluated and documented with a physical exam in accordance with each investigational site's SOC.

- *HD History and Status:* Determine and document if and how the participant has been and / or is receiving HD (AVF, CVC, etc.). Refer to Section 6.4.1 for HD data to be collected.

- *Documentation of AEs:* Documentation of occurrence and / or status of AEs since the last follow up (refer to Section 8).

- *Documentation of Interventions:* Any access circuit interventions the participant has undergone since the index procedure and / or prior follow-up.

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.

## 6.5 Participant Investigation Completion and Premature Discontinuation

Following the index procedure, every participant into whom the WavelinQ™ EndoAVF System was introduced should remain in the clinical investigation until completion of the required follow-up period. The follow-up period for this clinical investigation is 24 months (730 ± 30 days) for treated participants and 30 days (± 5 days) for participants into whom the WavelinQ™ EndoAVF System was introduced during the index procedure but procedure success was not achieved. A treated participant is considered to have completed the investigation if the participant has completed the formal follow-up period associated with this clinical investigation through the 24-Month follow-up as described in the Schedule of Activities (Section 1.3).

However; a participant's participation may be prematurely discontinued. Additional participants will not be enrolled to replace those who withdraw from the clinical

investigation. Potential reasons for discontinuation may include, but are not limited to the following:

- *Withdrawn Consent:* The participant may at any time request to discontinue their participation in the clinical investigation. The PI must attempt to identify and document the reasons for discontinuation. 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.

- *Withdrawal by PI:* Participation may be immediately discontinued by the PI if, in the opinion of the PI, the participant would be exposed to inappropriate risk by continuing in the clinical investigation. Additionally, the PI may discontinue a participant's participation with prior written approval from the Sponsor if the participant is repeatedly noncompliant with clinical investigation procedures.

- *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.

- *Participant Death:* The participant becomes deceased. If known, the cause of death must be documented and an AE eCRF must be completed.

- *Clinical Investigation Termination:* The clinical investigation is terminated by the Sponsor (see Section 12.9).

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.

# 7 STATISTICAL METHODS

This section includes a summary of the planned statistical analyses and an overview of the statistical methods. The Statistical Analysis Plan (SAP) will be finalized prior to Database Lock and will include the technical and detailed descriptions of the statistical analyses summarized herein.

## 7.1 Overview of Clinical Investigation Design

This clinical investigation will be a global, multi-center, prospective, post-market, confirmatory, interventional, non-randomized, single arm clinical investigation to further evaluate the safety and effectiveness of the WavelinQ™ EndoAVF System for endovascular fistula creations in the ulnar and radial vessels when accessed from the wrist (and / or upper arm) arteries and concomitant veins in the parallel or anti-parallel configuration.

## 7.2 Analysis Populations

The analysis populations will be defined as follows:

- The ITT population will consist of all participants into whom the WavelinQ™ Endovascular System was introduced including those in whom procedure success was not achieved.

- An As-Treated (AT) population will include all treated participants, which includes all ITT participants but excludes those into whom the WavelinQ™ Endovascular System was introduced but procedure success was not achieved.
  - The AT population is composed of two subpopulations: The incident population and the prevalent population as defined in Section 4.5.2.

- 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 AT 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.

All effectiveness endpoints will be analyzed primarily based on the AT population. All safety endpoints will be analyzed primarily based on the ITT population. PP analyses may also be performed for the primary endpoints. They will only serve as sensitivity analyses for the primary analyses.

## 7.3 Sample Size Considerations

The sample size for the study of one-hundred and fifty (150) treated participants was established to assure adequate power for the primary safety and effectiveness endpoints as

well as to result in a sufficient sample size (when accounting for attrition) for assessment of the secondary and exploratory endpoints, specifically for those that only apply to subsets of the overall population (i.e. the incident population and wrist arterial procedure access population).

1) *Primary Safety Endpoint* – The proportion of participants with freedom from device- or procedure-related SAEs through 30 days (ITT Population).
   - Assumptions:
     - The freedom from device- or procedure-related SAE rate for AVFs created using the WavelinQ™ EndoAVF System is estimated at 92.6% through 30 days based on pre-market data;
     - The PG is set at 82.6% using a 10% non-inferiority margin;
     - The rate of attrition through 30 days is assumed to be 10%; and
     - The Type 1 error is 0.05 (two-sided).
   - Sample Size:
     - A sample size of 150 treated participants [135 evaluable] will give over 92.5% power with a two-sided type I error of 0.05 as calculated using PASS 2019 (One Proportion Exact Test).

2) *Primary Effectiveness Endpoint* – Interventions Post Creation to Facilitate AVF Use and / or Maintain AVF Use (Facilitation and / or Maintenance Interventions) through the Timepoint of the 6-Month Follow-Up of the Last Active Treated Participant (AT Population)
   - Assumptions:
     - The number of interventions post creation to facilitate AVF use and / or maintain AVF use after AVF creation using the WavelinQ™ EndoAVF System is estimated at 3.0 / PY, a conservative assumption based on pre-market data;
     - The PG is set at 5 / PY to align with the targets and recommendations of the 2019 update of the KDOQI Clinical Practice Guideline for Vascular Access of ≤ 2 interventions to facilitate and ≤ 3 interventions to maintain AVF use;
     - The rate of attrition through 6-, 12-, and 24-months, including lost to follow-up, death, and other clinical investigation premature withdrawals is assumed to be 20%, 40%, and 60%, respectively; and
     - The Type 1 error is 0.05 (two-sided).
   - Sample Size:
     - A sample size of 150 treated participants, yielding more than 100 PY by the time the last active treated participant completes their 6-month follow-up, will give over 99% power with a two-sided type I error of 0.05 as calculated using PASS 2019 (One-Sample Poisson Rate Test).

Hence, the sample size of 150 treated participants will provide approximately 92.5%*99%= 91.5% power for the co-primary endpoints.

## 7.4 Primary Endpoints

### 7.4.1 Primary Safety Endpoint

The primary safety endpoint is the proportion of AVF with freedom from device-related or procedure-related SAE through 30 days as defined in Section 4.1.1.

### 7.4.2 Primary Safety Endpoint Hypothesis Test

Objective: To assess if the 30 day primary safety rate endpoint for the WavelinQ™ EndoAVF System is greater than the safety PG.

The primary safety endpoint will be evaluated by the following hypothesis:

**$H_0$:** The primary safety endpoint of proportion of AVF with freedom from SAE for the WavelinQ™ EndoAVF System treated participants through 30 days ($P_{WS}$) is less than or equal to that of the PG of 82.6%.

**$H_1$**: The primary safety endpoint of proportion of AVF with freedom from SAE for the WavelinQ™ EndoAVF System treated participants through 30 days ($P_{WS}$) is greater than that of the PG of 82.6%.

That is:

**$H_0$**: $P_{WS} \leq 82.6\%$

**$H_1$**: $P_{WS} > 82.6\%$

Rejection of the null hypothesis will signify that the 30 day safety of the WavelinQ™ EndoAVF System is greater than the safety PG of 82.6%.

The primary safety analysis will be conducted on the ITT population. A two-sided p-value will be derived based on an exact binomial test comparing to the PG of 82.6% and the 95% confidence interval (CI) will be provided. The WavelinQ™ EndoAVF System will be considered to have achieved the safety objective and will reject the null hypothesis if the two-sided p-value is less than 0.05, equivalently, the lower bound of the 95% CI is greater than 82.6%.

### 7.4.3 Primary Effectiveness Endpoint

The primary effectiveness endpoint of the clinical investigation is an effectiveness measure based on the number of interventions post creation to facilitate AVF use and /

or maintain AVF use through the timepoint of the 6-month follow-up of the last active treated participant as defined in Section 4.1.2.

7.4.4 Primary Effectiveness Endpoint Hypothesis Test

Objective: To assess if the number of interventions post creation to facilitate AVF use and / or maintain AVF use (Facilitation and / or Maintenance Interventions) per PY for the WavelinQ™ EndoAVF System is less than the PG.

The primary effectiveness endpoint will be evaluated by the following hypothesis:

**$H_0$:** The number of interventions post creation to facilitate AVF use and / or maintain AVF use (Facilitation and / or Maintenance Interventions) per PY of participants treated with the WavelinQ™ EndoAVF System ($R_{WE}$) is greater than or equal to that of the PG of 5 post creation facilitation and maintenance interventions / PY.

**$H_1$**: The number of interventions post creation to facilitate AVF use and / or maintain AVF use (Facilitation and / or Maintenance Interventions) per PY of participants treated with the WavelinQ™ EndoAVF System ($R_{WE}$) is less than that of the PG of 5 post creation facilitation and maintenance interventions / PY.

That is:

**$H_0$**: $R_{WE} \geq 5$ post creation facilitation and maintenance interventions / PY

**$H_1$**: $R_{WE} < 5$ post creation facilitation and maintenance interventions / PY

Rejection of the null hypothesis will signify that the number of interventions post creation to facilitate AVF use and / or maintain AVF use (Facilitation and / or Maintenance Interventions) per PY of AVFs created using the WavelinQ™ EndoAVF System is less than the PG of 5 post creation facilitation and maintenance interventions / PY.

The primary effectiveness analysis will be conducted on the AT population after the last active treated participant completes their 6-month follow-up; by this time, all participants still in the clinical investigation will have at least 6-months of data. The number of Facilitation and / or Maintenance Interventions per PY will be estimated by Poisson regression model with only the intercept term, and the estimate and 95% CI will be provided, and the p-value comparing to the PG will be calculated by a chi-square test.

## 7.5 Secondary Endpoints

The secondary endpoints will be summarized with descriptive statistics (without formal statistical hypothesis testing) using the ITT population for the safety endpoints and the AT population for the effectiveness endpoints. For time-to-event endpoints, the KM production limit method will be used to determine the rate. For categorical variables, summary statistics will include frequency counts and percentages. For rate variables, summary statistics including number of event / PY. For continuous variables, summary statistics will include mean, standard deviation, minimum, median, and maximum. CIs (95%) will be provided using appropriate assumptions based on the variable type. Refer to Section 4.2 for any applicable definitions.

### 7.5.1 Safety

- Device- and Procedure-Related SAEs evaluated through 6- and 24-months.

### 7.5.2 Effectiveness

- Physiological Maturation evaluated through 6-weeks.
- Cannulation Success assessed through 6-months.
- Cumulative Functional Patency evaluated through 12-months.

## 7.6 Exploratory Endpoints

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

## 7.7 General Considerations

### 7.7.1 Subgroup Analyses

Primary and secondary endpoints may be explored by subgroup, including but not limited to:

- Sex;
- Age;
- Site of anastomosis (ulnar-ulnar; radial-radial; other); and
- Location of arterial procedure access (wrist; upper arm).

A full list of subgroups will be detailed in the Statistical Analysis Plan, which will be approved prior to database lock. The subgroup analyses will be summarized using descriptive statistics.

### 7.7.2 Poolability Analysis by Geographical Region and Investigational Site

A poolability analysis by geographical region and by investigational sites will be performed on the primary endpoints. Sites with less than 10 treated participants will be pooled by site number to form combined site(s) with at least 10 treated participants.

### 7.7.3 Handling of Missing Data

Investigation 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.

For the primary safety endpoint, a conservative approach will be used for the handling of missing data: If a participant has a specified event (device-related or procedure-related SAE), the participant will be included irrespective of if the participant prematurely discontinues prior to the 30 day timepoint; if a participant prematurely discontinues before 30 days without the occurrence of a specified event, the participant will be considered not evaluable and will not be included in the primary safety endpoint analysis.

For the primary effectiveness endpoint, the Poisson regression model will be used to analyze the data. In the Poisson regression model, missing data handling is a standard part of the analysis: If a treated participant prematurely discontinues prior to the data cut, that participant's study duration will be considered as the period of time between the index procedure and their premature discontinuation, and the corresponding number of facilitation and/or maintenance interventions in that specific duration will be used for analysis.

## 7.8 Analysis Timing

The primary reporting will occur when the last active treated participant has completed their 6-month follow-up. A final analysis will be completed when all participants have completed, or prematurely discontinued before, their 24-month follow-up. Note that to support regulatory submissions in the U.S. pertaining to the procedure access at the wrist arteries exploratory endpoint and ad-hoc analyses may be conducted at intervals other than those defined in this section looking specifically at data pertaining to arterial procedure access at the wrist.

# 8 SAFETY MONITORING AND REPORTING

The PI is responsible for the detection, documentation and reporting of events and any new information concerning reported events to the Sponsor that meet the criteria and definitions set forth in this section. These events will be collected for ITT participants and collection thereof will begin immediately following the start of the index procedure (defined to start at the time of the initial skin puncture to gain vessel access). Events occurring prior to the index procedure, will be documented as medical history. Events and the status thereof will be collected through the final investigation required participant follow-up visit or premature discontinuation.

## 8.1 Definitions of Events

### 8.1.1 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 the WavelinQ™ EndoAVF System and whether anticipated or unanticipated. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to the use of the WavelinQ™ EndoAVF System.

### 8.1.2 Serious Adverse Events (SAEs)

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

8.1.3 Adverse Device Effect (ADE)

An ADE is an AE that is considered to be related to the use of the WavelinQ™ EndoAVF System. This includes AEs resulting from insufficient or inadequate IFU, operation, or any malfunction of the WavelinQ™ EndoAVF System. Additionally, this definition includes any event resulting from use error or from intentional misuse of the WavelinQ™ EndoAVF System.

Note that a use error is defined as a user action or a 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.

8.1.4 Serious Adverse Device Effect (SADE) or Unanticipated (Serious) Adverse Device Effect (UADE / USADE)

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

An Unanticipated (Serious) Adverse Device Effect (UADE / USADE) is any (serious) ADE on health or safety or any life-threatening problem or death caused by, or associated with, the WavelinQ™ EndoAVF System, which by its nature, incidence, severity, or outcome has not been identified in the IFU and/or current risk assessment, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of participants.

## 8.2 Severity of Adverse Event

PIs will assess each AE for its severity (intensity) as experienced by the participant or user according to the following criteria:

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

- **Severe:** 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.

## 8.3 Relationship of AE to Device(s) / Procedure / AV Access Circuit

PIs will assess each AE for its relationship to the WavelinQ™ EndoAVF System, index procedure or the access circuit as follows:

- *Device Related:* AEs directly attributable to the WavelinQ™ EndoAVF System used as part of the index procedure.
- *Procedure Related:* AEs directly attributable to the index procedure.
    - *Wrist Arterial Procedure Access Related:* Procedure related AEs directly attributable to wrist arterial access if used during the index procedure.
- *AV Access Circuit Related:* This category should be restricted to AEs directly associated with the index AV access circuit defined as the continuum from the heart and the arterial inflow through the AV access to the venous outflow back to the heart.[8]

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

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

## 8.4 Reporting of Events

All AEs should be promptly recorded on the appropriate eCRF (including information on the date of the AE, treatment, resolution, and assessment of relatedness). The clinical course of the AE will be followed according to accepted SOC until the event resolves, stabilizes, or in the opinion of the PI, is no longer considered clinically significant. The PI must supply the Sponsor with information concerning the follow up and / or resolution of the AE. The additional reporting requirements for device- / procedure-related AEs / SAEs or UADEs / USADEs are as follows:

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

the Sponsor within 72 hours of knowledge of a UADE or death, as appropriate.

- It is the responsibility of the PI to notify the IRB / EC of applicable AEs in accordance with the governing IRB / EC requirements and / or regulatory authorities according to the local regulations in each participating country.
- UADEs / USADEs will be evaluated and assessed / escalated by the Sponsor per ISO 14155:2020(E) and as per local regulations.

#### 8.4.1 Non-Reportable AEs

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.

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.

## 8.5 Participant Death

Participant death, for any reason during the clinical investigation, must be reported to the Sponsor within one (1) working day of the investigational site becoming aware of the event.

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

## 8.6 Device Deficiencies

A device deficiency is 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 WavelinQ™ EndoAVF System. All device deficiencies will be recorded on the appropriate eCRF page and be promptly reported to the Sponsor. The device(s) should be returned to the Sponsor as outlined in the investigational site's regulatory binder. The site may also be contacted to provide additional information to allow the Sponsor to conduct a thorough investigation. This applies to:

- WavelinQ™ EndoAVF Systems used in the participant; or

- WavelinQ™ EndoAVF Systems in which the package was opened, but the device was not used; or
- WavelinQ™ EndoAVF Systems with which insertion attempts were made, but the WavelinQ™ EndoAVF System was not used in the participant.

If the device deficiency was associated with an AE, the reporting provisions for AEs, ADEs, SAEs, SADEs and UADEs / USADEs apply (see Section 8.4 and 12.4). 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 (see Section 12.4). It is the responsibility of the PI to notify the IRB / EC of such device deficiencies as, and if, applicable in accordance with the IRB / EC requirements and / or the Regulatory Authority's local regulations.

## 8.7 Serious Health Threat

A serious health threat is a 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. Serious health threats will be reported as per IRB / EC and regulatory requirements, if applicable.

## 8.8 Safety Committees

### 8.8.1 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.

### 8.8.2 Clinical Events Committee (CEC)

The CEC will be comprised of at least two (2) members (interventional radiologists, non-interventional / interventional nephrologists, or surgeons) who are not directly involved in the conduct of this clinical investigation. The CEC is responsible for the development of specific criteria used for the categorization of clinical events and clinical endpoints in the clinical investigation as determined by the CEC charter. The CEC will meet regularly to review and adjudicate all AEs defined in the charter. The CEC will have access to the eCRF associated with the reported AE for each participant. The Sponsor will forward all associated relevant de-identified documents (i.e., physician notes, operative reports, imaging, etc.) to the CEC upon request. The CEC will forward an adjudication report of AEs to the Sponsor in a timely fashion. Minutes

of all meetings will be recorded and distibuted as appropriate. The Sponsor will ensure that if applicable, appropriate information is provided to the Regulatory Authorities, the PIs, and all reviewing IRB / ECs.

# 9 RISK / BENEFIT ANALYSIS

## 9.1 Risk Assessment

The known possible risks associated with the use of the WavelinQ™ EndoAVF System are listed below and have been made available to the PI(s) in the IFU. Complications that may be associated with AEs, medical intervention and / or death that could occur with use of the WavelinQ™ EndoAVF System may include:

- aborted or longer procedure;
- additional procedures;
- bleeding, hematoma or hemorrhage;
- bruising;
- burns;
- death;
- electrocution;
- embolism;
- failure to mature;
- fever;
- increased risk of congestive heart failure;
- infection;
- numbness, tingling, and / or coolness;
- occlusion / stenosis;
- problems due to sedation or anesthesia;
- pseudoaneurysm;
- aneurysm;
- sepsis;
- steal syndrome or ischemia;
- swelling, irritation, or pain;
- thrombosis;
- toxic or allergic reaction;
- venous hypertension (arm swelling);
- vessel, nerve, or AVF damage or rupture;
- wound problem

The risks associated with use of the WavelinQ™ EndoAVF System have been identified by performing a Use Failure Mode and Effects Analysis as well as a Design Failure Mode and Effects Analysis (UFMEA and DFMEA) on the system and its use. The Sponsor also conducted non-clinical testing as well as clinical investigations to confirm that the WavelinQ™ EndoAVF System has element safety and effectiveness to create endoAVFs. A Risk-Benefit Analysis (RBA) was then subsequently performed. At the completion of the UFMEA, DFMEA and RBA, a Risk Management Report was generated to summarize the risk analysis process and provide documented evidence that all individual and cumulative risks associated with the use of the WavelinQ™ EndoAVF System have been adequately managed and reduced as low as possible. Any residual risks identified with the investigation intervention that are identified in the device RBA are also captured and tracked along with their mitigation strategies for this investigation using the investigation's Risk Analysis. Risks identified for associated / concomitant procedures are identified in Table 3 alongside their mitigation strategies.

**Table 3: Risk Assessment**

| Potential Risk of Clinical Significance | Summary of Risk | Mitigation Strategy |
|---|---|---|
| **Associated / Concomitant Procedures** | | |
| Risks associated with sedation and / or anesthesia | These risks can include:<br>• Nausea<br>• Vomiting<br>• Hematoma at injection site<br>• Sore throat / hoarse voice<br>• Damage to teeth<br>• Brain damage<br>• Death | • As delineated in Section 12.1 the PI as well as any additional operators (as applicable) must be experienced in the field of application.<br>• 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).<br>• The CIP required follow-up ensures close participant monitoring for AEs throughout the course of the investigation (Section 6.4). |
| Risks associated with angiography | These risks can include:<br>• Kidney damage<br>• Allergic reaction | • As delineated in Section 12.1 the PI as well as any additional operators (as applicable) must be experienced in the field of application.<br>• Clinical Eligibility Criteria must be met and documented using prior to treatment including assessment of the participants eligibility to receive contrast media (Section 5.1).<br>• The CIP required follow-up ensures close participant monitoring for AEs throughout the course of the investigation (Section 6.4). |
| Risks associated with vessel embolization placement, if completed. | These risks can include:<br>• Allergic reaction<br>• Hemolysis<br>• Migration<br>• Occlusion of unintended vessel<br>• Recanalization<br>• Stroke<br>• Tissue ischemia<br>• Vessel trauma including perforation, rupture, or extravasation<br>• Others, as delineated in the embolization device labeling and IFU | • As delineated in Section 12.1 the PI as well as any additional operators (as applicable) must be experienced in the field of application.<br>• The CIP required follow-up ensures close participant monitoring for AEs throughout the course of the investigation (Section 6.4). |

## 9.2 Benefit Assessment

There are no guaranteed benefits from participation in this clinical investigation; however, the potential benefits that may result from the endoAVF procedure using the WavelinQ™ EndoAVF System may include:

- Higher likelihood of a usable AVF, as less trauma to the vessels may reduce adverse or abnormal inflammatory and healing responses within the vessel wall resulting in lower rates of stenosis and thrombosis which are the leading causes for failure in AVFs created using traditional surgical methods.
- Reduced risk of infection, reduced participant discomfort, and reduced cosmetic deformation since no incision or prosthetic materials (including stitches) are required to create the endoAVF.
- Shorter endoAVF maturation / HD suitability time potentially leading to earlier endoAVF cannulation commencement and decreased CVC exposure time.

## 9.3 Overall Benefit: Risk Conclusion

Neither the risk management output, including the results of non-clinical testing (bench testing, biocompatibility testing), prior clinical investigations nor the market surveillance history reveal any unacceptable residual risks and these risks have been disclosed through the IFU (and herein in Section 9.1).

Furthermore, this CIP is specifically designed to manage and minimize risks through careful participant selection, thorough training of investigators, adherence to the pre-determined timepoints to assess participant clinical status and regular clinical monitoring visits by Sponsor appointed monitoring personnel. Additional risks identified during the clinical investigation will be assessed, evaluated, and reported by the Sponsor (if applicable). Prior to clinical investigation participation, the PI must explain to each participants the risks and benefits of this clinical investigation.

Taking into consideration the measures taken to minimize risk to participants in this clinical investigation, the potential risks identified in association with the WavelinQ™ EndoAVF System are justified by the anticipated benefits that may be afforded to participants with established non-reversible kidney failure that are in need of receiving HD.

# 10 DATA COLLECTION AND RECORD MAINTENANCE

## 10.1 Case Report Forms (CRF) and Source Documentation

The PI is responsible for and will assure the accuracy, attribution, completeness, legibility and timeliness of all clinical investigation documentation and data. Source documents shall be created and maintained by the investigation site team throughout the clinical investigation as well as documentation of the type and location of these source documents. All copies of the retained original source document shall be certified, as indicated by a dated signature by a member of the investigation site team.

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.

## 10.2 Source Documentation Access

Auditors, monitors, the Sponsor, and Regulatory Authorities may have access to the medical records related to this clinical investigation. Original or certified copies of all relevant clinical findings, observations, and other activities throughout the clinical investigation must be recorded and maintained in the medical file of each enrolled participant.

The PI will permit clinical investigation related monitoring, audits, IRB / EC 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).

## 10.3 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 including but not limited to those used for CRF tracking, data review, database cleaning, and issuing/resolving data queries. Procedures for validations and data storage will also be contained within the DMP.

### 10.4 Record Retention

The PI shall retain all clinical investigation records for a minimum of ten (10) years after the date on which the clinical investigation is terminated / completed. The data for some of these records may be available in computerized form but the final responsibility for maintaining clinical investigation records remains with the PI. 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 PI 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 applicable regulatory authority not later than ten (10) working days after the transfer occurs.

# 11 QUALITY CONTROL AND ASSURANCE

## 11.1 Control of the Investigation Device

The WavelinQ™ EndoAVF System is Conformité Européene (CE) marked and will be evaluated in a post-market fashion for its approved indication in the EU, the United Kingdom (UK). Sites in these regions 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 WavelinQ™ EndoAVF Systems that have failed or malfunctioned should be returned to the Sponsor. If the malfunctioned WavelinQ™ EndoAVF System has been used (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.

## 11.2 Monitoring

Monitoring shall be conducted according to the monitoring plan as well as in accordance with established standard operating procedures and is intended to verify that the rights and well-being of the participants are protected, that the reported data are accurate, complete, and verifiable from source documents, and that the conduct of the investigation complies with this CIP, any amendments (if applicable), in addition to applicable standards, regulations, and IRB / EC requirements. The clinical investigation monitors are designated as trained and qualified agents of the Sponsor and are assigned to oversee the conduct and progress of the clinical investigation. The clinical investigation monitors will be the principal communication link between the Sponsor and the PI and shall be independent from the investigational sites.

The clinical investigation monitors may assist in pre-qualifying potential investigational sites. Upon investigational site selection, the clinical investigation monitors will periodically conduct on-site inspection and monitoring of sites and records, to ensure continued compliance with this CIP and adequacy of the PI and the site to conduct the clinical investigation. In addition, the monitor will verify that the WavelinQ™ EndoAVF System is being used in accordance with the CIP instructions and IFU. A summary of monitoring visits is provided in the subsequent sections. It is important that the PI(s) and the relevant investigational site team members are available during the monitoring visits and that sufficient time is devoted to the process.

### 11.2.1 Site Initiation Visits (SIVs)

Before the clinical investigation may commence at an investigational site, the monitor will conduct a SIV. The purpose of this visit is to ensure the PI and clinical investigation site team understand the proper conduct of and required provisions for this clinical investigation as well as their responsibilities. As such, this visit will include a detailed

review of this CIP and associated documents. Additionally the visit serves as a means to verify that all necessary documents (refer to Section 12.3) and materials are on file at the investigational site, that investigation device training has been completed (as per Section 12.2), and confirm that IRB / EC approval has been received.

11.2.2 Interim Monitoring Visits (IMVs)

After initiation of the clinical investigation at an investigational site, the monitor will maintain personal contact with the PI and investigation site team through routine monitoring activities as specified in the monitoring plan for this clinical investigation.

These routine monitoring activities will serve as a means for the monitor to assess continued compliance to this CIP and associated documents as well as compliance to standards and regulatory requirements. These activities will verify that:

- Only authorized members of the investigation site team are participating in the clinical investigation according to their delegated responsibilities;
- The WavelinQ™ EndoAVF System is being used according to the CIP and IFU;
- There are adequate provisions to continue and maintain all documents and records throughout the duration of this clinical investigation as required by applicable regulations and that there are adequate investigation site resources and materials;
- There is adequate participant enrollment and access to an adequate number of potential participants;
- Signed and dated ICFs are obtained for each participant (or if applicable, their legally authorized representative (LAR)) before any clinical investigation-related procedures are undertaken and that the ICF used for this process is the version approved by the IRB / EC for the specific investigational site;
- There is accurate and complete data reporting and documentation (including the comparison and up to 100% verification of eCRFs with source documentation for critical fields);
- CRFs, queries, and appropriate corrections are complete, recorded in a timely manner and consistent with source documents and CIP requirements;
- Participant accountability and compliance is maintained and documented;
- There is complete and timely safety event monitoring, collection, and reporting per CIP requirements;
- Deviations have been appropriately recorded and reported;
- All required and necessary clinical investigation documents, reports, notifications, applications, submissions, approvals, as well as correspondence and the most updated versions thereof are maintained in the investigational site's files and are accurate, complete, timely, legible, dated and identify the clinical investigation;
- There is continued maintenance and calibration of clinical investigation-specific equipment and documentation thereof (if applicable);

- Any corrective and preventative actions have been implemented and are effective (if applicable);
- Applicable national privacy laws have been and are being followed; and
- There is continued IRB / EC acceptance of this clinical investigation.

The monitor will evaluate and summarize the results of each visit in written reports, identifying any ongoing issues with any investigational site and specifying recommendations for resolution of noted deficiencies.

11.2.3 Final Monitoring Visit

At the completion of the clinical investigation, the clinical investigation monitor will conduct a final site close-out visit (COV). The purpose of this visit may include but is not limited to collecting all outstanding clinical investigation data documents, confirming that the PI's files are accurate and complete, reviewing the record retention requirements with the PI, and ensuring that all applicable requirements for closure of the clinical investigation are met. The actions and observations made at this visit will be recorded and filed.

## 11.3 Audits and Inspections

The investigational sites may also be subject to quality assurance audit by personnel of the Sponsor (and its affiliates), as well as by regulatory representatives and other applicable authorities. If the site is selected for an audit, the PI(s) and the relevant investigational site team members will make themselves available during the visit. The PI must agree to the inspection of all clinical investigation 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 PI is aware of an upcoming inspection / audit by the Health Authorities, the PI will promptly inform the Sponsor. As agreed with the PI, Sponsor personnel may be present at the site during the inspection.

## 11.4 Deviations from the CIP and Medical Emergencies

A deviation is defined as an event where the PI or investigation site team members did not follow, intentionally or unintentionally, the requirements of this CIP.

Except when necessary to protect the life or physical well-being of a participant, deviations from the CIP are not permitted. It is the PI's responsibility to ensure that there are no deviations from this CIP, except when necessary to protect the life or physical wellbeing of a participant in an emergency or unanticipated circumstance. Except in emergency situations, a deviation requires prior approval by the Sponsor. If the deviation affects the

scientific soundness of this CIP or the rights, safety, or welfare of a participant, prior IRB / EC approval is required.

Any and all deviations must be recorded on the appropriate eCRF regardless of whether medically justifiable, Sponsor approved or taken to protect the participant in an emergency. 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 alternative intervention followed by written confirmation that describes the emergency action and outcomes, within five (5) working days from the date of the emergency action or in accordance with the governing IRB / EC's requirement, whichever is more stringent. Significant deviations must be reported to the Sponsor within five (5) working days. Significant deviations are defined as deviations that occur to protect the life or physical well-being of a participant in an emergency, or deviations that may affect the scientific soundness of the clinical investigation, or deviations pertaining to the rights, safety or welfare of human participants. PIs will also adhere to procedures for reporting clinical investigation deviations to and obtaining approval from their IRB / EC in accordance with their specific IRB / EC reporting policies and procedures. Refer to Section 12.4 for the deviation reporting requirements.

Upon evaluation by the Sponsor of the deviation(s), corrective and preventative actions may be required to prevent additional deviations, such as retraining of the investigational site, implementation of additional investigational site procedures, and more frequent monitoring. If these steps fail, more serious measures may be taken, up to and including termination of enrollment at the site.

# 12 ADMINISTRATIVE REQUIREMENTS

## 12.1 Investigator and Site Selection

The PIs selected for this clinical investigation must be of good standing as an investigator and knowledgeable in relevant areas of clinical research (including with the methods to obtain informed consent) to ensure adherence to the requirements of this CIP, the referenced standards and applicable national regulations, including the protection of human participants. The PI as well as any additional operators (as applicable) must also be experienced in the field of application and operators must be trained in the use of the WavelinQ™ EndoAVF System (refer to Section 12.2). Other investigation site team members must have appropriate qualifications, training, and experience to assume responsibility for the proper conduct of this clinical investigation and the site must have the infrastructure available to ensure adherence to this CIP and enrollment of sufficient numbers of evaluable participants. The curriculum vitae (CV) of the PI(s), Sub-Investigator(s) and Research Coordinator(s) will be maintained in the Sponsor's files as documentation of qualification by training and experience.

The PI will sign the Investigator Agreement pages of this CIP, agreeing to comply with all applicable government regulations and the requirements of this clinical investigation. The PIs and Sub-Investigators shall also disclose potential conflicts of interest, including financial, that can interfere with the conduct of the clinical investigation or interpretation of results.

Federal databases will be searched to ensure that the PIs, Sub-Investigators, and / or the site are not prohibited from engaging in federally sponsored clinical research. Any site that becomes deactivated prior to initial enrollment, either by the Sponsor or by the individual site itself, may be replaced.

New members of the investigation site team may be added throughout the course of the clinical investigation, but these new members shall only start their assignment after receiving adequate training on the clinical investigation requirements and documentation thereof (Note EC approval of new members of the investigation site team can also be required before commencement of their responsibilities).

## 12.2 Training

In addition to each PI and applicable clinical investigation team member being trained on this CIP and clinical investigation procedures during the SIV, device training will be provided by the Sponsor. This device training is required for each PI and Sub-Investigator that will operate the WavelinQ™ EndoAVF System. Operators are not permitted to use the WavelinQ™ EndoAVF System on enrolled participants in this clinical investigation if they have not completed the training and been approved in writing as an operator by the Sponsor.

## 12.3 Required Documents

A PI 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 clinical investigation activities:

- Signed and executed Non-Disclosure Agreement (NDA) by PI and appropriate party at the Sponsor;
- CVs, signed and dated within 2 years of clinical investigation start for the PI and Sub-Investigator(s);
- CVs for Research Coordinator(s);
- Signed CSA by PI (or designee);
- Signed Investigator Agreement (CIP Signature Page) by PI and Sub-Investigator(s);
- Signed "Financial Disclosure Statement" by PI and Sub-Investigator(s);
- Signed "Training Log" for all delegated investigation site team members;
- Site "Delegation of Authority Log";
- Written approval from the IRB / EC of both this CIP and ICF, and any other applicable CIP specific material; and
- IRB / EC Membership List, Assurance of Compliance Form, or equivalent.

## 12.4 Reporting Requirements

At a minimum, the PI or authorized designee shall inform the Sponsor of the following events according to the notification timelines in Table 4. Additional information required to be reported by the investigational sites IRB / EC must be completed according to the notification timelines established by the IRB / EC. Copies of these additional reports are to be provided to the Sponsor.

**Table 4: Reports and Notifications Required from Clinical Investigators**

| Event / Report Type: | Notification to: | Time to Notification: |
|---|---|---|
| Device- / procedure-related AEs / SAEs, as well as ADEs / SADEs, or UADEs / USADEs | Sponsor and IRB / EC (if applicable) | As soon as possible, but no later than one (1) working day after site awareness and per local IRB / EC requirements. Relevant documentation to be submitted to the Sponsor no later than three (3) working days (see Section 8.4). |
| Death | Sponsor and IRB / EC (if applicable) | As soon as possible, but no later than one (1) working day after site awareness and per local IRB / EC requirements (see Section 8.5). |

| Event / Report Type: | Notification to: | Time to Notification: |
|---|---|---|
| Device Deficiencies | Sponsor and IRB / EC (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.<br>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 (see Section 8.6) |
| Requests for or Reports of Significant Deviations | Sponsor and IRB / EC (if applicable) | As soon as possible, but no later than five (5) working days after emergency / deviation occurs (see Section 12.4). |
| Emergency Situations | Sponsor and IRB / EC (if applicable) | Immediately if an emergency situation arises in which the safety of a participant may require immediate alternative intervention followed by written confirmation that describes the emergency action and outcomes, within five (5) working days from the date of the emergency action or in accordance with the governing IRB / EC's requirement. (see Section 11.4). |
| Failure to Obtain ICF | Sponsor and IRB / EC (if applicable) | Within five (5) working days after index procedure. |
| Withdrawal of IRB / EC Approval | Sponsor | Immediately by telephone followed by a copy of the notification within five (5) working days. |
| Investigation Suspension / Premature Termination | IRB / EC | The PI must notify the IRB / EC of all terminations / suspensions.<br>The PI must notify the IRB / EC in writing as soon as possible but no later than within ten (10) working days (or sooner as required by the IRB / EC) if the premature termination is related to safety or compliance issues (see Section 12.7). |
| Clinical Investigation Progress Report | Sponsor and IRB / EC | At regular intervals or annually. |
| Notice of Inspection or Audit by the Health Authorities | Sponsor | As soon as possible after becoming aware of the impending inspection / audit. |
| Transfer of Clinical investigation records | Sponsor and regulatory authority (if applicable) | Within ten (10) working days after the transfer occurs. |

## 12.5 Registration of the Clinical Investigation

A description of this clinical investigation will be made available on a publicly accessible database (e.g., http://www.clinicaltrials.gov), in compliance with applicable regulations

(e.g., Title VIII of Public Law 110-85 as FDA Amendments Act of 2007 (FDAAA) / ISO 14155). This content shall be updated as required per applicable national regulations.

### 12.6 Publication Policy

At the conclusion of this clinical investigation, an article may be prepared for publication in a reputable scientific journal. Formal presentation(s) or publication(s) of data collected from this clinical investigation will be considered as a joint publication by the PI(s) and the appropriate personnel of the Sponsor. Authorship will be based on the generally accepted criteria of the International Committee of Medical Journal Editors (ICMJE) and determined by mutual agreement.

The publication of the principal results from any single-center experience within the clinical investigation 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.

### 12.7 Close-Out, Premature Termination, or Suspension of the Clinical Investigation

The completion of this clinical investigation shall coincide with the last visit of the last active treated participant upon the completion of follow up. The Sponsor shall notify all PIs and if required, the Regulatory Authorities of the completion of this investigation. PIs or authorized designees shall notify their respective IRB / EC of the clinical investigation completion and forward documentation of this notification to the Sponsor.

The Sponsor reserves the right to suspend enrollment or prematurely terminate the clinical investigation at any time as set forth in the CSA. If suspicion of an unacceptable risk, including serious health threat, to participants arises during the clinical investigation, or when so instructed by the IRB / EC or regulatory authorities, the Sponsor shall suspend the clinical investigation while the risk is assessed. The Sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be mitigated is confirmed.

In the event of suspension of enrollment or premature termination of the clinical investigation, the Sponsor will send a report outlining the circumstances to the IRB / EC, and all PIs and Regulatory Authorities (if applicable). A suspended or terminated clinical investigation may not be reinitiated without approval of the reviewing IRB / EC and Regulatory Authorities (if applicable). In the event of clinical investigation premature termination or suspension, treated participants should be followed through the 24-month follow-up period or as deemed appropriate for the circumstances of premature termination or suspension. The specific follow-up requirements will be communicated along with the notice of premature termination or suspension.

The Sponsor may also suspend enrollment or terminate the clinical investigation 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 CIP or other clinical research requirements. Written notice will be submitted to the PI in advance of such termination or suspension. In the event of clinical investigation premature termination or suspension at a site, treated participants at that site should be followed through the 24-month follow-up period or as deemed appropriate for the circumstances of premature termination or suspension. The specific follow-up requirements will be communicated along with the notice of premature termination or suspension.

In the event of suspension of the clinical investigation at a specific site, the Sponsor will send notification to the site, the regulatory authority (if applicable) and the site must report the suspension to the IRB / EC. Documentation of the IRB / EC communication must be provided to the Sponsor. The clinical investigation may not be reinitiated at the site without written approval of the Sponsor and without approval of the reviewing IRB / EC and regulatory authority (if applicable). The written approval of the IRB / EC must be provided to the Sponsor prior to reinitiating the clinical investigation. The Sponsor will notify other site PIs if the premature termination or suspension at the site was for safety reasons.

If deemed appropriate, the PI or authorized designee shall promptly inform enrolled participants of suspension or premature termination and once again in the event of clinical investigation resumption. The PI must notify the IRB / EC in writing as soon as possible but no later than within ten (10) working days if the premature termination is related to safety or compliance issues.

## 12.8 Amendments

The CIP and associated clinical investigation documentation shall be amended as needed throughout the clinical investigation in accordance with the Sponsor's written procedures for the control of documents and document changes.

If the amendment impacts the integrity of the clinical investigation, the data collected before and after the amendment shall be analyzed statistically to assess the effect of the amendment on performance, effectiveness, or safety analysis. This analysis shall be included in the clinical investigation report. Note that for each amendment of the CIP, the CRFs shall be evaluated to determine if an amendment of these documents is also necessary.

# 13 ETHICAL AND REGULATORY CONSIDERATIONS

## 13.1 Regulatory Status

The WavelinQ™ EndoAVF System is CE marked and will be evaluated in a post-market fashion for its approved indication in the EU and the UK. Appropriate regulatory approvals will be obtained in other regions prior to initiating the clinical investigation in those regions, if applicable.

## 13.2 IRB / EC Approval and Communications

PIs or authorized designees must submit this CIP together with all locally required documentation (at minimum the CIP, ICF, patient facing materials (if any), participant recruitment procedures / advertising materials (if any), and CVs of the PI(s)) to an appropriate IRB / EC and obtain clinical investigation-specific written approval (favorable opinion) before being allowed to participate in the clinical investigation. Before commencement of the clinical investigation, the PI or authorized designee must provide the Sponsor with written documentation of IRB / EC approval identifying the documents and amendments (if applicable) on which the opinion was based. The IRB / EC must give written renewal of the original approval at least annually to continue the clinical investigation. A copy of each written renewal must be provided to the Sponsor.

The PI or authorized designee is also responsible for fulfilling any conditions of approval imposed by the IRB / EC, such as regular safety reporting (SAEs), reporting of and / or requests for major CIP deviation(s), reporting of clinical investigation progress / timing, approval of resumption of a suspended clinical investigation, etc. The PI or authorized designee will provide the Sponsor with copies of associated reports, communications and / or approvals.

The IRB / EC will be notified of any amendments to the CIP, as well as possible associated information and consent form changes, where applicable, and written favorable opinion / approval will be obtained prior to implementation, as applicable and evidence thereof is to be supplied to the Sponsor. For non-substantial changes (e.g. minor logistical or administrative changes, change of telephone numbers, etc.) not affecting the rights, safety and well-being of human participants or not related to the clinical investigation objectives or endpoints, a simple notification to the IRB / EC and, where appropriate, regulatory authorities can be sufficient.

## 13.3 Informed Consent and National Privacy Laws

Prior to any non-SOC clinical investigation related procedure, the PI (or authorized designee) must explain to each prospective participant in layman's terms, the nature of the clinical investigation, its purpose, its expected duration, as well as the risks and benefits of clinical investigation participation. The informed consent process must avoid any coercion or undue improper influence on, or inducement of, the patient to participate and must not

waive (or appear to waive) the legal rights of the patient in any way. Also, prospective participants 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., General Data Protection Regulation (GDPR) in the EU) will be followed in this clinical investigation. The prospective participants must be informed of their right to withdraw from the clinical investigation 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 clinical investigation will not jeopardize their future medical care. Prospective participants will be informed of their right to new information and / or findings relating to the clinical investigation, and the process by which this information is made available.

After this explanation, given sufficient time to review the informed consent and decide whether to participate, before any clinical investigation procedure is conducted, and before entering the clinical investigation, the prospective participant must voluntarily provide consent in accordance with ISO 14155:2020(E) (see Section 13.3.1 for special circumstances). The PI (or authorized designee) must ensure that the ICF receives a personally dated signature from the participant (see Section 13.3.1 for special circumstances) after agreeing to participate in this clinical investigation. The PI or authorized designee that conducted the informed consent must also provide a personally dated signature on the form. Documentation of the informed consent process shall be captured in the participant's source documentation and the original signed ICF maintained with the essential clinical investigation files. The participant will receive a copy of his / her signed ICF.

Part of the IRB / EC approval must include approval of an ICF that is specific to this investigation. The PI or authorized designee must administer this approved ICF to each prospective clinical investigation participant and obtain the participant's signature (see Section 13.3.1 for special circumstances) on the ICF prior to any non SOC clinical investigation related procedure. The ICF may be modified to suit the requirements of the individual site. The PI or authorized designee will provide the Sponsor or authorized designee with a copy of the approved ICF for his / her site. The ICF templates are standalone documents to facilitate revision(s) as necessary, without requiring a CIP amendment.

New information that arises throughout the course of the investigation which may relate to the participant's willingness to continue participation in the clinical investigation will be evaluated for the appropriate methods of disseminating and disclosure (if deemed applicable) to participants by the Sponsor and the PI.

### 13.3.1 Special Circumstances for Informed Consent

Note that the process described in this section is subject to local IRB / EC approval and national regulations. PIs must follow the allowable procedures for their investigational sites with respect to special circumstances for informed consent.

Informed consent may be given by the LAR only if a prospective participant is unable to make the decision to participate in a clinical investigation (e.g. patient with a mental, intellectual disability). In such cases, the prospective participant shall also be informed about the clinical investigation within his / her ability to understand. Note that this is subject to national regulations.

Informed consent shall be obtained through a supervised oral process if a prospective participant or LAR is unable to read or write. An independent and impartial witness shall be present throughout the process. The written ICF and any other information shall be read aloud and explained to the prospective participant or his / her LAR. And, whenever possible, either the participant or his / her LAR shall sign and personally date the ICF. The witness shall sign and personally date the ICF attesting that the information was accurately explained, and that informed consent was freely given.

The nature of this clinical investigation does not involve emergency treatments consent must always be obtained prior to the completion of any clinical investigation related procedure that is not SOC.

### 13.3.2 Confidentiality

Participant confidentiality and confidentiality of data shall always be observed by all parties involved throughout the clinical investigation. All information and data sent to the Sponsor or its designees concerning participants or their participation in the clinical investigation will be considered confidential. All data used in the analysis and reporting of this clinical investigation will be used in a manner without identifiable reference to the participant.

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 PI consents to visits and inspections by personnel of the Sponsor and its affiliates or designees, as well as Regulatory and Health Authority (e.g. FDA) representatives and shall provide direct access to all source data during and after the clinical investigation for monitoring, audits, IRB / EC reviews and regulatory inspections. As required, the PI or institution shall obtain permission for direct access to source

documents from the participant, hospital administration and regulatory authorities before starting the clinical investigation.

### 13.4 Statement of Compliance

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

- ISO 14155:2020(E) and GCP;
- Ethical principles of the Declaration of Helsinki adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, in its current revision; and
- Applicable sections of the national laws and regulations.

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

# 14 REFERENCES

1. Meichelboeck W. ESRD 2005 A worldwide overview. 4th international congress of the vascular access society, Berlin, Germany, 2005. www.vascularaccesssociety.com

2. United States Renal Data System (USRDS) 2008 Annual Report.

3. GBD chronic kidney disease collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: A systematic analysis for the global burden of disease study 2017. Lancet. 2020;395:709–33.

4. Kramer A, et al. The European renal association – European dialysis and transplant association (ERA-EDTA) registry annual report 2016: A summary. *Clinical Kidney Journal.* 2019:1-19.

5. Sidawy AN, et al. Recommended standards for reports dealing with arteriovenous hemodialysis access. *J. Vasc. Surgery.* 2002;35(3):603-10.

6. Xue JL, et al. The association of initial hemodialysis type with mortality outcomes in elderly Medicare ESRD patients. *Am J Kidney Disease*. 2003;42(5):1013-9.

7. Dhingra RK. Type of vascular access and mortality in U.S. hemodialysis patients. *Kid Int.* 2001;60:1443-51.

8. Lok CE, Huber TS, Lee T, et al. KDOQI vascular access guideline work group. KDOQI clinical practice guideline for vascular access: 2019 update. *Am J Kidney Dis.* 2020;75(4)(suppl 2):S1-S164.

9. Sidawy AN, et al. The society for vascular surgery: Clinical practice guidelines for surgical placement and maintenance of arteriovenous hemodialysis access. *J Vasc Surgery.* 2008;48(5S):2S-25S.

10. Beathard GA, et al. Definitions and end points for interventional studies for arteriovenous dialysis access. *Clin J Am Soc Nephrol.* 2918;13(3):501-12.

11. Asif A, Roy-Chaudhury P, and Beathard GA. Early arteriovenous fistula failure: A logical perspective of how and why to intervene. *Clin J Am Soc Nephrol.* 2006;1:332-39.

12. Schwab J. and Beathard GA. The hemodialysis catheter conundrum: Hate living with them, but can't live without them. *Kidney International.* 1999;56:1-17.

13. Dember L, Beck G, Allon M, et al. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: A randomized controlled trial. *JAMA.* 2008;299(18):2164-71.

14. Lok C. Six-month patencies of the endovascular arteriovenous fistula (EndoAVF) from the Novel Endovascular Access Trial (NEAT). *J. Vasc. Surg.* 2016;63(7S).

15. Rajan DK, Ebner A, Desai SB, Rios JM and Cohn WE. Percutaneous creation of an arteriovenous fistula for hemodialysis access. *J. Vasc. Interv. Radiol.* 2015;26:484–90.

16. Robbin ML, Greene T, Cheung AK, et al. Arteriovenous fistula development in the first 6 weeks after creation. *Radiology.* 2016;279(2):620-29.

17. Umphrey HR, Lockhart ME, Abts CA, Robbin ML. Dialysis grafts and fistulae: planning and assessment. *Ultrasound Clin.* 2011;6(4):477–489.

18. Shenoy S, et al. Clinical trial end points for hemodialysis vascular access: Background, rationale, and definitions. *Clin J Am Soc Nephrol.* 2018;13:490-4.

19. Lee T, Mokrzycki M, Moist L, Maya I, Vazquez M, Lok C. Standardized definitions for hemodialysis vascular access. *Semin Dial.* 2011;24:515–524. Doi: 10.1111/j.1525-139X.2011.00969.x.

# 15 APPENDICES

## 15.1 Appendix A – Abbreviations and Acronyms

| Abbreviation | Term |
|---|---|
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| AT | As-Treated |
| AV | Arteriovenous |
| AVF | Arteriovenous Fistula |
| AVG | Arteriovenous Graft |
| Bard | C.R. Bard, Inc. |
| BD | Becton Dickinson and Company |
| BDPI | BD Peripheral Intervention |
| CE | Conformité Européene |
| CEC | Clinical Events Committee |
| CI | Confidence Interval |
| CIP | Clinical Investigation Plan (Clinical Protocol) |
| CSA | Clinical Study Agreement |
| COV | Close-Out Visit |
| CV | Curriculum Vitae |
| CVC | Central Venous Catheter |
| DFMEA | Design Failure Mode and Effects Analysis |
| DMP | Data Management Plan |
| DUS | Duplex Ultrasound |
| eCRF | Electronic Case Report Form |
| EC | Ethics Committee |
| endoAVF | Endovascular Arteriovenous Fistula |
| EQ-5D | European Quality of Life-5 Dimensions |
| ESKD | End Stage Kidney Disease |
| ESU | Electrosurgical Unit |
| EU | European Union |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HD | Hemodialysis |
| ICF | Informed Consent Form |
| ICMJE | International Committee of Medical Journal Editors |
| IFU | Instructions for Use |
| IMV | Interim Monitoring Visit |
| IRB | Institutional Review Board |
| ISO | International Organization for Standardization |
| ITT | Intent to Treat |

| Abbreviation | Term |
|---|---|
| KDOQI | National Kidney Foundation Kidney Disease Outcomes Quality Initiative |
| KM | Kaplan-Meier |
| KRT | Kidney Replacement Therapy |
| LAR | Legally Authorized Representative |
| LTF | Lost to Follow-Up |
| MM | Medical Monitor |
| NDA | Non-Disclosure Agreement |
| PG | Performance Goal |
| PI | Principal Investigator |
| PP | Per-Protocol |
| PY | Patient Years |
| RBA | Risk-Benefit Analysis |
| QOL | Quality of Life |
| RF | Radiofrequency |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SF-VAQ | Short Form-Vascular Access Questionnaire |
| SIV | Site Initiation Visit |
| SOC | Standard-of-Care |
| SVS | Society for Vascular Surgery |
| UFMEA | Use Failure Mode and Effects Analysis |
| UK | United Kingdom |
| U(S)ADE | Unanticipated (Serious) Device Effect |
| USRDS | United States Renal Data System |
| WBC | White Blood Cell |

## 15.2 Appendix B – Definitions

| Term | Definition |
|---|---|
| **Access Abandonment (Permanent Abandonment)** | Defined as the point at which the access can no longer be used for one or two needle prescribed HD as it may be unable to provide adequate flows and / or is deemed unsafe for the participant, and the associated problem cannot be corrected by any further intervention, including medical, surgical, or endovascular interventions or rest.[8,19] Participants with an abandoned index AVF will continue with follow-up through 24-months and data will be collected on safety and interventions.<br><br>A HD AV access is <u>not</u> considered abandoned:<br>• If the participant discontinues use of the AV access due to kidney transplant, initiation of PD, or participant preference.<br>• During the maturation period or while waiting for a second stage procedure unless the PI determines the participant requires and they then receive an alternative HD vascular access.<br>• During planned interventions, including transposition.<br>• If all reasonable efforts have not been attempted (and documented) to improve the condition of the access for it to be used.<br><br>A discontinuation of use of the clinical investigation AVF for any reason that does not meet this definition of access abandonment will be considered a temporary interruption. |
| **Access Circuit Censoring Events** | Include participant transfer to PD, kidney transplantation or the event of a participants premature discontinuation in the investigation due to withdrawn consent, withdrawal by PI, LTF, or participant death (refer to Section 6.5 for definitions). |
| **Access Site for Cannulation** | A vascular site of entry to reach the blood for HD. Also referred to as the cannulation area or cannulation zone. |
| **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. These may include procedures to facilitate maturation and / or cannulation of the AVF, procedures to maintain use of the AVF, procedures to ensure HD continuity, as well as procedures to address AEs. |

| Term | Definition |
|---|---|
| **Adverse Device Effect (ADE)** | An ADE is an AE that is considered to be related to the use of the WavelinQ™ EndoAVF System. This includes AEs resulting from insufficient or inadequate IFU, operation, or any malfunction of the WavelinQ™ EndoAVF System. Additionally, this definition includes any event resulting from use error or from intentional misuse of the WavelinQ™ EndoAVF System. |
| **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 WavelinQ™ EndoAVF System and whether anticipated or unanticipated. For users or other persons, this definition is restricted to events related to the use of the WavelinQ™ EndoAVF System.<br><br>**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) in Table 1 of Section 4.4 but exclusive of adjunctive and second stage procedures. |
| **Anastomosis**[8] | A communication between an artery and a vein by surgical or endovascular techniques. |
| **Aneurysm**[8] | An abnormal dilation of the blood vessel or part of the vessel wall; in the case of vascular access, it may result from disease or trauma of the vessel wall. |
| **Angiography** | An X-ray procedure that uses contrast agent and a camera (fluoroscopy) to assess and capture flows or blockages in arteries and veins. May also be referred to as angiogram, fistulogram, venogram or arteriogram. |
| **As Treated (AT) Population** | This population will include all treated participants, which includes all ITT participants but excludes those into whom the WavelinQ™ Endovascular System was introduced but procedure success was not achieved.<br><br>The AT population is composed of two subpopulations: The incident population and the prevalent population as defined in Section 4.5.2. |
| **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. |

| Term | Definition |
|---|---|
| **Audit trail** | Documentation that allows reconstruction of the course of events. |
| **AV Access Circuit[8]** | Defined as the continuum from the heart and the arterial inflow through the AV access to the venous outflow back to the heart. |
| **AV Access Circuit Related AE** | AEs directly associated with the index AV access circuit. |
| **Bleeding Diathesis** | A disorder that involves the tendency to hemorrhage, or bleed. Hypercoagulability causes this condition. This condition is also known as bleeding tendency or predisposition. |
| **Cannulation Success** | The interval of time between HD AV access creation to first successful use for HD using 2-needle cannulation and proportion of participants with successful first use for HD using 2-needle cannulation. |
| **(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). |
| **Clinically significant lesion (stenosis)[8]** | Defined as one that contributes to clinical signs and symptoms without other cause, with or without a sustained change in surveillance measurements (e.g., change in blood flow [Qa] or venous pressures) in the dialysis access circuit. Such a lesion is found during monitoring of vascular access and shows >50% narrowing relative to adjacent normal vein diameter by angiography or ultrasound. |
| **Complications[8]** | • *Thrombotic flow–related complications or dysfunction:* Complications specifically related to the risk of or occurrence of thrombosis that leads to a clinically important reduction in intra-access flow that threatens the required access patency to achieve prescribed dialysis and/or results in clinical signs and symptoms (e.g., stenosis or thrombosis).<br>• *Non–thrombotic flow–related complications or dysfunction:* Such complications may or may not threaten flow or patency but are associated with clinical signs and symptoms (e.g., AV access aneurysms, steal syndrome).<br>• *Infectious complications or dysfunction:* Any infection involving the vascular access (intraluminal/access, extraluminal/access, peri-access, i.e., cannulation or entry site) that results in clinically important infectious signs and symptoms. |
| **Cumulative Functional Patency** | The time from first successful HD AV access use for HD using 2-needle cannulation to access abandonment, when the access reaches an access censoring event as specified a priori in this CIP, or analysis timepoint / clinical investigation end. |

| Term | Definition |
|---|---|
| **Cumulative Patency** | The time from HD AV access creation to access abandonment, when the access reaches a censoring event as specified a priori in this CIP, or analysis timepoint / clinical investigation end. This includes intervening manipulations (surgical or endovascular interventions) intended to support maturation or cannulation, as well as those to maintain or re-establish functionality of the access.[18] |
| **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 WavelinQ™ EndoAVF System. |
| **Device Related AE** | AEs directly attributable to the WavelinQ™ EndoAVF System used as part of the index procedure. |
| **End Stage Kidney Disease (ESKD)** | 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. |
| **Facilitation Interventions** | Defined as those procedures that are intended to facilitate functionality of the index AVF (i.e. those intended to support the maturation or cannulation of arterialized vein segments) and / or a procedure to address an AE related to the facilitation of index AVF functionality (Refer to Table 1). |
| **Functional Maturation** | The proportion of participants with successful prescribed HD with 2-needle cannulation of the AVF for three (3) continuous weeks. Additionally, the time from HD AV access creation to the first day of the 3-week period |
| **Functional HD Usability** | The proportion of participants dialyzed using successful 2-needle access of the AVF created as part of this clinical investigation for ≥ 75% of HD sessions over a continuous 28-day period. Additionally, the time from HD AV access creation to the first day of the 28-day period. |

| Term | Definition |
|---|---|
| **HD Continuity Interventions** | Defined as those procedures that are intended to ensure the continuity of HD (not including diagnostic studies) other than those related to the facilitation or maintenance of index AVF functionality and / or a procedure to address an access related AE other than those related to the facilitation or maintenance of index AVF functionality. HD continuity interventions include all CVC related interventions up until the placement of a subsequent AV access following abandonment of the index AVF. HD continuity interventions exclude any intervention performed on a non-index AV access other than the placement of the non-index AV access itself. |
| **HD AV Access Continuity** | The ability for a participant to receive an alternate HD AV access in the same arm as the index AVF. This endpoint applies to participants for whom their index AVF is abandoned. |
| **Hypercoagulable State** | Blood clotting disorder. |
| **Incident Participant** | Participants who have not previously and who were not actively receiving HD prior to or at the time of the index procedure but are in need of a vascular access as determined by the referring clinician. This category is further sub-divided into pre-KRT participants, those that have never had any form of KRT and pre-HD, those that have never had HD as KRT. |
| **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 AVF / AV Access Circuit** | The index AVF / AV access circuit refers to the AVF / AV access circuit originally created as part of this clinical investigation at the time of the index procedure. |
| **Index Procedure** | The procedure intended to create the investigation AVF (index AVF) using the WavelinQ™ EndoAVF System defined to begin at the time of the initial skin puncture to gain vessel access and end at the time of last sheath removal (start of access site closure). |

| Term | Definition |
|---|---|
| **Infiltration Injury[8]** | A vessel injury related to cannulation or the dialysis procedure and can be categorized as below:<br>- Minor cannulation injury – an injury that may result in bleeding infiltration and swelling that may be treated with conservative measures such as ice and rest for 1-2 days but cannulation can be re-attempted for the next dialysis session. The access should be successfully re-cannulated with 2 needles in < 7 days. Note that even a minor cannulation injury may require the use of a temporary catheter.<br>- Major cannulation injury – an injury that results in significant bleeding infiltration and swelling that requires recovery for >7 days.<br>- Severe cannulation injury – an injury that results in significant bleeding complications that requires one of: blood transfusion, emergency room visit, hospitalization, radiological or surgical intervention. |
| **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. |
| **Intent to Treat (ITT) Population** | All treated participants including those for whom RF energy was not administered but the WavelinQ™ Endovascular System was introduced. |
| **Intervention(s)** | Procedures that are not pre-determined or planned that are performed *after* the index procedure (adjunctive procedures are those performed *during* the index procedure and second stage procedures are expected procedures that are determined a priori or at the time of the index procedure). Interventions require the completion of the Intervention eCRF. For this clinical investigation, interventions are further classified as facilitation, maintenance, and HD continuity interventions (Refer to Table 1). |
| **Investigational Site** | Institution or site where the clinical investigation is carried out. |
| **Juxta-Anastomotic Area** | Defined as the arterial area extending 5cm before and the venous area extending 5cm after the anastomosis. |
| **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". |

| Term | Definition |
|---|---|
| **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. |
| **Maintenance Interventions** | Defined as those procedures that are intended to maintain / re-establish functionality of the index AVF and / or a procedure to address an AE related to the maintenance of index AVF functionality. |
| **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 with this CIP, written procedures, applicable standards, and the applicable regulatory requirements. |
| **Neointimal hyperplasia**[8] | The myoendothelial proliferation of cells and matrix that produces stenosis in AV accesses. |
| **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. |
| **Peri-Anastomotic Area** | Defined as the venous area extending from the juxta-anastomosis area to the start of the perforating vein. |
| **Per-Protocol (PP) Population** | 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 AT 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. |
| **Physiological Maturation** | An AVF having at least 500 mL / min of flow in the brachial artery and an outflow vein diameter of ≥ 4 mm as measured by DUS.[16,17] AVFs that meet the definition of functional maturation will automatically meet physiological maturation. |

| Term | Definition |
|---|---|
| **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. |
| **Pre-HD Participant** | Participants who have not previously and who were not actively receiving HD prior to the index procedure but are in need of a vascular access as determined by the referring clinician. |
| **Pre-KRT Participant** | Incident participants who have not previously and who were not actively receiving any form of KRT prior to the index procedure but are in need of a vascular access as determined by the referring clinician. |
| **Prevalent Participant** | Participants who have previously and / or who were actively receiving HD prior to 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. |
| **Primary Functional Patency** | The time from first successful HD AV access use for HD using 2-needle cannulation to the first one of the following events: access thrombosis; any facilitation or maintenance intervention intended to support maturation or cannulation as well as those to maintain or re-establish functionality*; access abandonment (as defined in Section 4.4); the access reaches an access censoring event as specified a priori in this CIP; or analysis timepoint / clinical investigation end. *Excludes second stage procedures. |
| **Primary Patency** | The time from HD AV access creation to the first one of the following events: access thrombosis; any facilitation or maintenance intervention intended to support maturation or cannulation, as well as those to maintain, or re-establish functionality*; access abandonment (as defined in Section 4.4); the access reaches an access censoring event as specified a priori in this CIP; or analysis timepoint / clinical investigation end.[18] *Excludes adjunctive and second stage procedures. |
| **Procedure access Site** | A site of vessel 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 endoAVF creation using the WavelinQ™ EndoAVF System after procedural vessel access has been obtained as confirmed via intraprocedural angiography and / or verified via DUS. |

| Term | Definition |
|---|---|
| **Pseudoaneurysm[8]** | A collection of blood outside the vessel (walled off by surrounding tissue), communicating with the fistula or prosthetic graft through a defect (e.g., needle hole) in the wall. |
| **Recirculation[8]** | The return of dialyzed blood to the systemic circulation without full equilibration.<br>- *Cardiopulmonary recirculation:* Resulting from the return of dialyzed blood without full equilibration with all systemic venous return.<br>- *Access recirculation:* Resulting from the admixture of dialyzed blood with arterial access blood without equilibration with the systemic arterial circulation. Occurs under conditions in which blood pump flow is greater than intra-access flow. |
| **Recruitment** | Active efforts to identify participants who can be suitable for enrolment into the clinical investigation. |
| **Screen Failure** | A participant who is excluded from this clinical investigation as based on the eligibility criteria. |
| **Second Stage Procedures** | Facilitation Interventions (as defined subsequently) intended to support the cannulation of arterialized vein segments that are determined to be needed a priori to or at the time of the index procedure (i.e. pre-planned facilitation interventions intended to support cannulation). Second stage procedures will not count against the intervention or patency endpoints and will require completion of the Second Stage Procedures eCRF. |
| **Serious Adverse Device Effect (SADE)** | ADE that has resulted in any of the consequences characteristic of a SAE. |
| **Serious Adverse Event** | An AE that led to any of the following:<br>• Death; or<br>• Serious deterioration in the health of the participant, users or other persons as defined by one or more of the following:<br>- A life-threatening illness or injury; or<br>- A permanent impairment of a body structure or a body function including chronic diseases; or<br>- In-patient or prolonged existing hospitalization; or<br>- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; or<br>• Fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment.<br><br>**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. |

| Term | Definition |
|---|---|
| **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 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. |
| **Steal Syndrome**[8] | Compromised perfusion and ischemia of tissue after construction of an AV access due to diversion of arterial blood flow into the AV access away from the peripheral system, leading to a range of signs and symptoms, such as mild numbness to severe motor impairment or skin ulceration to gangrene necessitating major amputation. |
| **Stenosis**[8] | The constriction or narrowing of the blood vessel; a stricture. |
| **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. |
| **Temporary Interruption** | A discontinuation of use of the clinical investigation AVF for any reason that does not meet the definition of access abandonment. |
| **Thrombosis** | The formation or presence of a blood clot resulting in vessel occlusion. |
| **Treated Participant** | Defined as a participant that has met all eligibility criteria, into whom the WavelinQ™ EndoAVF System was introduced and in whom procedure success was achieved. |
| **Transposition**[8] | The movement of a vein from its normal position by elevation and / or by lateral movement to bring the vein closer to the skin to permit improved maturation and / or easier cannulation or use for HD. |

| Term | Definition |
|---|---|
| **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 WavelinQ™ 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. |
| **Vascular Access at HD Initiation** | The vascular access HD modality used at the initiation of HD following the index procedure (CVC, AVG, clinical investigation AVF, or alternate AVF). Use of the clinical investigation AVF at initiation includes both one- and two-needle cannulation and may be presented as a combined total as well as by type of needle access. |
| **Wrist Arterial Procedure Access Related AE** | Procedure related AEs directly attributable to wrist arterial access if used during the index procedure. |