Statistical Analysis Plan

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Approval

Individual or Function	Name	Signature/Date
Statistician (Author)	Shu Zhang	This document is signed electronically in the eTMF system
Project Manager	Simon Lubek	This document is signed electronically in the eTMF system
Statistics Functional Manager	Ying Wan	This document is signed electronically in the eTMF system
Business Representative	Anna Lovas	This document is signed electronically in the eTMF system

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1 Introduction

This document provides details of the statistical analysis plan (SAP) for the Bard Peripheral Vascular, Inc. WAVE Global Clinical Investigation (CIP Number BDPI-19-005). The primary reporting will occur when the last active 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.

1.1 Background and Rationale

End Stage Kidney Disease (ESKD) currently affects over 3.5 million people worldwide. 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. 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. 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.

1.2 Objectives

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 of the CIP for specific objectives and Section 4.5 of the CIP for endpoint rationales.

2 Investigation Description

2.1 Investigation Design

This is a global, multi-center, prospective, post-market, confirmatory, interventional, non-randomized, single-arm clinical investigation evaluating arteriovenous fistula (AVF) creation by means of the WavelinQ™ EndoAVF System in patients who require a vascular access for hemodialysis (HD).

2.2 Investigation Population

This investigation will enroll participants who are either already receiving HD at the time of screening, regardless of access type (central venous catheter (CVC), AVF, arteriovenous graft (AVG)) (prevalent participants), or who are anticipated to require HD within 6 months post HD arteriovenous (AV) access creation (incident participants).

As a post market investigation, the eligibility criteria will be in line with the device Instructions for Use (IFU) and with prior / concurrent clinical investigations of the WavelinQ™ EndoAVF System. There will be no formal limitations on the patient populations enrolled with regards to incident or prevalent patients.

2.3 Randomization and Blinding

This is a single-arm investigation, no randomization and blinding are involved.

2.4 Sample Size

The sample size for the investigation 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.

2.5 Interim Analyses

No interim analysis is planned.

The primary reporting will occur when the last active treated participant has completed the 6-month follow-up (referred as 6-month reporting). A final analysis will be completed when all participants have completed, or prematurely discontinued before, their 24-month follow-up (referred as final reporting). 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.

2.6 Investigation Procedure

The point at which the informed consent form (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. Enrolled participants who are excluded from this clinical investigation, based on eligibility criteria listed in the CIP Section 5.1, are considered ***screen failures***.

A ***treated participant*** in this clinical investigation 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. 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 electronic Case Report Form (eCRF). Participation for these participants will end at time of the index procedure.

The schedule of activities is shown as below:

	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.

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.

2.7 Endpoints

Note: The term access abandonment is synonymous with permanent abandonment for the purposes of these investigation documents. Access abandonment (permanent abandonment) is an abandonment that meets the definition in Section 4.4 of the CIP. The term access discontinuation is used to refer to any discontinuation of use of the access that does not meet these criteria of the definition and may also be referred to as a "temporary interruption" as per the CIP.

2.7.1 Primary Endpoints

There are two co-primary endpoints for this clinical investigation: an endpoint to evaluate safety and another to evaluate effectiveness.

2.7.1.1 Primary Safety 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.

2.7.1.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the number of interventions post creation to facilitate and / or maintain AVF use through the timepoint of the 6-month follow-up of the last active treated participant.

2.7.2 Secondary Endpoints

2.7.2.1 Safety

The secondary safety endpoint is the proportion of participants with freedom from CEC adjudicated device-related or procedure-related SAEs. This endpoint will be assessed through 6 and 24 months.

2.7.2.2 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. This endpoint will be assessed through 6 weeks post creation.

2.7.2.3 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.

2.7.2.4 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. Note: access abandonment refers to permanent abandonment.

2.7.3 Exploratory Endpoints

2.7.3.1 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.

2.7.3.2 Adjunctive Procedure

The number of adjunctive procedures performed. Adjunctive procedure refers to procedure(s) completed after the creation of the clinical investigation AVF and 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, as well as procedures to address AEs.

2.7.3.3 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.

2.7.3.4 Physiological Maturation

As defined for the secondary endpoint in Section 2.7.2.2, this endpoint will be evaluated through additional time points.

2.7.3.5 Cannulation Success

As defined for the secondary endpoint in Section 2.7.2.3, this endpoint will be evaluated through additional time points.

2.7.3.6 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.

2.7.3.7 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 tome from HD AV access creation to the first day of the 28-day period.

2.7.3.8 Interventions

Intervention related endpoints are categorized as follows:

- Interventions Post Creation to Facilitate AVF Use (Facilitation Interventions): as defined for the primary effectiveness endpoint in Section 2.7.1.2 and evaluated separately.
- Interventions Post Creation to Maintain AVF Use (Maintenance Interventions): as defined for the primary effectiveness endpoint in Section 2.7.1.2 and 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), 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.

2.7.3.9 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; the access reaches an access censoring event as specified a priori in this CIP; or analysis timepoint / clinical investigation end. *Excludes adjunctive and second stage procedures. Note: access abandonment refers to permanent abandonment.

2.7.3.10 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. Note: access abandonment refers to permanent abandonment.

2.7.3.11 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; the access reaches an access censoring event as specified a priori in this CIP; or analysis timepoint / clinical investigation end. *Excludes second stage procedures. Note: access abandonment refers to permanent abandonment.

2.7.3.12 Cumulative Functional Patency

As defined for the secondary endpoint in Section 2.7.2.4, this endpoint will be evaluated through additional time intervals. Note: access abandonment refers to permanent abandonment.

2.7.3.13 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.

2.7.3.14 DUS Perforator Vein and Juxta-anastomotic 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.

2.7.3.15 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.

2.7.3.16 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 Screening, 6-week, 6-month, 12-month, and 24-month.

2.7.3.17 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.

2.8 Acceptance Criteria

The primary safety endpoint will be evaluated against a PG of 82.6% with the two-sided type I error level at 0.05.

The primary effectiveness endpoint will be evaluated against a PG of $\leq$ 5 interventions with the two-sided type I error level at 0.05.

3 Intended Statistical Software and Data Information

3.1 Intended Statistical Software

All data processing, summarization, and analyses will be performed using Statistical Analysis System (SAS), Version 9.4 software package.

3.2 Data Information

Derived data specification can be found in Appendix 2.

4 Analysis Population Set(s)

4.1 Population Definitions

The analysis populations will be defined as follows:

- The Intent-to-Treat (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:
    - Incident population: 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 subgroup population will be identified if the question of "Has the Subject had any Kidney Replacement Therapy (KRT) up until time of Index Procedure (Kidney Transplant, Peritoneal Dialysis and/or Hemodialysis)?" on the Dialysis History/Onset page is answered as No, or if the question is answered as Yes but "Hemodialysis" is not selected.
    - Prevalent population: Participants who have previously and/or who were actively receiving HD prior to the index procedure. This subgroup population will be identified if the question of "Has the Subject had any Kidney Replacement Therapy (KRT) up until time of Index Procedure (Kidney Transplant, Peritoneal Dialysis and/or Hemodialysis)?" on the Dialysis History/Onset page is answered as Yes and "Hemodialysis" is selected.
- 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.

5 Statistical Analysis/Calculations

5.1 Primary Endpoints

5.1.1 Primary Safety Endpoint

The primary safety endpoint is the proportion of participants with freedom from CEC adjudicated device- or procedure-related 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.

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 device- or procedure-related SAE will be identified if:

On the Adverse Event Adjudication page, Serious (SAE) is checked as Yes, and Relationship to Study Device is or Relationship to Procedure is Possibly Related or Definitely Related.

The binary definition is shown as below:

- If the device or procedure-related SAE start date occurs before or on Day 30, the participant is considered as having an event.
- If the participant discontinued before the beginning of 30-day follow-up visit window (30-5 = Day 25) without having the device- or procedure-related SAE, the participant is considered not evaluable and will not be included in the analysis.
- Otherwise, if the participant is in the investigation without having the device-related SAE and has passed the 30-day follow-up visit by the cutoff date of database lock, the participant is considered as not having an event.

The primary safety analysis will be conducted based on evaluable participants only in 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% two-sided confidence interval (CI) will be provided using the Clopper-Pearson method. 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%. The primary safety analysis will be repeated on the PP population.

Additionally, as a supportive analysis, Kaplan-Meier (KM) analysis will be used to analyze the primary safety endpoint.

- If the device or procedure-related SAE occurs before or on Day 30, the participant is considered as having the event at the corresponding start date.
- If the participant was transferred to PD, or had a kidney transplant, or had permanent abandonment, or had access discontinuation, or discontinued before Day 30 without having device or procedure-related SAE, the participant is considered as censored at the earliest date among these events (i.e., PD start date, kidney

transplant date, date of permanent abandonment, date of access discontinuation, last date of available study data including the unscheduled visit date).

- Otherwise, if the participant did not have a device or procedure-related SAE and has passed Day 30 by the cutoff date of database lock, the participant will be censored at Day 30 for this analysis.

The analysis will be evaluated on the ITT population. The number of participants with events, number of participants censored, time to event (days), and proportion of participants with events along with the 95% CI will be presented.

5.1.2 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.

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 patient year (PY) of participants treated with the WavelinQTM EndoAVF System (RWE) 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 WavelinQTM EndoAVF System (RWE) is less than that of the PG of 5 post creation facilitation and maintenance interventions / PY.

That is:

H_0: RWE $\geq$ 5 post creation facilitation and maintenance interventions / PY

H_1: RWE $<$ 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.

Facilitation and/ or maintenance intervention will be identified if:

On the Post-Procedure Intervention page, Date of Post Procedure Intervention is not NULL and before or on the cutoff date of the database lock, and Type of Intervention is checked as Facilitation and/ or Maintenance. Note in the event that there are multiple treatments performed during the same procedure driven by multiple reasons, each reason driving the intervention will be counted as a separate intervention.

For each participant, 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 is expressed as:

(Number of observed facilitation and/or maintenance interventions * 365) / Length of investigation duration (Days)

Length of investigation duration (Days) is from the date of index procedure to the cutoff date of database lock (cutoff date – date of index procedure +1). If a participant discontinued early, then the last date of available study data (including the unscheduled visit date) will be used to calculate the length of investigation duration (last date of

available study data – date of index procedure +1). If a participant's endoAVF has permanent abandonment the date of permanent abandonment will be used to calculate the length of investigation duration (permanent abandonment date – date of index procedure +1).

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 using the Wald method, and the p-value comparing to the PG will be calculated by a Chi-square test. The analysis will be repeated on the PP population.

5.1.3 Poolability of Investigational Sites

The primary endpoints will be summarized by. Sites with fewer than 10 treated participants will be pooled by site number to form combined sites with at least 10 participants. For the primary safety endpoint, logistic regression will be used to estimate; for the primary effective endpoint, Poisson regression will be used.

5.1.4 Subgroup Analysis

The following subgroup variables are included in the subgroup analysis:

- Sex
- Age
    - ≤50 vs. >50 Years
    - ≤75 vs. >75 Years
- Site of anastomosis (Recorded on the Procedure Overview eCRF page: "Which Artery/Vein was Used to Create the endoAVF"):
    - Ulnar / Radial / Other
- Location of arterial procedure access (Recorded on the Procedure Overview eCRF page: "Which Artery was Used to Gain Access"):
    - Brachial / Ulnar / Radial / Other
    - Wrist Artery Access (Ulnar & Radial) / Non-Wrist Artery Access (Brachial)
- Second Stage Procedures identified at Index Procedure (Recorded on the Procedure Overview eCRF page: "Is a Second Stage Procedure Planned?")

5.2 Secondary Endpoints

5.2.1 Safety

The proportion of participants with freedom from CEC adjudicated device-related or procedure-related SAEs will also be assessed through 6-months (Day 180) and 24-months (Day 730) post creation, using the same definition as the primary safety endpoint. The proportion and the 95% CI will be provided using the Clopper-Pearson method. Additionally, for exploratory purposes, the endpoint will be assessed through 6-weeks, 3-months, 12 months, and 18 months post creation.

5.2.2 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. Participants with AVFs that meet the definition of functional maturation (defined as successful prescribed HD with 2-needle cannulation of the AVF for three (3) continuous weeks) will automatically meet physiological maturation. This endpoint will be assessed through 6 weeks post creation. Additionally, for exploratory purposes, the endpoint will be assessed through 30 days, 3 months, 6 months, 12 months, 18 months, and 24 months post creation.

The event of physiological maturation will be identified if:

> On the EndoAVF Dialysis page, Date of First 2-Needle Cannulation of 3 Week Continuous Dialysis is not NULL and within a specific visit (e.g., within 49 days for 6 weeks post creation). This meets the functional maturation.
>
> *or*
>
> On the Core Lab Analysis - Duplex Ultrasound: EndoAVF Arm page, Average Brachial Artery Volume Flow under the Brachial Artery/Vein Assessments section is >= 500 mL / min and any outflow vein diameter (including Distal Upper Arm Cephalic Vein Diameter, Mid Upper Arm Cephalic Vein Diameter, Proximal Upper Arm Cephalic Vein Diameter, Distal Upper Arm Basilic Vein Diameter, Mid Upper Arm Basilic Vein Diameter, Proximal Upper Arm Basilic Vein Diameter, Median Cubital Vein Diameter) under the Outflow Veins Section is >= 4 mm. In case the core lab DUS is not available, the corresponding information from the Duplex Ultrasound: EndoAVF Arm page will be used to determine the physiological maturation. Additionally, as a supportive analysis, only the core lab DUS data will be used to determine the physiological maturation. Data is considered not evaluable if the core lab DUS is not available.

The binary definition for physiological maturation is shown as below:

- If physiological maturation occurs on or before the end of a specific visit window (e.g., 42+7 = Day 49 for the 6-week visit), the participant is considered as having an event.
- If the participant was transferred to PD, or had a kidney transplant, or had access discontinuation, or discontinued before the beginning of a specific visit window (e.g., 42-7 = Day 35 for 6-week visit) without physiological maturation, the participant is considered not evaluable and will not be included in the analysis.
- Otherwise, if the participant did not achieve physiological maturation and has passed the specific visit window by the cutoff date of database lock, the participant is considered as not having an event. If the participant had access permanent abandonment prior to achieving physiological maturation and has passed the specific visit window by the cutoff date of database lock, the participant is considered as not having an event.

This endpoint will be evaluated on the AT population. The proportion of physiological maturation and the 95% two-sided CI will be provided using the Clopper-Pearson method. For the 6-month reporting, the physiological maturation rate up to 6-months (up to Day 210) will be presented. For the final reporting, the physiological maturation rate up to 24-months (up to Day 760) will be presented.

Similar analysis will be done for exploratory purposes, for physiological maturation defined as an AVF having at least 500 mL / min of flow in the brachial artery and an outflow vein diameter of ≥ 5 mm as measured by DUS.

5.2.3 Cannulation Success

Cannulation success is defined as with successful first use for HD using 2-needle cannulation. This endpoint will be evaluated through 6 months. Additionally, for exploratory purposes, the endpoint will be evaluated through 30 days, 6 weeks, 3 months, 12 months, 18 months, and 24 months.

The event of cannulation success will be identified if:

On the EndoAVF Dialysis page, "Date endoAVF First Used with 2 Needles for Hemodialysis" is not NULL and within a specific visit (e.g., within 210 days for 6 months post creation).

Kaplan-Meier (KM) analysis will be used to estimate the time from HD AV access creation (the date of index procedure) to first successful use for HD using 2-needle cannulation through certain post creation visit.

- If cannulation success occurs, the participant is considered as having the event at the corresponding date.
- If the participant was transferred to PDs, or had a kidney transplant, or had access discontinuation, or discontinued before the end of a specific visit window (e.g.180+30 = Day 210 for 6-month visit) without cannulation success, the participant is considered as censored at the earliest date among these events (i.e. PD start date, kidney transplant date, date of access discontinuation, or last date of available study data including the unscheduled visit date).
- Otherwise, if the participant did not achieve cannulation success and has passed the specific visit window by the cutoff date of database lock, the participant will be censored at the end of the reporting time window (e.g., 180+30 = Day 210 for the 6-month reporting, 730+30 = 760 for the 24-month reporting) for this analysis. If the participant had access permanent abandonment prior to achieving cannulation success and has passed the specific visit window by the cutoff date of database lock, the participant will be censored at the date of permanent abandonment.

This endpoint will be evaluated on the AT population. The number of participants with events, number of participants censored, time to event (days), and proportion of participants with events along with the 95% CI will be presented at 6-months post creation using the KM method. For the 6-month reporting, the cannulation success rate up to 6-months (up to Day 210) will be presented. For the final reporting, the cannulation success rate up to 24-months (up to Day 760) will be presented.

5.2.4 Cumulative Functional Patency

The time interval of cumulative functional patency is defined as the time from first successful HD AV access use for HD using 2-needle cannulation to access abandonment. This endpoint will be evaluated through 12-months. Additionally, for exploratory purposes, the endpoint will be evaluated through 6 months, 18 months, and 24 months.

Only the participants who have started 2-needle HD using the endoAVF will be considered as evaluable for this endpoint.

Access Abandonment (Permanent Abandonment) will be identified if:

On the EndoAVF Dialysis page, Date endoAVF Successfully Used with 2 Needles for Hemodialysis is not NULL and within a specific visit (e.g., within 395 days for 12 months).

and

On the EndoAVF Abandonment page, Date of Abandonment is not NULL and within a specific visit (e.g. within 395 days for 12 months), the question of "All Possible Attempts Have Been Made to Improve the Condition of the Access" is checked as Yes, and the question of "Could Further Endovascular Interventions

Salvage the Access" is checked as No, and the question of "Could Further Surgical Revisions Salvage the Access?" is checked as No, and Reason for Abandonment is selected as "The Access is No Longer Viable" or "The Access is Viable but there are Complications that Require the Abandonment of the Access".

The binary definition for cumulative functional patency is shown as below:

- If permanent abandonment, as detailed above, occurs on, or before, a specific visit (e.g., 365+30 = Day 395 for 12 months post creation), the participant is considered as having an event (loss of cumulative functional patency).
- If the participant was transferred to PD, or had a kidney transplant, or had access discontinuation, or discontinued before the beginning of a specific visit (e.g., 365-30 = Day 335 for 12 months post creation) without permanent abandonment, the participant is considered not evaluable and will not be included in the analysis.
- Otherwise, if the participant did not have permanent abandonment and has passed the specific visit window by the cutoff date of database lock, the participant is considered as not having an event.

This endpoint will be evaluated on the AT population and on the AT population with attainment of first successful HD AV access use for HD using 2-needle cannulation (on the EndoAVF Dialysis page, Date endoAVF Successfully Used with 2 Needles for Hemodialysis is not NULL). The proportion of cumulative functional patency (100% - event rate) and the 95% two-sided CI will be provided using the Clopper-Pearson method. For the 6-month reporting, the cumulative functional patency rate will be presented for 6-months (up to Day 210). For the final reporting, the physiological maturation rate up to 24-month (up to Day 760) will be presented.

5.3 Exploratory Endpoints

5.3.1 Procedure Success

Procedure success is defined as successful endoAVF creation. The event of procedure success will be identified if:

On the Procedure Overview page, the question of "Was WavelinQ endoAVF Successfully Created?" is checked as Yes, and the question of "Was Final Result Confirmed via Angiography or Duplex Ultrasound?" is also checked as Yes.

This endpoint will be evaluated on the ITT population. The proportion of participants with procedure success will be reported with the 95% two-sided CI using the Clopper-Pearson method.

5.3.2 Adjunctive Procedure

A participant is considered of having adjunctive procedure if:

On the Adjunctive Procedures page, Treatment is not null.

This endpoint will be evaluated on the AT population. The number and proportion of participants with adjunctive procedures, total number of procedural adjunctive procedures, and the number and proportion of each treatment type of adjunctive procedure will be reported.

5.3.3 Vascular Access at HD Initiation

The vascular access HD modality used at the initiation of HD following the index procedure is captured on the Dialysis History/Onset page. To get the data needed for this calculation, the question of "If the subject is not currently on Hemodialysis, did the subject start hemodialysis during the study?" is YES and Start Date of Dialysis is not NULL, and Vascular Access Used for First Dialysis Session is not NULL. When endoAVF is selected for

Vascular Access Used for First Dialysis Session, the 1- or 2-needle cannulation information will be obtained from the EndoAVF Dialysis page. When the question of "Was endoAVF First Used with 1-Needle for Hemodialysis" is checked as Yes and the corresponding date is not NULL, it is considered as 1-Needle cannulation. When the question is checked as No and Date endoAVF Successfully Used with 2 Needles for Hemodialysis is not NULL, it is considered as 2-Needle cannulation.

This endpoint will be evaluated on the AT Incident population. The total number of all types of vascular accesses and proportion of each type will be reported. For Study endoAVF, the proportions of 1-Needle and 2-Needle cannulation will also be provided.

5.3.4 Functional Maturation

Functional maturation is defined as successful prescribed HD with 2-needle cannulation of the AVF for three (3) continuous weeks.

Functional maturation will be identified if:

On the EndoAVF Dialysis page,

- Date of First 2-needle Cannulation of 3 Week Continuous Dialysis is not NULL *and*
- Date is before or on the cutoff date of the database lock.

Kaplan-Meier (KM) analysis will be used to estimate the time from HD AV access creation (the date of index procedure) to functional maturation. The following definition will be applied:

- If functional maturation occurs, the participant is considered as having the event, and date of first 2-needle cannulation of 3-week continuous dialysis will be used in the analysis.
- If the participant was transferred to PD, or had a kidney transplant, or had access discontinuation, or discontinued before a specific visit without attaining functional maturation, the participant is considered as censored the participant at the earliest date among these events (i.e. PD start date, kidney transplant date, date of access discontinuation, or last date of available study data including the unscheduled visit date).
- Otherwise, if the participant did not achieve functional maturation and has passed the specific visit window by the cutoff date of database lock, the participant will be censored at the end of the reporting time window (e.g., 180+30 = Day 210 for the 6-month reporting, 730+30 = 760 for the 24-month reporting) for this analysis. If the participant had access permanent abandonment prior to achieving functional maturation and has passed the specific visit window by the cutoff date of database lock, the participant will be censored at the date of permanent abandonment.

This endpoint will be evaluated on the AT population and on the AT population with endo AVF successfully used with 2 needles for hemodialysis (on the EndoAVF Dialysis page, Date endoAVF Successfully Used with 2 Needles for Hemodialysis is not NULL). The number of participants with events, number of participants censored, time to event (days), and proportion of participants with events along with the 95% CI will be presented at 6-weeks, 3-, 6-, 12-, 18-, and 24-months post creation using the KM method. For the 6-month reporting, the functional maturation rate up to 6-months (up to Day 210) will be presented. For the final reporting, the functional maturation rate up to 24-months (up to Day 760) will be presented.

Similar analysis will be done for successful prescribed HD with 2-needle cannulation of the AVF for two (2) continuous weeks.

5.3.5 Functional HD Usability

Functional HD usability is defined as 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.

Functional HD usability will be identified if:

On the EndoAVF Dialysis page,

- Percent of Sessions Using 2-Needle is ≥75 *and*
- Date of First 2-Needle Cannulation in 28 Day Period is not null and before the cutoff date of database lock.

Kaplan-Meier (KM) analysis will be used to estimate the time from HD AV access creation (the date of index procedure) to the first day of the 28-day period. The following definition will be applied:

- If functional HD usability occurs, the participant is considered as having the event, and date of first 2-needle cannulation in 28-day period will be used for the analysis.
- If the participant was transferred to PD, or had a kidney transplant, or had access discontinuation, or discontinued before the end of a specific visit window (e.g. Day 210 for 6 months post creation) without attaining functional HD usability, the participant is considered as censored at the earliest date among these events (i.e. PD start date, kidney transplant date, date of access discontinuation, last date of available study data including the unscheduled visit date).
- Otherwise, if the participant is still in the investigation without functional HD usability and have passed the specific visit window by the cutoff date of database lock, the participant will be censored at the end of the reporting time window (e.g., 180+30 = Day 210 for the 6-month reporting, 730+30 = 760 for the 24-month reporting) for this analysis. If the participant had access permanent abandonment prior to achieving functional HD usability and has passed the specific visit window by the cutoff date of database lock, the participant will be censored at the date of permanent abandonment.

This endpoint will be evaluated on the AT population and on the AT population with endo AVF successfully used with 2 needles for hemodialysis (on the EndoAVF Dialysis page, Date endoAVF Successfully Used with 2 Needles for Hemodialysis is not NULL). The number of participants with events, number of participants censored, time to event (days), and proportion of participants with events along with the 95% CI will be presented at 6-weeks, 3-, 6-, 12-, 18-, and 24-months post creation using the KM method. For the 6-month reporting, the functional HD usability rate up to 6-months (up to Day 210) will be presented. For the final reporting, the functional HD usability rate up to 24-months (up to Day 760) will be presented.

5.3.6 Interventions

The following endpoints 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.

1) Intervention Post Creation to Facilitate AVF Use

Using the same definition as specified in Section 5.1.2, the number of Facilitation Interventions (On the Post-Procedure Intervention page, Date of Post Procedure Intervention is not NULL and before or on the cutoff date of the database lock, and Type of Intervention is checked as Facilitation) per PY will be estimated by Poisson regression model with only the intercept term, and the estimate and 95% CI will be provided using the Wald method. Additionally, a sensitivity analysis will be completed where the definition of facilitation interventions

is driven by the date of first successful 2-needle cannulation (Date endoAVF Successfully Used with 2 Needles for Hemodialysis on the EndoAVF Dialysis eCRF) where any intervention occurring prior to this date is counted as a facilitation intervention. Note in the event that there are multiple treatments performed during the same procedure driven by multiple reasons, each reason driving the intervention will be counted as a separate intervention.

2) Intervention Post Creation to Maintain AVF Use

Using the same definition as specified in Section 5.1.2, the number of Maintenance Interventions (On the Post-Procedure Intervention page, Date of Post Procedure Intervention is not NULL and before or on the cutoff date of the database lock, and Type of Intervention is checked as Maintenance) per PY will be estimated by Poisson regression model with only the intercept term, and the estimate and 95% CI will be provided using the Wald method. Additionally, a sensitivity analysis will be completed where the definition of maintenance interventions is driven by the date of first successful 2-needle cannulation (Date endoAVF Successfully Used with 2 Needles for Hemodialysis on the EndoAVF Dialysis eCRF) where any intervention occurring on or after this date is counted as a maintenance intervention. Note in the event that there are multiple treatments performed during the same procedure driven by multiple reasons, each reason driving the intervention will be counted as a separate intervention.

3) All Interventions Post Creation

Similarly, the number of all Interventions post creation (On the Post-Procedure Intervention page, Date of Post Procedure Intervention is not NULL and before or on the cutoff date of the database lock, and Type of Intervention is not NULL) per PY will be estimated by Poisson regression model with only the intercept term, and the estimate and 95% CI will be provided using the Wald method. Note in the event that there are multiple treatments performed during the same procedure driven by multiple reasons, each reason driving the intervention will be counted as a separate intervention. Note that for this endpoint, unlike for Facilitation and Maintenance Interventions, as HD Continuity Interventions may occur after permanent abandonment, if a participant's endoAVF has permanent abandonment the last date of available study data (including the unscheduled visit date) will be used rather than the date of permanent abandonment.

4) All Interventions After First Use

As defined for the exploratory endpoint of all interventions post creation with duration of evaluation adjusted to start from first successful HD AV access use.

The first successful HD AV access use will be identified if:

On the EndoAVF Dialysis page:

- Date endoAVF Successfully Used with 2 Needles for Hemodialysis is not NULL.

The number of all Interventions after first successful HD AV access use per PY will be estimated by Poisson regression model with only the intercept term, and the estimate and 95% CI will be provided using the Wald method.

For all the endpoints described above, total number of interventions and number of interventions at each time point will be summarized.

5.3.7 Primary Patency

The time interval for primary patency is defined as 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.

The failure for primary patency will be identified for the first occurrence of one of the followings:

- Access thrombosis: on the Post-Procedure Intervention page, Type is checked as "Thrombosis"; or on the Core Lab Analysis - Duplex Ultrasound: EndoAVF Arm page, and Type is checked as "Thrombosis"; Note: if the result from the Core Lab Analysis - Duplex Ultrasound: EndoAVF Arm page is not available, use the corresponding information from the Duplex Ultrasound: EndoAVF Arm to determine Thrombosis.
- Intervention: on the Post-Procedure Intervention page, Date of Post Procedure Intervention is not NULL, and Type of Intervention is checked as "Facilitation - Support AVF Cannulation", and/or "Facilitation – Support AVF Maturation" and/ or "Maintenance";
- Access Abandonment (Permanent Abandonment): on the EndoAVF Abandonment page, Date of Abandonment is not NULL, and the question of "All Possible Attempts Have Been Made to Improve the Condition of the Access" is checked as Yes, and the question of "Could Further Endovascular Interventions Salvage the Access" is checked as No, and the question of "Could Further Surgical Revisions Salvage the Access?" is checked as No, and Reason for Abandonment is selected as "The Access is No Longer Viable" or "The Access is Viable but there are Complications that Require the Abandonment of the Access".

Kaplan-Meier (KM) analysis will be used to estimate the time interval of primary patency. The following definition will be applied:

- If any failure event(s) as described above occurs, the participant is considered as having the event (loss of primary patency), and the first failure event date will be used in the analysis.
- If the participant was as transferred to PD, or had a kidney transplant, or had access discontinuation, or discontinued before the end of a specific visit window (e.g., 180+30 = Day 210 for 6-month visit) without the event, the participant is considered as censored the earliest date among these events (i.e., PD start date, kidney transplant date, date of access discontinuation, last date of available study data including the unscheduled visit date).
- Otherwise, if the participant did not have any failure event and has passed a specific visit by the cutoff date of database lock, the participant will be censored at the end of the reporting time window (e.g., 180+30 = Day 210 for the 6-month reporting, 730+30 = 760 for the final 24-month reporting) for this analysis.

This endpoint will be evaluated on the AT population. The number of participants with events, number of participants censored, time to event (days), and proportion of participants with event free along with the 95% CI will be presented at 30-days, 6-weeks, 3-, 6-, 12-, 18-, and 24-months post creation using the KM method.

5.3.8 Cumulative Patency

The time interval for cumulative patency is defined as the time from HD AV access creation to access abandonment.

Kaplan-Meier (KM) analysis will be used to estimate the time interval of cumulative patency. The following definition will be applied:

- If permanent abandonment (as detailed in Section 5.2.4) occurs, the participant is considered as having the event (loss of cumulative patency), and the corresponding abandonment date will be used in the analysis.
- If the participant was as transferred to PD, or had a kidney transplant, or had access discontinuation, or discontinued before the end of a specific visit window (e.g., Day 210 for 6-month visit) without the event, the participant is considered as censored at the earliest date among these events (i.e., PD start date, kidney

transplant date, date of access discontinuation, last date of available study data including the unscheduled visit date).

- Otherwise, if the participant is still in the investigation without the event and has passed a specific visit by the cutoff date of database lock, the participant will be censored at the end of the reporting time window (e.g., 180+30 = Day 210 for the 6-month reporting, 730+30 = 760 for the 24-month reporting) for this analysis.

This endpoint will be evaluated on the AT population. The number of participants with events, number of participants censored, time to event (days), and proportion of participants with event free along with the 95% CI will be presented at 6-, 12-, 18-, and 24-months post creation using the KM method.

5.3.9 Primary Functional Patency

As defined for primary patency with duration of evaluation adjusted to start from first successful HD AV access use for HD using 2-needle cannulation. See Section 5.3.7 for defining the failure for primary functional patency.

The binary definition for primary functional patency is shown as below:

- If any failure event(s) as described in Section 5.3.7 occurs on or before the end of a specific visit window (e.g., 180+30 = Day 210 for 6-month visit), the participant is considered as having an event (loss of primary functional patency).
- If the participant was as transferred to PD, or had a kidney transplant, or had access discontinuation, or discontinued before the end of a specific visit window (e.g., 180+30 = Day 210 for 6-month visit) without the event, the participant is considered not evaluable and will not be included in the analysis.
- Otherwise, if the participant did not have any failure event(s) and has passed the specific visit window by the cutoff date of database lock, the participant is considered as not having an event.

This endpoint will be evaluated on the AT population and on the AT population with attainment of first successful HD AV access use for HD using 2-needle cannulation (on the EndoAVF Dialysis page, Date endoAVF Successfully Used with 2 Needles for Hemodialysis is not NULL). The proportion of primary functional patency (100% - event rate) and the 95% two-sided CI will be provided using the Clopper-Pearson method. For the 6-month reporting, the primary functional patency rate up to 6-months (up to Day 210) will be presented. For the final reporting, the primary functional patency rate up to 24-months (up to Day 760) will be presented.

5.3.10 CVC Exposure /Use

5.3.10.1 Duration of CVC Use Since Index Procedure

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. The duration of CVC use since index procedure will be evaluated at 30-days, 6-weeks, 3-, 6-, 12-, 18-, and 24-months post creation for the participants with a CVC in place (or placed) at the index procedure. This analysis will only be performed for the participants with a CVC in place (or placed) at the index procedure from the AT population.

For each participant, the “true” Date of Removal of the first CVC placement will be identified, i.e., when a participant has a chain of CVC placements where the Date of Placement of an exchanged CVC is within one day of the Date of Removal of the previous CVC, it is considered as a CVC replacement, and the last Date of Removal of the chain of CVC placements will be used for the analysis.

Kaplan-Meier (KM) analysis will be used to estimate the time to CVC removal since the index procedure.

- If CVC removal occurs, the participant is considered as having the event, and the corresponding date of removal will be used in the analysis.
- If the participant was transferred to PD, or had a kidney transplant, or discontinued before the end of a specific visit window (e.g. Day 210 for 6 months post creation) without CVC removal, the participant is considered as censored at the earliest date among these events (i.e. PD start date, kidney transplant date, last date of available study data including the unscheduled visit date).
- Otherwise, if the participant is still in the investigation without having the CVC removed and have passed a specific visit by the cutoff date of database lock, the participant will be censored at the end of a specific visit window (e.g., 180+30 = Day 210 for the 6-month reporting, 730+30 = 760 for the 24-month reporting) for this analysis.

The number of participants with events, number of participants censored, time to event (days), and proportion of participants with events along with the 95% CI will be presented.

5.3.10.2 Time to CVC Removal

Same analysis as 5.3.10.1. The analysis will be performed for the entire AT population. For participants that do not have a CVC in place (or placed) at the time of the index procedure, the time to CVC removal of the first placed CVC chain after the index procedure will be included.

5.3.10.3 Frequency of CVC Placements

The number of CVC placements will be evaluated at 30-days, 6-weeks, 3-, 6-, 12-, 18-, and 24-months post creation on the AT population. The number of CVC placements will include the CVC already in place at the index procedure. When a participant has a chain of CVC placements (where the Date of Placement of an exchanged CVC is within one day of the Date of Removal of the previous CVC), the analysis will be done in both ways: (1) only the first CVC replacement is counted, and (2) each CVC replacement is counted separately.

5.3.10.4 Total Days of CVC Exposure

Total days of CVC exposure will be calculated by (Date of Removal minus Date of Placement +1 summed across all CVCs a participant is exposed to during the follow up). When the CVC placement occurs prior to index procedure, Date of Index Procedure will be used for the calculation. If the participant is still in the investigation without having a CVC removed by the cutoff date of database lock, the cutoff date of database lock will be used for the calculation. When a participant has a chain of CVC placements where the Date of Placement of an exchanged CVC is within one day of the Date of Removal of the previous CVC, it is considered one CVC placement, and the corresponding total days of CVC exposure will be accumulated. This endpoint will be assessed on the AT population.

5.3.10.5 Total Days of CVC Use

Total days of CVC use is collected as the Number of Dialysis Sessions Using CVC Post Index Procedure on the CVC Usage page. When a participant has a chain of CVC placements where the Date of Placement of an exchanged CVC is within one day of the Date of Removal of the previous CVC, it is considered one CVC placement, and the corresponding total days of CVC use will be accumulated for that participant. This endpoint will be assessed on the AT population.

5.3.11 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 AT population participants through 6 weeks.

Juxta/Peri-Anastomotic Area and Perforator Vein Patency will be collected on the Core Lab Analysis - Duplex Ultrasound: EndoAVF Arm page. Patent is defined as there is no evidence of occlusion or stenosis ≥ 50% as noted by DUS imaging. If the result from the Core Lab Analysis - Duplex Ultrasound: EndoAVF Arm page is not available, use the corresponding information from the Duplex Ultrasound: EndoAVF Arm for this analysis. The Juxta/Peri-Anastomotic Area and Perforator Vein Patency data will be summarized by descriptive statistics for the AT population.

5.3.12 Wrist Arterial Procedure Access Considerations

A separate SAP will address these considerations.

5.3.13 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 Screening/Baseline, 6-weeks, 6-, 12-, and 24-months follow-up visits.

The SF-VAQ has four domains: overall satisfaction (one item), physical symptoms (four items), social functioning (four items), and complications (four items). The score with the 7-point scale will be used for each item: 1= Strongly Disagree, 2= Somewhat Disagree, 3=Disagree a Little, 4= No opinion, 5= Agree a Little, 6= Somewhat Agree, and 7 = Strongly Agree. The score will be summarized with descriptive statistics for each item and each domain at the Screening/Baseline, 6-week, 6-, 12-, and 24-month follow-up visits for the AT population. Change in score from the baseline value will also be summarized for each follow-up visit.

The EQ-5D-5L measures five dimensions of health: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Data and change from baseline value will be summarized at each visit for each of the five health domains and Subject's Own Health State for the AT population.

5.3.14 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 AT population participants for whom their index AVF is abandoned. The alternate type(s) of HD AV access(es) placed in these participants will be collected.

The participants for whom their index AVF is abandoned or in whom they have access discontinuation will be identified if:

On the EndoAVF Abandonment eCRF page, Reason for Abandonment is not NULL.

And

On the Post-Procedure Intervention eCRF page, the question of “Was a New Vascular Access Created” is checked as Yes.

The counts and percentages of the alternate type(s) of HD AV access(es) will be summarized.

6 Summary of General Investigation Data

6.1 Participant Disposition

The summary of the number of participants enrolled, intent to treated (ITT), as treated (AT), investigation device inserted but participant not treated, completed the investigation, and discontinued from the investigation by reason of discontinuation will be provided. Screen failures will be summarized for each inclusion/exclusion criteria that were not met.

6.2 Deviations

The major or minor deviations will be classified as in Appendix 3. The number of participants with deviations and major deviations will be summarized with descriptive statistics by nature of the deviation by treatment. Deviations will be listed with date of occurrence and the nature of deviation. This summary will be reported based on the ITT population. A separate listing for eligibility violations/deviations (on the Eligibility Verification, the question of "Did Subject meet ALL Eligibility Criteria" is marked as No, and on the Screen/Baseline Subject Disposition eCRF page, Subject's Treatment Status is selected as "Study Device Inserted") will be generated.

6.3 Demographics and Baseline Variables

Demographics and baseline characteristics will be summarized with descriptive statistics using the AT population. Summary statistics for categorical variables will include frequency counts and percentages and for continuous variables will include mean, standard deviation, minimum, median, and maximum.

Demographics and baseline characteristics variables include:

- Age at Time of Informed Consent (year)
- Sex (Male, Female)
- Ethnicity (Hispanic/Latino, Not Hispanic or Latino)
- Race (American Indian or Alaskan Native, Asian (including subcategories), Black or African American, Native Hawaiian or Other Pacific Islander, White and Other)
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI, kg/m^2)
- Radial Pulses
- Motor Deficit

6.4 Physical Exam

Physical exam will be collected at the Screening/Baseline, Discharge, 30 Day, 6 Week, 6 Month, and 12 Month visits. Physical exam data will be summarized for each visit for the AT population.

6.5 Vital Signs

Vital signs will be collected at the Screening/Baseline, Discharge, 30 Day, 6 Week, 6 Month, and 12 Month visits. Vital signs and the change from screening/baseline will be summarized for each visit for the AT population. Note:

The vital sign measurements on the non-target limb (recorded on the Procedure Overview eCRF page) will be used as the baseline value for the comparisons.

6.6 Concurrent Illnesses and Medical Conditions

The participant's medical history (including Risk Factors, Kidney Disease, Cardiovascular Disease, Other Disease) will be summarized for the AT population.

6.7 Prior and Concurrent Medications

Not applicable.

6.8 AVG and AVF History

The AVG and AVF history data at screen/baseline will be summarized with descriptive statistics for the AT population. A separate summary will be provided for the AT population showing accesses in the same limb as the endoAVF.

6.9 Dialysis History/Onset

The Dialysis History/Onset data will be summarized with descriptive statistics for the AT population.

6.10 Device Failure, Malfunctions and Defects

Device deficiencies/malfunctions will be tabulated by the failure code. This summary will be reported based on the ITT population.

6.11 Procedure Overview

The procedure overview data will be summarized with descriptive statistics for the AT population.

6.12 Duplex Ultrasound

The duplex ultrasound data for both site-reported and core lab will be summarized with descriptive statistics for each visit for the AT population.

6.13 Hemodialysis/AV Access Circuit Assessment

The Hemodialysis/AV access circuit assessment data will be summarized with descriptive statistics for each follow-up visit for the AT population.

6.14 Post Procedure Interventions

The post procedure interventions data will be summarized with descriptive statistics for the AT population.

6.15 Second Stage Procedures

The second stage procedures data will be summarized with descriptive statistics for the AT population.

6.16 EndoAVF Abandonment

The EndoAVF abandonment data will be summarized with descriptive statistics for the AT population.

7 Safety Analysis

7.1 Adverse Event

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.

A separate CEC (Clinical Events Committee) will be formed to adjudicate AEs as defined in their respective charter. AEs will be adjudicated for seriousness and relatedness as reported by trial investigators. This does not apply to the user AEs.

An overall summary including the number and percentage of participants with at least one AE, total number of AEs, total number of SAEs, AEs by relationship to the Device/Index Procedure (Including Wrist Arterial Procedure Access, Embolization Device, and Closure Device)/AV Access Circuit, and AEs by severity of the event will be summarized for the ITT participants. In addition, the following summary tables will be provided:

- Number of AEs by System Organ Class (SOC) and Preferred Terms (PT)
- Number of SAEs by System Organ Class (SOC) and Preferred Terms (PT)
- Number of AEs by relationship to Study Device by System Organ Class (SOC) and Preferred Terms (PT)
- Number of AEs by relationship to Procedure by System Organ Class (SOC) and Preferred Terms (PT)
- Number of AEs by severity by System Organ Class (SOC) and Preferred Terms (PT)

A listing of all AEs, as well as of the SAEs and UADEs will be provided.

8 References

[1] C. et al. Gamble. Guidelines for the content of statistical analysis plans in clinical trials. *JAMA*, 318 (23):2337–2343, 2017.

9 SAP Revision History

Version Number	Rationale for Change	Section or Page Affected	Description of Change
1.0	Original SAP		

10 Appendix

Appendix 1.1 Tables/Listing/Figures Shell for 6-Month Reporting

Appendix 1.2 Tables/Listing/Figures Shell for Final Reporting

Appendix 2 Derived Data Specification

Appendix 3 Deviations: Major/Minor Classification