Cover Page for Statistical Analysis Plan
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Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	Ellipsys Vascular Access System Post Market Surveillance (PS) Study
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Tracy Bergemann, PhD /Distinguished Statistician
2.0	• Language updated to align with CIP v4.0. Added additional analysis regarding potential adjunctive procedures, per FDA request.	Tracy Bergemann, PhD /Distinguished Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
AVF	Arteriovenous (AV) Fistula
CEC	Clinical Events Committee
CI	Confidence Interval
CVC	Central Venous Catheter
EDC	Electronic Data Capture
HD	Hemodialysis
PS	Post-market Surveillance
PTA	Percutaneous Transluminal Angioplasty
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
VAQ	Vascular Access Questionnaire

3. Introduction

This document outlines the detailed statistical methods to be implemented for the data collected within the scope of the Ellipsys Vascular Access System Post Market Surveillance Study. This Statistical Analysis Plan (SAP) has been designed to document, before data are analyzed, the rationale for the study design, and the planned analyses that will be included in study reports. The purpose of this plan is to provide a framework within which answers to the study objectives can be achieved in a statistically rigorous fashion, without bias or analytical deficiencies.

Specifically, the plan has the following purpose: To prospectively outline the types of analyses and presentations of data that will form the basis for conclusions to be reached that will answer the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of statistical analysis in the medical device industry.

4. Study Objectives

The primary objectives of this post-market surveillance study are to support short-term safety of the device and procedure and further assess long-term safety and effectiveness in subjects treated by newly trained providers of the Ellipsys Vascular Access System in the creation of a native AV fistula (AVF) via percutaneous access in subjects who are on hemodialysis and are medically indicated for the creation of an upper limb anastomosis.

4.1 Primary Objectives

The primary objectives will assess safety and effectiveness in subjects by measuring the early occlusion rate, the long-term serious adverse event (SAE) rate and cumulative patency.

4.1.1 Primary Endpoints

To evaluate the Ellipsys Vascular Access System, this study design shall include three primary endpoints; two based on the safety of the device during treatment and post-operative outcomes and one based on the effectiveness performance of the device. The primary endpoints are as follows:

Primary Safety Endpoints

Early occlusion:

Early occlusion defined as the percentage of subjects with a total occlusion within 7 days of the AVF creation procedure.

Study related serious adverse events through 12 months:

Rate of serious adverse events through 12 months related to the device, study procedure or secondary procedure to maintain or reestablish patency.

An independent clinical events committee (CEC) will assess and adjudicate any potential relationship to the device and/or procedures per the criteria set in the CEC charter.

Primary Effectiveness Endpoint

Cumulative patency through 12 months post-AVF creation:

Cumulative patency is defined as freedom from access abandonment from time of access creation.

4.2 Secondary Objectives

Secondary objectives include descriptive analyses of secondary endpoints as well as acute procedural observations and clinical utility measures. There are no formal hypothesis tests or sample size requirements for the secondary objectives.

4.2.1 Secondary Endpoints

The following secondary endpoints to be evaluated in this study are as follows:

1. Primary patency through 12 months post-AVF creation:

Defined as freedom from access thrombosis or any intervention designed to facilitate, maintain or reestablish patency measured from time of access creation through 12 months.

2. Assisted primary patency through 12 months post-AVF creation:
Defined as freedom from access thrombosis from time of access creation through 12 months.

3. Secondary procedure Rate:
Defined as the percentage of subjects having one or more surgical or percutaneous interventions designed to mature or maintain the AVF or re-establish flow. Secondary procedures are procedures subsequent to completion of the AVF creation procedure. This endpoint will also be summarized by type of procedure, indication, procedure success and association with any adverse events (AEs).

4. Overall patient safety:
A full characterization of all adverse events during the study.

4.3 Ancillary Objectives

Ancillary objectives include descriptive analyses of ancillary endpoints as well as acute procedural observations and clinical utility measures.

4.3.1 Ancillary Endpoints

The following ancillary endpoints to be evaluated in this study are as follows:

1. Functional Patency Rate Through 12 months: *Defined as freedom from access abandonment from the time of first two-needle cannulation.*
2. Physiological Maturation Rate at 3, 6, and 12 months: *Defined as the percentage of access sites with access vessel minimum blood flow rate ≥ 500mL/min and minimum diameter ≥ 5mm as measured by duplex ultrasound.*
3. Functional Cannulation Success Through 12 months: *Defined as the time to achieve successful use of the endovascular AVF, with two-needle access and at least two hours of dialysis through the access, for more than two-thirds of the dialysis sessions over a continuous 28-day period after access creation.*

4. Days of Central Venous Catheter (CVC) Exposure through 12 months

5. Subject Satisfaction using the Vascular Access Questionnaire (VAQ) at 6 months

6. Nurse-Cannulator Satisfaction at 3, 6, and 12 months
Subjective and objective parameters will be assessed including fistula characteristics, cannulator training, skills and experience cannulating this type of fistula.

5. Investigation Plan

This study is a prospective, non-randomized, multi-center, single-arm, observational, post-market surveillance (PS) study of the Ellipsys Vascular Access System. The study will be conducted by newly trained providers in subjects on hemodialysis and medically indicated for creation of an upper limb anastomosis. Subjects will be followed for 12 months (+2 month window) following the AVF creation procedure.

6. Determination of Sample Size

The sample size is not driven by a statistical hypothesis. To ensure that a minimum of 100 subjects will be evaluable at the 12-month follow-up visit, a minimum of 134 subjects will be enrolled in the study. This sample size estimate allows for a 25% drop-out rate (100/.75 = 134 subjects) which may result due to a higher than normal attrition rate seen in this study population due to the natural history of the disease state. Newly trained users from up to 14 sites in the United States will participate in the study. Each study site will enroll no more than 20% of the total enrollment (134 subjects), with a maximum of 27 subjects.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

A STROBE flow diagram will be used to describe the disposition of study subjects for analysis of the primary objectives.

Figure 1 shows an example of a blank STROBE flow diagram. Subject enrollment status will be presented for all enrolled subjects, followed by number of subjects with a procedure attempt, number of subjects with successful access creation and follow-up compliance thereafter. Subject enrollment will also be presented for each site as the number of subjects enrolled, number with procedure attempts, and number with access created.

An access failure occurs when the Ellipsys device is not deployed due to access failure defined as 1) the needle or wire cannot be introduced, or 2) vessel spasm precludes continuing the procedure. Subjects with an access failure may be re-scheduled for another attempt at access or followed through discharge and exited. If the second access attempt is also not successful, these subjects will be considered access failures and followed for safety through clinic discharge. If the second access attempt is more than 30 days after the initial screening, the subject will be re-screened and given a new subject identification number; the new number will be linked to the previous subject identification number in Electronic Data Capture (EDC) to prevent subjects being included twice in the analysis.

Subject visit compliance, and end of study status will be presented for enrolled subjects in whom the procedure has been attempted and the Ellipsys Vascular Access System deployed, whether successful or not. For each study visit, the following information will be tallied: in window visits, out of window visits, early terminations, deaths, and missed visits. Overall follow-up compliance will be reported as number of subjects who had a follow-up visit within or out of window divided by total number of eligible subjects. The number and percentage of subjects who did/did not complete the study will be summarized overall as well as for each reason for withdrawal or early termination.

Follow-up:

Study exit might include the following reasons:

- Study completed
- Subject lost to follow-up
- Subject death
- Subject did not meet inclusion/exclusion criteria
- Subject was not treated with the study device
- Subject did not provide consent
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g. medically justified, inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)

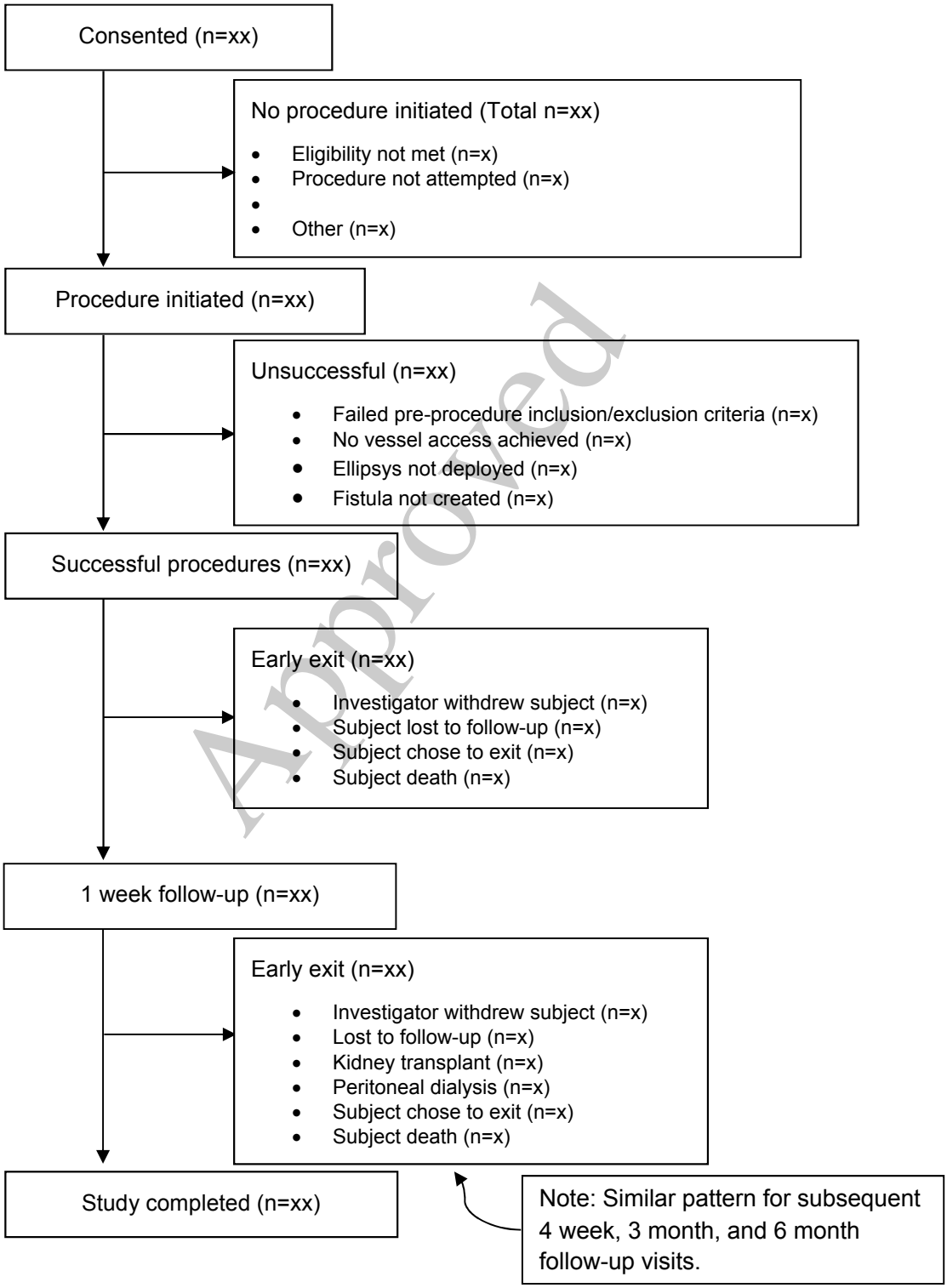
Analysis:

Analysis can only be completed for subjects that have case report forms saved complete.

Allocation:

Since the Ellipsys post-market surveillance study is not a randomized study, all study subjects that are enrolled are allocated to the intervention (i.e. are treated with the Ellipsys Vascular Access System).

Figure 1 – Example of STROBE Flow Diagram



7.1.2 Clinical Investigation Plan (CIP) Deviations

Protocol deviations will be summarized as the number of events as well as the number and percentage of subjects.

Deviations may include, but are not limited to the following:

- Failure to obtain informed consent prior to participation
- Incorrect version of the informed consent form used
- Failure to obtain IRB approval before the start of enrolling subjects in the study
- Included subject did not meet inclusion/exclusion criteria
- Required testing and/or measurements not done or incorrectly done
- Subject did not attend follow-up visit
- Follow-up visit was completed outside window
- Unauthorized use of Ellipsys system outside of CIP
- Adverse events/Unanticipated Adverse Device Effects (UADE) or device deficiencies not reported in the required timeframe as specified in the CIP
- Source data permanently lost
- Enrollment of subjects during lapse of IRB approval
- Enrollment limits exceeded

7.1.3 Analysis Sets

The study populations are defined as follows:

- The **Safety population** is defined as all enrolled subjects in whom the procedure has been attempted and the Ellipsys Vascular Access System deployed, whether successful or not.

  The Safety Population may include device failures. A device failure is defined as a malfunction of the Ellipsys Vascular Access System during use that precludes creation of a percutaneous AV fistula. A second Catheter may be deployed or a second Controller may be used to complete the procedure.

  The Safety population may include procedure failures. A procedure failure is when the Ellipsys Vascular Access System is deployed and functions per specification, however, the AV fistula creation is unsuccessful due to incorrect placement in the patient anatomy. If this is observed immediately after deployment and the introducer sheath or guidewire is still in place, a second deployment may be attempted to complete the procedure.

- The **Treated population** is defined as all subjects in the Safety population with AVF successfully created.

Summaries of baseline parameters will be based on the Safety population. Summaries of the primary safety analyses will be based on the Safety population. Primary effectiveness and secondary endpoint analyses will be based on the Safety and/or Treated population, as indicated in the following sections. In the event a subject has more than one AVF access attempt, the first attempt will be used in summaries and analyses of the Safety population, and the final attempt will be used in summaries and analyses of the Treated population.

7.2 General Methodology

For continuous variables, the number of observations, mean, standard deviation (SD), median, minimum, and maximum will be calculated, unless otherwise stated. For categorical variables, frequencies and percentages will be calculated. Exact binomial confidence limits will be calculated based on Wilson-score methods.

Survival analysis will also be performed for time-to-event endpoints using the Kaplan-Meier method. In cases where adjustment for competing risks is necessary, cumulative incidence curves will also be provided.

To assess the continued safety of the AVF creation procedure post-market, a subset of study endpoints will be descriptively compared to the pre-market study (DEN170004) results where possible. Comparisons will be performed using the Safety population for each study.

7.3 Handling of Missing, Unused, and Spurious Data and Dropouts

For all study endpoints that use time-to-event analysis as the primary analysis, patients lost to follow-up or who have died will be treated as censored or as a competing risk for observation of the endpoint. In instances where partial dates are provided, information from the partial date and other dates provided for the patient will be use to determine a plausible range of possible dates, and then the midpoint of that range will be used.

Missing data for primary safety objective #1 may result from a study procedure attempted but not completed, or loss to follow-up or death prior to endpoint assessment. Missing data for secondary and ancillary endpoints may result from clinical assessments unable to be performed due to a remote visit, or unanswered questions on the Subject and Cannulator Satisfaction surveys. Additionally, not all ultrasound measurements of artery and vein diameters and mean flow rates will be available due to normal variations in subject anatomy. These missing values will be excluded from summaries and analyses. In general, imputation of missing data will not be performed for descriptive statistics.

7.4 Adjustments for Multiple Comparisons

In general, although this post-market study has multiple primary endpoints, they are not hypothesis-driven and therefore their results will be presented descriptively with no adjustments for multiple comparisons. For comparisons between pre-market results and post-market results, however, these comparisons will account for multiple comparisons. Two comparisons between the pre-market study (DEN170004) and the post-market study are anticipated, for Primary Safety Objective #1, and components of Secondary Objective #4. A Bonferroni adjustment to the alpha-level to determine the quantile for the confidence intervals (CIs) in those analysis will be performed. Thus, confidence intervals for these comparisons will be based on 97.5% CIs rather than 95% CIs.

7.5 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be presented for the Safety population.

Demographic characteristics including age, gender, body mass index, ethnicity, and race will be summarized using descriptive statistics and 95% CIs.

Relevant co-morbidities and surgical history will be presented as the number and percentage of subjects with each condition or procedure. Surgical history is collected separately for each side of the body and will be presented in relation to the side of the body on which the study AVF was created: Ipsilateral (same side) or Contralateral (opposite side).

Relevant demographic and baseline characteristics will be descriptively compared to the pre-market study (DEN170004). If the studies differ with respect to demographics, additional analyses or adjustments may be required for endpoint comparisons between studies.

Relevant concomitant medication use at baseline will be presented as the number and percentage of subjects taking aspirin, Plavix, Coumadin, other anti-coagulant medications, or other anti-platelet medications, as well as the indication(s) for treatment.

The time since hemodialysis (HD) started and current method of HD will be summarized descriptively.

7.6 Treatment Characteristics

Subjects may have an additional AVF access attempted if the first attempt does not lead to successful AVF creation. Summaries of AVF creation procedures will be presented for the Safety population.

Descriptive summaries will be presented for pre-procedure ultrasound vein mapping, pre- and intra-operative medication use, elapsed time for each stage of the procedure, and procedure outcomes, including the number and percentage of subjects for whom:

- access was achieved,
- the device was deployed,
- an AVF was created,
- an intra-operative percutaneous transluminal angioplasty (PTA) procedure was performed,
- AVF was patent at discharge,
- any AEs occurred, and
- the number of access attempts leading to a successful AVF creation procedure.

The summary of the intra-operative PTA procedure will include largest balloon size used, location of the PTA, and whether any complications occurred.

For subjects who did not have a fistula created, the reasons will be tabulated.

Post-procedure ultrasound measurements of artery and vein mean flow rates and diameters will be summarized descriptively. Not all measures will be available due to normal variations in subject anatomy; missing values will be ignored.

Relevant concomitant medication use during the study will be summarized at each visit for the Safety population, and will be presented as the number and percentage of subjects taking aspirin, Plavix, Coumadin, other anti-coagulant medications, or other anti-platelet medications.

7.7 Evaluation of Objectives

7.7.1 Primary Effectiveness Objective

Cumulative Patency through 12 months post AVF creation

Analysis Dataset:

Treated Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

Cumulative patency will be summarized for the Treated population using a Kaplan-Meier curve through at least 12 months. Analyses will include patency/survival probabilities and 95% confidence interval bands through the 12-month visit. The confidence interval will be calculated using a typical transformation of the survival function: log(S(t)). Subjects not completing the study will be censored after their last available visit. A sensitivity analysis shall be performed where a cumulative incidence curve is estimated and death will be accounted for as a competing risk. The cumulative incidence curve will be descriptively compared to 1-S(t) where S(t) is the survival function estimated by the Kaplan-Meier method.

The observed cumulative incidence estimate may be calculated using the "cmprsk" library in R, with code similar to the following:

```
cmpout1 <- cuminc(time,event)
```

The event variable is 0 if censored, 1 if an event occurs and 2 if a death occurs. Similar code in SAS is possible using the following:

```
proc lifetest;
   time T*event(0) / failcode=1;
run;
```

where T is the time variable, event takes a value of 1 for primary events, a value of 0 as a censored observation indicator, and all other values as competing events.

Endpoint Definition:

Cumulative patency is defined as freedom from access abandonment from time of access creation. An abandoned dialysis access is one that can no longer be used for one or two needle prescribed dialysis because it is unable to provide adequate blood flow and/or is deemed unsafe for the patient, and the associated problem cannot be corrected by any intervention either medical, endovascular or surgical. Access abandonment due to kidney transplant, for example, shall not contribute to the endpoint and date of censoring is the date their access is abandoned. For time-to-event analysis, day 0 is time of

access creation and final date is day of event or day of last follow-up. The definition of cumulative patency is derived from reporting standards by Sidawy, et al and Shenoy, et al [1,2].

Additional Analysis:

- Cumulative patency post- surgical or endovascular intervention
- The association between early occlusion and cumulative patency through 12 months will be summarized for the Treated population. Kaplan-Meier curves and associated life tables will be generated summarizing cumulative patency comparing curves for subjects who experience and do not experience early occlusions.
- The association between the number of secondary procedures required to facilitate maturation or maintain the functionality of a patent access and cumulative patency through 12 months will be summarized for the Treated population. Kaplan-Meier curves and associated life tables will be generated summarizing cumulative patency for subjects having 0, 1, 2, 3 and 4 or more secondary procedures.

7.7.2 Secondary Objective #1

Primary Patency through 12 months post AVF creation

Analysis Dataset:

Treated Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

Primary patency will be summarized for the Treated population using a Kaplan-Meier curve through at least 12 months. Analyses will include patency/survival probabilities and 95% confidence interval bands through the 12-month visit. The confidence interval will be calculated using a typical transformation of the survival function: log(S(t)). Subjects not completing the study will be censored after their last available patency assessment. A sensitivity analysis shall be performed where a cumulative incidence curve is estimated and death will be accounted for as a competing risk. The cumulative incidence curve will be descriptively compared to 1-S(t) where S(t) is the survival function estimated by the Kaplan-Meier method.

The observed cumulative incidence estimate may be calculated using the “cmprsk” library in R, with code similar to the following:

cmpout1 <- cuminc(time,event)

The event variable is 0 if censored, 1 if an event occurs and 2 if a death occurs. Similar analysis will be conducted on the subcomponents of the endpoint.

Endpoint Definition:

Primary patency is defined as freedom from access thrombosis or any intervention designed to facilitate, maintain or reestablish patency in a thrombosed access from time of access creation. Subsequent to the completion of the AVF creation procedure, consistent with the Training Manual for this staged procedure, the site investigator will assess if an additional PTA balloon maturation or other procedure is needed to promote maturation when outflow is <400 ml/min. Therefore, these specific maturation procedures will not be included in the primary patency endpoint. For time-to-event analysis, day 0 is time of access creation and final date is day of event or day of last follow-up. The definition of primary patency is derived from reporting standards by Sidawy, et al and Shenoy, et al [1,2].

Additional Analysis:

- Primary patency post- surgical or endovascular intervention

7.7.3 Secondary Objective #2

Assisted Primary Patency through 12 months post AVF creation

Analysis Dataset:

Treated Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

Assisted primary patency will be summarized for the Treated population using a Kaplan-Meier curve through at least 12 months. Analyses will include patency/survival probabilities and 95% confidence interval bands through the 12-month visit. The confidence interval will be calculated using a typical transformation of the survival function: log(S(t)). Subjects not completing the study will be censored after their last available visit. A sensitivity analysis shall be performed where a cumulative incidence curve is estimated and death will be accounted for as a competing risk. The cumulative incidence curve will be descriptively compared to 1-S(t) where S(t) is the survival function estimated by the Kaplan-Meier method.

The observed cumulative incidence estimate may be calculated using the “cmprsk” library in R, with code similar to the following:

cmpout1 <- cuminc(time,event)

The event variable is 0 if censored, 1 if an event occurs and 2 if a death occurs.

Endpoint Definition:

Assisted primary patency is defined as freedom from access thrombosis from time of access creation. For time-to-event analysis, day 0 is time of access creation and final date is day of event or day of last follow-up. The definition of assisted primary patency is derived from reporting standards by Sidawy, et al and Shenoy, et al [1,2].

Additional Analysis:

- Assisted primary patency post- surgical or endovascular intervention
- Assisted primary patency post- functional cannulation success

7.7.4 Secondary Objective #3

Rate of Secondary Procedures

Analysis Dataset:

Treated Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

Secondary procedure rate will be summarized cumulatively through 12 months as the number of procedures per person-years as well as the number and percentage of subjects having one or more procedures in the Treated population. This summary will be presented overall and by type of procedure (surgical or percutaneous). Additionally, the number of secondary procedures will be summarized categorically as the number and percentage of subjects with 0, 1, 2, 3, or 4 or more procedures.

Summaries specific to PTA/balloon maturation interventions will be provided. These summaries will be based on secondary procedures that include a PTA/balloon maturation intervention, whether performed alone or in combination with other interventions. The summaries will be presented for interventions performed post-AVF creation through 12 months. The summaries will include the number of PTA interventions performed, whether the PTA was performed in combination with other interventions, the rate of intervention in person-years, the location and average balloon size. Similar summaries will be provided for stent, embolization, and valvulotomy interventions, presented cumulatively through 12 months.

This endpoint will also be summarized by type of procedure (e.g. banding, balloon maturation, transposition/elevation/ superficialization, etc.), indication (due to stenosis, due to AE, etc.), procedure success and association with any AEs.

Endpoint Definition:

Secondary procedures are surgical or percutaneous interventions designed to mature or maintain the AVF or re-establish flow. Secondary procedures are procedures subsequent to completion of the AVF creation procedure.

Additional Analysis:

- The association between the occurrence of acute anastomotic disruption or pseudoaneurysm and the secondary procedure rate for the Treated population. The mean number of secondary procedures will be summarized cumulatively and stratified by subjects who experienced anastomotic disruption or pseudoaneurysm and those who did not.
- The association between the occurrence of early occlusions and the secondary procedure rate for the Treated population. The mean number of secondary procedures will be summarized for subjects who experienced an early occlusion and those who did not.

7.7.5 Ancillary Objective #1

Functional Patency Rate Through 12-months

Analysis Dataset:

Treated Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

Functional patency will be summarized for the Treated population using a Kaplan-Meier curve through at least 12 months. Analyses will include patency/survival probabilities and 95% confidence interval bands through the 12-month visit. The confidence interval will be calculated using a typical transformation of the survival function: log(S(t)). Subjects not completing the study will be censored after their last available visit.

Endpoint Definition:

Functional patency is defined is defined as freedom from access abandonment from time of first two-needle cannulation. An abandoned dialysis access is one that can no longer be used for one or two needle prescribed dialysis because it is unable to provide adequate blood flow and/or is deemed unsafe for the patient, and the associated problem cannot be corrected by any intervention either medical, endovascular or surgical. Access abandonment due to kidney transplant, for example, shall not contribute to the endpoint and date of censoring is the date their access is abandoned. For time-to-event analysis, day 0 is time of first two-needle cannulation and final date is day of event or day of last follow-up.

7.7.6 Ancillary Objective #2

Physiological Maturation Rate at 3-, 6-, and 12-months

Analysis Dataset:

Treated Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

Physiological maturation will be summarized at each relevant follow-up visit as the number and percentage of subjects achieving the endpoint along with exact two-sided 95% confidence limits for the percentage, calculated via the Wilson method. The endpoint will be summarized separately at 3, 6 and 12 months.

Endpoint Definition:

Physiological maturation is defined in an access site as access vessel minimum blood flow rate ≥ 500mL/min and minimum diameter ≥ 5mm as measured by duplex ultrasound.

7.7.7 Ancillary Objective #3

Functional Cannulation Success Through 12-months

Analysis Dataset:

Treated Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

Functional cannulation success will be summarized for the Treated population using a Kaplan-Meier curve through at least 12 months. Incidence of success will be characterized as 1-S(t) where S(t) is the survival function estimated by the Kaplan-Meier method. Analyses will include probabilities and 95% confidence interval bands through the 12-month visit. The confidence interval will be calculated using a typical transformation of the survival function: log(S(t)). Subjects not completing the study will be censored after their last available visit. For time-to-event analysis, day 0 is date of access creation and final date is day 28 of a 28-day window, in the case of an event, or day of last follow-up.

A sensitivity analysis may be performed where a cumulative incidence curve is estimated and death will be accounted for as a competing risk. The cumulative incidence curve will be descriptively compared to the Kaplan-Meier estimate of incidence.

The observed cumulative incidence estimate may be calculated using the “cmprsk” library in R, with code similar to the following:

```
cmpout1 <- cuminc(time,event)
```

The event variable is 0 if censored, 1 if an event occurs and 2 if a death occurs.

Endpoint Definition:

Functional cannulation is defined as the time to achieve successful use of the endovascular AVF, with two-needle access and at least two hours of dialysis through the access, for more than two-thirds of the dialysis sessions over a continuous 28-day period after access creation.

7.7.8 Ancillary Objective #5

Subject Satisfaction using the Vascular Access Questionnaire (VAQ) at 6 Months

Analysis Dataset:

Treated Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

The VAQ will be summarized for subjects in the Treated population whose primary access is the study AVF. Summaries will present the number and percentage of subjects not bothered by any symptoms and the number and percentage of subjects at least moderately bothered by each symptom. Descriptive statistics for the overall VAQ score will be provided.

Endpoint Definition:

Subject satisfaction with the AVF is assessed at the 6-month visit using the Vascular Access Questionnaire (VAQ), a series of 17 questions measuring how much subjects are bothered by problems related to their primary vascular access. Responses range from 0 (Not at all) to 4 (Extremely) and the 17 items are summed to produce a score. The VAQ summary score ranges from 0 to 68 with a higher value indicating that the subject has a more negative view of their vascular access.

7.7.9 Ancillary Objective #6

Nurse-Cannulator Satisfaction at 3-, 6-, and 12-months

Analysis Dataset:

Treated Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

Baseline cannulator training will be summarized using the responses from the first study AVF cannulated by each cannulator. Cannulator experience with the study AVF will be presented for the Treated population at each timepoint, summarizing each question descriptively. Missing responses will not be included.

Endpoint Definition:

Subjective and objective parameters will be assessed including fistula characteristics, cannulator training, skills and experience cannulating this type of fistula. Cannulator training and experience cannulating the study AVF is assessed at approximately 3, 6, and 12 months post AVF creation. If subject has not started receiving dialysis through the study AVF at the time of the scheduled follow-up visit, the Cannulator Satisfaction Survey will not be completed.

7.8 Safety Evaluation

In addition to the safety objectives outlined below, a table compiling all observed device deficiencies that could have led to a serious adverse device effect will be provided. An enumeration of deaths will also be provided.

7.8.1 Primary Safety Objective #1

Early Occlusion

Analysis Dataset:

Safety Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

Early occlusion will be summarized by presenting the number, percentage, and two-sided 95% CI for the percentage of subjects with early occlusion. Early occlusion will be presented overall and separately by type and location of the occlusion.

Endpoint Definition:

Early occlusion is defined as the percentage of subjects with total occlusion within 7 days (≤ 7) of the AVF creation procedure. These events will be based on the adjudication by an independent CEC. The percentage is calculated where the numerator is the number of patients with total occlusion within 7 days of the AVF creation procedure and the denominator is the number of patients in the Safety Analysis set.

Additional Analysis:

- To assess the short-term safety of the AVF creation procedure, early occlusion will be descriptively compared to the pre-market study (DEN170004). Early occlusion will be compared using the percentage and 97.5% CI for each study (CI adjusted for multiple comparisons). If there are differing representations of baseline characteristics between the two studies, they will be adjusted for in the analysis.

7.8.2 Primary Safety Objective #2

Study related serious adverse events through 12 months

Analysis Dataset:

Safety Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

The study-related SAE rate will be summarized for the Safety population using a Kaplan-Meier curve through at least 12 months. Analyses will include survival probabilities and 95% confidence interval bands through the 12-month visit. Subjects not completing the study will be censored after their last available visit. A sensitivity analysis shall be performed where a cumulative incidence curve is estimated and death will be accounted for as a competing risk. The cumulative incidence curve will be descriptively compared to 1-S(t) where S(t) is the survival function estimated by the Kaplan-Meier method.

The observed cumulative incidence estimate may be calculated using the "cmprsk" library in R, with code similar to the following:

cmpout1 <- cuminc(time,event)

The event variable is 0 if censored, 1 if an event occurs and 2 if a death occurs.

Endpoint Definition:

The rate of SAEs through 12 months related to the device, study procedure, or secondary procedure to maintain or reestablish patency. For time-to-event analysis, day 0 is day of first attempted AVF creation procedure and final date is day of event or day of last follow-up. An independent CEC will assess and adjudicate any potential relationship to the device and/or procedures per the criteria set in the CEC charter.

Additional Analysis:

Subcomponents of the SAE rate endpoint will also be provided, with subcomponents defined as related to the device, related to the study procedure, or related to the secondary procedure to maintain or reestablish patency.

7.8.3 Secondary Objective #4

Overall patient safety

Analysis Dataset:

Safety Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

Study-related AEs occurring during the study will be presented for the Safety population cumulatively and for each of the following study intervals:

Peri-operative: within 7 days (≤ 7 days) of the AVF creation procedure

Post-operative: 8 days to 3 months after the AVF creation procedure

Follow-up: more than 3 months after the AVF creation procedure

AEs will be summarized as the number of events as well as the number and percentage of subjects experiencing one or more of the following event types:

- Any study-related AE:
  - Cumulative
  - Peri-operative
  - Post-operative
  - Follow-up
- AE related to:
  - study device
  - study procedure
  - intra-procedure (index) or planned balloon angioplasty (PTA) maturation procedures
- Cannulation-related AE
- AE resulting from or related to a secondary procedure
- SAE
- UADE
- Stenosis

SAE incidence will be summarized by system organ class and event as the number of events as well as the number and percentage of subjects experiencing each event. The above summaries will be presented cumulatively and for each study interval. For the four different study intervals, subjects are included in the denominator of percentage calculations if their follow-up has extended at least to the beginning of that study time interval. Non-SAE will be presented in manner similar to SAE.

Endpoint Definition:

All adverse events related to the device, procedure, secondary procedures to maintain or re-establish patency, or any serious adverse event shall be reported. An independent CEC will assess and adjudicate any potential relationship to the device and/or procedures per the criteria set in the CEC charter. Stenosis events will be reported based on the MedDRA terms AVF site stenosis or AVF occlusion.

Additional Analysis:

- To assess the safety of the AVF creation procedure, rates for SAEs, UADEs, and procedure-related AEs will be descriptively compared to the pre-market study (DEN170004) results by presenting the rate and 97.5% CI for each study (CI adjusted for multiple comparisons). This comparison will be presented for the peri-operative and post-operative study intervals. If there are differing representations of baseline characteristics between the two studies, they will be adjusted for in the analysis.

7.8.4 Ancillary Objective #4

Days of Central Venous Catheter Exposure Through 12-months

Analysis Dataset:

Safety Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

CVC use and exposure during the study will be summarized descriptively for subjects in the Safety population. The summary will include the number and percentage of subjects with CVC use during the study, broken down as:

- CVC present at study procedure
- CVC placed prior to AVF maturation
- Additional CVC placed during the study

The overall CVC exposure in days will be summarized descriptively.

Endpoint Definition:

Days of CVC exposure through 12 months.

7.9 Changes to Planned Analysis

None

8. Validation Requirements

Analysis datasets and statistical analyses will be generated using SAS® software, version 9.4 or later and/or R software, version 4.0 or later. Minimum validation requirements for the programs written to execute the analyses in this SAP:

- Primary objectives: Level I
- Secondary objectives: Level I
- Ancillary objectives: Level II
- Deviation table and listing: Level III

9. References

1 Sidawy AN, Gray R, Besarab A, Henry M, Ascher E, Silva M, Miller A, Scher L, Trerotola S, Gregory RT, Rutherford RB, Kent KC. Recommended standards for reports dealing with arteriovenous hemodialysis accesses. Journal of Vascular Surgery. 2002; 35: 603-610.

2 Shenoy S, Allon M, Beathard G, Brouwer-Maier D, Dember LM, Glickman M, Lee C, Litchfield T, Lok C, Huber T, Roy-Chaudhury P, Work J, West M, Wasse H. Clinical trial end points for hemodialysis vascular access. Clin J Am Soc Nephrol. 2018; 13: 490-494.

10. Statistical Appendices

10.1 Mapping of Variables

Endpoint definitions are provided for all study objectives in Section 7. The locations of these study endpoints on the study eCRFs are specified in more detail and documented in RAD: Cabinets/MCRI/APV/Studies/Ellipsys PS/General Trial Folder/8.0 Data Management/8.01 Data Management Oversight/Endpoint Mapping File Ellipsys PS.xls.

10.2 Additional Analysis

The following additional analyses may be performed.

1. *Characterization of adjunctive procedures*

   Analysis Dataset:

   Safety Analysis Set per section **Error! Reference source not found.**.

   Analysis Method:

Adjunctive procedures will be summarized as a listing. The type of procedure (e.g. banding, coils, stents, etc.), indication (due to stenosis, due to AE, etc.), procedure success and association with any AEs will be provided.

Endpoint Definition:

Adjunctive procedures are defined as any additional procedure that occurred during the AVF creation procedure. Balloon angioplasty during the AVF creation procedure is not considered an adjunctive procedure.

2. *Ultrasound measurements of artery and vein diameter and mean flow rate*

Analysis Dataset:

Treated Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

Ultrasound measurements of artery and vein diameters and mean flow rates will be summarized descriptively. Mean flow rate and diameter recorded at visits prior to identifying a well-defined target vessel will be summarized by vessel. Once a well-defined target vessel is identified, mean flow rate and diameter associated with the target vessel will be summarized both by vessel and in an aggregated manner.

Endpoint Definition:

Measurement of artery and vein diameter and flow rate by Duplex ultrasound.

2. Target vessel location

Analysis Dataset:

Treated Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

The number of subjects with each target vessel location at 3, 6, and 12 months shall be enumerated. Any changes in target vessel location during the study shall be noted.

3. Investigator assessments of arterial, venous, and AVF patency

Analysis Dataset:

Treated Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

The number of subjects with confirmed patency at each visit shall be enumerated.

4. Hemodialysis access

Analysis Dataset:

Treated Analysis Set per section **Error! Reference source not found.**.

Analysis Method:

Current hemodialysis status for each subject will be summarized 6 and 12 months. The summary will include the number and percentage of subjects on hemodialysis, the most recent access site, Kt/V if the most recent access is the study AVF, and any reasons why the most recent site is not the study AVF. Additionally, the number and percentage of subjects not on hemodialysis will be presented with the reasons.

End of study AVF status will be summarized for the Treated population as the last known AVF status for each subject, including:

- AVF functioning with no intervention
- AVF functioning with intervention, no occlusion
- AVF functioning with intervention, after occlusion
- AVF functioning but not being used
- AVF abandoned prior to initial function
- AVF abandoned after initial function
- Subject not on HD