Cover Page for Study Protocol

Clinical Investigation Plan Title: Ellipsys Vascular Access System Post Market Surveillance (PS) Study

ClinicalTrials.gov Identifier: NCT04484220

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Medtronic

**Clinical Investigation Plan**

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| **Clinical Investigation Plan/Study Title** | Ellipsys Vascular Access System Post Market Surveillance (PS) Study |
| **Clinical Investigation Plan Identifier** | MDT20052 (PS200001) |
| **Study Product Name** | Ellipsys Vascular Access System |
| **Sponsor/Local Sponsor** | Medtronic Vascular, Inc.<br>2300 Berkshire Lane<br>Plymouth, MN 55441<br>USA |
| **Document Version** | 4.0 |
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**Confidentiality Statement**

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# 1. Glossary

| Term | Definition |
|---|---|
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| AV | Arteriovenous |
| AVF | Arteriovenous Fistula |
| CEC | Clinical Event Committee |
| CFR | Code of Federal Regulation |
| CIP | Clinical Investigation Plan |
| CMS | Centers for Medicare & Medicaid Services |
| CRF | Case Report Form |
| CRO | Clinical Research Organization |
| CTA | Clinical Trial Agreement |
| CV | Curriculum Vitae |
| CVC | Central Venous Catheter |
| DD | Device Deficiency |
| DoH | Declaration of Helsinki |
| DTL | Delegated Task List |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| ESRD | End Stage Renal Disease |
| FD | Financial Disclosure |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act |

| Term | Definition |
|---|---|
| GCP | Good Clinical Practice |
| HD | Hemodialysis |
| HIPAA | Health Insurance Portability and Accountability Act |
| IC | Informed Consent |
| ICH | International Conference of Harmonization |
| IDE | Investigational Device Exemption |
| IFU | Instructions For Use |
| IRB | Institutional Review Board |
| ISO | International Organization for Standardization |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| PS | Post-market Surveillance |
| PTA | Percutaneous Transluminal Angioplasty |
| PTFE | Polytetrafluoroethylene |
| QoL | Quality of Life |
| RA | Regulatory Authority |
| RVD | Reference Vessel Diameter |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SID | Subject Identification Number |
| UADE | Unanticipated Adverse Device Effect |

| Term | Definition |
|---|---|
| VAQ | Vascular Access Questionnaire |

## 2. Synopsis

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|---|---|
| **Title** | Ellipsys Vascular Access System Post Market Surveillance (PS) Study |
| **Clinical Study Type** | Observational, post-market surveillance |
| **Product Name** | Ellipsys Vascular Access System |
| **Sponsor** | Medtronic Vascular, Inc.<br>2300 Berkshire Lane<br>Plymouth, MN 55441<br>USA |
| **Indication under investigation** | The Ellipsys System is indicated for the creation of a proximal radial artery to perforating vein anastomosis via a retrograde venous access approach in patients with a minimum vessel diameter of 2.0mm and < 1.5mm of separation between the artery and vein at the fistula creation site who have chronic kidney disease requiring dialysis. |
| **Investigation Purpose** | To evaluate the safety and effectiveness of the Ellipsys Vascular Access System in the creation of a native AV fistula via percutaneous access in subjects who are on hemodialysis and are medically indicated for the creation of an upper limb anastomosis. |
| **Product Status** | The Ellipsys Vascular Access System was granted marketing authorization under de novo classification under regulation 513 (f)(2). The device is commercially available for the indication being studied. |
| **Primary Objective** | The primary objective of this post-market surveillance study is to support the 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 via percutaneous access in subjects who are on hemodialysis and are medically indicated for the creation of an upper limb anastomosis. |
| **Primary Endpoints** | **Primary Safety Endpoints**<br>*Early Occlusion*<br>Early occlusion is defined as the percentage of subjects with total occlusion within 7 days of the AVF creation procedure.<br>*Study Related Serious Adverse Events through 12 months*<br>Serious adverse event related to the device, study procedure or secondary procedure to maintain or re-establish patency through 12 |

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| | months<br><br>**Primary Effectiveness Endpoint**<br>*Cumulative Patency through 12 months post-AVF creation*<br>Cumulative patency is defined as the interval from time of access creation until access abandonment |
| **Secondary Objective** | Secondary objectives include descriptive analyses of secondary endpoints as well as acute procedural observations and clinical utility measures. |
| **Secondary Endpoints** | 1. Primary Patency through 12 months<br>2. Assisted Primary Patency through 12 months<br>3. Secondary Procedures<br>4. Overall Patient Safety |
| **Study Design** | Prospective, multi-center, single-arm, non-randomized, observational, post-market surveillance (PS) study |
| **Sample Size** | Minimum of 134 subjects |
| **Inclusion/Exclusion Criteria** | General Inclusion Criteria<br>1. Male or non-pregnant female ≥ 18 years old and ≤ 80 years old<br>2. Life expectancy of at least one year per investigator's opinion<br>3. Diagnosed with end-stage renal disease ESRD or chronic kidney disease on hemodialysis<br>4. Patients deemed medically eligible for upper extremity autogenous AV fistula creation, per institutional guidelines and/or clinical judgement<br>5. Adequate quality vein based on pre-operative assessment:<br>a. Adjacent vein diameter of ≥ 2.0mm at target anastomosis site<br>b. Confirmed clinically significant outflow<br>6. Adequate quality radial artery based on pre-operative assessment:<br>a. Arterial lumen diameter of ≥ 2.0mm at target anastomosis site<br>7. Adequate collateral arterial perfusion with patent palmar arch demonstrated by Barbeau Test or Allen's Test<br>8. Radial artery-adjacent vein proximity of ≤ 1.5mm measured lumen edge-to-lumen edge as determined by pre-procedural ultrasound and confirmed pre-procedure<br>9. Patient is able to provide written informed consent and attend follow up examinations at the enrolling institution<br>Imaging-based Inclusion Criteria |

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| | 10. Confirmed radial artery-adjacent vein proximity of ≤1.5mm measured lumen edge-to-lumen edge as determined by pre-procedural ultrasound and confirmed pre-procedure<br>11. Confirm radial artery and adjacent vein diameter of ≥ 2.0mm at target anastomosis site<br>General Exclusion Criteria<br>1. Pre-existing ipsilateral vascular disease interfering with the study procedure or potentially confounding the study results including:<br>a. Documented or suspected central venous stenosis (≥ 50%) or<br>b. Upper extremity arterial stenosis or<br>c. Vascular disease at the radial artery/adjacent vein site<br>2. Prior vascular surgery at or proximal (central) to the AVF target site interfering with AVF maturation or other ipsilateral surgery that could potentially confound the study results such as prior axillary dissection or mastectomy<br>3. History of steal syndrome from a previous surgical ipsilateral hemodialysis vascular access which required intervention or abandonment<br>4. Systolic pressures < 100mgHg at time of screening<br>5. Suspected or confirmed skin disease at the skin entry site<br>6. Edema of the upper extremity on the ipsilateral side<br>7. Immunocompromised subjects due to underlying disease or immunosuppressant therapy such as sirolumus (Rapamune®) or Prednisone at a dose > 10mg per day<br>8. Known bleeding diathesis, coagulation disorder, or medications putting the subject at increased risk, per investigator's judgement<br>9. Patients with acute or active infection<br>10. Scheduled kidney transplant within 6 months of enrollment<br>11. Participation in another clinical investigation (excluding retrospective studies or studies not requiring a consent form)<br>12. History of substance abuse or anticipated to be non-compliant with medical care or study requirements based on investigator's judgement<br>13. Patient has an active COVID-19 infection with ongoing sequela or hospitalization for treatment of COVID-19. |
| **Study Procedures and Assessments** | Subjects successfully enrolled in this study are to be followed for 12 months (+ 2-months window) post AVF creation. Follow-up |

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| | assessments are be scheduled for 1 week, 4 weeks, 3, 6, and 12 months. |
| **Safety Assessments** | In addition to the primary safety endpoint analysis, adverse event (AE) assessments through the 12-month follow-up will be collected and reported. Refer to Section 11 for additional details on types of AEs to be collected and their associated reporting requirements. |
| **Statistics** | **Primary Safety Endpoint:**<br>Early occlusion will be summarized for the Safety population by presenting the number, percentage, and 95% confidence interval. Early occlusion in the post-market study will be descriptively compared to the pre-market study by presenting the percentages and 97.5% confidence intervals for each study.<br><br>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. A sensitivity analysis shall be performed where a cumulative incidence curve is estimated and death will be accounted for as a competing risk.<br><br>**Primary Effectiveness Endpoint:**<br>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. 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. |
| **Title** | Ellipsys Vascular Access System Post Market Surveillance (PS) Study |

# 3. Introduction

## 3.1 Background

More than 500,000 Americans are affected by chronic end stage renal disease (ESRD) necessitating dialysis to stay alive. One fifth of all hemodialysis patients will die each year and another 125,000 new patients will begin dialysis during that same period. Worldwide, there are 1.9 million people on hemodialysis.

In 2019, the National Kidney Foundation updated the Kidney Disease Outcomes Quality Initiation (KDOQI) Clinical Practice Guideline for Vascular Access to include a more patient-focused approach to ESRD management. The intent of the newly adopted “Life-Plan” is to provide each patient with an

individualized plan for their current dialysis access needs while keeping in mind future access needs. The Fistula First initiative increased creation of arteriovenous fistulas (AVF) to more than 60% of US patients. Still, creation of a fistula remains a challenging surgical procedure for even the most experienced surgeon. It is a technically demanding open procedure that attaches small blood vessels together. Surgery times to create the AV fistula can range from 30 to 90 minutes requiring the use of magnifying loupes and delicate sewing techniques. There is also a high rate of primary failures of AV fistulas, up to 50% in some centers. When an upper-arm fistula fails, the patient's future vascular access options are also negatively impacted. This complication rate and surgical difficulty in creating an AV fistula are believed to have driven the wide- spread use of PTFE grafts because of the relative ease of the surgical technique, despite their poorer clinical outcomes. While the Fistula First initiative reduced PTFE graft use, chronic venous catheter (CVC) utilization remained unchanged.

A strong clinical need exists for a reliable, percutaneous endovascular access system to create a native AV fistula not involving reliance on an open surgical procedure. Endovascular interventions are well-established in medical practice and are substantiated to minimize the risks to patients of anesthesia complications, wound healing, bleeding, and infection. The tissue and other bodily trauma associated with open surgical procedures are much greater when compared to minimally invasive techniques. As more tissue is exposed to the air in an open surgical procedure, the risk of infection is greatly increased. The surgical trauma of a cut-down procedure includes vessel dissection with an increased risk of bleeding. As such the medical option of an open surgical procedure is inferior to the safer, less traumatic, endovascular procedure. The reduced tissue trauma may benefit the patient by reducing pain and recovery time. Further, the minimally invasive procedure allows for intravascular sealing of the vein and artery leaving the vasculature around the AVF site undisturbed.

The Ellipsys Vascular Access System (Ellipsys System) has demonstrated clinical safety and efficacy in a U.S. IDE pivotal clinical trial and was granted De Novo marketing clearance on June 22, 2018.

## 3.2 Purpose

Medtronic, Inc. is sponsoring this post-market surveillance study to evaluate the safety and effectiveness of the Ellipsys System in the creation of a native AV fistula via percutaneous access in subjects who are on hemodialysis and are medically indicated for the creation of an upper limb anastomosis.

# 4. Objectives and Endpoints

## 4.1 Objectives

### 4.1.1 Primary 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 System in the creation of a native AV fistula via percutaneous access in subjects who are on hemodialysis and are medically indicated for the creation of an upper limb anastomosis.

### 4.1.2 Primary Endpoints

To evaluate the Ellipsys System, this study design shall include three primary endpoints; two to evaluate 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**

1. **Early Occlusion**

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

2. **Study Related Serious Adverse Event (SAE) Rate Through 12 months**

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

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

**Primary Effectiveness Endpoint**

1. **Cumulative Patency Through 12 months Post-AVF Creation:**

   Defined as freedom from access abandonment from time of access creation.

### 4.1.3 Secondary Objectives

The following secondary objectives include descriptive analyses of secondary endpoints as well as acute procedural observations and clinical utility measures.

### 4.1.4 Secondary Endpoints

The 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 re-establish 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.

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 adverse events during the study.

### 4.1.5 Ancillary Objectives

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

### 4.1.6 Ancillary Endpoints

The 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 (DUS).

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. Study Design

This is a prospective, multicenter, non-randomized post-market surveillance study evaluating the Ellipsys System for the creation of a native AV fistula in subjects who are on hemodialysis and are medically indicated for the creation of an upper limb anastomosis. All eligible subjects who provide informed consent and meet all inclusion/exclusion criteria are to be enrolled into this study. Total enrollment is 134 subjects at up to 14 US sites. There is no minimum enrollment requirement at each site; however, no individual site may enroll more than 27 study subjects.

## 5.1 Duration

Once enrolled, subjects shall remain in the study through completion of the required follow-up duration unless the subject withdraws consent, the investigator withdraws the subject, or Medtronic terminates the study for any reason. The enrollment phase is expected to take approximately 13 months. The follow-up duration for each subject is 12 months. The total expected duration of the study is approximately 30 months.

## 5.2 Rationale

The clinical performance of the Ellipsys System shall be evaluated through a prospective, multicenter, non- randomized post-market surveillance study in a total of 134 subjects. The study has been designed to further characterize the short and long-term safety and effectiveness of the Ellipsys System to create an AV fistula in subjects on hemodialysis.

# 6. Product Description

## 6.1 General

The Ellipsys System is intended for use as a less invasive means to create an AV fistula via percutaneous access. The Ellipsys System mechanically approximates a vein and artery to create an anastomosis in the vasculature of the upper limb in order to produce an AV fistula.

The Ellipsys System is comprised of the Ellipsys Catheter and the Ellipsys Power Controller. The Ellipsys Catheter is placed percutaneously using Seldinger technique to place a guidewire and appropriately sized introducer Sheath into the selected vein in close proximity to the selected artery. The Ellipsys Catheter is advanced through the sheath over the guidewire and actuated at the selected anastomosis site and the vein and artery are approximated.

The Power Controller is used to create the anastomosis once the vessels are in the appropriate relative positions. The Ellipsys Catheter is then removed from the vessel and the skin access site is closed using standard percutaneous closure techniques. The Ellipsys System will be deployed and in use for less than 2 hours with no element of the device left behind.

The micropuncture set, Guidewire and Introducer Set are commercially available, off-the-shelf medical devices.

## 6.2 Manufacturer

The Ellipsys System is manufactured in accordance with standard procedures and specifications under 21 CFR 820 and EN ISO13485. The manufacturer is listed below:

Medtronic Inc. (formerly Avenu Medical Inc.)
27123 Calle Arroyo, Suite 2101
San Juan Capistrano, CA
92675 USA

## 6.3 Packaging

The Ellipsys System is comprised of two main components: the Ellipsys Catheter and the Ellipsys Power Controller. The Ellipsys Catheter is provided in sterile packaging and is meant as a single-use disposable device. The Ellipsys Power Controller is reusable and non-sterile.

## 6.4 Intended Population

The Ellipsys System is indicated for the creation of a proximal radial artery to perforating vein anastomosis via a retrograde venous access approach in patients with a minimum vessel diameter of

2.0mm and less than 1.5mm of separation between the artery and vein at the fistula creation site who have chronic kidney disease requiring dialysis.

## 6.5 Equipment

Any test equipment critical to be used for assessing endpoints (e.g., Duplex Ultrasound, etc.) will be maintained/calibrated according to the study sites' standard protocol.

## 6.6 Product Use

The Instructions for Use (IFU) is available separate from this CIP. Devices used in this study will be taken from commercial inventory at the study sites.

## 6.7 Product Training Materials

The Investigator delegated to performing the Ellipsys EndoAVF creation procedure (Index Procedure) will be evaluated to ensure that he/she is qualified by training, education, and experience. Each investigator must meet the predefined 'Newly Trained Provider' requirements prior to site activation

### 6.7.1 Newly Trained Provider

The following stipulations must be met for an investigator to qualify as a 'Newly Trained Provider':

Investigator must fulfill both of the following:

- Did not participate in the IDE study, or participated but performed Ellipsys endoAVF creation in ≤2 subjects in the IDE study
- Performed a total of ≤10 Ellipsys cases in study or commercial settings at the time of site/investigator selection for the post-approval study.

Investigator must complete appropriate training including:

- Completion of non-patient-based training, including vascular mapping and device model training
- Completion of patient-based training by one of the following:
    - ≥1 patient based Ellipsys endoAVF creation, proctored by a sponsor assigned trainer or a trained investigator, or
    - ≥3 documented prior experience of Ellipsys endoAVF creation in a clinical trial or commercial setting

Training completion documentation must be collected for at least one 'Newly Trained Provider' prior to site activation.

## 6.8 Product Receipt and Tracking

Product accountability will not be performed for this study. Devices will be taken from commercial inventory at study sites.

## 6.9 Product Storage

It is the responsibility of the investigator to correctly handle and store market released product. These products will be used according to their labeling.

## 6.10 Product Accountability

Product accountability will not be maintained for this study as the products used are market released in the U.S.

Product delivery

Commercially available product supply will be managed in a manner consistent with other market-released products.

Product receipt and tracking

All products used in this study will be market released in the geographies they are used. Device Traceability may be required per local laws and regulations. If there are additional local requirements related to the Ellipsys System beyond what is collected by Medtronic on the eCRF, this is the Investigator's responsibility and should be recorded in the subject's medical records, but will not be collected by Medtronic (e.g., national registration card number, identification code linked to names and contact information, log of all subjects enrolled in the study, lot or batch number).

# 7. Study Site Requirements

## 7.1 Investigator/Investigation Site Selection

All investigators managing the subject's endoAVF must be qualified practitioners and experienced in the diagnosis and treatment of subjects with ESRD. All 'Newly Trained Provider' physicians must be trained in the handling of the Ellipsys System.

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The investigator/investigation site must meet the following minimum criteria:

1. Investigator/site is qualified by training, education, and has relevant experience appropriate to the use of the product and associated procedures.
    a. Operating physician must be trained in the surgical or percutaneous creation of AV fistulas and/or be trained in minimally invasive percutaneous procedures (e.g., endovascular interventions).
2. Investigator must have experience with medical devices and/or regulated studies.
    a. Site has participated in at least one pre-market study in the last 5 years.
3. Investigator must have interest in the therapy proposed for this investigation.
4. Investigator/site expects to have adequate staff, time and resources to the conduct the study throughout the duration of the study. Each site must have a designated research coordinator assigned to the study.
5. Investigator/site has access to an adequate number of eligible subjects.
6. Ability to perform duplex ultrasounds.
7. Investigator/site has access to hemodialysis treatment records for enrolled subjects throughout follow-up period according to the study protocol.

8. Site has at least one Investigator (Principal or Sub-Investigator) that meets the definition of a Newly Trained User (i.e. has performed ≤10 Ellipsys cases in a clinical trial or commercial setting OR participated in the Ellipsys IDE Study but performed ≤2 Ellipsys EndoAVF creation study procedures).
9. Investigator/site has the ability to comply with the protocol, required procedures, applicable Institutional Review Board (IRB) and national/local regulations.
10. Investigator is not debarred, disqualified, or working under sanctions in applicable regions. *U.S. Sites: Investigator has not been excluded from participation in all Federal Health Care programs (e.g. Medicare, Medical, Medicaid). Investigator is not on the list of FDA list of investigators who have been disqualified, restricted, or debarred from conducting clinical studies.*
11. Anticipated study startup timeline, including contracting and IRB and regulatory submission and approval (if applicable) is acceptable.
12. Anticipated competition for same subject population from competitive ongoing studies is at an acceptable rate.

Study site personnel training will be completed and documented prior to participation in this study.

## 7.2 Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train study site personnel on the clinical investigation plan, informed consent, and on data collection and reporting tools. If new members join the study site team, they will receive training on the applicable study requirements relevant to their role before contributing to the study.

Prior to performing study related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- IRB approval (and voting list, as required by local law) of the current version of the CIP and IC.
- RA approval or notification (as required per local law)
- Fully executed CTA
- Financial disclosure (if applicable)
- CV of investigators and key members of the investigation study site team (as required).
- Documentation of delegated tasks
- Documentation of study training.
- Additional requirements imposed by local regulations, the IRB and RA shall be followed, if appropriate.

In addition, all participating study site staff must be trained on the current version of the CIP as well as on the applicable study requirements depending on their role and must be delegated by the principal investigator to perform study related activities.

Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to performing study related activities.

## 7.3 Role of the Sponsor Representatives

Sponsor representatives may provide support at the study site as required for the study under supervision of the Principal Investigator, including:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support at the EndoAV Fistula Creation Procedure, Week 1, and Week 4 follow-up visits, and as needed during EndoAVF cannulation for hemodialysis under the supervision of a study investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at study sites
- Monitoring and auditing activities
- Duplex ultrasound and vein mapping training visits as well as maturation procedure consultation, as needed

# 8. Selection of Subjects

## 8.1 Study Population

This study will be conducted in subjects diagnosed with ESRD or chronic kidney disease on hemodialysis who are medically indicated for the creation of an upper limb anastomosis. Patients who provide informed consent shall be enrolled into this study.

## 8.2 Subject Enrollment

Only subjects who provide written informed consent, meet all inclusion criteria (section 8.3) and none of the exclusion criteria (section 8.4), are considered eligible for enrollment at each study site. When a subject and the principal investigator or authorized designee, as required, have personally signed and dated the IC, the subject is considered enrolled in the study. The date the subject signed the IC must be documented in the subject's medical records.

The decision to use the Ellipsys System will occur at the time of the procedure, based on confirming pre-procedural Inclusion Criteria. The target vessels will be assessed for size and quality (i.e., location, tortuosity, stenosis, degree of calcification) using vascular ultrasound. If a subject's AVF becomes occluded and is abandoned, the subject will not be eligible for re-enrollment into the post market surveillance study. The following criteria will be used to determine the patient's eligibility for enrollment in the study.

## 8.3 Inclusion Criteria

Patients must meet all of the following general inclusion criteria:

1. Male or non-pregnant female ≥ 18 years of age and ≤ 80 years of age
2. Life expectancy of at least one year, in the investigator's opinion
3. Diagnosed with ESRD or chronic kidney disease on hemodialysis.

4. Patients deemed medically eligible for upper extremity autogenous AV fistula creation, per institutional guidelines and/or clinical judgment
5. Adequate quality vein based on pre-operative assessment
   a. Adjacent vein diameter of ≥2.0 mm at target anastomosis site
   b. Confirmed clinically significant outflow
6. Adequate quality radial artery based on pre-operative assessment
   c. Arterial lumen diameter of ≥2.0 mm at target anastomosis site
7. Adequate collateral arterial perfusion with patent palmar arch as demonstrated by Barbeau Test or Allen's Test.
8. Radial artery-adjacent vein proximity ≤1.5 mm measured lumen edge-to-lumen edge as determined by pre-procedural ultrasound and confirmed pre-procedure
9. Patient is able to provide written informed consent and attend follow-up examinations at the enrolling institution

**Imaging-based Inclusion Criteria**

The following criteria are to be assessed during the study Index procedure immediately prior to use of the Ellipsys device:

10. Confirm radial artery-adjacent vein proximity ≤1.5 mm measured lumen edge-to-lumen edge as determined by pre-procedural ultrasound and confirmed pre-procedurally
11. Confirm radial artery and adjacent vein diameter of ≥2.0 mm at target anastomosis site

## 8.4 Exclusion Criteria

Patients must not meet any of the following general exclusion criteria:

1. Pre-existing ipsilateral vascular disease interfering with the study procedure or potentially confounding the study results including:
   a. Documented or suspected central venous stenosis (≥ 50%) or
   b. Upper extremity arterial stenosis or
   c. Vascular disease at the radial artery / adjacent vein site
2. Prior vascular surgery at or proximal (central) to the AVF target site interfering with AVF maturation or other ipsilateral surgery that could potentially confound the study results such as prior axillary dissection or mastectomy
3. History of steal syndrome from a previous surgical ipsilateral hemodialysis vascular access which required intervention or abandonment
4. Systolic pressures < 100 mg Hg at the time of screening
5. Suspected or confirmed skin disease at the skin entry site
6. Edema of the upper extremity on the ipsilateral side
7. Immunocompromised subjects due to underlying disease or immunosuppressant therapy such as sirolimus (Rapamune®) or Prednisone at a dose of > 10 mg per day

8. Known bleeding diathesis, coagulation disorder or medications putting the subject at increased risk, in the Investigator's judgment
9. Patients with acute or active infection
10. Scheduled kidney transplant within 6 months of enrollment
11. Participation in another clinical investigation (excluding retrospective studies or studies not requiring a consent form)
12. History of substance abuse or anticipated to be non-compliant with medical care or study requirements based on investigator judgment
13. Patient has an active COVID-19 infection with ongoing sequela or hospitalization for treatment of COVID-19.

# 9. Study Procedures

Refer to Figure 1 for a study flow diagram from patient screening through AVF creation. Subjects enrolled in the study and who undergo a successful AVF creation procedure will be followed for 12 months.

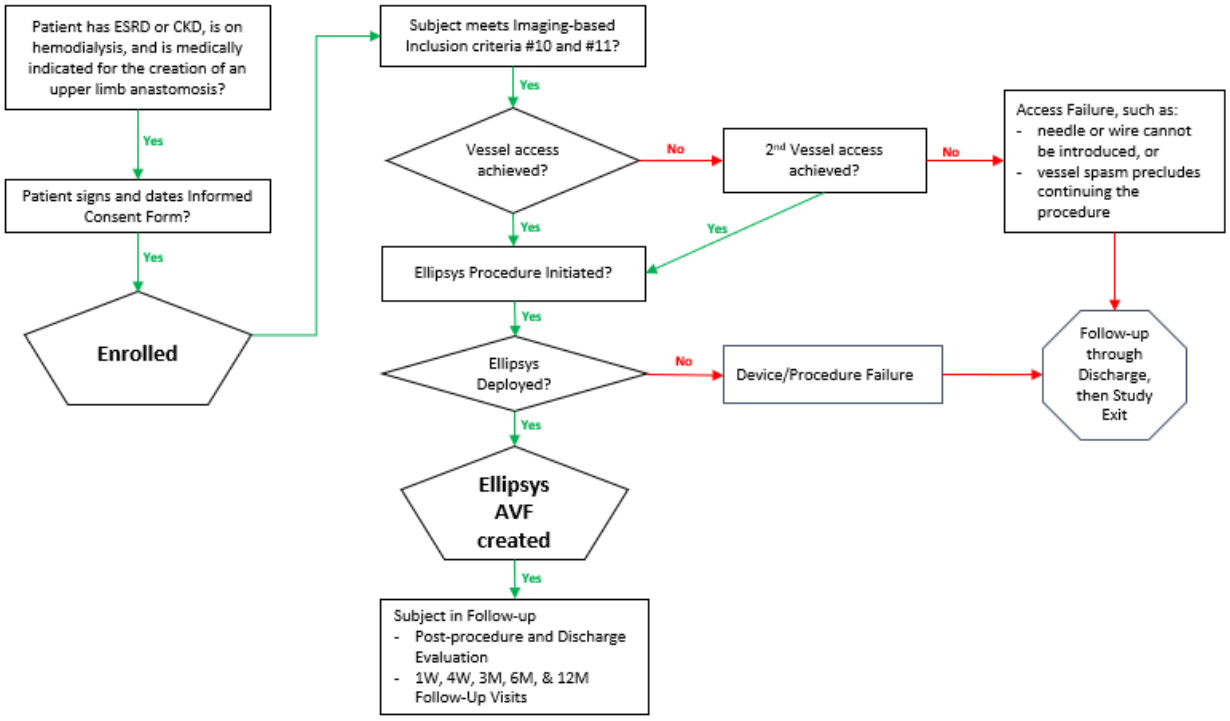


**Figure 1: Flow Diagram from Patient Screening to Subject Follow-Up**

## 9.1 Schedule of Events

The clinical study will require follow-up visits at post-procedure/discharge, 1 week, 4 weeks, 3-, 6-, and 12-months post-index procedure. Table 1 shows a detailed overview of the schedule of clinic evaluations and follow-up visits. Most of the required tests and procedures are considered standard of care for subjects who have a surgical or percutaneous AV fistula created.

**Table 1: Schedule of Assessments and Visit Windows**

| Data Collection Requirement / Assessment | Baseline | Index Procedure | Post-Procedure / Discharge | 1 Week (± 2 days) | 4 Weeks (± 7 days) | 3 Months (± 14 days) | 6 Months (± 30 days) | 12 Months (+ 60 days) |
|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | |
| Demographics, Clinical Evaluation, & Vital Signs | X | | | | | | | |
| Duplex Ultrasound | X[1] | X[1] | X | X | X | X | X | X |
| Study Procedure | | X | X | | | | | |
| AVF Evaluation | | | | X | X | X | X | X |
| Secondary Procedures[2] | | X[5] | X | X | X | X | X | X |
| Hemodialysis Records | | | | | X[3] | X[3] | X[3] | X[3] |
| Subject Satisfaction (VAQ) | | | | | | | X | |
| Cannulator Satisfaction Survey | | | | | | X | X | X |
| Adverse Events and Device Deficiencies[4] | X | X | X | X | X | X | X | X |
| Medications | X | X | | X | X | X | X | X |

[1]The Baseline and Pre-procedure Duplex Ultrasounds are to be performed and assessed by the Investigator/designee only, they will not be submitted to the DUS Core Lab. Beginning with the post-procedure DUS exam through follow-up completion, all DUS images are to be performed according to the Ellipsys PS DUS Protocol and submitted to the DUS Core Lab for analysis.

[2]Additional procedures needed to mature or maintain the AVF or re-establish flow to meet the prescribed dialysis parameters. The need for such procedures will be assessed subsequent to completion of the AVF creation procedure.

[3]Collection through successful 2-needle access of study AVF for >2/3 of sessions over a continuous 28-day period.

[4]Adverse Event and Device Deficiencies assessment is required from the moment the subject is enrolled in the study (i.e. subject signed and dated the informed consent form).

[5] If an adjunctive procedure is required during the AVF creation procedure, the details of the procedure will be documented on the Adjunctive/Secondary Procedure CRF and will indicate that the adjunctive procedure occurred during the AVF creation procedure.

## 9.2 Data Collection

Data collection requirements are summarized in Table 2 below.

**Table 2: Data Collection Requirements for Enrolled Subjects**

| Category | Sub-Category | PIC Signed | Required eCRFs | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Consent | Inclusion/ Exclusion | Baseline | Medical History | Procedure | Secondary Procedure | Subject Visits | Dialysis Treatment Record | Vascular Access Questionnaire | Cannulator Satisfaction Survey | Dialysis Catheter Use | AE | Device Deficiency | Study Exit |
| Enrolled[1] | Safety Population[2] | X | X | X | X | X | X | X | X | X | X | X | X | X[3] | X[3] | X |
| | Access Failure[4] | X | X | X | X | X | X[4] | | | | | | | X[4] | | X |
| | Device Failure[5] | X | X | X | X | X | X | | | | | | | X[3] | X[5] | X |
| | Procedure Failure[6] | X | X | X | X | X | X | | | | | | | X[3] | X[3] | X |

[1]**Enrolled:** subject who signed and dated the informed consent form.

[2]**Safety population:** enrolled subjects for whom the procedure is attempted, and the Ellipsys System is deployed.

[3]As applicable

[4]**Access failure:** enrolled subjects in whom the Ellipsys device is not deployed due to 1) the needle or wire cannot be introduced, or 2) vessel spasm precludes continuing the procedure. These subjects may be re-scheduled for another attempt at access later the same day or within 30 days. If no second attempt is made or the second attempt is not successful, these subjects will be considered access failures and will be followed for safety through clinic discharge. Two Procedure eCRFs are to be completed for subjects in this category. If an AE occurs prior to discharge, subject will be followed for safety until resolution.

[5]**Device failure:** a malfunction of the Ellipsys 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. A Device Deficiency eCRF must be completed to report the device failure.

[6]**Procedure failure:** the Ellipsys 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.

## 9.3 Scheduled Follow-up Visit Windows

After receiving notice of successful device application, Medtronic will provide the target dates and windows for each visit to the study site if applicable. Should a subject miss a visit or the visit fall outside the pre-specified window, a protocol deviation must be reported, and the original follow-up schedule maintained for subsequent visits.

Data analyses include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a protocol deviation. Follow-up visit windows are listed in Table 3 and are based on days post-AVF creation.

**Table 3: Study Follow-Up Visit Windows**

| Study Follow-up Visit | Window (Calculated days post-AVF creation procedure) |
|---|---|

| | Window Start (days post-procedure) | Target (days post-procedure) | Window End (days post-procedure) |
|---|---|---|---|
| **1 Week** (± 2 days) | Day 5 | Day 7 | Day 9 |
| **4 Weeks** (± 7 days) | Day 23 | Day 30 | Day 37 |
| **3 Months** (± 14 days) | Day 76 | Day 90 | Day 104 |
| **6 Months** (± 30 days) | Day 150 | Day 180 | Day 210 |
| **12 Months** (+ 60 days) | Day 360 | Day 360 | Day 420 |

## 9.4 Subject Screening

Patient eligibility for a surgical or percutaneous AVF will be assessed based on standard of care institutional guidelines which may include medical history, physical examination, blood pressure, ultrasound vascular mapping and other parameters. Those patients who are eligible for a surgical or percutaneous AVF may be considered for inclusion in this study. Patients who meet all general screening criteria will be asked to participate in the study. Patients who fail to meet one or more of the I/E criteria will be considered screening failures. If the patient agrees to participate, a personally signed and dated informed consent will be obtained. These subjects may then proceed with study specific screening procedures, including the pre-procedure confirmatory vascular mapping by ultrasound.

Institutional screening procedures may be used to fulfill study criteria if the investigator assesses that the subject's condition has remained stable. Female subjects will be assessed by history and/or review of medical records for reproductive potential and if necessary, a pregnancy test will be done to exclude pregnancy. Subjects who sign and date the informed consent form will be enrolled in the study and proceed with the study procedure.

## 9.5 Subject Consent

Informed consent is defined as a legally effective documented confirmation of a subject's or their legally authorized/designated representative voluntary agreement to participate in a particular study after information has been given and explained to the subject on all aspects of the study that are relevant to the subject's decision to participate. This process includes obtaining an informed consent (IC) Form that has been approved by the study site's IRB and signed and dated by the subject or their legally authorized/designated representative. A subject may only consent after information has been given and explained to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate.

Prior to enrolling subjects, the IC Form must be approved by the IRB. The document(s) must be controlled (i.e. versioned and/or dated) to ensure it is clear which version(s) were approved by the IRB. Any adaptation of the sample IC Form must be reviewed and approved by Medtronic and the IRB reviewing the application prior to enrolling subjects. The sample IC Form is available separate from this CIP.

The investigator must notify the subject or their legally-authorized/designated representative of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study. If relevant, consent may be requested from subjects to confirm their continued participation.

Prior to initiation of any study-specific procedures, IC must be obtained from the subject or their legally authorized/designated representative. Some general inclusion/exclusion criteria that are standard of care may be evaluated prior to the subject signing the IC Form. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize study sites to submit subject information to the study sponsor. The IC process must be conducted by the principal investigator or an authorized designee, and the IC Form must be given to the subject or their legally authorized/designated representative in a language he/she is able to read and understand. The process of IC must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other study site personnel. The IC process shall not waive or appear to waive subject's legal right. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the IC form, to inquire about details of the study, and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the study, the IC Form must be signed and personally dated by the subject and investigator or authorized designee, as required by the IRB.

A copy of the IC Form, signed and dated, must be provided to the subject and his/her authorized designee.

If the IC is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures. It is best practice for the IC process to be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write, witnessed (impartial witness) IC will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the IC. The IC should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated consent to participate in the study.

The original of the signed IC Form must be filed in the hospital/clinical chart and/or with the subject's study documents.

The IC must be available for monitoring and auditing.

## 9.6 Enrollment

A subject is considered enrolled when the consent process has been finalized and the IC Form has been signed and dated. The date the subject or the subject's authorized/designated representative signed the IC and Data Protection Authorization, as required by law, must be documented in the subject's medical records. A log of all subjects enrolled in the study should be maintained. Enrollment can be a stand-

alone visit or can occur on the same day as the baseline visit. Once consent is obtained, report adverse events/deaths, study deviations and subject exits as they occur.

## 9.7 Baseline

The baseline visit can be a stand-alone visit or can be performed on the same day prior to the AVF creation procedure.

The following information is required to be collected at the baseline visit:

- Demographics
- Clinical Evaluation
- Vital Signs
- Medical/Surgical History
- Medications
- Hemodialysis History
- Baseline Duplex Ultrasound (vascular mapping) is performed and assessed by the Investigator to confirm the subject meets pre-procedure inclusion criteria 10 and 11. It will not be submitted to the DUS Core Lab.
- Adverse events are required from the moment the subject is enrolled in the study (i.e. subject signed and dated the informed consent form)

## 9.8 AV Fistula Creation Procedure (Day 0)

The following information is required to be collected at the AV Fistula creation procedure (Index Procedure) visit:

- Date of procedure
- Visit type: Initial Study Procedure or Reattempt Study Procedure
- Pre-procedure Duplex Ultrasound (vascular mapping) is performed and assessed by the Investigator to confirm the subject meets pre-procedure inclusion criteria 10 and 11. It will not be submitted to the DUS Core Lab.
- Pre- and Intra-Operative Medications
- Procedure Times
- Ellipsys Catheter and Power Controller Identification
- Procedure information (including access, device deployment, fistula creation, and post-AVF balloon dilation)
- Post-procedure Duplex Ultrasound (submit to DUS Core Lab) vessel dimensions and flow rates
- Assess fistula patency at discharge
- Adverse event is required from the moment the subject is enrolled in the study (i.e. subject signed and dated the informed consent form)
- If a complication or adverse event occurs intra-procedure, the details should be captured in the Adverse Event CRF and the Device Deficiency CRF if applicable

- If an adjunctive procedure is required during the AVF creation procedure, the details of the procedure will be documented on the Adjunctive/Secondary Procedure CRF and will indicate that that the adjunctive procedure occurred during the AVF creation procedure. Ballooning performed during the AVF creation procedure is not recorded on the Adjunctive/Secondary Procedure CRF, only on the Procedure CRF.
- Document any technical issues with the procedure

Adjunctive procedures are defined as any procedure done during the endo AVF creation procedure. These procedures will be documented on the Adjunctive/Secondary Procedure CRF. Balloon angioplasty is not considered an adjunctive procedure and details of balloon angioplasty during the endo AVF creation procedure will be captured on the Procedure CRF.

There may be cases where 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. These subjects may be re-scheduled for another attempt at access later the same day or within 30 days. If no second attempt is made or the second attempt is not successful, these will be considered access failures. These subjects will be followed for safety through clinic discharge.

Ultrasound and/or angiographic evaluation during the AVF creation procedure following AVF creation using the Ellipsys System and balloon dilation, will be used to determine the absence/presence of vessel dissection/perforation, evidence of distal emboli and possible hemorrhagic events. Post-procedure ultrasound and/or angiography will be performed and analyzed by the investigator. The post-procedure ultrasound will be submitted to the DUS Core Lab for analysis. If any secondary procedures listed in section 9.11 are required to mature or maintain the AVF or re-establish flow subsequent to completion of the AVF procedure, they will be documented in the Adjunctive/Secondary Procedure CRF and the AE CRF if applicable.

## 9.9 Recommended Antiplatelet/Anticoagulant Regimen

Based on the institutional standard of care and the judgement of the treating physician, subjects may be started or maintained on an anti-platelet or anti-coagulant regimen prior to or during the procedure and/or initial follow-up. The following measures are recommended to minimize risk of early thrombosis and/or occlusion:

1. Pre-procedure loading dose of 300 mg Plavix and 325 mg Aspirin given at index procedure
2. Intra-procedure injection of 3000 units heparin via the access sheath once radial artery access is achieved

## 9.10 Scheduled Follow-up Visits

Scheduled visits will occur at 1 Week, 4 Weeks, 3-, 6-, and 12-Months post-AVF creation. At each post-procedure follow-up visit, the subject's physical and vascular status will be assessed.

The following information is required to be collected at follow-up visits:

- Duplex Ultrasound (submit to DUS Core Lab) vessel dimensions and flow rates
- Evaluation of study AV Fistula
- Evaluation of upper extremity with access site created by study AVF
- Medications

- Secondary Procedures
- Hemodialysis Records
- Adverse Events
- Cannulator Satisfaction Survey (3-, 6-, and 12-month visits only), see Appendix 2: Cannulator Satisfaction Survey. If subject has not started receiving dialysis through the study AVF at the scheduled follow-up visit, the Cannulator Satisfaction Survey should not be completed
- Subject VAQ (collected at the 6-month visit only), see Appendix 1: Vascular Access Questionnaire

## 9.11 Secondary Procedures

Secondary Procedures are surgical procedures or percutaneous interventions that may be needed to mature or maintain the AVF or to re-establish flow to meet the prescribed dialysis parameters. The need for such procedures will be assessed by the Investigator subsequent to completion of the AVF procedure.

Secondary procedures do not include procedures performed during the procedure to create the study AVF, see section 9.8 for details of the AV fistula creation procedure. Secondary procedures are procedures subsequent to completion of the AVF procedure.

Additional secondary procedures can include, but are not limited to:

- Banding
- Branch Ligation
- Embolization Coils
- Embolization Plugs
- Percutaneous transluminal angioplasty (PTA)
- Stenting
- Transposition / Elevation / Superficialization
- Valvulotomy

Secondary Procedure information will be collected via the Adjunctive/Secondary Procedure CRF and an Adverse Event CRF, if applicable. If the above procedures are required during the AVF creation, they are considered adjunctive procedures, the details and timing of the procedure will be recorded on the Adjunctive/Secondary Procedure CRF, section 9.8 provides details and definition for adjunctive procedures.

## 9.12 Assessment of Efficacy

The primary effectiveness endpoint is described in section 4.1.2 as cumulative patency through 12 months post-AVF creation. Cumulative patency is defined as freedom from access abandonment from time of access creation.

## 9.13 Assessment of Safety

The primary safety endpoints are described in section 4.1.2 and are defined as follows:

- Early occlusion is defined as the percentage of subjects with total occlusion within 7 days of the AVF creation procedure
- Study related serious adverse event rate is defined as the rate of serious adverse events related to the device, study procedure or secondary procedure to maintain or re-establish patency through 12 months.

A full description of adverse events and reporting can be found in section 11.

## 9.14 Recording Data

Data entered into the electronic database must be traceable to source documents. Source documentation is defined as the first time data appear, and may include original documents, data, and records (e.g., hospital records, clinical and office charts, procedure reports, laboratory notes, memoranda, subjects' questionnaires or evaluation checklists, recorded data from automated instruments, and copies or transcriptions certified after verification as being accurate copies).

In general, eCRFs (or paper copies) may not serve as source documents. An exception may be the completion of QoL Questionnaires and clinical scales. Source documentation for data elements not routinely captured in medical records may vary from study site to study site; the study site may use source document worksheets if identified as source documents.

The investigator must ensure the availability of source documents from which the information on the eCRFs was derived. The type and location of source documents should be documented. Where printouts of electronic medical records, are provided as source documents, or where copies of source documents are retained as source documents, those should be certified. Certification must contain (1) the signature of the individual making the copy, (2) the date the copy was made and (3) a statement attesting to the accuracy and completeness of the copy.

The source documents must be made available for monitoring or auditing by Medtronic's representative or representatives of the competent authorities and other applicable regulatory agencies.

The CRF may be considered source for the following data collection elements:

- AE eCRF
  - Date study site became aware of event
- DD eCRF
  - Date study site became aware of event
- Subject Death
  - Date study site became aware of death
- Deviations
  - Reason for deviation

## 9.15 Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the CIP or the CTA. 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/ Adverse Device Effects 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

Investigators are required, whenever possible, to obtain prior approval from Medtronic before initiating changes in or deviations from the investigational plan, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval shall be documented in writing and maintained in the study files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g., subject did not attend scheduled follow-up visit), the event, however, is still considered a deviation.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB as well as Medtronic as soon as possible but no later than five (5) working days from the date of the deviation occurrence.

Reporting of all deviations should comply with IRB policies and/or local laws and/or regulatory agencies and must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation. Subject specific deviations shall be reported on the Protocol Deviation eCRF; all non-subject specific deviations (e.g. unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator Agreement, etc.) shall be reported to Medtronic in writing.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions which may include amending the CIP, conducting additional training, terminating the investigation, etc. Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment at that site until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic may provide site-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

## 9.16 Subject Exit, Withdrawal or Discontinuation

Every subject should be encouraged to remain in the study until they have completed the required follow-up per the CIP. Subjects shall be included in the analyses up to the time that consent was withdrawn. Subjects who discontinue participation prior to study completion shall be included in the analysis of results but shall not be replaced in the inclusion of total study subjects.

### 9.16.1 Study Exit

A study exit eCRF is required for all subjects. Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing system and/or procedure related AEs are resolved or unresolved with no further actions planned. Following exit, subjects will continue to receive standard medical care.

Subjects are urged to remain in the study as long as possible but may be exited from the study for any of the following situations:

- 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)

### 9.16.2 Study Completed

At the completion of the 12-month follow-up visit, subjects will be exited from the study. The 12-month follow-up visit and exit visit should be combined, and both a 12-month follow-up CRF and a Study Exit CRF need to be completed.

### 9.16.3 Lost to Follow-up

A subject is considered to be lost to follow-up if at least two attempts to contact the subject are unsuccessful. If a subject fails to return for follow-up visits, the site will contact the subject at the last known telephone number and/or dialysis center of record. The method of attempt (e.g., one letter and one phone record, or two letters) must be documented in the subject's medical record. In addition, regulation set forth by the governing IRB must be followed.

If all reasonable attempts to locate the subject fail, the subject will be considered lost to follow-up. A Study Exit CRF should be completed.

### 9.16.4 Subject Chooses to Exit (i.e. Revokes Consent)

A subject can withdraw from the study at any time. If the subject wishes to exit from the study (i.e. the subject revokes consent), the study site is required to document the reason for exit on the Exit CRF. In addition, study sites shall follow the regulations set forth by the governing IRB.

### 9.16.5 Investigator Withdraws Subject

No subjects should be withdrawn by investigators unless compelling medical justification is present. It is recommended investigators discuss any withdrawals with the study team prior to withdrawing subjects. If an Investigator Withdrawal is necessary, the following data should be collected prior to subject withdrawal if possible:

- Reason for subject withdrawal
- Rationale and/or documented safety concern

# 10. Risks and Benefits

## 10.1 Potential Risks

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance. As with any intravascular procedure there are risks such as vessel dissection, perforation and infection that can occur. The clinical risks of using the Ellipsys Vascular Access System are related to the ability to create and achieve AV Fistula maturation to support hemodialysis. Table 4 lists the events that can be reasonably associated with surgical or percutaneous AV fistula creation, chronic kidney disease, vascular intervention, or may result from the use of the Ellipsys Vascular Access System.

**Table 4: Potential Adverse Events**

| Vascular Events | Local Tissue Effects | Systemic Events | Other |
|---|---|---|---|
| • Vessel spasm<br>• Perforation of target or adjacent vessels<br>• Dissection of target or adjacent vessels<br>• Aneurysm or pseudoaneurysm<br>• Other injury to artery or vein, including intimal injury and resultant hyperplasia<br>• Thrombosis - total or partial occlusion due to clot formation or blockage within vessel<br>• Venous insufficiency or engorgement<br>• Arterial or venous hypertrophy<br>• Arterial or venous stenosis<br>• Arterial Steal Syndrome | • Bleeding (hemorrhage), extravasation or hematoma at the fistula or catheter insertion site requiring intervention<br>• Pain at the catheter insertion site<br>• Soft tissue damage<br>• Bruising, hematoma<br>• Ischemia<br>• Hyperemia<br>• Nerve damage of the upper extremity<br>• Transient functional impairment<br>• Edema of upper extremity | • High output cardiac failure<br>• Myocardial infarction<br>• Clinically significant changes in blood pressure<br>• Embolization of air, tissue, device or thrombus<br>• Stroke or transient ischemic attack<br>• Pulmonary arterial hypertension<br>• Death | • Electrical shock<br>• Allergic reaction to medications or device materials<br>• Infection or sepsis<br>• Failure to create an AVF during index procedure |

| | | | |
|---|---|---|---|
| • Venous hypertension<br>• Secondary surgical intervention to repair vascular injuries<br>• Loss of site for percutaneous AV fistula creation<br>• Acute anastomotic or vessel disruption due to PTA or other catheter-based manipulation | | | |

There are no incremental risks introduced to the subject as a result of participation in this study.

## 10.2 Risk Minimization

Potential risks with this study are minimized by selecting Investigators who are trained in the use of the study device and trained to the study protocol, by clearly defining inclusion/exclusion criteria to ensure only appropriate subjects are enrolled. In addition, the investigator performs a continuous monitoring, assessment, and documentation of any risks.

## 10.3 Potential Benefits

The Ellipsys System may offer no benefit. The potential benefit of having an AV fistula created with the Ellipsys System is reduced side effects as compared to standard therapy. The information gained from this study may be of benefit to other persons with the same medical condition.

## 10.4 Risk-Benefit Rationale

As with any intravascular procedure there are risks such as vessel dissection, perforation and infection that can occur. The clinical risks of using the Ellipsys Vascular Access System are related to the ability to create and achieve AV Fistula maturation to support hemodialysis. In the premarket study, there were no unanticipated adverse events. The adverse events reported were generally comparable to those associated with using other interventional intravascular devices and with standard open surgical AV fistula creation. The materials, manufacturing processes, and sterilization methods are well characterized, and verification testing mitigated the likelihood of unexpected events.

Potential risks with this study are minimized by selecting Investigators who are trained in the use of the study device and trained to the study protocol, by clearly defining inclusion/exclusion criteria to ensure only appropriate subjects are enrolled. In addition, the investigator performs a continuous monitoring, assessment, and documentation of any risks.

Medtronic shall establish a CEC to independently review and evaluate subject health status, device performance, and identify any safety concerns regarding subjects' wellbeing. Medtronic has further minimized the possibility of risks by completing product testing prior to the use of the Ellipsys System in this clinical study, implementing quality control measures into production processes, providing

guidelines for subject selection and evaluation, and providing adequate instructions and labeling. The Indication, warnings, and contraindications are provided in the device IFU.

# 11. Adverse Events and Device Deficiencies

## 11.1 Adverse Events

AE definitions are provided in Table 5. For this post-market surveillance study, only those adverse events related to the device, procedure, or secondary procedures, and any serious adverse events are required to be reported (including SAEs, ADEs, and SADEs). Such events shall be collected throughout the study duration, starting at the time of signing the IC through study exit.

Reporting of these events to Medtronic will occur on an AE eCRF and should begin at the time of study enrollment. Each event must be reported separately. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened.

Any medication/treatment associated with the treatment of an AE must be reported

Subject deaths are also required to be reported. Refer to Section 11.5 for AE reporting requirements.

## 11.2 Device Deficiency

The DD definition is provided in Table 5. DD information will be collected throughout the study and reported to Medtronic. Note that DD that result in an AE to the subject should be captured as an AE only.

DD that did not lead to an AE but could have led to a SADE (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate (no later than 72 hours of the investigator's/site's first knowledge of the event) reporting on a Device Deficiency eCRF (see Table 7).

## 11.3 Processing Updates and Resolution

For any changes in status of a previously reported adverse event or DD (i.e. change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE or DD form. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject dies or exits the study, or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to study completion, all efforts should be made to continue following the subject until all unresolved AEs are resolved, unresolved with no further actions planned, or site closure, whichever occurs first.

At the time of study exit, all collected adverse events that are unresolved must be reviewed and an update to the original AE must be reported.

## 11.4 Definitions/Classifications

For the purpose of this clinical study, Medtronic shall define and classify the following events per ISO14155:2020 and 21 CFR 812.3. Note that these regulations are used for definitions only. the study is not following either for reporting requirements as this is a post market surveillance study following 21 CRF 822.

**Table 5: Adverse Event and Device Deficiency Definitions**

| Event Type | Definition |
|---|---|
| **Adverse Event (AE)**<br>(ISO 14155:2020, 3.2) | Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated<br>NOTE 1: This definition includes events related to the investigational medical device or the comparator.<br>NOTE 2: This definition includes events related to the procedures involved.<br>NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. |
| **Serious Adverse Event (SAE)**<br>(ISO 14155:2020, 3.45) | AE that led to any of the following<br>a) death,<br>b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:<br>1) a life-threatening illness or injury, or<br>2) a permanent impairment of a body structure or a body function, including chronic disease, or<br>3) in-patient or prolonged hospitalization, or<br>4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,<br>c) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment<br>NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE. |
| **Adverse Device Effect (ADE)**<br>(ISO 14155:2020, 3.1) | AE related to the use of an investigational medical device<br>NOTE 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.<br>NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device.<br>NOTE 3: this includes 'comparator' if the comparator is a medical device. |
| **Serious Adverse Device Effect (SADE)**<br>(ISO 14155:2020, 3.44) | Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. |

| | |
|---|---|
| **Unanticipated Adverse Device Effect (UADE)** (21 CFR 812.3(s)) | Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. |
| **Device Deficiency** (ISO 14155:2020, 3.19) | Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.<br>NOTE 1: DD include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling.<br>NOTE2: This definition includes device deficiencies related to the investigational medical device or the comparator. |

For each reported AE, the causal relationship between the AE, the study device and the study procedure shall be classified as not related, possible, probable, or causal.

The causal relationships for device-related and procedure-related are defined in Table 6.

**Table 6: Adverse Event Causal Relationship Definitions**

| Related to | Definition |
|---|---|
| **Ellipsys System** | Adverse events directly attributable to use of the device including introduction, use and removal from the vessel. |
| **Study (Index) Procedure** | Adverse events that occur within 30 days of the index procedure where the Ellipsys System was used unless specifically shown not to be related to that index procedure.<br>Except the introduction, use and removal of the device including:<br>- initially accessing the vessel<br>- any catheter/wire exchanges during the study procedure not directly involving the study device, e.g., related to a completion angiogram |
| **Secondary Procedure** | Adverse events directly related to any aspect of the secondary procedure except the introduction, use and removal of device. |
| **Intra-procedure (Index) PTA/balloon angioplasty or Planned PTA/balloon Maturation Procedure** | Adverse events directly related to the intra-procedure (index) or planned PTA/balloon maturation procedure (peri-procedure AEs and late AEs) including:<br>- introducing, inflating, deflating or removing the balloon catheter<br>- intimal injury, acute anastomotic disruption, extravasation, hematoma, pseudoaneurysm<br>- peri-anastomotic stenosis, intimal hyperplastic lesions |

| | |
|---|---|
| | NOTE: As stated in the Ellipsys System IFU (available separate from the CIP), PTA/balloon maturation procedures to increase flow to the optimal access vessel was required in 99% of the Ellipsys IDE study subjects overall. The majority of these were performed to increase the anastomosis and juxta-anastomotic diameter and were unrelated to any clinical pathology. It is expected that similar procedures will be performed by the study investigator post-procedure and designated as such on the Secondary Procedure Form. |
| **Cannulation** | Adverse events directly related to cannulating a mature AV fistula target vessel to conduct dialysis, or other complications that can occur during or after dialysis such as bleeding, hematoma, etc. |

## 11.5 Reporting of Adverse Events

The investigator is required to assess and document in the medical record all SAEs, ADEs, SADEs, and DDs (per the definitions in Table 5) observed in subjects from the time of study enrollment. AEs shall be followed until the event has resolved or until study exit. In case of permanent impairment, the event shall be followed until the event stabilizes and the overall clinical outcome has been ascertained.

Reporting of AEs and DDs shall end once the subject exits the study. In any case where AEs are unresolved at the time of study exit, this shall be documented on the eCRF.

The investigator is responsible for reporting AEs to Medtronic and their local IRB (per IRB reporting requirements) as outlined in Table 7 below, by completing the Adverse Event eCRF and/or Device Deficiency eCRF. For the purposes of this CIP, planned/elective procedures for pre-existing conditions are not considered or reported as AEs as long as the pre-existing condition is not aggravated or exacerbated after a study procedure. A list of AEs that may be associated with the device and/or the interventional procedure is provided in Section 10.1.

**Table 7: Adverse Event Reporting Guidelines (Site Reporting to Medtronic*)**

| Event Type | Timeframe for Event Reporting | Requirement for Event to be Reported |
|---|---|---|
| Serious Adverse Event (SAE) | As soon as possible, but **within 10 working days** from the investigator's/site's first knowledge of the event | Through Study Exit |
| Adverse Device Effect (ADE) | | |
| Serious Adverse Device Effect (SADE) | | |
| Device Deficiency (DD) | | |
| | | |
| Device Deficiency (DD) that did not lead to AE but could have led to a SADE | **Immediately** or no later than **72 hours** from the investigator's/sites' first knowledge of the event | Through Study Exit |

*Study sites are responsible for reporting AEs/Device Deficiencies to the IRB per the IRB reporting policy

For any study related emergency, the investigators can contact the Medtronic Clinical Research Specialist assigned to the site, or any member of the Medtronic clinical study team. Contact information for the clinical study team are listed on the Study Contact List in the Investigator Site File.

## 11.6 Product Complaint Reporting

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless of whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the FDA as required per applicable regulations.

# 12. Data Review Committees

## 12.1 Clinical Events Committee Review

The Clinical Events Committee (CEC) is an independent committee of medical experts established to assess important endpoints of the study and determine whether each meet protocol-specified criteria. These endpoints may include certain categories of adverse events or other occurrences that arise during the study. The CEC reviews pertinent subject data, including, but not limited to, the patient medical chart, laboratory or pathology findings, imaging data, postmortem reports, and other relevant data for subjects participating in the study.

The CEC will consist of a minimum of three (3) non-Medtronic employed physicians that are not participating investigators for the study, including a CEC chairperson. The CEC is charged with the categorization of selected adverse events and clinical endpoints in the study, using criteria established at the outset of the study and specified by the CIP and the CEC Charter.

Database automated alerts and the independent Medical Monitor at Medtronic's designated Contract Research Organization (CRO) will identify clinical events requiring adjudication as specified in the CEC Charter. The CEC will regularly evaluate and adjudicate these events, as well as other events as may be requested by Medtronic.

The CEC will be established and led by:

Syntactx

4 World Trade Center

150 Greenwich Street, 44th Floor

New York, NY 10007

## 12.2 Duplex Ultrasound Core Lab

The Duplex Ultrasound Core Laboratory (DUS Core lab) is responsible for developing protocol requirements, reviewing DUS exams, interpreting subject DUS data, and providing feedback on the quality of the DUS exams to participating sites. The DUS Core lab shall review, analyze, and record data

on the Duplex Core laboratory Assessment eCRF. The DUS Core laboratory's interpretation of all DUS exams shall be used for the data analyses.

The DUS Core lab responsible for analyzing all DUS exams is:

Vascular Ultrasound Core Laboratory (VasCore)
Massachusetts General Hospital
One Bowdoin Square, 10th Floor
Boston, MA 02114

# 13. Statistical Design and Methods

This is a prospective, non-randomized, multi-center post-market surveillance study using newly trained study sites. The objective of this post-market surveillance study is to further support the short-term safety of the device and procedure and the 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.

General methods as well as methods used for each study objective are outlined below. To assess the continued safety of the AVF creation procedure post-market, a subset of study safety endpoints will be descriptively compared to the pre-market study (DEN170004) results where possible. Further details will be documented in the Statistical Analysis Plan (SAP). Any deviation to the pre-specified statistical analyses will be noted in the study final report.

## 13.1 General Aspects of Analysis

Data analysis will be performed by Medtronic employed statisticians. All statistical analyses will be generated using SAS version 9.4 or later or R version 4.0 or later software. Demographic and baseline characteristics will be summarized descriptively and will include age, gender, ethnicity, race, body mass index and relevant co-morbidities (including diabetes and hypertension). For continuous variables, descriptive statistics will be presented including the number of subjects with the measurement, mean, standard deviation, median, minimum and maximum. For categorical variables, descriptive statistics will include the number with the characteristic, the number evaluated, and the percentage.

Subject enrollment and accountability, visit attendance, and end of study status will be displayed using a STROBE diagram and descriptive statistics, as appropriate. At each study visit, the following information will be tallied: completed visits, missed visits, deaths, study withdrawals, and lost to follow-up. Compliance with study visits will be summarized as the percent of subjects available at each visit.

The study populations are defined as follows:

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

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

Subject status will be presented for all enrolled subjects. 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.

Missing data for the primary endpoints may result from a study procedure attempted but not completed, or loss to follow-up or death prior to endpoint assessment. In time-to-event analysis, where applicable, patients lost to follow-up or who have died will be treated as censored or as a competing risk for observation of the primary endpoint.

Missing data for secondary 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, ultrasound measurements of artery and vein diameters and mean flow rates may be unavailable 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.

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 in those analysis will be performed. Thus, confidence intervals for these comparisons will be based on 97.5% confidence intervals rather than 95% confidence intervals.

## 13.2 Primary Objective(s)

There are no formal hypothesis tests or sample size requirements for the primary objectives.

### 13.2.1 Primary Safety Objective #1

*Early 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.

**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.

**Determination of Subjects/Data for Analysis:**

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.

### 13.2.2 Primary Safety Objective #2

*Study related serious adverse events through 12 months*

**Endpoint Definition:**

The rate of SAEs through 12 months related to the device, study procedure, or secondary procedure to maintain or re-establish 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.

**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.

**Determination of Subjects/Data for Analysis:**

Safety Analysis Set

### 13.2.3 Primary Effectiveness Objective

*Cumulative Patency through 12 months post AVF creation*

**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.

**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. 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.

**Determination of Subjects/Data for Analysis:**
Treated Analysis Set

**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.

## 13.3 Secondary Objectives

There are no formal hypothesis tests or sample size requirements for the secondary objectives.

### 13.3.1 Secondary Objective #1

*Primary Patency through 12 months post AVF creation*

**Endpoint Definition:**
Primary patency is defined as freedom from access thrombosis or any intervention designed to facilitate, maintain or re-establish patency in a thrombosed access from time of access creation. Subsequent to 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.

**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. 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.

**Determination of Subjects/Data for Analysis:**
Treated Analysis Set

**Additional Analysis:**

Primary patency post-surgical or endovascular intervention

### 13.3.2 Secondary Objective #2

*Assisted Primary Patency through 12 months post AVF creation*

**Endpoint Definition:**

Assisted primary patency is defined as freedom from access thrombosis from time of access creation.

**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. 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.

**Determination of Subjects/Data for Analysis:**

Treated Analysis Set

### 13.3.3 Secondary Objective #3

*Rate of Secondary Procedures*

**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.

**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.

**Determination of Subjects/Data for Analysis:**
Treated Analysis Set

**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.

### 13.3.4 Secondary Objective #4

*Overall Patient Safety*

**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.

**Analysis Method:**
Secondary 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
- SAE

- UADE
- AE related to:
  - study device
  - study procedure
  - intra-procedure or planned balloon angioplasty (PTA) maturation procedures
- Cannulation-related AE
- AE resulting from or related to a secondary procedure
- 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. These summaries will be presented cumulatively and for each study interval. Non-SAE will be presented in manner similar to SAE.

**Determination of Subjects/Data for Analysis:**
Safety Analysis Set

**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.

## 13.4 Ancillary Objective(s)

Ancillary objectives include descriptive analyses of ancillary endpoints as well as clinical utility measures. No formal statistical test procedures are planned.

### 13.4.1 Ancillary Objective #1

*Functional Patency Rate Through 12-months*

**Endpoint Definition:**
Defined as freedom from access abandonment from the time from two-needle cannulation.

**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. Subjects not completing the study will be censored after their last available visit.

**Determination of Subjects/Data for Analysis:**
Treated Analysis Set

### 13.4.2 Ancillary Objective #2

*Physiological Maturation Rate 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.

**Analysis Methods:**

Physiological maturation will be summarized 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 at 3, 6, and 12 months.

**Determination of Subjects/Data for Analysis:**

Treated Analysis Set

### 13.4.3 Ancillary Objective #3

*Functional Cannulation Success Through 12-months*

**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.

**Analysis Methods:**

Functional cannulation success will be summarized for the Treated population using a Kaplan-Meier curve through at least 12 months. Analyses will include probabilities and 95% confidence interval bands through the 12-month visit. Subjects not completing the study will be censored after their last available visit.

**Determination of Subjects/Data for Analysis:**

Treated Analysis Set

### 13.4.4 Ancillary Objective #4

*Days of Central Venous Catheter Exposure Through 12-months*

**Endpoint Definition:**

Days of CVC exposure through 12 months.

**Analysis Methods:**

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.

**Determination of Subjects/Data for Analysis:**

Safety Analysis Set

### 13.4.5 Ancillary Objective #5

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

**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 VAQ summary score ranges from 0 to 68 with higher values indicating more negative views of vascular access.

**Analysis Methods:**

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.

**Determination of Subjects/Data for Analysis:**

Treated Analysis Set

### 13.4.6 Ancillary Objective #6

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

**Endpoint Definition:**

Cannulator training and experience cannulating the study AVF is assessed at approximately 3, 6, and 12 months post AVF creation.

**Analysis Methods:**

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.

**Determination of Subjects/Data for Analysis:**

Treated Analysis Set

## 13.5 Sample Size Determination

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 domestic centers 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.

# 14. Ethics

## 14.1 Statement(s) of Compliance

The study will be conducted according to ICH Good Clinical Practice (GCP), the Declaration of Helsinki (DoH), and regulations of the United States, including data protection laws, the Clinical Trial Agreement and the Clinical Investigation Plan. GCP includes review and approval by an independent IRB before initiating a study, continuing review of an ongoing study by an IRB, and obtaining and documenting the freely given informed consent of a subject before initiating the study.

Ultimately, all study sites will follow and comply with:

- Principles of DoH
- 21 CFR Part 11: Electronic Records, Electronic Signatures
- 21 CFR Part 50: Protection of Human Subjects
- 21 CFR Part 54: Financial Disclosure by Clinical Investigators
- 21 CFR Part 56: IRBs
- 21 CFR Part 822: Postmarket Surveillance
- The CTA
- The procedures described within this CIP

The study will be publicly registered prior to in accordance with the 2007 FDAAA and DoH on http://clinicaltrials.gov (PL 110-85, section 810(a)).

Approval of the CIP and CIP amendments is required from the following groups prior to any study procedures at a study site:

- Medtronic
- Principal Investigators (where required by local law/regulations)
- An independent medical IRB.

Similarly, approval of subsequent revisions to the CIP is required at each study site from the above-mentioned groups prior to implementation of the revised CIP at the study site. Any additional requirements imposed by the IRB or regulatory authority shall be followed, if appropriate.

# 15. Study Administration

## 15.1 Monitoring

Monitoring and monitoring oversight shall be provided by Medtronic and detailed in a Monitoring Plan separate from this CIP. Representatives of Medtronic (i.e. contractors and authorized designees) may also act as the study monitors to the site. A list of the study monitors shall be kept separate from the Monitoring Plan and provided separately from the clinical study contact list.

Monitoring for the study, including site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan. An adaptive, risk-based monitoring methodology will be applied to this study. An assessment of study risk, critical data, and processes was conducted to define the appropriate monitoring methodology and rigor. Considerations assessed include, but are not limited to study objectives, purpose, design, complexity, size, critical data (including the endpoints), degree of deviation from normal clinical practice (standard of care) and regulatory requirements.

Monitoring visits may be conducted periodically to assess study site progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to IR approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs in accordance to the study-specific monitoring plan. Monitors review study site regulatory and study compliance by identifying observations of non-compliance and communicating those observations along with recommendations for preventative/corrective actions to study site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular study site.

### 15.1.1 Monitoring Visits

Monitoring visits may be conducted periodically to assess study site progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to IR approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs in accordance with the study-specific monitoring plan. Monitors review study site regulatory and study compliance by identifying observations of non-compliance and communicating those observations along with recommendations for preventative/corrective actions to study site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular study site.

## 15.2 Data Management

Data will be collected using an electronic data management system for studies. CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to pseudonymize for instance, where the subject's name cannot be removed from the data carrier, such as duplex ultrasound images.

Procedures in the CIP require source documentation. Source documentation will be maintained at the study site. Source documents, which may include worksheets, subject medical records, programmer printouts, and interrogation files, must be created and maintained by the investigational study site team.

## 15.3 Direct Access to Source Data/Documents

Medtronic may conduct audits at participating study sites. The purpose of an audit is to verify the performance of the monitoring process and the study conduct, independently of the personnel directly involved in the study. RAs, such as the FDA, may also perform inspections at participating study sites. The investigator and/or institution shall permit Medtronic, IRBs and RAs direct access to source data and documents during monitoring, audits and regulatory inspections.

## 15.4 Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique SID to each subject. Records of the subject/SID relationship will be maintained by the study site. The SID number is to be recorded on all study documents to link them to the subject's medical records at the study site. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. In the US, "Protected Health Information" (PHI) will be maintained in compliance with the HIPAA of 1996. To maintain confidentiality, the subject's name or any other PHI should not be recorded on any study document other than the IC. This scenario will be covered in the IC. In the event a subject's name/PHI is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel. Data relating to the study might be made available to third parties (for example in case of an audit performed by RA), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

## 15.5 Warranty

Warranty information is provided in the product packaging for the Ellipsys System and additional copies are available upon request.

## 15.6 CIP Amendments

Any revisions or amendments to the CIP or IC document, along with a statement of justification for the changes, will be submitted to all affected RAs (FDA, CA) and governing ECs, according to applicable regulations. All amendments to the CIP shall be agreed upon between Medtronic and the principal investigator(s), or the coordinating investigator. Approval by regulatory agencies and ECs (where applicable) must be obtained prior to implementing a CIP revision at the study site.

## 15.7 Record Retention

All study-related documents must be retained for a period of at least 2 years after study closure (or longer if required by local law). Medtronic will inform the investigator/study site when these documents are no longer required to be retained.

No study document or image will be destroyed without prior written agreement between Medtronic and the investigator. The investigator should take measures to prevent accidental or premature destruction of documents. Should the investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to Medtronic.

Medtronic will retain the study records according to Medtronic corporate policy and record retention schedule.

### 15.7.1 Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after the date on which the investigation is terminated.

- All correspondence between the IRB, sponsor, monitor, RA and the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
  - Signed and dated IC (signed by subject)
  - Observations of SAEs/ADEs/DDs
  - Medical history
  - Index Procedure and follow-up data
  - Documentation of the dates and rationale for any deviation from the protocol.
- List of investigation study sites.
- Financial Disclosure.
- Subject Enrollment & Identification log.
- All approved versions of the CIP, IC.
- Signed and dated CTA.
- CV of principal investigators and key members of investigation study site team.
- Documentation of delegated tasks.
- IRB approval documentation. Written information that the investigator or other study staff, when member of the IR, did not participate in the approval process. Approval documentation must include the IRBs composition, where required per local law.
- Study training records for study site staff.
- Any other records that FDA and local regulatory agencies require to be maintained.
- Final Study Report including the statistical analysis.

### 15.7.2 Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records:

- All correspondence which pertains to the investigation
- Signed Investigator Trial Agreements, FD, delegated task list
- All approved IC templates, and other information provided to the subjects and advertisements, including translations
- Copies of all IRB approval letters and relevant IRB correspondence and IRB voting list/roster/letter of assurance
- Names of the institutions in which the study will be conducted
- Names/contact addresses of monitors
- Monitoring visit reports
- Statistical analyses and underlying supporting data
- Final report of the study
- The CIP, study related reports, and revisions
- Study training records for study site personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained.

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in stored in secured file cabinets at Medtronic during the course of this study.

After closure of the study Medtronic will archive records and reports indefinitely.

## 15.8 Reporting Requirements

### 15.8.1 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects, device deficiencies, deaths, and any deviations from the clinical investigation plan. If any action is taken by an IRB with respect to this study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Safety data investigator reporting requirements are listed in Section 11.5. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

**Table 8: Investigator Reports**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Withdrawal of IRB approval | Sponsor and Relevant Authorities | The investigator must report a withdrawal of approval by the reviewing IRB of the investigator's part of the investigation within 5 working days. |
| Study Deviations | Sponsor and IRB | Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. |
| Final Report | IRBs and Relevant Authorities | This report must be submitted within 3 months of study completion or termination. |

### 15.8.2 Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the table below. In addition to the reports listed below, Medtronic shall, upon request of the reviewing IRB, or FDA, provide accurate, complete and current information about any aspect of the investigation.

**Table 9: Sponsor Reports**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Interim Reports | IRB and FDA | Interim reports will be submitted according to the approved postmarket surveillance plan (every six months for the first two years and then annually for duration of study). (21 CFR 822.38) |
| Final report | Investigators, IRB, and FDA | A final report will be submitted to the FDA, investigators, and IRBs within six months after completion or termination of this clinical study. |
| Study deviation | Investigators | Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation.<br>Study site specific study deviations will be submitted to investigators periodically. |

| Report | Submit to | Description/Constraints |
|---|---|---|
| Other | IRB, FDA | Accurate, complete, and current information about any aspect of the investigation. |
| Premature termination or suspension of clinical study | IRB, Investigators, and FDA, where applicable | Medtronic will provide prompt notification of termination or suspension and reason(s) to investigator and where required to IRB and FDA. |

## 15.9 Publication and Use of Information

Publications from the Ellipsys PS Study will be handled according to Standard Operating Procedures and as indicated in the CTA.

## 15.10 Suspension or Early Termination

Medtronic or the FDA may decide to suspend or prematurely terminate the clinical study (e.g. if AEs associated with the Ellipsys System are identified which might endanger the safety or welfare of the subject). If the clinical study is terminated prematurely or suspended, Medtronic shall promptly inform the investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB and the study subjects. In the case of early study suspension or termination, investigators are responsible to continue to follow subjects to monitor safety outcomes per investigational site standard of care.

### 15.10.1 Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or FDA, whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing IRB oversight is required until the overall study closure process is complete. Refer to section 9.16 for additional information regarding study exit procedures.

### 15.10.2 Early Termination or Suspension

Early Termination is the closure of a study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single study site. Suspension is a temporary postponement of study activities related to enrollment. This is possible for the whole study or a single study site.

#### 15.10.2.1 Investigator/study site termination or suspension

Possible reasons for investigator or study site termination or suspension include but are not limited to:

- Failure to obtain initial IRB approval or annual renewal of the study
- Persistent non-compliance to the clinical investigation (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment

- Noncompliance to regulations and the terms of the CTA (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring observations in a timely manner, etc.)
- IRB suspension of the study site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

### 15.10.3 Procedures for Termination or Suspension

#### 15.10.3.1 Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the FDAs where required
- In the case of study termination or suspension for reasons other than a temporary IRB approval lapse, the investigator will promptly inform the IRB
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

#### 15.10.3.2 Investigator-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the IRB
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

#### 15.10.3.3 Institutional Review Board-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with IRB policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)

- The investigator will promptly inform the subjects, or legally-authorized designees or guardians and/or the personal physician of the subjects, with the rationale for the study termination or suspension

# 16. References

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# 17. Appendices

Appendix 1: Vascular Access Questionnaire

Appendix 2: Cannulator Satisfaction Survey

Appendix 3: List of Investigators

## Appendix 1: Vascular Access Questionnaire

Ellipsys PS Vascular Access Questionnaire

**Vascular Access Questionnaire (VAQ)**

During the past 4 weeks, how much were you bothered by each of the following problems related to your primary vascular access (e.g. fistula/graft or catheter/line)? (Circle the number that best describes your situation.)

What was your primary vascular access over the last 4 weeks

- ○ Dialysis Catheter
- ○ Study AVF (arteriovenous fistula)
- ○ Other

Other, specify _____

| | Not at all | A little | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|---|
| a. Pain | o 0 | o 1 | o 2 | o 3 | o 4 |
| b. Bleeding | o 0 | o 1 | o 2 | o 3 | o 4 |
| c. Bruising | o 0 | o 1 | o 2 | o 3 | o 4 |
| d. Swelling | o 0 | o 1 | o 2 | o 3 | o 4 |
| e. Redness | o 0 | o 1 | o 2 | o 3 | o 4 |
| f. Infection | o 0 | o 1 | o 2 | o 3 | o 4 |
| g. Clotting | o 0 | o 1 | o 2 | o 3 | o 4 |
| h. The appearance of your access | o 0 | o 1 | o 2 | o 3 | o 4 |
| i. Worries about whether your access is working well to clean the blood properly | o 0 | o 1 | o 2 | o 3 | o 4 |
| j. Having to come early to the dialysis unit because of your access | o 0 | o 1 | o 2 | o 3 | o 4 |
| k. Having to leave late from the dialysis unit because of your access | o 0 | o 1 | o 2 | o 3 | o 4 |
| l. Problems sleeping because of your access | o 0 | o 1 | o 2 | o 3 | o 4 |
| m. Having to be careful to protect your access | o 0 | o 1 | o 2 | o 3 | o 4 |
| n. Your access interfering with your daily activities (eg work or other regular daily activities) | o 0 | o 1 | o 2 | o 3 | o 4 |
| o. Your access interfering with your social and leisure activities | o 0 | o 1 | o 2 | o 3 | o 4 |
| p. Worries about being hospitalized because of problems with your access | o 0 | o 1 | o 2 | o 3 | o 4 |
| q. Worries about how long your access will last | o 0 | o 1 | o 2 | o 3 | o 4 |

## Appendix 2: Cannulator Satisfaction Survey

**Ellipsys PS** — **Cannulator Satisfaction**

**Cannulator Training and Experience**

| | |
|---|---|
| Initials of Cannulator<br>Use first letter of first, middle and last name | |
| Training | o LICENSED VOCATIONAL NURSE<br>o PATIENT CARE TECHNICIAN<br>o REGISTERED NURSE<br>o OTHER |
| Other, specify | |
| How long have you been independently cannulating AVFs (arteriovenous fistulas) | Months |
| How long have you been independently cannulating AVFs (arteriovenous fistulas) | Years |
| Have you ever cannulated a surgical AVF (arteriovenous fistula) | o NO o YES |
| Earliest surgical AVF (arteriovenous fistula) you've cannulated | o GREATER THAN OR EQUAL TO 12 WEEKS POST-OP<br>o LESS THAN 12 WEEKS POST-OP |
| Have you cannulated a percutaneous AVF (pAVF) before this subject | o NO o YES |

**Experience with this Subject**

| | |
|---|---|
| Date you most recently cannulated this subject | DD-MON-YYYY |
| Was the AVF (arteriovenous fistula) marked prior to cannulation | o NO o YES |
| Was visualization of the AVF (arteriovenous fistula) acceptable | o NO o YES |
| If NO, explain | |
| Was palpation of the AVF (arteriovenous fistula) acceptable | o NO o YES |
| If NO, explain | |
| Is cannulating length acceptable | o NO o YES |
| If NO, explain | |
| Is AVF (arteriovenous fistula) depth acceptable | o NO o YES |
| If NO, explain | |
| Was a tourniquet used | o NO o YES |
| Number of attempts with the arterial needle | |
| Satisfied with ease of cannulating (arterial needle) | o NO o YES |
| If NO, explain | |
| Number of attempts with the venous needle | |
| Satisfied with ease of cannulating (venous needle) | o NO o YES |
| If NO, explain | |
| Comments | |
| Completed by | o CANNULATOR<br>o STUDY COORDINATOR<br>o OTHER |
| Other, specify | |

**Appendix 3: List of Investigators**

(Provided under separate cover)

# 18. Version History

| Version | Summary of changes | Author(s)/Title |
|---|---|---|
| 1.0 | • Version 1.0, 03/JAN/2020 initial revision for updated 522 order of 10/JAN/2020 | Avenu Medical |
| 1.1 | • Version 1.1, 25/FEB/2020 update per interactive review discussion on 14/FEB/2020 | Avenu Medical |
| 1.2 | • Version 1.2, 23/MAR/2020 update per new 522 order on 10/JAN/2020 | Avenu Medical |
| 1.3 | • Version 1.3 final, 23/APR/2020 | |

| | | |
|---|---|---|
| 2.0 | • CIP transferred into MDT 056-F275 template<br>• Study Sponsor updated from Avenu Medical to Medtronic Vascular Inc.<br>• Primary and Secondary Endpoints updated; Ancillary Endpoints added<br>• Definition of Newly Trained Provider added<br>• Inclusion Criteria updated to remove requirement for urine/blood pregnancy test<br>• Exclusion Criteria added to exclude patients with an active COVID-19 infection or relevant history of COVID-19<br>• Unscheduled Visit removed as a follow-up visit type<br>• Reportable adverse events limited to only those adverse events related to the device, procedure, or secondary procedures, and any serious adverse events (including SAEs, ADEs, SADEs, and UADEs) | Stephanie Brucato, Principal Clinical Research Specialist |

| | | |
|---|---|---|
| 3.0 | • CIP transferred to version D of MDT 056-F275 template<br>• Sponsor address updated<br>• General Inclusion Criterion 7 updated to include Allen's Test<br>• General Exclusion Criterion 13 updated<br>• Number of allowable sites increased to up to 14<br>• Maximum number of subjects allowable per site increased to 27<br>• Section 9.11 added to define Secondary Procedures<br>• Throughout document Removed 'UADE' from site reportable adverse events<br>• Section 11.4 Updated Table 6 of to 'Intra- procedure (index) PTA balloon angioplasty or planned PTA/balloon maturation procedure' and added definition note for 'planned PTA/balloon maturation procedure'<br>• Section 11.4 Table 6 Added 'Cannulation' | Stephanie Brucato, Senior Principal Clinical Research Specialist |
| 4.0 | • CIP transferred to version E of MDT 056-F275 template<br>• All references to Secondary Procedure CRF have been updated to Adjunctive/Secondary Procedure CRF<br>• Section 2, updated to correct a numbering error<br>• Section 2, safety assessment section updated to correct incorrect reference section<br>• Section 9.1, table 1 footnote 2 updated to clarify when the | Heather Catchpole, Senior Clinical Research Specialist |

| | | |
|---|---|---|
| | determination of secondary procedures begins<br>• Section 9.8 updated to add 'If a complication or adverse event occurs intra-procedure, the details should be captured in the Adverse Event CRF ' and 'If any secondary procedures are required to mature or maintain the AVF or re-establish flow subsequent to completion of the AVF procedure, they will be documented in the Adjunctive/Secondary Procedure CRF and the AE CRF if applicable. '<br>• Sections 9.8 and 9.11 updated to add instructions for procedures done during the AVF creation.<br>• Section 9.11 updated to further clarify definition of secondary procedures<br>• Section 9.11 updated to include reminder to complete AE CRF if the secondary procedure is done because of an adverse event<br>• Section 9.15 Deleted unanticipated and (UADE) for consistency<br>• Section 11.1 updated for consistency to indicate Adverse events are collected from the point of enrollment through study exit<br>• Section 13.3.1 updated to clarify definition of secondary procedure<br>• Section 13.3.3 updated to clarify definition of secondary procedure<br>• Section 17 moved before section 18 to correct numbering order | |