



**CLINICAL STUDY PROTOCOL
CP-0011 REV. 1.0**

07 JANUARY 2015

**Multicenter, Observational, Post-Market, Real World Study to
Assess Outcomes of Patients Treated with the AFX System
compared to other EVAR devices for Endovascular Abdominal
Aortic Aneurysm Repair**

**LEOPARD: Looking at EVAR Outcomes by Primarily
Analysis of Randomized Data**

Table of Contents

Section	Page
1. INVESTIGATOR SIGNATURE PAGE.....	4
2. STUDY CONTACT PERSONNEL.....	5
2.1. SPONSOR	5
3. PROTOCOL SYNOPSIS	6
4. STUDY OVERVIEW	10
4.1. OBJECTIVE	10
4.2. BACKGROUND	10
4.3. STUDY GOVERNANCE	10
4.4. STUDY DEVICE	11
4.5. STUDY DESIGN	11
4.6. ENROLLMENT CLOSE	12
5. STUDY POPULATION AND PROCEDURES	12
5.1 INCLUSION CRITERIA	13
5.2 EXCLUSION CRITERIA	13
5.2 PATIENT ASSESSMENT AND SCREENING	13
5.3 ENROLLMENT CRITERIA	13
5.4 PATIENT INFORMED CONSENT.....	13
5.5 ENROLLMENT AND RANDOMIZATION	13
5.6 IMPLANTATION PROCEDURE.....	14
5.7 FOLLOW UP REQUIREMENTS.....	14
6. STUDY EVALUATIONS.....	15
6.1. PRIMARY STUDY ENDPOINTS	15
6.2. SECONDARY STUDY ENDPOINTS	15
6.3. ADDITIONAL EVALUATIONS.....	16
6.4. SUB-STUDY EVALUATIONS.....	16
7. ELECTRONIC CASE REPORT FORMS	16
8. DATA MANAGEMENT	16
9. STATISTICAL CONSIDERATIONS	17
9.1 GENERAL CONSIDERATIONS	17
9.2 STATISTICAL METHODS	17
9.3 DISTRIBUTION OF THE PATIENTS.....	19
9.4 HANDLING MISSING VALUES	19
10. ADVERSE EVENT REPORTING.....	19
10.1 ADVERSE EVENT DEFINITIONS	19
10.2 ADVERSE EVENT REPORTING	20
10.3 DEFINITIONS	21
10.3.1 DEFINITIONS ASSOCIATED WITH THE COMPOSITE PRIMARY ENDPOINT ARC	21
10.3.2 ADVERSE EVENT DEFINITIONS	22
10.3.3 OTHER DEFINITIONS	23

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11. RESPONSIBILITIES	23
11.1 SPONSOR RESPONSIBILITIES	23
11.2 INVESTIGATOR RESPONSIBILITIES.....	24
11.3 INDEPENDENT EVENT REVIEWER RESPONSIBILITIES.....	24
11.4 INDEPENDENT PHYSICIAN RESPONSIBILITIES	25
12 CONFIDENTIALITY AND PATIENT RIGHTS.....	25
12.1 CONFIDENTIALITY	25
12.2 PATIENT RIGHTS	25
13 ETHICAL CONSIDERATIONS.....	25
14 MONITORING.....	26
15 STUDY TERMINATION	26
16 PUBLICATION	26

1. INVESTIGATOR SIGNATURE PAGE

I agree to conduct the study as detailed in this Clinical Investigational Plan and in accordance with all applicable regional laws and regulations. In addition, I agree to provide all the information requested in the case report forms presented to me by the sponsor in a manner to assure completeness, legibility and accuracy.

I agree to actively enroll patients into this study and confirm that I do not have any material conflicts including participation in any clinical investigations for similar types of medical devices.

I will provide copies of this study protocol and all necessary information about this study to the study staff under my supervision. I will discuss this material with them and ensure they are fully informed about the device under investigation as well as all aspects concerning the conduct of this study.

I also agree that all information provided to me by the sponsor, including pre-clinical data, protocols, case report forms, and any verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be relayed in confidence to the Institutional Review Board or to regulatory authorities.

In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than the sponsor, or the Institutional Review Board(s), the core labs, or the independent medical reviewer. Any such submission will indicate that the material is confidential.

I will supervise the conduct of the clinical investigation to be performed in compliance with the clinical investigational plan, Good Clinical Practice (GCP)/ICH, the Declaration of Helsinki, ISO 14155:2011 and all applicable regulatory and ethical requirements.

Investigator Signature

Date

Investigator Printed Name

2. STUDY CONTACT PERSONNEL

2.1. SPONSOR

SPONSOR CONTACT
<p>Avyaya Sharma Director Clinical Affairs Tel: 949.595.7276 Fax: 949.595.7382 Endologix, Inc. 2 Musick Irvine, CA 92618 USA asharma@endologix.com</p>

3. PROTOCOL SYNOPSIS

Title of the Study	Multicenter, Post-Market, Real World Study to Assess Outcomes of Patients Treated with the AFX System compared to other EVAR devices for Endovascular Abdominal Aortic Aneurysm Repair: LEOPARD (Looking at EVAR Outcomes by Primary Analysis of Randomized Data)
Study Devices	AFX Endovascular AAA system and other approved Endovascular AAA stent graft systems
Study Sponsor	Endologix, Inc. 11 Studebaker Irvine, CA 92618 USA
Steering Committee	The governance of the study will be provided by a Steering Committee (SC) comprised of physicians experienced in EVAR and considered global Thought Leaders in the field. The purpose of the Steering Committee is to provide scientific direction and oversight to the LEOPARD Study involving Endologix's EVAR System, AFX. Essential responsibilities of the SC include study design and protocol review, regular assessments of the Trial progress to ensure the endpoints of the study are met, and to provide guidance and advice to the investigators for patient selection, timely enrollment and study progress. In addition, the SC will be called on to help interpret results and serve as expert faculty for other investigators. Details of the SC are available on file, in the SC Charter.
Objectives	Objective of this post-market study is to evaluate Endologix AFX endovascular AAA system with <i>anatomical</i> fixation against other approved Endovascular systems with <i>proximal</i> fixation.
Study Design	Prospective, randomized, multi-center study designed to evaluate the outcomes of contemporary EVAR in a real world population. Patients will be followed procedurally to discharge, at 1, 6 (standard of care follow-up), 12 months and annually through to 5 years (total follow-up commitment).
Investigational Sites	Up to 80 sites with experience in standard endovascular repair (EVAR). Each participating investigator must be certified on the AFX system and comparator devices. Any investigator wishing to employ percutaneous endovascular repair (PEVAR) must also provide documentation of certification on the procedure using the particular device.
Subject Population	Up to 800 patients. Consented patients diagnosed with AAA who are considered candidates for endovascular repair and meet the study eligibility criteria.
Data Capture	Electronic Case Report Forms (eCRF) will be used for data collection. Internet access is required for data entry.
Monitoring	Source data verification will be performed by means of intermittent on-site and/or off-site monitoring.
Study Timelines	Expected study start: Q4 -2014 Expected enrollment duration: 18 months

Independent Adverse Event Review	Independent physician(s) will adjudicate all Serious Adverse Events (SAE), Adverse Device Effects (ADE) and Serious Adverse Device Effects (SADE) reported by the sites within this study. Independent physician(s) will complete the eCRF data capture form for all adjudicated events.
Imaging Assessment	All imaging will be evaluated by an independent core lab.
Inclusion Criteria	<ol style="list-style-type: none"> 1. Male or female at least 18 years old 2. Subjects with minimum of 2 year life expectancy 3. Subjects have signed the informed consent document for data release 4. Subjects with infrarenal AAA who are assessed by the investigator to be eligible for endovascular Abdominal Aortic Aneurysm Repair with the study devices
Exclusion Criteria	<ol style="list-style-type: none"> 1. Currently participating in another study where primary endpoint has not been reached yet 2. Known allergy to any of the device components 3. Pregnant (females of childbearing potential only) 4. Subjects with pre-existing EVAR, i.e. in need of repair/intervention of a previously failed EVAR.
Study Design	<p>The LEOPARD Study is designed to compare the anatomically stabilized AFX Endograft System to a reference group of proximally fixated EVAR devices. Patients will be randomized between the two groups.</p> <p>Randomization will be 1:1. Each investigator will select one comparator device of their choice before enrolling the first patient. The study will sequentially evaluate non-inferiority and superiority hypotheses.</p> <p>Randomization Scheme:</p> <div style="text-align: center;"> <pre> graph TD A[Patient Population per Investigator] --> B[AFX] A --> C[Reference Group (One Device Selected Prospectively by Each Participating Investigator)] </pre> </div>

<p>Primary Endpoint</p>	<p>One year survival in absence of Aneurysm Related Complications. ARC is a composite of the most relevant EVAR outcomes and includes:</p> <ul style="list-style-type: none"> • Peri-Operative Death (≤ 30 days) • Rupture • Conversion to OSR • Endoleaks; post-operative • Migration (≥ 10mm) • Aneurysm Enlargement (≥ 5mm) • Endograft Limb Occlusions • Reinterventions for device- or aneurysm-related complications <p>Any imaging driven observation at 365 days \pm 60 days will be included in the one year evaluation window</p>
<p>Secondary Endpoints</p>	<ul style="list-style-type: none"> • MAEs at 30 Days, 12 Months and Annually • ARC Post 12 Months up to Five Years • Aneurysm Related Mortality • Endoleaks Classified by Type • Loss of Neck Apposition • AAA Related Secondary Procedures up to Five Years • Device integrity • Any adjunctive procedures necessitated during the implant procedure. <p>Steering committee may add additional secondary endpoints as required during the study.</p>
<p>Additional Evaluations</p>	<ul style="list-style-type: none"> • Total Endovascular time; from catheter introduction to catheter removal • Anesthesia Time • Fluoroscopy Time • Contrast Volume used • Total Procedure Time; from cut-down to closure • Time in ICU • Total Radiation Exposure • Additional Imaging <p>Steering committee may add additional secondary endpoints as required during the study.</p>
<p>Sub-Studies</p>	<p>Economic Sub-study Subset of the study population will be part of an economic outcomes assessed by site specific billing information.</p> <p>Patient Related outcomes: Subset of the study population will be assessed on patient related outcomes with EVAR specific tools for quality of life evaluation.</p>

<p>Statistical Considerations</p>	<p>The primary endpoint will be evaluated in both the AFX and proximally fixated device groups. The relative performance of the two groups will be evaluated through one-sided tests for non-inferiority and superiority. Combining the superiority and non-inferiority trials into a single closed testing procedure allows for maintenance of a controlled Type 1 error rate. An 8% margin will be used for the non-inferiority test. If the non-inferiority null hypothesis is rejected, the null hypothesis for superiority will be investigated.</p> <p>Hypotheses for Non-inferiority: Null Hypothesis: $H1_0: \mu_A - \mu_B \leq -8\%$ (AFX is inferior with respect to the primary endpoint) Alternative: $H1_1: \mu_A - \mu_B > -8\%$ (Statistical evidence of non-inferiority)</p> <p>Hypotheses for Superiority: Null Hypothesis: $H2_0: \mu_A - \mu_B \leq 0$ (The two device groups have equal effect) Alternative: $H2_1: \mu_A - \mu_B > 0$ (Statistical evidence of superiority)</p> <p>The study size has been selected to provide 80% power for the superiority test. The sample size required for non-inferiority testing is relatively smaller; thus, the power of the non-inferiority test approaches 100%.</p>																																																																
<p>Suggested Schedule of Tests</p>	<p>Patient eligibility will be assessed by the Investigator per institutional standard of care pre-procedural imaging. Blood work and physical exam will also be collected as per routine schedule at each institution.</p> <p>Following Institutional Review board approval and patient written informed consent, the patient will be screened for eligibility. Subjects will be followed procedurally and to hospital discharge and per institutional standard of care thereafter through to 5 years (total follow-up commitment).</p> <p>The following table outlines a typical site follow-up schedule which will be altered to meet standard of care at individual sites.</p> <table border="1" data-bbox="386 1157 1554 1713"> <thead> <tr> <th>Suggested Schedule of Tests:</th> <th>Screening/ Baseline</th> <th>Procedure</th> <th>Pre-Discharge</th> <th>1 month FUP</th> <th>6 months FUP</th> <th>1 Year FUP</th> <th>>1 to 5 Years FUP</th> </tr> </thead> <tbody> <tr> <td>Inclusion/ Exclusion</td> <td>x</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Demographics/ Medical History</td> <td>x</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Physical Exam†</td> <td>x</td> <td></td> <td>x</td> <td>x</td> <td>x</td> <td>x</td> <td>x</td> </tr> <tr> <td>Blood Labs‡</td> <td>x</td> <td></td> <td>x</td> <td>x</td> <td>x</td> <td>x</td> <td>x</td> </tr> <tr> <td>Contrast-enhanced CT scan</td> <td>x[¥]</td> <td></td> <td></td> <td>x*</td> <td></td> <td>x*</td> <td>x*</td> </tr> <tr> <td>Procedural Information</td> <td></td> <td>x</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Adverse Events</td> <td></td> <td>x</td> <td>x</td> <td>x</td> <td>x</td> <td>x</td> <td>x</td> </tr> </tbody> </table> <p>†The physical exam includes overall health, physical assessment, and vital signs. ‡Blood labs typically include serum creatinine and hemoglobin, if collected. ¥ High resolution (<3mm slice spacing), contrast and non-contrast CT scan is preferred up to 3 months prior to the scheduled procedure *If institution's standard of care for EVAR involves another imaging modality e.g. duplex ultrasound, that modality may be collected alternatively.</p>	Suggested Schedule of Tests:	Screening/ Baseline	Procedure	Pre-Discharge	1 month FUP	6 months FUP	1 Year FUP	>1 to 5 Years FUP	Inclusion/ Exclusion	x							Demographics/ Medical History	x							Physical Exam†	x		x	x	x	x	x	Blood Labs‡	x		x	x	x	x	x	Contrast-enhanced CT scan	x [¥]			x*		x*	x*	Procedural Information		x						Adverse Events		x	x	x	x	x	x
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Procedural Information		x																																																															
Adverse Events		x	x	x	x	x	x																																																										

4. STUDY OVERVIEW

4.1. OBJECTIVE

The objective of this post-market study is to evaluate Endologix AFX endovascular AAA system with *anatomical* fixation against other approved Endovascular systems with *proximal* fixation. Multiple U.S clinical centers will be involved in the study to include a broad range of experience. Imaging data will be evaluated by an independent core lab.

4.2. BACKGROUND

Since the pioneering work of Dr. Parodi and Dr. Volodos in the late 1980s and early 1990s, there have been few pivotal moments in the history of endovascular repair of AAA (EVAR). The EVAR-1/2, DREAM, OVER and ACE trials have demonstrated early benefits of EVAR over open surgical repair but each of these studies included patients with prior generation endografts; many of which are rarely or never implanted today. The gradual evolution of EVAR practice since then expanded the use of the technique in a growing number of aortic anatomies outside the boundaries tested in clinical trials. Such practices have recently been questioned, reversing in some instances the utilization of EVAR as the technique of choice in AAA repair. Unfortunately, all current evidence on so-called “hostile” versus “friendly” anatomies is limited to the retrospective analyses of the single-center cohorts treated with multiple generations of devices. In the age of increasing patient awareness and fiscal scrutiny over therapeutic outcomes, new prospective data on EVAR outcomes in the contemporary patient populations is long overdue.

The evolution of EVAR technology has led to two distinct device concepts currently available in clinical practice. One concept incorporates the bifurcated component positioned high in the aneurysm sac and tubular limb components extended distally into iliac arteries. Such endograft systems rely on penetrating hooks and barbs for *proximal* fixation within the aorta. The majority of device manufacturers adopted this concept, producing devices with different proximal stent configurations (suprarenal versus infrarenal), stent designs, and graft materials. The alternative concept, developed by Endologix, relies on the bifurcated endograft component positioned directly on the native aortic bifurcation, with the proximal component extending cranially into the aortic neck. Fixation of the endograft on the aortic bifurcation (anatomic fixation) and the associated freedom to optimize the proximal configuration without constraints of the fixation elements, results in a system that most closely resembles the anatomy of the native aorta and the seal zones extended by the pressure of the native blood flow (ActiveSeal™), with potential advantages of optimized hemodynamics, migration resistance, and aneurysm exclusion.

The purpose of the LEOPARD study is to evaluate the outcomes of contemporary EVAR in a real world population using two distinct endograft concepts (*proximal* versus *anatomic* fixation).

The multicenter, Level 1 randomized evidence generated by LEOPARD will serve as modern reference for future therapy developments, the way the earlier trials serve that purpose today. In addition, the LEOPARD study will provide the insight into the performance of the individual device designs in a broad set of patient anatomies guidance on EVAR strategy and clinical presentations, leading to the definitive choices in the years to come.

4.3. STUDY GOVERNANCE

The governance of the study will be provided by a Steering Committee (SC) comprised of physicians experienced in EVAR and considered thought leaders in the field. The purpose of the Steering

Committee is to provide scientific direction and oversight to the LEOPARD Study involving Endologix's EVAR System, AFX. Essential responsibilities of the SC include study design and protocol review, regular assessments of the Trial progress to ensure the endpoints of the study are met, and to provide guidance and advice to the investigators for patient selection, timely enrollment and study progress. In addition, the SC will be called on to help interpret results and serve as expert faculty for other investigators.

Details of the SC are available in the Steering Committee Charter and are kept on file.

4.4. STUDY DEVICE

The devices used in this study are endovascular stent grafts approved by the FDA to treat abdominal aortic aneurysms. All devices are commercially available in the U.S. and, for the purposes of this study, include the latest iteration of the following devices:

1. Endologix AFX[®] System (Test device)
2. Cook Zenith[®] System(Comparator device)
3. Gore Excluder System(Comparator device)
4. Medtronic Endurant System (Comparator device)

The description, specifications and indications/instructions for use may be found in their respective Instructions for Use. It is noted the AFX[®] System is anatomically fixated distally while the remaining three devices are fixated proximally within the aorta using penetrating barbs or hooks.

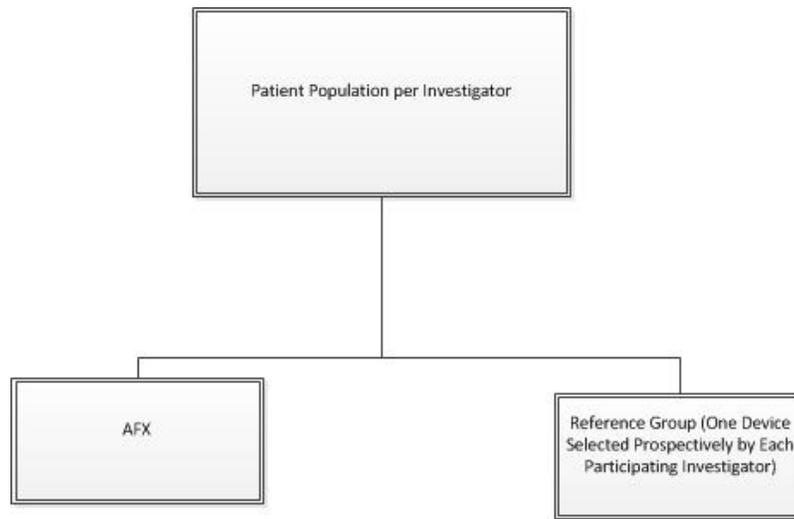
This study will allow for use of iterative changes to all devices indicated above.

4.5. STUDY DESIGN

The LEOPARD study is a prospective, randomized, multi-center study, intended to evaluate the outcomes of contemporary EVAR (Endovascular Aneurysm Repair) in a real world population. The study is designed to compare the anatomically stabilized AFX Endograft System to a reference group of proximally fixated EVAR devices. Patients will be randomized between the two groups.

Randomization will be 1:1. Each investigator will select one comparator device of their choice before enrolling the first patient and this device will serve as the comparator device for that investigator throughout the course of enrollment. The study will sequentially evaluate non-inferiority and superiority hypotheses.

Randomization Scheme:



All subjects undergoing EVAR with either the AFX System or the reference group of other EVAR devices will be followed procedurally to discharge, at 1, 6 (standard of care follow-up), 12 months and annually through to 5 years (total follow-up commitment).

After this protocol and the patient Informed Consent Form (ICF) are reviewed and approved by the local Institutional Review Board (IRB), potential subjects having infrarenal AAA will be offered participation in the study. This will be accomplished through the patient's reading of the informed consent form and discussion of the study with the patient by the Investigator and site personnel. Agreement to participate and to attend all protocol required follow-up visits will be documented with the patient's signature on the informed consent form.

4.6. ENROLLMENT CLOSE

Total enrollment for the study is up to 800 patients. When the sponsor has been notified that the necessary number of patients has been enrolled, the sites will be notified to discontinue enrollment. However, all consented patients will still be allowed to receive the treatment for their study arm. This may result in a small number of additional patients in the trial. All such patients will be included in study analysis.

5. STUDY POPULATION AND PROCEDURES

Up to 80 sites with experience in EVAR and up to 800 subjects will participate in this study. Each participating Investigator will be required to be certified on both the AFX system and their choice of comparator device. Any investigator wishing to employ percutaneous endovascular repair (PEVAR) must also provide documentation of certification on the procedure using the particular device. Following completion of the ICF, the Investigator will commence patient screening and enrollment. Certification must be completed in accordance with each manufacturer's certification process.

5.1 INCLUSION CRITERIA

A patient who meets all of the following criteria may be considered as a potential study subject:

1. Male or female at least 18 years old
2. Subjects with minimum of 2 year life expectancy
3. Subjects have signed the informed consent document for data release
4. Subjects with infrarenal AAA who are assessed by the investigator to be eligible for endovascular Abdominal Aortic Aneurysm Repair with the study devices

5.2 EXCLUSION CRITERIA

A patient who does not meet any of the following criteria may be considered as a potential study subjects:

1. Currently participating in another study where the primary endpoint has not been reached yet.
2. Known allergy to any of the device components
3. Pregnant (females of childbearing potential only)
4. Subjects with pre-existing EVAR, i.e. in need of repair/intervention of a previously failed EVAR.

5.2 PATIENT ASSESSMENT AND SCREENING

Patients will be consecutively assessed for inclusion in the study by the investigator according to standard of care. A log of all these assessments will be maintained. This will include information on any patients deemed unable to participate and the reasons for such.

5.3 ENROLLMENT CRITERIA

Patients who fulfill all eligibility criteria and sign the ICF will be considered as a study candidate. The randomization process will be initiated to determine the primary study device for each study candidate. A study candidate is considered an enrolled subject in the study only upon the insertion of the delivery system for the associated primary study device. Any other adjective procedures before insertion of the delivery system for the primary device will be captured for all study candidates.

5.4 PATIENT INFORMED CONSENT

Written informed consent, documented on the ICF in accordance with Good Clinical Practice standards and study center regulations, shall be obtained from each patient. The Investigator will retain a copy of the signed informed consent document in each patient's record, and provide a copy to the patient. There is no incremental risk and data will be collected anonymously.

5.5 ENROLLMENT AND RANDOMIZATION

Patient enrollment into this study is based on the site evaluation of patient conformance with the protocol-specified selection criteria (§5.1 and §5.2), and the Investigator's assessment of suitability for treatment with either the AFX-System or the comparator device. Blood work and physical exam will also be collected as per standard of care at each institution.

Once consented and assessed for inclusion in the study, the Investigator will elect to randomize the patient by entering required information into the EDC. Upon entering this information the patient will be randomized to receive the AFX® System or the comparator device. The randomization

result will be generated and accessible to the site prior to the scheduled procedure date.

Enrollment in the study only occurs upon advancement of the study device into the subject's vasculature.

5.6 IMPLANTATION PROCEDURE

The EVAR procedure is performed according to the device IFU to which the patient has been randomized and the institutional standard of care. Patient sedation, vascular access and procedural techniques will be handled at the discretion of the Investigator.

5.7 FOLLOW UP REQUIREMENTS

Subjects will be followed procedurally and to hospital discharge and at 1, 6 (standard of care follow-up), 12 months and annually through five years (total follow-up commitment).

The following table outlines a suggested follow-up schedule which may be altered to meet standard of care at individual sites.

Suggested Schedule of Tests:	Screening / Baseline	Procedure	Pre-Discharge	FUP 1 1 month 30± 15 days	FUP 2 6 Month 182± 30 days	FUP 3 1 Year 365± 60 days	>1 to 5 Years FUP (± 90 days window)
Inclusion/Exclusion	x						
Demographics/Medical History	x						
Physical Exam [†]	x		x	x	x	x	x
Blood Labs [‡]	x		x	x	x	x	x
Contrast-enhanced CT scan	x [§]			x [§]	x*	x [§]	x*
Procedural Information		x					
Adverse Events		x	x	x	x	x	x
[†] The physical exam includes overall health, physical assessment, and vital signs. [‡] Blood labs typically include serum creatinine and hemoglobin, if collected [§] High resolution (<3mm slice spacing), contrast and non-contrast CT scan is preferred up to 3 months prior to the scheduled procedure *If the institution's standard of care for EVAR subjects involves another imaging modality e.g. duplex ultrasound, that modality may be collected alternatively.							

6. STUDY EVALUATIONS

6.1. PRIMARY STUDY ENDPOINTS

Primary Study Endpoints The primary study endpoint is one -year survival in the absence of Aneurysm Related Complications (ARC). ARC is a composite of the most relevant EVAR related outcomes and includes:

- Peri-operative death (≤ 30 days)
- Aneurysm rupture
- Conversion to Open Surgical Repair (OSR)
- Endoleaks; post-operative
- Endograft migration (≥ 10 mm)
- Aneurysm enlargement (≥ 5 mm compared to 1 month CT study)
- Endograft occlusion
- Reinterventions for device- or aneurysm-related complications

The outcomes above comprising of the ARC composite endpoint are defined in Sections 10.3

Imaging driven observations will be based on the one year evaluation window (365 days \pm 60 days). If there are two diagnostic images available within the window, it will be up to the discretion of the core lab to analyze one or both images to ensure an overall accurate evaluation of the patient.

6.2. SECONDARY STUDY ENDPOINTS

Secondary endpoints to be assessed include:

1. Major Adverse Events (MAEs) at 30 Days, 12 Months and Annually:
 - Mortality (all-cause)
 - Bowel Ischemia
 - Myocardial Infarction
 - Paraplegia
 - Renal Failure
 - Respiratory Failure
 - Stroke
 - Procedural Blood Loss $\geq 1,000$ mL
2. ARC Post 12 Months up to Five Years
3. Individual components of ARC Post 12 Months and up to Five Years
4. Aneurysm Related Mortality
5. Endoleaks Classified by Type
6. Loss of Neck Apposition
7. AAA Related Secondary Procedures up to Five years
8. Device Integrity
9. Any adjunctive procedures necessitated during the implant procedure.

The Steering Committee may add additional secondary endpoints, as required during the study.

6.3. ADDITIONAL EVALUATIONS

Additional evaluations include the following procedural and in-hospital evaluations:

- Total Endovascular time; from catheter introduction to catheter removal
- Anesthesia Time
- Fluoroscopy Time
- Contrast Volume used
- Total Procedure Time; from cut-down to closure
- Time in ICU
- Total Radiation Exposure
- Additional Imaging

The Steering Committee may add additional evaluations, as required during the study.

6.4. SUB-STUDY EVALUATIONS

Economic Sub-Study

Subset of the study population will be part of an economic outcomes assessment.

Patient Related outcomes:

Subset of the study population will be assessed on patient related outcomes with EVAR specific tools for quality of life evaluation.

7. ELECTRONIC CASE REPORT FORMS

The study will utilize an electronic Case Report Form (eCRF) system for data collection. All site staff will be trained on correct eCRF completion prior to site activation. Only trained personnel will receive access and be able to enter data in the eCRF. All eCRF pages will be electronically signed by the investigator at each site. Each subject will be anonymized and given a specific study number in the eCRF.

8. DATA MANAGEMENT

The data required for the study will be entered by the investigation sites into eCRF. Detailed edit checks will ensure a high quality standard of the data entered in the database. Additionally, data management will review the collected data and issue possible queries. Queries should be resolved by the investigation site on an ongoing basis. When all study data is complete, the database will be locked and data analyzed.

9. STATISTICAL CONSIDERATIONS

9.1 GENERAL CONSIDERATIONS

Primary analyses will be based on Intention-to-Treat (ITT) populations.

Randomization will be centralized using permuted block design. A randomization schedule will be generated with a random number generator in the SAS System®. To maximize the chance that all blocks are filled, the randomization result will be generated and accessible to the site no earlier than 48 hours prior to the planned procedure day. Sites/investigators will be blinded to block size. Due to the use of a large number of sites with relatively a small number of patients within specific sites, stratification by institution will not be performed. Stratification using risk factors will not be performed.

For additional information on the randomization process, refer to §5.5.

Statistical analyses will be performed using SAS System®, Version 9.4 or later.

9.2 STATISTICAL METHODS

All continuous variables in the composite endpoint will be evaluated to 1 year (day 365 post-implant), whereas imaging-driven variables will be evaluated to a 1 year window (day 365 +/- 60 days). The day of implantation will be set as day 0. Early events are defined as those occurring from the date of the procedure up to 30 calendar days post-operatively. Late events are defined as those occurring from after 30 calendar days post-operatively (from day 31 forward).

The null hypotheses for both non-inferiority and superiority will be evaluated with one-sided alpha levels of 0.05.

If the non-inferiority null hypothesis is rejected, the null hypothesis for superiority will be investigated.

Hypotheses for Non-Inferiority:

Null Hypothesis: $H_{1_0}: \mu_A - \mu_B \leq -8\%$ (AFX is inferior with respect to the primary endpoint)

Alternative: $H_{1_1}: \mu_A - \mu_B > -8\%$ (Statistical evidence of non-inferiority)

Hypotheses for Superiority:

Null Hypothesis: $H_{2_0}: \mu_A - \mu_B \leq 0$ (The two device groups have equal effect)

Alternative: $H_{2_1}: \mu_A - \mu_B > 0$ (Statistical evidence of superiority)

Data for the primary endpoint will be presented as point estimates for both the treatment (AFX device) and control (proximally fixated devices), along with a 95% confidence interval for the difference. The lower bound of a one sided 95% confidence interval is used to evaluate the non-inferiority and superiority null hypotheses.

Quantitative parameters will be described using the following summary descriptive statistics: number of non-missing values, mean, standard deviation, median, first and third quartiles, and minimum and maximum values.

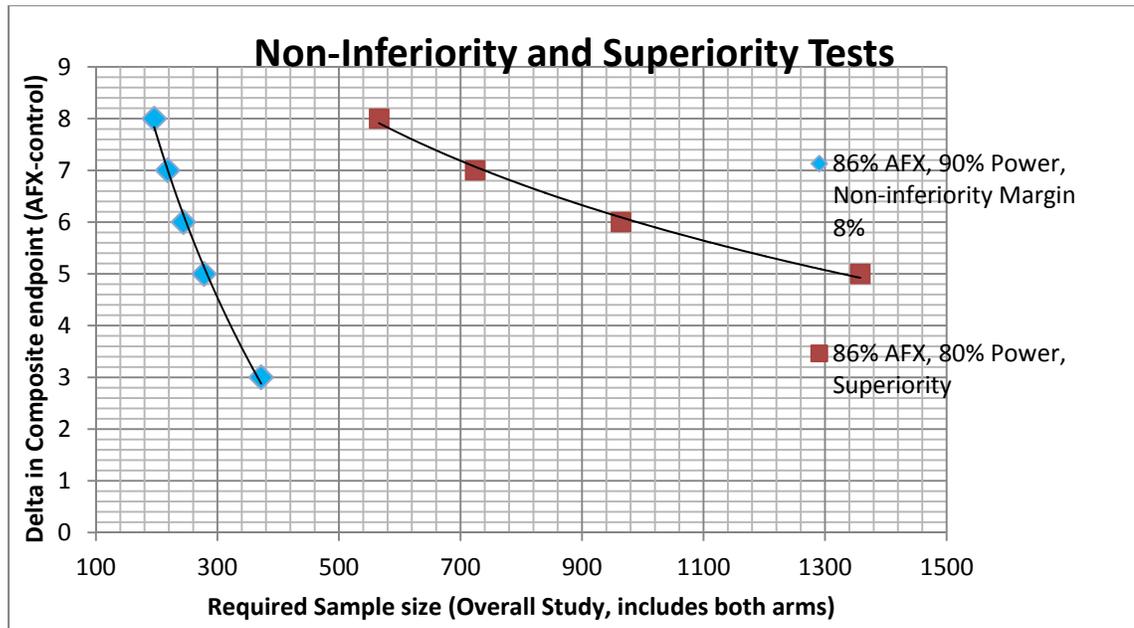
Qualitative parameters will be described overall using frequencies and percentages. Percentages will be calculated on the number of non-missing observations. In all cases, the number of missing values will be specified.

Kaplan-Meier estimates will be generated for the composite endpoint components that are continuous in nature (not imaging-driven), to one year.

Sample Size Determination:

Given an alpha error rate of 0.05, a desired power of 90%, and assuming a success rate (in terms of the primary endpoint) of 86% for AFX with a 8% advantage over the control group, the sample size required to demonstrate non-inferiority is 154 subjects in total. As shown in the sample size plot below, in order to have enough power to evaluate all hypotheses the sample size for this study is driven by the evaluation of superiority. In this case, an alpha error rate of 0.05, power of 80%, success rate of 86% for AFX, and a relative 8% advantage in AFX's favor requires 566 patients. A 7% advantage in AFX's favor requires 724 patients. An approximate drop-out rate of 10%/1-year indicates 804 patients should be enrolled to provide 724 patients at 1 year. The sample size has been determined with PASS version 12.0.2.

The plot below shows required sample sizes for different relative advantages of the AFX group.



9.3 DISTRIBUTION OF THE PATIENTS

The number of patients in the ITT population, as well as the distribution across sites will be presented.

Descriptive statistical data will be used to draw up the characteristics of subjects at the time of enrollment (demographics, baseline data).

9.4 HANDLING MISSING VALUES

In order to provide unbiased and informative findings, no replacement of missing values is planned for any parameters. In all applicable cases, reported analysis will mention the number of missing values for each outcome in the ITT population.

10. ADVERSE EVENT REPORTING

The safety of the device will be monitored throughout the study by assessment of serious adverse events (SAE), adverse device effects (ADE) and serious adverse device effects (SADE). All SAEs will be recorded in the eCRF system and will be assessed by independent physician(s) as well the internal Complaint Handling Department in order to comply with Vigilance reporting.

Independent physician(s) will adjudicate all SAEs, ADEs and SADEs reported by the sites within this study. For all adjudicated events, the independent physician(s) will be required to complete the eCRF data capture form.

Non-serious adverse events will not be evaluated in this study (Definitions according to ISO 14155:2011(E)).

10.1 ADVERSE EVENT DEFINITIONS¹

1. Serious Adverse Event (SAE)

An SAE is a serious adverse event that

- a) led to death
- b) led to serious deterioration in the health of the subject, that either resulted in
 - a life-threatening illness or injury, or
 - a permanent impairment of a body structure or a body function, or
 - in-patient or prolonged hospitalization, or
- c) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- d) led to fetal distress, fetal death or a congenital abnormality or birth defect

2. Unanticipated Adverse Events

Investigators shall submit to Endologix and to the reviewing ethics committee/IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible,

¹ Clinical investigation of medical devices for human subjects, good clinical practice. ISO 14155:2011.

but in no event later than 10 working days after the investigator first learns of the effect. Investigators must submit to Endologix documentation of the report made to the ethics committee.

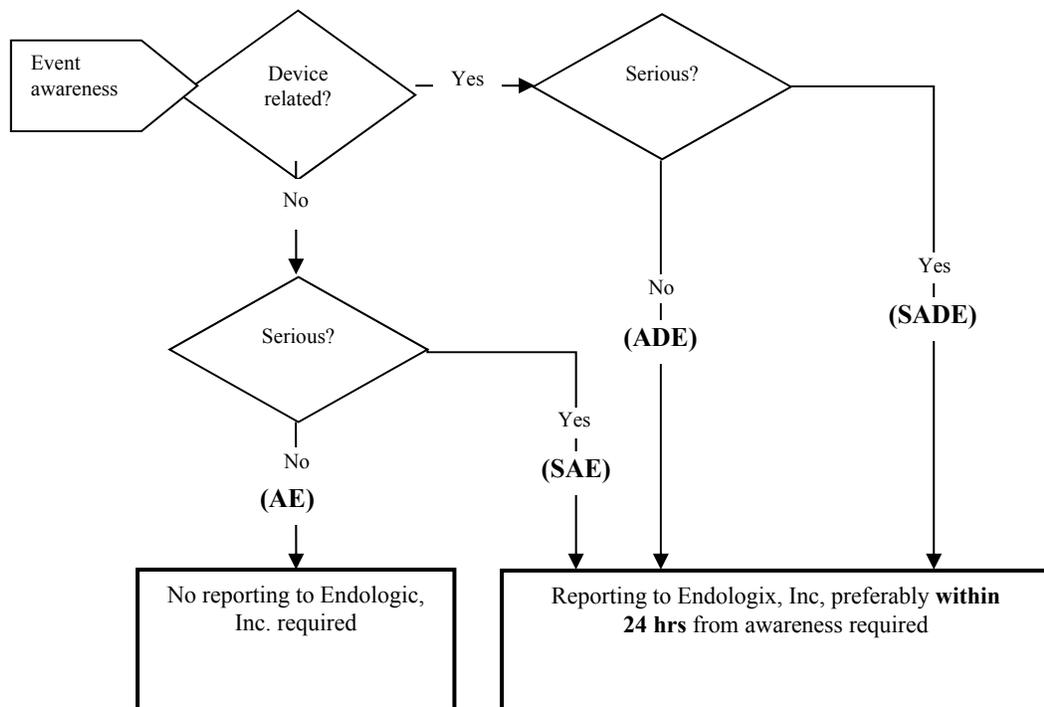
NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP (Clinical Investigation Plan), without serious deterioration in health, is not considered an SAE.

The **relation to the investigational device** is classified by the investigator as either:

- Related or
- Not related

10.2 ADVERSE EVENT REPORTING

The investigator must report any SAE **in the eCRF** to Endologix, Inc. as soon as possible when he becomes aware of the event, preferably **within 24 hours of awareness** of the event. The decision tree for the event reporting looks as follows:



10.3 DEFINITIONS

10.3.1 Definitions Associated with the Composite Primary Endpoint ARC

ARC is defined as the primary study endpoint is an assessment at one year, where survival is in the absence of Aneurysm Related Complications (ARC). ARC is a composite of the most relevant EVAR related outcomes and includes:

- *Aneurysm Rupture*: Loss of continuity in the aneurysm wall (aortic or iliac if present) at any time point. The latter can be determined by CT/MR imaging, operative findings, or post-mortem evidence of blood outside of the wall of the aneurysm.
- *Conversion to Open Surgical Repair (OSR)*: open surgical repair of the abdominal aortic aneurysm due to unsuccessful delivery or deployment of the stent graft, due to complications or other clinical situations that precluded successful endovascular treatment, or at any time following initial successful endovascular treatment for any reason.
- *Endoleaks*: clear evidence of contrast within the aneurysm sac
 - *Endoleak Type Ia* – contrast material in the aneurysm sac adjacent to the proximal seal zone and/or between the endograft and the inner wall of the proximal attachment site.
 - *Endoleak Type Ib* - contrast material in the aneurysm sac adjacent to the distal seal zone and/or between the endograft and the inner wall of the distal attachment site.
 - *Endoleak Type II* – contrast material along the posterior sac wall with visualization of lumbar artery or the inferior mesenteric artery
 - *Endoleak Type III* – contrast material in contact with the endograft, not in direct contact with the neck.
- *Migration* (≥ 10 mm): core lab reported stent distal movement >10 mm from the original implant location relative to the center of the distal renal artery; as compared to the 1month CT scan location
- *Aneurysm Sac Enlargement*: aneurysm sac diameter increase of ≥ 5 mm in late follow-up as compared to the initial post-operative measurement.
- *Endograft Limb Occlusions*: defined as total obstruction of blood – irrespective of whether a secondary intervention is necessary.
- *Stenosis*: defined as a reduction in lumen $>50\%$ by, for example, thrombus, intimal hyperplasia, or endograft kink/twist.

Elaboration of the above definitions can be found in the CEC Manual of Operations.

10.3.2 Adverse Event Definitions

The following event definitions will be applied during this study.

- *Death* is defined as any death occurring during the study period, regardless of cause.
 - *Aneurysm-related death* is defined as any death occurring within 30 days from the date of the procedure, regardless of cause, and death due to aneurysm rupture or death within 30 days of any secondary procedure intended to treat the aneurysm.
 - *Cardiac-related death* is defined as death due to arrhythmia, heart failure (including cardiogenic shock), or myocardial infarction
 - *Pulmonary-related death* is defined as death due to pulmonary edema, respiratory failure, or pulmonary embolism
 - *Vascular-related death* is defined as death due to stroke, cerebral hemorrhage, or other clear vascular event that is not categorized as cardiac-related or pulmonary-related or aneurysm-related.
 - *Other* is to be used to identify a death due to any event that cannot be clearly categorized as above, but where some information is available.
 - *Unknown* is to be used to identify a death where no information is available.
- *Procedural Technical Failure* is defined as a failure of the AFX[®] System or comparator devices to be delivered and deployed, such that the procedure is not completed, or the device failure results in a serious complication, or residual Type I and Type III endoleaks which occur and cannot be resolved during the index procedure.
- *Major Adverse Event* is defined as an event occurring during the study that meets one of the following criteria:
 - *All-Cause Death* (see above).
 - *Bowel Ischemia*: the lack of adequate blood flow to the intestines that requires intensification of medical therapy or surgical/endovascular intervention.
 - *Myocardial Infarction*: increase of one or more cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following: myocardial ischemia; ECG changes indicative to new ischemia (new ST-T changes or left bundle branch block (LBBB)); development of pathological Q-waves in the ECG; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
 - *Paraplegia*: paralysis of the lower extremities inclusive of the lower trunk;
 - *Renal Outcomes*:
 - *Renal Dysfunction* – a decrease of > 30% in eGFR or an increase in pre-operative serum creatinine level at two consecutive intervals

- *Renal Failure* – permanent dialysis dependence or kidney transplant
- *Stroke*: a sudden development of neurological deficit due to vascular lesions of the brain such as hemorrhage, embolism, or thrombosis that persists for >24 hours;
- *Procedural Blood Loss >1,000mL*: estimated blood loss during the index procedure $\geq 1,000\text{mL}$.
- *Unanticipated Adverse Device Effect (UADE)* is 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 nature, severity or degree of incidence. Additionally, an unanticipated adverse event includes any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

10.3.3 Other Definitions

- *Luminal Thrombus Requiring Intervention*: any endovascular surgical intervention after completion of the AFX® System implantation for resolution of endograft thrombosis.
- *Distal Ischemia*: new onset of compromised peripheral blood flow resulting in femoral or peripheral arterial occlusion or stenosis (attributable to the index procedure or to the endograft and not related to natural progression of atherosclerotic disease) causing a threat to the viability of the limb and requiring surgical or percutaneous intervention; or stent graft occlusion requiring any intervention.
- *Occlusion requiring intervention*: intervention for stent graft occlusion
- *Secondary Endovascular Procedure*: any non-diagnostic intervention after the index procedure intended to correct or repair an endoleak, device stenosis or occlusion, migration, aneurysm sac expansion and/or a device defect (including infection);
- *Successful Implantation*: Successful delivery and deployment of the device.
- *Intention-to-Treat*: analysis of the results of an experiment is based on the initial treatment assignment and not on the treatment eventually received.

11. RESPONSIBILITIES

11.1 SPONSOR RESPONSIBILITIES

This study is conducted under the responsibility of Endologix, Inc. USA. Only Endologix staff and designees approved by Endologix, Inc. will participate in this study. Endologix is responsible as the Sponsor to ensure:

- Proper site and investigator selection
- Availability of signed investigator agreements prior to study initiation
- Availability of regulatory and IRB approval prior to the initiation of the study at any site

- Management and monitoring of the study with special attention to verification of all clinical requirements, adherence to protocol, good clinical practices and compliance with applicable government and institutional regulations
- Furthermore, the sponsor is responsible for ensuring proper regulatory approvals are obtained, and reporting to regulatory authorities per applicable regulations
- Sites are supported and adequately trained on the device.

11.2 INVESTIGATOR RESPONSIBILITIES

It's the **investigator's** and **investigation site staff's** responsibility to conduct this study in accordance with relevant rules and regulations, including but not limited to, this study protocol, the signed investigator agreement, Good Clinical Practices, all applicable laws and regulations and any conditions or restrictions imposed by the reviewing IRB. This includes compliance with requirements related to IRB approval and reporting, and proper patient informed consent prior to participation in the study. The investigator is also responsible for protecting the rights, safety, and welfare of the subjects under his/her care.

- Each investigator is responsible for supervising all procedures conducted under this protocol at his/her institution.
- Furthermore, the investigator is responsible for ensuring that data are completely, accurately, and promptly recorded on each patient's eCRFs and related documents are available to verify the accuracy of the eCRFs, and for ensuring the clinical monitor has access to all necessary records to ensure the integrity of the data

In order to be considered for the participation in the study the investigator must:

- Provide the sponsor with a complete signed study contract
- Acquire and provide all applicable approvals, including but not limited to, the relevant IRB.
- **The Investigator must complete the above process and start enrollment within 3 months from the date he/she receives the needed regulatory documents for the study. If this deadline cannot be met the investigator and his/her team may not be able to participate in this study. At this time the sponsor may opt to enroll an alternative site.**

In addition, all local regulations must be adhered to; in particular those which afford greater protection to the safety of study subjects. Suitably qualified and trained clinical personnel of the investigation site must ensure compliance with the protocol, adherence to ethical and regulatory obligations and proper maintenance of study records.

By signing the protocol signature page, the investigator agrees to conduct the study according to protocol.

11.3 INDEPENDENT EVENT REVIEWER RESPONSIBILITIES

An independent physician(s) will adjudicate all SAEs, ADEs and SADEs reported by the sites within this study. The independent physician will complete the eCRF data capture form for all the adjudicated events.

11.4 INDEPENDENT PHYSICIAN RESPONSIBILITIES

All images obtained in this study will be assessed by independent physician(s) and measurements of the assessment will be recorded in the eCRF, to ensure uniform and unbiased image assessment throughout the study.

12 CONFIDENTIALITY AND PATIENT RIGHTS

12.1 CONFIDENTIALITY

Study subjects will be identified only by a unique subject number used in all correspondence and the study database. The investigator and the investigation site team shall maintain patient confidentiality during all site audits and inspections and in all documentation. The investigator will keep a list containing the names of all patients along with their assigned study subject number.

All information provided to the investigator relevant to the device, as well as information obtained during the course of the study, will be regarded as confidential. The investigator and all members of his or her study team agree not to disclose or publish such information in any way to any third party without prior written permission from Endologix, Inc. which will not be unreasonably withheld, except as required by law. The Investigator will take all measures to ensure patient confidentiality is maintained at all times. All subject data must be anonymized before retrieval from the clinical site.

12.2 PATIENT RIGHTS

The subject has the right to withdraw from the study at any time and without reason.

Upon early withdrawal from the study, the eCRFs should be completed as far as possible and the reasons for withdrawal should be documented if possible.

13 ETHICAL CONSIDERATIONS

No data identifying the subject and no other confidential data will be recorded. No procedures and examinations are required in addition to those that are standard of care in each participating site. The knowledge gained from this study might provide information to improve the treatment of patients with AAA eligible for endovascular treatment and/or the device.

This study is performed in accordance with the Declaration of Helsinki and in accordance with Good Clinical Practice.

14 MONITORING

The eCRF will **not** be considered as source document.

Source data verification will be performed by means of intermittent on-site and/or off-site monitoring. Details will be outlined in the monitoring plan.

15 STUDY TERMINATION

The study can be terminated or suspended prematurely at a specific investigation site or in total due to low compliance to the CIP, lack of enrolled subjects or that it becomes apparent that the study can no longer fulfill its aims. Endologix, Inc. can do so at its own discretion without having any further obligations to the study site(s).

16 PUBLICATION

Endologix, Inc. intends to publish the results of this study. Endologix, Inc. reserves the right to include the report of this study in any regulatory documentation or submission or in any informational materials prepared for the medical profession. The ownership of the data shall at all times be held by Endologix, Inc. Only Investigators from centers with high protocol compliance, fast enrollment and complete data sets from all follow-up visits will be considered as authors on publications.

Any single center within the study is not permitted to publish its own data prior to the publication of the multi-center data at any time throughout the study.

Endologix, Inc. agrees that after publication of multicenter data investigators shall be permitted to present at symposia, national or regional professional meetings, and to publish in journals, theses or dissertations, or otherwise of their own choosing, methods and results of the study. Any prior publication in any way or form is not permitted, unless approved in writing by Endologix, Inc.