CLINICAL TRIAL PROTOCOL
CP-0011 REV. 02

REVISION 01: 07 JANUARY 2015
REVISION 02: 29 AUGUST 2021

Multicenter, Observational, Post-Market, Real World Trial 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

Protocol Number: CP-0011

National Clinical Trial (NCT) Identified Number: NCT02407457

National Principal Investigator: Dr. Christopher Kwolek, MD

SUMMARY OF CHANGES FROM PREVIOUS REVISION

Revision	DCO#	Date	Affected Section(s)	Summary of revisions made	Rationale
02	21-0542	29 August 2021	Entire document	Changed study with trial, general formatting and minor adjustments.	FDA suggestion being a Randomized Controlled Trial rather study.
			2	Changed Sponsor Contact.	Provide most up to date contacts
			3	Updated all the information changed in the document and that are reported into the synopsis.	To stay consistent with the changes made.
			4.3	Included that the Steering Committee has been used only for the start-up of the trial.	As the Steering Committee has not been used afterward as we have an Independent Adjudicator and the Corelab.
			4.5	Included that the 6 months visit is not required as any other visit as standard of care will be followed for the follow-up.	To be clear on the schedule of activities and lack of specific requirements for the follow-up and imaging.
			5.8	Included details on the exit date for patients undergoing a conversion. Included table with schedule of activities.	For consistency and to provide specific definition and guidelines on the study exit dates for these patients. Included the schedule of activities as per standard of care to provide details on follow-up.
			7	Added the definition for technical failure.	More clarity.
			10.1	Changed to Modified Intention to Treat (mITT) population and added the definition and included reference to the Statistical Plan.	To make sure to include in the analysis only the patients that effectively undergone an EVAR procedure.
			10.2	Changed the sample size determination.	The sample size has been changed to reflect the adequate sample size for evaluating non inferiority and not superiority as originally planned.
			11	Included MAE and events that might meet the endpoint as monitored events, included that non serious adverse event with no relationship with the device won't be considered. Included details on events to be adjudicated by the	More clarity.

				independent adjudicator.	
			11.1.1	Included definition of UADE.	More clarity.
			11.2	Included definition of SAE.	More clarity.
			12.1	Updated a few definitions.	Consistency.
			12.2.	Updated AE definition.	Consistency and clarity.
			12.3	Updated MAE definition and included definition of type of deaths.	Consistency and clarity.
			13.3	Included UADE in the list of events to be adjudicated.	For consistency with the Adjudication plan.
			13.4	Included Corelab.	Including Corelab review of the images provided by site.
			16	Included into the Monitoring section references to the current COVID-19 situation and consequent updates included in the monitoring plan.	To reflect the changes done to the monitoring plan.
			16.1	Included sub-section on protocol deviation.	Missing before.

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1 INVESTIGATOR SIGNATURE PAGE

I agree to conduct the trial 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 trial 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 trial protocol and all necessary information about this trial to the trial 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 trial.

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 trial. 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 trial or its progress will be provided to anyone not involved in the trial other than the sponsor, or the Institutional Review Board(s), the Core Lab(s), 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 and all applicable regulatory and ethical requirements.

_____ _____

Investigator Signature Date

_____

Investigator Printed Name

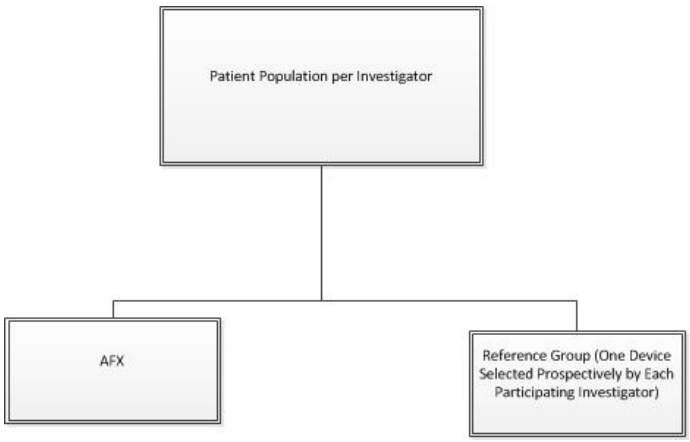
2. TRIAL CONTACT PERSONNEL

2.1 SPONSOR

SPONSOR CONTACT
Carola Ciancioso **Director Clinical Affairs** Tel: 0039 392 91 04 786 Endologix 2 Musick Irvine, CA 92618 USA cciancioso@endologix.com

3 PROTOCOL SYNOPSIS

Title of the Trial	Multicenter, Post-Market, Real World Trial to Assess Outcomes of Patients Treated with the AFX System compared to other EVAR devices for Endovascular Abdominal Aortic Aneurysm Repair: **LEOPARD** (**L**ooking at **E**VAR **O**utcomes by **P**rimary **A**nalysis of **R**andomized **D**ata)
Trial Devices	AFX Endovascular AAA System and other approved Endovascular AAA stent graft systems
Trial Sponsor	Endologix 2 Musick Irvine, CA 92618 (USA)
Steering Committee	Initial governance of the trial was 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 was to provide scientific direction and oversight to start with the LEOPARD Trial involving Endologix's EVAR System, AFX. Essential responsibilities of the SC included trial design and protocol review and to provide guidance and advice to the Investigators for patient selection and timely enrollment. Details of the SC are available on file, in the SC Charter.
Objectives	Objective of this post-market trial is to evaluate Endologix AFX endovascular AAA system with *anatomical* fixation against other approved Endovascular systems with *proximal* fixation.
Trial Design	Prospective, randomized, multi-center trial 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 consented patients diagnosed with AAA who are considered candidates for endovascular repair and meet the trial 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 a combination of on-site and centralized monitoring using Endologix procedures.
Trial Timelines	Enrollment started: 23 March 2015 Enrollment Completion: Q3 2017 5-year Follow-Up Completion: Q4 2022
Independent Adverse Event Review	Independent physician(s) will adjudicate all Major Adverse Events (MAE), Adverse Device Effects (ADE), Serious Adverse Device Effects (SADE) and Unanticipated

	Adverse Device Effects (UADE) reported by the sites within this trial. Independent physician(s) will complete the eCRF data capture form for all adjudicated events.
Imaging Assessment	Available imaging will be evaluated by an independent Core Lab.
Inclusion Criteria	1. Male or female at least 18 years old 2. Subjects with minimum of 2 years 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 trial devices
Exclusion Criteria	1. Currently participating in another trial 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.
Trial Randomization	The LEOPARD Trial 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. The trial will sequentially evaluate non-inferiority and superiority hypotheses. Randomization Scheme: 

Primary Endpoint	One year survival in absence of Aneurysm Related Complications. ARC is a composite of the most relevant EVAR outcomes and includes: - 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 Any imaging driven observation at 365 days ± 60 days will be included in the one year evaluation window
Secondary Endpoints	• MAEs at 30-Days, 12 Months and Annually • ARC Post 12 Months up to Five Years • Aneurysm Related Mortality • Endoleaks Classified by Type • AAA Related Secondary Procedures up to Five Years • Device integrity • Any adjunctive procedures necessitated during the implant procedure
Additional Evaluations	• Total Endovascular time; from catheter introduction to catheter removal • Anaesthesia Time • Fluoroscopy Time • Contrast Volume used • Total Procedure Time; from cut-down to closure • Time in ICU • Total Radiation Exposure • Additional Imaging

Statistical Considerations	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. 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) 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) The original trial size was selected to provide 80% power for the superiority test. The original sample size required, for non-inferiority testing, is relatively smaller; thus, the power of the non-inferiority test approaches 100% with the revised sample size.
Suggested Schedule of Tests	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. 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). **Table 1** outlines a typical site follow-up schedule which will be altered to meet standard of care at individual sites.

Table 1: Typical Site Follow-Up Schedule (may be altered to meet standard of care at sites)

Suggested Schedule of Tests	Screening/Baseline	Procedure	Pre-Discharge	1 Month FUP	6 Month FUP	1 Year FUP	>1 to 5 Year FUP's
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 institution's standard of care for EVAR involves another imaging modality e.g., duplex ultrasound, that modality may be collected alternatively.*

4 TRIAL OVERVIEW

4.1 OBJECTIVE

The objective of this post-market trial 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 trial 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 practices has since 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, 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 trial 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 earlier trials serve that purpose today. In addition, the LEOPARD trial will provide insight into the performance of the device design in a broad range of patient anatomies, guidance on EVAR strategy and clinical presentations, leading to the definitive choices in the years to come.

4.3 INITIAL TRIAL GOVERNANCE

The initial governance of the trial 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 start-up of the LEOPARD Trial involving Endologix's EVAR System, AFX. Essential responsibilities of the SC include trial design and protocol review and to provide guidance and advice to the Investigators for patient selection and timely enrollment.

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

4.4 TRIAL DEVICE

The devices used in this trial 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 trial, 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 trial will allow for use of iterative changes to all devices indicated above.

4.5 TRIAL DESIGN

The LEOPARD trial is a prospective, randomized, multi-center trial, intended to evaluate the outcomes of contemporary EVAR (Endovascular Aneurysm Repair) in a real-world population. The trial 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 trial will sequentially evaluate non-inferiority and superiority hypotheses.

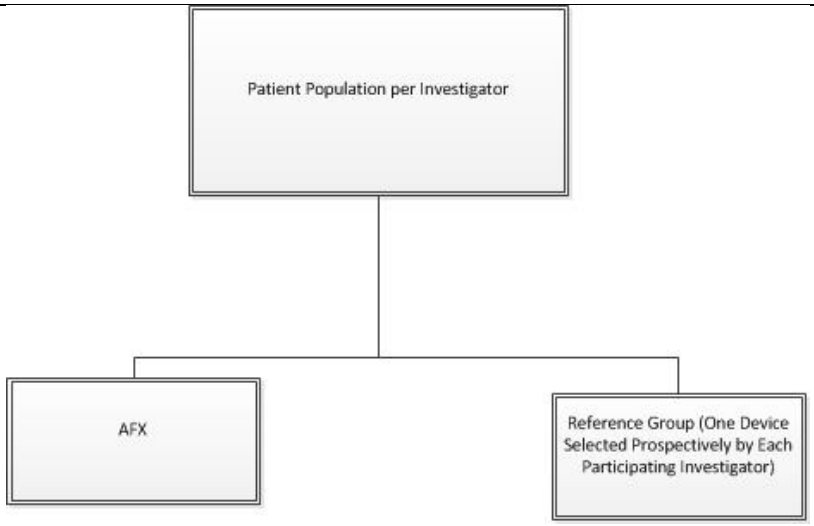


Figure 1: Randomization Scheme

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, no specific trial visit is required), 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 trial. This will be accomplished through the patient's reading of the informed consent form and discussion of the trial 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 trial 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 trial arm. This may result in a small number of additional patients in the trial. All such patients will be included in trial analysis.

5 TRIAL POPULATION AND PROCEDURES

Up to 80 sites with experience in EVAR and up to 800 subjects will participate in this trial. 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 trial subject:

1. Male or female at least 18 years old
2. Subjects with minimum of 2 years 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 trial devices.

5.2 EXCLUSION CRITERIA

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

1. Currently participating in another trial 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.

5.3 PATIENT ASSESSMENT AND SCREENING

Patients will be consecutively assessed for inclusion in the trial 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.

5.4 ENROLLMENT CRITERIA

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

5.5 PATIENT INFORMED CONSENT

Written informed consent, documented on the ICF in accordance with Good Clinical Practice standards and trial 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.

5.6 ENROLLMENT AND RANDOMIZATION

Patient enrollment into this trial is based on the site evaluation of patient conformance with the protocol-specified selection criteria (see **§5.1**), 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 trial, 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 trial only occurs upon advancement of the trial device into the subject's vasculature.

5.7 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.

5.8 FOLLOW-UP REQUIREMENTS

Subjects will be followed procedurally and to hospital discharge and at 1, 6 (standard of care follow-up; no specific trial visit is required), 12 months and annually through five years (total follow-up commitment).

Table 2 outlines a suggested follow-up schedule which may be altered to meet standard of care at individual sites.

If a subject undergoes conversion to open surgical repair, the subject will continue follow-up for 30-days post-conversion, at which point the subject will exit. If the subject has not been discharged from the conversion hospitalization within 30-days, the date of discharge will be the date of trial exit.

Table 2: Suggested Follow-Up Visit Schedule

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 TRIAL EVALUATIONS

6.1 PRIMARY TRIAL ENDPOINTS

The primary trial 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 (≥ 10mm)
- Aneurysm enlargement (≥ 5mm compared to 1-month CT)
- Endograft occlusion
- Reinterventions for device- or aneurysm-related complications

The outcomes above comprising of the ARC composite endpoint are defined in **§12.1**.

Imaging driven observations will be based on the one-year evaluation window (365 days ± 60 days). If there are two diagnostic images available within the window, the convention will be to use any image with a positive finding.

6.2 SECONDARY TRIAL ENDPOINTS

Secondary endpoints to be assessed up to five years include:

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

7 ADDITIONAL EVALUATIONS

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

1. Procedural Technical Failure

2. Total Endovascular time; from catheter introduction to catheter removal
3. Anesthesia Time
4. Fluoroscopy Time
5. Contrast Volume used
6. Total Procedure Time; from cut-down to closure
7. Time in ICU
8. Total Radiation Exposure

The 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.

8 ELECTRONIC CASE REPORT FORMS

The trial 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 trial number in the eCRF.

9 DATA MANAGEMENT

The data required for the trial 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 trial data is complete, the database will be locked, and data analyzed.

10 STATISTICAL CONSIDERATIONS

10.1 GENERAL CONSIDERATIONS

Primary analyses will be based on modified Intention-to-Treat (mITT) populations. An Intention-to-Treat (ITT) analysis population consists of all randomized subjects. While the intent of the trial is to implant all randomized subjects, some randomized subjects will not undergo implantation due to unforeseen issues. If this were to occur in a substantial number of subjects, it is possible that the results may be biased towards non-inferiority as the groups would become increasingly similar. Thus, a mITT population is defined, which consists of all randomized subjects that subsequently underwent EVAR. All endpoints in this trial, unless otherwise specifically noted, will be evaluated against the mITT analysis population.

Randomization will be centralized using permuted block design. A randomization schedule will be generated with a random number generator in the SAS System®. Sites/Investigators will be blinded to block size. Due to the use of a large number of sites with a relatively small number of patients within specific sites, stratification by institution will not be performed. The intent is to allocate similar numbers of subjects between the two treatment groups across the total number of sites, to provide maximum power. Additionally, stratification using risk factors will not be performed.

Additional information is available in the Statistical Analysis Plan (SAP). Statistical analyses will be performed using SAS System®, Version 9.4 or later.

For additional information on the randomization process, refer to **§5.6**.

10.2 STATISTICAL METHODS

All non-imaging-driven 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: $H1_0: \mu_A - \mu_B \leq -8\%$ (AFX is inferior with respect to the primary endpoint)

Alternative: $H1_1: \mu_A - \mu_B > -8\%$ (Statistical evidence of non-inferiority)

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)

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 across the duration of the trial.

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 an 8% advantage over the control group, the sample size required to demonstrate non-inferiority is 154 subjects in total. In order to have enough power to evaluate all hypotheses the sample size for this trial was 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 original protocol thus called for enrollment of up to 800 subjects. The enrollment was completed at 455 subjects after an unplanned analysis supported that the superiority evaluation was futile. With a total of 455 subjects enrolled, 410 are assumed to reach the 1-year endpoint after 10% dropout. This sample size results in 99% power for the non-inferiority test under original assumptions, and thus the trial is considered adequately powered for evaluating non-inferiority. The sample size has been determined with PASS version 12.0.2.

10.2.1 DISTRIBUTION OF THE PATIENTS

The number of patients in the mITT 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).

10.2.2 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 mITT population.

10.2.3 DATA ANALYSIS

In the original analyses, the ARC endpoint has been evaluated by site reported events only. Now that Corelab data is available, it will be considered during the future evaluations of the data.
In future analyses, the data presented will utilize CoreLab findings in addition to site-reported findings. The analyses will defer to CoreLab results when the site and CoreLab disagree. In the absence of CoreLab-reviewed data, events will be assessed by the site. In addition to this, the clinical data and evaluation of the patients will be considered when reviewing data, and the clinical history of the patient as well as the review of the independent adjudicator may overrule site and Corelab findings.

11 ADVERSE EVENT REPORTING

The safety of the device will be monitored throughout the trial by assessment of serious adverse events (SAE), adverse device effects (ADE) serious adverse device effects (SADE), and major adverse events (MAE), or events that may potentially meet an endpoint. All SAEs will be recorded in the eCRF system and will be assessed by the Sponsor. Additionally, applicable events will be assessed by the internal Complaint Handling Department in order to comply with adverse event reporting. Non-serious adverse events with no device relationship that do not meet a trial endpoint, will not be evaluated in this trial (definition according to ISO 14155:2011(E)).

Independent adjudication will occur for all ADEs, MAEs and SADEs reported by the sites within this trial. For any adjudicated events, the adjudicator or designee will be required to complete the eCRF data capture form.

11.1 ADVERSE EVENT DEFINITIONS[1]

11.1.1 UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

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 (US 21 CFR 812.3).

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

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, **but no later than 24-hours 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, as well as the relation to the index procedure is classified by the Investigator as either "Related" or "Unrelated".

11.2 SERIOUS ADVERSE EVENTS (SAE)

Per ISO 14155, a SAE is a serious adverse event that

a) Led to death,
b) Led to serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:
    1) A life-threatening illness or injury, or
    2) A permanent impairment of a body structure or body function, including chronic diseases, or
    3) In-patient or prolonged hospitalization, or
    4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure of a body function,
c) Led to fetal distress, fetal death or a congenital abnormality or birth defect, including physical or mental impairment.

The Investigator must report any SAE **in the eCRF** to Endologix, Inc. as soon as they become aware of the event, preferably **within 24-hours of awareness** of the event. Refer to **Figure 2** for the decision tree for event reporting:

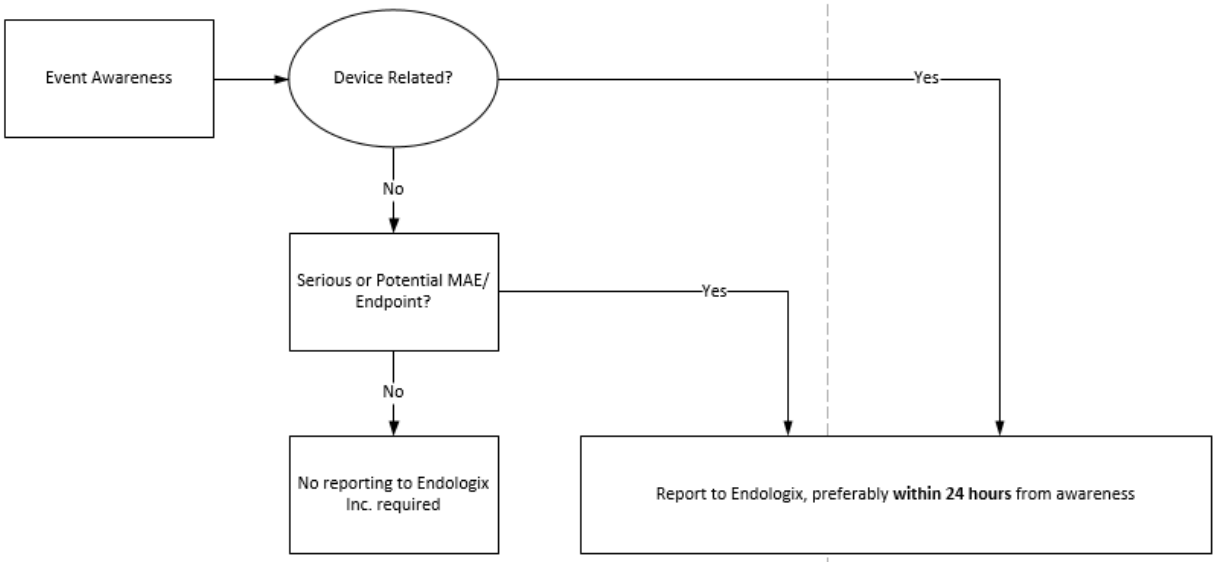


Figure 2: Reporting Decision Tree

12 DEFINITIONS

12.1 DEFINITIONS ASSOCIATED WITH THE COMPOSITE PRIMARY ENDPOINT ARC

The primary trial 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 include:

- *Aneurysm Rupture*: bleeding or leaking of blood from the aneurysm subsequent to the index procedure.
- *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. Excludes post-mortem explant of the trial device.
- *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 IIIa** – Component disconnect
  - **Endoleak Type IIIb** – Mid-graft hole
- *Migration (≥10mm):* stent distal movement ≥10mm from the original implant location relative to the center of the distal renal artery; as compared to the 1-month CT scan location.
- *Aneurysm Sac Enlargement*: aneurysm sac diameter increase of ≥5mm in late follow-up as compared to 1-month CT scan location.
- *Endograft Limb Occlusions*: defined as total obstruction of blood within the lumen of a device limb – irrespective of whether a secondary intervention is necessary.
- *Endograft 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 Adjudication Charter.

12.2 ADVERSE EVENT DEFINITIONS

An adverse event (AE) is defined as any untoward medical occurrence, unintended disease, injury or untoward clinical sign (including abnormal laboratory values) in subjects, users or other persons, whether or not related to the medical device (ISO 14155). For the purposes of this study, adverse events that are not related to the study device will not be captured as shown in **Figure 2**.

12.3 MAJOR ADVERSE EVENT

An event occurring during the trial that meets one of the following criteria:

- *All-Cause Mortality*:
- Death is defined as any death occurring during the trial period, regardless of cause.
    - *Aneurysm-related death:* is defined as any death occurring within 30-days from the date of the index 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 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.
- *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 Failure* – permanent dialysis dependence or kidney transplant
- *Respiratory Failure:* respiratory failure requiring ventilator support beyond 24 hours post-procedure
- *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;
- *Index Procedural Blood Loss >1,000mL:* estimated blood loss during the index procedure ≥1,000mL.

12.4 OTHER DEFINITIONS

- *Luminal Thrombus Requiring Intervention*: any endovascular surgical intervention after completion of the device 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.
- *Modified Intention-to-Treat:* analysis of the results of implanted patients is based on the initial treatment assignment and not on the treatment eventually received.

13 RESPONSIBILITIES

13.1 SPONSOR RESPONSIBILITIES

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

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

- Management and monitoring of the trial 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

13.2 INVESTIGATOR RESPONSIBILITIES

It's the Investigator's responsibility to conduct this trial in accordance with relevant rules and regulations, including but not limited to, this trial 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 trial. 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 trial the Investigator must:

- Provide the sponsor with a complete signed trial 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 trial. If this deadline cannot be met the Investigator and his/her team may not be able to participate in this trial. 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 trial 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 trial records.

By signing the protocol signature page, the Investigator agrees to conduct the trial according to protocol.

13.3 INDEPENDENT EVENT REVIEWER RESPONSIBILITIES

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

13.4 INDEPENDENT CORE LAB RESPONSIBILITIES

All images obtained in this trial will be assessed by an external, independent Core Lab and measurements of the assessment will be recorded in the eCRF, to ensure uniform and unbiased image assessment throughout the trial.

14 CONFIDENTIALITY AND PATIENT RIGHTS

14.1 CONFIDENTIALITY

Trial subjects will be identified only by a unique subject number used in all correspondence and the trial 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 trial subject number.

All information provided to the Investigator relevant to the device, as well as information obtained during the course of the trial, will be regarded as confidential. The Investigator and all members of his or her trial 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.

14.2 PATIENT RIGHTS

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

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

15 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 trial might provide information to improve the treatment of patients with AAA eligible for endovascular treatment and/or the device.

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

16 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 (CMP). Considering the COVID-19 public health emergency, the monitoring plan has been updated accordingly to include changes to the original plan that could become necessary due to the extraordinary situation. The *Conduct of Clinical Trials of Medical products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards* has been reviewed and used to identify and outline the most suitable changes.

16.1 PROTOCOL DEVIATION

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization, or Good Clinical Practice (ICH GCP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2 and 4.5.3
- 5.1 Quality Assurance and Quality Control , Section 5.1.1
- 5.20 Noncompliance, Sections 5.20.1 and 5.20.2

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Considering the COVID-19 public health emergency, the monitoring plan has been updated accordingly to include changes to the identification of protocol deviations related to delayed or missed follow-up visits as well as delayed or missed images.

17 TRIAL TERMINATION

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

18 PUBLICATION

Endologix intends to publish the results of this trial. Endologix reserves the right to include the report of this trial 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. Only Investigators from centers with high protocol compliance, fast enrollment, complete data sets from all follow-up visits, and participation on manuscript development will be considered as authors on publications.

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

Endologix 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 trial. Any prior publication in any way or form is not permitted, unless approved in writing by Endologix.