CLINICAL TRIAL PROTOCOL
CP-0004 Rev. 06

Prospective, Multicenter, Single Arm Safety and Effectiveness Trial of the Endologix Fenestrated Stent Graft System for the Endovascular Repair of Juxtarenal/Pararenal (JAA/PAA) Aneurysms

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1) **Instructions for Use (IFUs)**
2) **Informed Consent Form**
3) **Case Report Forms**
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Revision 06 Change Summary[1]

Section (Page)	Change and Reason for the Change
All Pages	Changed Protocol revision number from 04 to 06 and date from August 08, 2012 to February 27, 2014 Reason: Reflect the revision change
2.1 (8)	Updated the study contacts. Reason: Reflect change in study personnel.
11.1 (60)	Changed to include reference to the Ventana Medical Advisory Board (VMAB). Reason: Reflect the inclusion of the VMAB as part of the Ventana Patient Safety Surveillance Program.
11.5	Updated Monitoring Plan to include contact information of current study personnel Reason: Reflect change in study personnel.

Revision 05 Change Summary

Section (Page)	Change and Reason for the Change
All pages	Changed protocol revision number from 04 to 05 and Date from August 08, 2012 to March 07, 2013. Reason: Reflect the revision change.
TOC	Removed Instructions for Use (IFU) as an attachment. Reason: The IFU is provided with the device.
2.1 (8)	Updated the study contacts. Reason: Reflect change in study personnel.
Synopsis	Removed references to Attachment 1 Instructions for Use (IFU). Reason: the IFU is provided with the device.
7.1 (21)	Removed statements which specified commercial devices sizes. Reason: Section was modified in the event that new commercial device sizes are introduced.
7.4 (25)	Removed references to Attachment 1 Instructions for Use (IFU). Reason: The IFU is provided with the device.
8.7.1 (35)	Updated the definition for relationship to device and procedure. Reason: to clarify device related vs procedure related adverse events.
8.7.2 (35) 8.7.3 (36	Updated adverse event report requirements to IRBs to specify as applicable. Reason: To correspond with local IRB reporting requirements.

[1] This document is version 06 of Protocol CP-0004. Version 05 was submitted and approved but not implemented. Hence the current protocol is not reflective of those changes.

Revision 04 Change Summary

Section (Page)	Change and Reason for the Change
All pages	Changed protocol revision number from 03 to 04 and Date from November 2011 to August 08, 2012. Reason: Reflect the revision change.
Synopsis	Updated sections Inclusion Criteria, Exclusion Criteria, and Schedule of Tests Reason: Reflect revisions within the protocol
5.2 (15)	Revised inclusion criterion (d)(1) to read: "Adequate ipsilateral iliac/femoral access compatible with the required delivery systems (diameter ≥8 mm)" Reason: For simplicity and clarity to the sites.
5.2 (16)	Added inclusion criterion 17: Aortic diameter at the most caudal renal artery of 18 to 36mm Reason: For consistency with the IFU. Change was requested by the DSMB.
5.3 (16)	Added exclusion criteria (x): Pre-existing renal stent and (y): Pre-planned need for concomitant procedure (e.g., surgical conduit for vascular access, hypogastric artery embolization/coil, renal artery angioplasty). Reason: To simplify the patient screening process.
7.1 (21)	Updated the delivery system description Reason: To reflect the IFUs in the attachments.
7.2 (23)	Clarified the training requirements for investigators and sub-investigators. Reason: For readability and clarification.
8.3 (26)	Updated patient numbering scheme Reason: For simplicity and clarity to the sites.
8.5 (27)	Correct the flow chart to be consistent with section 8.6 for long term follow-up Reason: For consistency with the protocol
8.6 (28)	Updated the CT scan protocol to require slice spacing at 2mm or less. Reason: As recommended by the Core Laboratory for ease of analysis.
8.6 (31)	Added intraoperative angiography in procedural documentation requested Reason: For clarification on desire for intra-operative imaging.
8.6 (33)	Added explanation for missed patient visits and patient exit Reason: For readability and clarification.
8.7 (35)	Updated SAE notification process Reason: For clarity and readability
8.7 (37)	Update protocol deviation definitions Reason: For readability and clarification.
11.1 (58)	Updated definition for medical monitor Reason: For clarity and readability.
11.4 (61)	Updated documentation requirements Reason: Reflect final CRF design, study forms and study logs

Revision 03 Change Summary

Section (Page)	Change and Reason for the Change
All pages	Changed protocol revision number from 02 to 03 and Date from July 2011 to November 2011. Reason: Reflect the revision change.
2.1, 2.2 (6)	Updated contacts. Reason: Reflect current personnel.
5.3 (15)	Revised exclusion criterion (i) to remove waiver for patients on dialysis. Reason: Editorial correction (error).
8.6 (27-31)	Editorial revisions and corrections. Reason: For readability and clarification.
10 (39-52)	Revised/clarified elements of the statistical analyses. Reason: To address FDA requests in its letters dated August 25, 2011 and October 21, 2011.
11.1 (55)	Renamed/item (d) from 'Core Lab' to 'Core Lab and Independent Physician Assessor' and added physician assessor role and responsibility. Reason: For added clarification to study sites.
Appendix 3	Updated CRFs to have same date as Protocol; Page 8: editorial corrections. Reason: For consistency with the protocol. Page 8: correction of inadvertent errors.

Revision 02 Change Summary

Section (Page)	Change and Reason for the Change
All pages	Changed protocol revision number from 01 to 02 and Date from May 2011 to July 2011. Reason: Reflect the revision change.
3 (7) 5.1 (14)	Changed maximum number of sites to participate from 20 to 25. Changed number of roll-in patients (1/site) from 20 to 25. Reason: Error correction only.
Appendix 1	Updated IFUs to add tradenames of the fenestrated device (Ventana™) and the renal stent graft device (Xpand™). Reason: Reflect newly assigned tradenames.
Appendix 2	Updated informed consent document to reflect correction to the number of sites and participants. Reason: For consistency with the protocol.
Appendix 3	Updated CRFs to have same date as Protocol; Page 2: changed renal artery length from 12mm to 13mm; Page 8: reformatted for readability and added boxes to record fluoro times at various steps. Reason: For consistency with the protocol. Page 2: correction of inadvertent error; Page 8: for clarity.

1. INVESTIGATOR SIGNATURE PAGE

I agree to conduct the study as detailed in the Investigational Plan and in accordance with all applicable 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 am not currently participating in any clinical investigations for similar types of medical devices.

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 Ethics Committee or 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, the Ethics Committee(s) or Institutional Review Board(s), the core labs, the independent clinical events committee, or the data safety monitoring board. Any such submission will indicate that the material is confidential.

Investigator Signature Date

Investigator Printed Name

2. STUDY CONTACT PERSONNEL

2.1. SPONSOR

PROJECT MANAGER	ADDITIONAL SPONSOR CONTACT
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2.2. CONTACT NAMES AND TELEPHONE NUMBERS

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3. PROTOCOL SYNOPSIS

Title:	Prospective, Multicenter, Single Arm Safety and Effectiveness Trial of the Endologix Fenestrated Stent Graft System for the Endovascular Repair of Juxtarenal/Pararenal (JAA/PAA) Aneurysms
Objective:	To study the safety and effectiveness of the Endologix Fenestrated Stent Graft System in the endovascular treatment of patients with juxtarenal and/or pararenal aortic aneurysms.
Design:	Multicenter, prospective, single arm
Study Devices:	Endologix, Inc. commercially-available bifurcated stent graft devices Endologix fenestrated JAA/PAA proximal extension stent graft devices Endologix renal stent graft devices
Study Sites:	Institutions with fixed imaging, an adequate research infrastructure, and well established experience in open repair of JAA/PAA, renal stenting techniques, and endovascular aneurysm repair techniques may participate. An investigational site may not enroll more than 20% of the total enrollment.
Patient Enrollment:	A maximum of 122 patients at up to 25 institutions will participate: *Roll-In Phase*: One patient/site will be treated in a roll-in phase. Therefore, a maximum of 25 patients will participate in this phase. This requirement may be waived at the discretion of Endologix for sites that participated in Pilot or Feasibility phase(s). *Trial Phase*: Up to 97 patients will participate in the Trial Phase. This number is based on a statistically justified sample size plus an allowance for deviations from assumptions. The power for passing the trial is 80%. All patients will be diagnosed with JAA/PAA with maximum diameter ≥5.5cm, or between 4.5 and 5.5cm and rapidly expanding (>0.5cm in six months), or >50% larger than the normal aortic diameter Confirmation of patient anatomical eligibility for the device will be based on the independent core lab assessment of the reconstructed high resolution, contrast enhanced CT scan performed within the prior three months. Following informed consent and anatomical eligibility confirmation, patient screening/baseline assessments will be performed. A review of screening case report forms and submitted documentation will be conducted by Endologix and a CONFIRM or DENY response will be provided to the site. Anatomically eligible, consenting, and confirmed patients will be scheduled for the procedure. Instructions for Use are provided in Attachment 1; the patient informed consent form is provided in Attachment 2; template case report forms are

provided in Attachment 3; and the investigator agreement is provided in Attachment 4.

Inclusion Criteria: Male or female at least 18 years old; informed consent understood and signed and patient agrees to all follow-up visits; have aortic aneurysm with maximum diameter ≥5.5cm, or between 4.5 and 5.5cm and rapidly expanding (>0.5cm in six months), or >50% larger than the normal aortic diameter.

Anatomically eligible for the Bifurcated System per the FDA-approved indications for use (IFU) and for the Fenestrated Stent Graft System:

- Adequate iliac/femoral access compatible with the required delivery systems (diameter ≥8 mm);
- Non-aneurysmal infrarenal aortic neck <15mm in length;
- Most caudal renal artery to aortoiliac bifurcation length ≥70mm
- SMA to aortoiliac bifurcation length ≥90mm;
- Proximal non-aneurysmal aortic neck below the SMA with: diameter 18 to 34 mm; length ≥15 mm; angle ≤60° to the aneurysm sac;
- Angle ≤60° (clock face) between the SMA and CA
- Renal arteries both distal to the SMA by ≤35mm, within ≤30mm of each other axially, with 4 to 8mm lumen diameter, and with clock face angle of 90° to 210° to each other
- Common iliac artery distal fixation site with: distal fixation length ≥15 mm; ability to preserve at least one hypogastric artery; diameter ≥10 mm and ≤23 mm; angle ≤90° to the aortic bifurcation.
- The Endologix Fenestrated Proximal Extension Stent must have the ability to overlap the bifurcated stent graft by at least 3cm.
- Aortic diameter at the most caudal renal artery of 18 to 36mm

Exclusion Criteria: Exclusionary criteria and conditions are as follows:

Life expectancy <2 years as judged by the investigator; Psychiatric or other condition that may interfere with the study; Participating in the enrollment or 30-day follow-up phase of another clinical study; Known allergy to any device component; Coagulopathy or uncontrolled bleeding disorder; Contraindication to contrast media or anticoagulants; Ruptured, leaking, or mycotic aneurysm; Aortic dissection Serum creatinine (S-Cr) level >2.0 mg/dL; Traumatic vascular injury; Active systemic or localized groin infection; Connective tissue disease (e.g., Marfan's Syndrome); Recent (within prior three months) cerebrovascular accident or myocardial infarction; Prior renal transplant; Length of either renal artery to be stented <13mm; Significant occlusive disease of either renal artery; An essential accessory renal artery; Indispensable inferior mesenteric artery; Aneurysmal disease of the descending thoracic aorta; Clinically significant mural thrombus circumferentially in the suprarenal segment; Prior iliac artery stent implanted that may interfere with delivery system introduction; Unsuitable vascular anatomy; Pregnancy (female patient of childbearing potential only); Existing renal stent; Pre-planned need for concomitant procedure (e.g. surgical conduit for vascular access, hypogastric artery embolization/coil, renal artery angioplasty)

Primary Endpoints:

Safety: Major adverse events at 1 month.[†]

Effectiveness: Treatment Success at 1 year. This is defined as procedural technical success and the absence of: aneurysm rupture; conversion to open surgical repair; Type I endoleak after 30 days; Type III endoleak; clinically significant migration; aneurysm enlargement; or secondary intervention for resolution of endoleak, limb occlusion, migration, aneurysm sac expansion and/or a device defect.[‡]

Additional Evaluations:

Additional evaluations include:

- Procedural and in-hospital evaluations: Anesthesia time; fluoroscopy time; contrast volume used; total procedure time; estimated blood loss; incidence of transfusion; time in ICU; time to hospital discharge.
- Death (all-cause and aneurysm-related) within 30 days, at 6 months, and at 1 to 5 years;
- Major adverse events after 30 days, at 6 months, and at 1 to 5 years;
- Individual major adverse event components within 30 days and at 1 to 5 years;
- Aneurysm rupture within 30 days, at 6 months, and at 1 to 5 years;
- Conversion to open repair within 30 days, at 6 months, and at 1 to 5 years;
- Adverse Events: All serious and non-serious events within 30 days, at 6 months, and at 1 to 5 years;
- Distal blood flow as assessed by ankle-brachial index evaluations pre-discharge and at 30 days, 6 months, and years 1 to 5;
- Endograft performance (aneurysm sac diameter change from the first post-operative visit; device migration; incidence of endoleak; incidence of limb occlusion) at 30 days, 6 months, and years 1 to 5;
- Renal function as assessed by estimated glomerular filtration rate (eGFR) pre-discharge and at 30 days, 6 months, and years 1 to 5;
- Renal stent graft patency and integrity at 30 days, 6 months, and years 1 to 5
- Stent graft (fenestrated/bifurcated) patency and integrity at 30 days, 6 months, and years 1 to 5;
- Secondary procedures within 30 days, at six months, and at years 1 through 5 for resolution of endoleak, limb occlusion, migration, aneurysm sac expansion and/or a device defect.

Schedule of Tests:

Pre-procedural high resolution, contrast-enhanced CT scan evaluation to determine anatomical eligibility for enrollment will be performed within three months of the procedure. A physical exam and laboratory testing will be performed prior to the procedure. Following ethics committee/IRB approval

[†]Defined as all-cause death, bowel ischemia; myocardial infarction, paraplegia, renal failure, and respiratory failure, stroke, and blood loss >1,000cc. Refer to protocol §8.7.7 for detailed definitions.

[‡]Refer to protocol §8.7.7 for detailed definitions.

and patient written informed consent, the patient will be screened for eligibility. Patients will be followed procedurally and to hospital discharge, and will then be followed at intervals: 1 month; 6 months; 1 year; and annually to 5 years. Tests and evaluations:

Schedule of Tests:	**Screening/ Baseline**	**Procedure (Day 0)**	**Pre-Discharge**	**1 Month***	**6 Months***	**1 to 5 Years***
Physical Exam[†]	x		x	x	x	x
Blood Labs[‡]	x		x	x	x	x
Contrast-Enhanced CT Scan[¥]	x			x	x	x
Ankle Brachial Index	x		x	x	x	x
Adverse Events		x	x	x	x	x

[†]The physical exam includes overall health and physical assessment and vital signs.

[‡]Blood labs include serum creatinine, blood urea nitrogen, hematocrit, and hemoglobin.

[¥]The baseline high resolution, contrast-enhanced CT scan (2mm or less slice spacing) performed within three months prior to enrollment will be reviewed by the independent core lab for patient eligibility determination. Evaluations of endograft performance, renal stent graft patency and integrity, and stent graft patency and integrity will be made based upon post-operative CT scan evaluations by the core laboratory.

*Follow-up windows are ±2 weeks (1 month visit); ±1 month (6 month visit); ±2 months (Year 1 visit); ±3 months (Years 2 through 5 visits)

Statistical Considerations:

Study Population: The intent to treat (ITT) population in this study consists of all patients who are enrolled and treated.

Trial Success, Safety: The primary safety analysis is ***Major Adverse Events (MAE)***, as previously defined. This analysis is limited to patients enrolled in the Trial Phase (i.e., roll-in patients are not included and will be reported as a separate feasibility group). The primary endpoint is to show that the % of patients with an MAE is statistically superior to that in the Endologix open surgical historical control group at 30 days. The hypothesis test will be evaluated by the exact test as a one-tailed test, using significance level α=0.025. Multivariable analyses will be used to assess predictors of trial success.

Trial Success, Effectiveness: The primary effectiveness analysis is ***Treatment Success***, as previously defined. This analysis is limited to patients enrolled in the Trial Phase (i.e., roll-in patients are not included and will be reported as a separate feasibility group). The primary endpoint is to show that the % of patients with Treatment Success is statistically superior to the target rate of 80% at one year. The hypothesis test will be evaluated using the exact binomial distribution as a one-tailed test, using significance level α=0.05. Multivariable analyses will be used to assess predictors of trial success.

Additional Evaluations: Appropriate statistical methodology will be used to analyze all additional evaluations.

4. TRIAL OVERVIEW

4.1. OBJECTIVE

The objective of this study is to assess the safety and effectiveness of the Endologix Fenestrated Stent Graft System for the endovascular repair of juxtarenal or pararenal (JAA/PAA) aortic aneurysms in suitable patients.

4.2. BACKGROUND

An extensive summary of current scientific literature regarding surgical and endovascular techniques and devices used in the repair of JAA or PAA is provided in the Clinical Investigator's Brochure (CIB). A brief summary is provided below:

An arterial aneurysm is a permanent, localized dilatation of an artery with an increase in diameter of 50% or more than the normal artery diameter. Although any artery may develop an aneurysm, most commonly an aneurysm is seen in the abdominal aorta, thoracic aorta, popliteal artery or common iliac artery. Abdominal aortic aneurysm (AAA) is a progressive disease characterized by structural deterioration, gradual expansion, and eventual rupture of the abdominal aorta if left untreated. AAA is the most common type of aortic aneurysm, with more than 90% occurring inferior to the renal arteries. This vascular disorder causes significant mortality and morbidity in the aged population and is a leading cause of death.[2]

The complexity of AAA is commonly characterized based on location and involvement with visceral vessels. Infrarenal AAA generally involves the infrarenal aorta and may involve the aortoiliac vasculature. A subset of infrarenal AAA extends up to the level of but does not involve the renal arteries, and is termed juxtarenal AAA (JAA). A small proportion of AAA involves the renal arteries and as such is termed pararenal AAA (PAA). Extension of the disease to and beyond the superior mesenteric artery (SMA) or celiac artery (CA) into the thoracic aorta describes thoracoabdominal aneurysms. These more complex aneurysms are beyond the scope of this study.

It is estimated that approximately 25% to 40% of infrarenal AAA are not suitable for endovascular repair due to unfavorable proximal neck anatomy (e.g., highly angulated, dilated, short [JAA], or encroaching on or involving the renal arteries [JAA or PAA]).[3,4] In most US studies of endovascular AAA repair, including that for the Endologix Powerlink System, the infrarenal non-aneurysmal neck length and angulation to the aneurysm sac requirements are ≥15mm and ≤60°, respectively; shorter

[2]Hoyert DL, Arias E, Smith B L, et al. Deaths: final data for 1999. Natl Vital Stat Rep 2001; 49(8):1-113.

[3]Carpenter JP, Baum RA, Barker CF, et al. Impact of exclusion criteria on patient selection for endovascular abdominal aortic aneurysm repair. J Vasc Surg 2001;34:1050-4.

[4]Arko FA, Filis KA, Seidel SA, et al. How many patients with infrarenal aneurysms are candidates for endovascular repair? J Endovasc Ther 2004;11:33-40.

lengths or greater angulation have been reported to increase the risk of migration and Type 1A endoleak and associated need for intervention.[5,6]

Owing to the increased risk of renal complications, mesenteric ischemia and other complications following open repair of JAA or PAA compared to infrarenal AAA or hybrid open visceral debranching techniques,[7] researchers have sought to extend a totally endovascular technique to repair of these aneurysms. To consider application of an endovascular method to JAA or PAA repair, it is essential to maintain the patency of visceral vessels (i.e., renal arteries; SMA; CA). Browne and colleagues reported their feasibility experience in the construction and implant of home made fenestrated stent grafts using Dacron graft and stainless steel Z-stents in the canine model.[8] Each fenestration was sized to approximate the size of the arterial ostium, an improvement over prior reports suggesting that oversizing of the fenestration may be necessary to ensure the ostia are not covered.[9] Six hours after implant, animals were sacrificed and the positioning of all fenestrations verified. No ostial obstruction was observed, and the devices were widely patent. Several single center clinical case reports have described the use of 'homemade' fenestrated stent grafts fashioned by physicians from commercially available stent grafts for the endovascular repair of JAA/PAA. Although cited as technically feasible in some patients, the broad application of this approach does not appear to be generally accepted by the medical community.

A number of single center and several multicenter reports of a custom device based on the Cook Zenith stent graft are available in the literature. The key limitation to this approach is the need to customize the design and manufacture of each stent graft to a particular patient anatomy. This requires a lengthy period of time for planning, manufacture, and delivery of the device. More recently, several publications attempt to propose methods for modifying this customization algorithm to broaden the applicability of a particular device to more than one patient. That is, to create an 'off-the-shelf' fenestrated stent graft device.

Endologix, Inc. has developed a Stent Graft System based on the approved AFX design that is specifically intended as a potential 'off-the-shelf' endovascular repair option for JAA/PAA. This design couples the commercially available bifurcated stent graft with a fenestrated/scalloped proximal extension and renal stent grafts with the intent to be applicable to approximately 80-90% of patients presenting with JAA/PAA.

[5]Leurs LJ, Kievit J, Dagnelie PC, et al. Influence of infrarenal neck length on outcome of endovascular abdominal aortic aneurysm repair. J Endovasc Ther 2006;13:640–8.

[6]AbuRahma A, Campbell J, Stone PA, et al. The correlation of aortic neck length to early and late outcomes in endovascular repair patients. J Vasc Surg 2009;50:738-48.

[7]Fulton JJ, Farber MA, Marston WA, et al. Endovascular stent-graft repair of pararenal and type IV thoracoabdominal aortic aneurysms with adjunctive visceral reconstruction. J Vasc Surg 2005;41:191-8.

[8]Browne TF, Hartley D, Purchas S, et al. A fenestrated covered suprarenal aortic stent. Eur J Vasc Endovasc Surg 1999;18:445-9.

[9]Park JH, Chung JW, Cho IW, et al. Fenestrated stent grafts for preserving visceral brnaches in the treatment of abdominal aortic aneurysms: preliminary results. J Vasc Interventional Radiology 1996;7:819-23.

4.3. TRIAL DESIGN

This is a multicenter, prospective, single arm clinical trial. Patients with JAA/PAA who are suitable candidates for endovascular repair using the Endologix Fenestrated Stent Graft System will be considered for enrollment.

After this protocol and the patient informed consent form are reviewed and approved by the local Ethics Committee or responsible Institutional Review Board, potential patients will be offered participation in the study. This will be accomplished through the patient's reading of the informed consent form in the patient's native language and discussion of the study with the patient by the investigator and site personnel. Agreement to participate and to attend all follow-up visits will be documented with the patient's signature on the informed consent form, with appropriate signatures of the site investigator and an impartial witness.

After providing written informed consent, screening and eligibility determinations will be performed. Patients will undergo a high resolution, contrast-enhanced computed tomography angiography (CT) scan of the relevant aortic and aortoiliac vasculature within three months of the scheduled procedure. Evaluation of the aortic and vascular anatomy suitability per this protocol, as depicted on the CT scan, will be performed by the site investigator and by an independent core laboratory. Other tests include a physical examination, review of patient medical history for exclusionary conditions, selected blood chemistry and hematology analyses, and ankle-brachial index determination.

Upon acceptance for enrollment, patients will be scheduled for the endovascular repair procedure.

Note: An investigational site may not enroll more than 20% of the total Trial Phase enrollment.

Following patient discharge from the hospital, the first follow-up visit will be made at one month (±2 weeks). A CT scan will be performed to assess aneurysm morphology and device integrity and patency, as well as the status of the renal arteries and implanted stent grafts. Subsequent follow-up will be made at six months, one year, and annually to five years.

Continued patient follow-up beyond five years is outside of the scope of this study. Nonetheless, all patients should be monitored and evaluated per the institutional standards of care for patients who receive an endovascular stent graft.

5. STUDY POPULATION

5.1. NUMBER OF PATIENTS

Up to 25 sites and up to 122 patients will participate in this trial. Following investigator training, each investigator will treat one patient during a roll-in phase. These (maximum 25) patients will not count toward the Trial Phase cohort. Note that the Roll-In phase requirement may be waived at the discretion of Endologix for a site that participated in the Pilot Study or Feasibility Study of this same device system.

During the Trial Phase, 97 patients are planned to be enrolled at the investigational sites. In both phases, screening results, including the independent core laboratory evaluation of the pre-operative CT scan, will be used to make a final determination as to patient suitability for enrollment. Patients must meet **all** inclusion criteria and **no** exclusion criteria in order to participate.

5.2. PATIENT INCLUSION CRITERIA

A patient who meets ***all of the following criteria*** potentially ***may be included*** in the study:

(a) Male or female at least 18 years old;

(b) Informed consent form understood and signed and patient agrees to all follow-up visits;

(c) Have abdominal aortic aneurysm with diameter ≥5.5cm, or between 4.5 and 5.5cm and rapidly expanding (>0.5cm in six months), or >50% larger than the normal aortic diameter;

(d) Anatomically eligible for the Bifurcated System and for the Fenestrated Stent Graft System per the indications for use (IFU):

1) Adequate ipsilateral iliac/femoral access compatible with the required delivery systems (diameter ≥8 mm)
2) Non-aneurysmal infrarenal aortic neck <15mm in length;
3) Most caudal renal artery to the aortoiliac bifurcation length ≥70mm;
4) SMA to aortoiliac bifurcation length ≥90mm;
5) Infra-SMA non-aneurysmal[†] aortic neck diameter 18 to 34 mm;
6) Infra-SMA non-aneurysmal aortic neck length ≥15 mm;
7) Infra-SMA non-aneurysmal aortic neck angle ≤60° to the aneurysm sac;
8) Angle ≤60° (clock face) between the SMA and CA;
9) Renal arteries both distal to the SMA by ≤35mm;
10) Renal arteries axially within ≤30mm of each other
11) Renal arteries both with luminal diameter of 4 to 8mm;
12) Renal arteries with an angle (clock face) of 90° to 210° to each other;
13) Common iliac artery distal fixation sites length ≥15 mm;
14) Common iliac artery distal fixation sites angle to the aortic bifurcation ≤90°;
15) Ability to preserve at least one hypogastric artery;
16) The Endologix Fenestrated Proximal Extension Stent must have the ability to overlap the bifurcated stent graft by at least 3cm.
17) Aortic diameter at the most caudal renal artery of 18 to 36mm

[†]Non-aneurysmal is defined as <20% diameter change over a length of at least 15mm below the SMA.

5.3. PATIENT EXCLUSION CRITERIA

A patient who meets ***any of the following criteria will not be included*** in the study:

(a) Life expectancy <2 years as judged by the investigator;
(b) Psychiatric or other condition that may interfere with the study;
(c) Participating in the enrollment or 30-day follow-up phase of another clinical study;
(d) Known allergy to any device component;
(e) Coagulopathy or uncontrolled bleeding disorder;
(f) Contraindication to contrast media or anticoagulants;
(g) Ruptured, leaking, or mycotic aneurysm;
(h) Aortic dissection;
(i) Serum creatinine (S-Cr) level >2.0 mg/dL;
(j) Traumatic vascular injury;
(k) Active systemic or localized groin infection;
(l) Connective tissue disease (e.g., Marfan's Syndrome);
(m) Recent (within prior three months) cerebrovascular accident or myocardial infarction;
(n) Prior renal transplant;
(o) Length of either renal artery to be stented <13mm;
(p) Significant occlusive disease of either renal artery (>70% stenosis);
(q) An essential accessory renal artery (supplies more than 25% of the renal parenchyma);[‡]
(r) Indispensable inferior mesenteric artery;
(s) Aneurysmal disease of the descending thoracic aorta;
(t) Clinically significant mural thrombus in the suprarenal segment;[¥]
(u) Prior iliac artery stent implanted that may interfere with delivery system introduction;
(v) Unsuitable vascular anatomy;
(w) Pregnancy (female patient of childbearing potential only);
(x) Existing renal stent;
(y) Pre-planned need for concomitant procedure (e.g. surgical conduit for vascular access, hypogastric artery embolization/coil, renal artery angioplasty)

[‡]Patients who undergo prior embolization of an essential accessory renal artery may be considered for trial enrollment.
[¥]Mural thrombus >5mm in thickness over >60% of the aortic circumference.

6. RESPONSE MEASURES

6.1. SAFETY

The safety endpoint is defined as the incidence of Major Adverse Events (MAE), defined as the composite of the following as determined by the independent Clinical Events Committee (CEC). Event definitions are provided in §8.7.7.

- *All-Cause Mortality*;
- *Bowel Ischemia*;
- *Myocardial Infarction*;
- *Paraplegia*;
- *Renal Failure*;
- *Respiratory Failure*;
- *Stroke;*
- *Blood Loss >1,000cc*

Refer to §10.6 for primary safety endpoint analysis details.

6.2. EFFECTIVENESS

The primary effectiveness endpoint is defined as the rate of Treatment Success at one year. Treatment Success is a composite of outcomes clinically relevant to the endovascular repair of JAA/PAA as follows. Event and related definitions are provided in §8.7.7.

- Procedural Technical Success;
- Absence of:
  - Aneurysm rupture;
  - Conversion to open repair;
  - Type I endoleak >30 days;
  - Type III endoleak;
  - Clinically significant migration;
  - Aneurysm enlargement;
  - Secondary intervention for resolution of endoleak, limb occlusion, migration, aneurysm sac expansion and/or a device defect

Refer to §10.7 for primary effectiveness endpoint analysis details.

6.3. ADDITIONAL EVALUATIONS

Additional evaluations include:

- **Procedural and In-Hospital Evaluations**:
  - Volume of contrast media used;
  - Fluoroscopy time;
  - Total procedure time;[‡]
  - Time in ICU;[§]
  - Estimated blood loss;
  - % requiring blood transfusion;
  - Anesthesia time;[¥]
  - Time to hospital discharge;[£]
- **Mortality**, all-cause and aneurysm-related, within 30 days, at six months, and years 1 through 5;
- **MAE Individual Components** within 30 days, at six months, and years 1 through 5;
- **Composite MAEs** after 30 days ,at six months, and years 1 through 5;
- **Aneurysm Rupture** within 30 days, at six months, and years 1 through 5;
- **Conversion to Open Repair** within 30 days, at six months, and years 1 through 5;
- **Adverse Events** (serious and non-serious) within 30 days, at six months, and years 1 through 5;
- **Distal Blood Flow** pre-discharge and at 30 days, six months, and years 1 through 5 as determined by ankle-brachial index measurements and changes over time.
- **Endograft Performance** (aneurysm sac diameter change from the first post-operative visit; device migration; incidence of endoleak) at 30 days, 6 months, and years 1 to 5;
- **Renal Function** pre-discharge and at 30 days, six months, and years 1 through 5, as assessed by the estimated glomerular filtration rate (eGFR) and changes over time;
- **Renal Stent Graft Patency and Integrity** within 30 days, at six months, and years 1 through 5, as determined by contrast-enhanced CT scan, and as assessed by the independent core laboratory, inclusive of:
  - Patent luminal flow
  - Absence of stent fracture
  - Absence of renal infarct >30%
  - Absence of kinking, stenosis, or occlusion (>60%)
  - Absence of graft failure

[‡]Elapsed time from the first break of skin to final closure (i.e., skin to skin time).

[¥]Elapsed time from the initiation to the end of the anesthesia protocol.

[§]Elapsed time from the first administration of anesthesia to release from the ICU or post-anesthesia care unit providing ICU-level care. If the patient is not admitted to the ICU, this is defined as 0 hours.

[£]Elapsed time from initiation of the procedure to physical discharge from the hospital.

- **Stent Graft (Fenestrated/Bifurcated) Patency and Integrity** within 30 days, at six months, and at years 1 through 5, as determined by contrast-enhanced CT scan, and as assessed by the independent core laboratory, inclusive of:
  - Patent luminal flow
  - Absence of kinking or occlusion
  - Absence of stent fracture
  - Absence of graft fatigue or failure
- **Secondary Procedures** within 30 days, at six months, and years 1 through 5 for resolution of endoleak, limb occlusion, migration, aneurysm sac expansion and/or a device defect.

7. STUDY MATERIALS

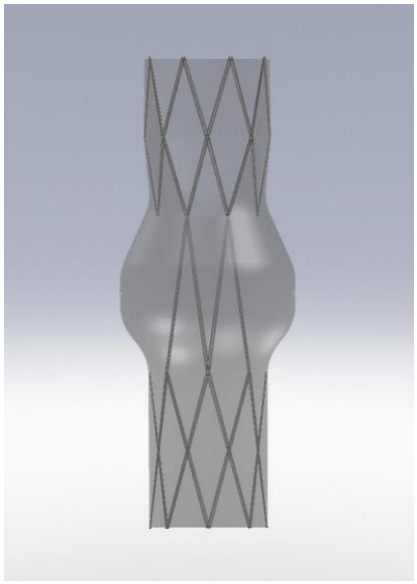
7.1. DEVICE DESCRIPTION

Bifurcated and Fenestrated Stent Grafts

Bifurcated stent grafts (**Figure 1**) are composed of a CoCr alloy wire stent cage[†] with a thin-walled, high density expanded polytetrafluoroethylene (ePTFE) graft cover that is attached proximally and distally to the stent cage with polypropylene suture. Bifurcated devices have body lengths ranging from 60 to 100mm. Limb dimensions include lengths ranging from 30mm to 55mm and diameters of 13 or 16mm to accommodate various patient anatomies. Devices are delivered endoluminally via the femoral artery over a .035" guidewire using a disposable catheter system having an introducer sheath. The pre-loaded stent graft is inserted and upon deployment and withdrawal of the delivery system, expands to the indicated diameter. Accessory limb extensions in straight, stepped, flared, and tapered configurations are available.

Figure 1. Bifurcated Stent Graft

Figure 2. Fenestrated Stent Graft Design



The investigational fenestrated proximal extension stent graft system consists of two primary components: an implantable fenestrated/scalloped stent graft and a disposable delivery catheter system. The pre-loaded stent graft is inserted endoluminally via the femoral artery over a .035" guidewire and upon deployment and withdrawal of the delivery system, expands to the indicated diameter.

[†]The incoming wire is certified to meet ASTM F1058:2002, *Standard Specification for Wrought 40Cobalt-20Chromium-16Iron-15Nickel-7Molybdenum Alloy Wire and Strip for Surgical Implant Applications (UNS R30003 and UNS R30008).*

The fenestrated proximal extension stent graft (**Figure 2**) is composed of a CoCr alloy wire stent cage (having the same elements as the bifurcated device above) with a thin-walled, high density continuous ePTFE graft cover that is attached proximally and distally to the stent cage with polypropylene suture. The stent grafts have total lengths of 120 or 140mm. All fenestrated stent grafts have a distal segment with 28mm diameter and 4 or 6cm length to ensure significant overlap (at least 3cm) with the bifurcated stent graft. The proximal segment has diameters of 24, 28, 32, and 36mm, indicated for vessel diameters between 18 and 34mm. A scalloped section with length of 4cm from the most proximal edge of the stent graft is present to align below the SMA and CA. The midsection contains oversized unsupported graft having circular 3-mm diameter fenestrations that can expand up to 10mm for cannulation of the renal arteries and introduction of appropriate renal stent grafts. Each of the fenestrations and scallop are reinforced using the same polypropylene suture used to attach the graft to the stent. For visualization under fluoroscopy, each fenestration includes a radiopaque marker encased in the graft around its circumference; the scallop includes radiopaque markers encased within the graft at the sides, and a marker at the center of its distal edge.

The mid-section of each stent has two 'W' stent segments (anterior and posterior) that serve to attach the proximal stent segment to the distal stent segment, while maintaining an open area laterally to avoid interference with the renal arteries or fenestrations. The ePTFE graft is continuous throughout the extension, with sutures present only at the ends, around the fenestrations, and at the scallop. Unique to this device, the graft is produced having a 28mm distal diameter, a 24 to 36mm proximal diameter (depending on the device), and a 35 to 47mm (depending on the device) midsection diameter. The distal and proximal graft segments conform to the stent diameter, whereas the mid section contains the fenestrations for the renal arteries and is loose fitting. This feature permits the fenestrations to be moved *in situ* to accommodate renal artery locations that are up to 35mm away radially from the nominal location. Eight models are designed to accommodate patient anatomies where the renal arteries are at approximately the same level, and another 16 are designed to accommodate anatomies where one renal artery is higher than the other.

The delivery systems are single use, disposable systems used to deploy the bifurcated and fenestrated accessory stent graft configurations. The commercially available bifurcated delivery system is an integrated design with inner main body and limb covers and sheath constraining the self-expandable stent graft in a compressed state. The main body and limb covers fully contain the stent graft body and limbs. As the deployment control cord is retracted and the constraints removed, the self-expanding stent graft is allowed to expand within the vessel under the control of the implanting physician. The catheter is compatible with a 0.035 inch guidewire.

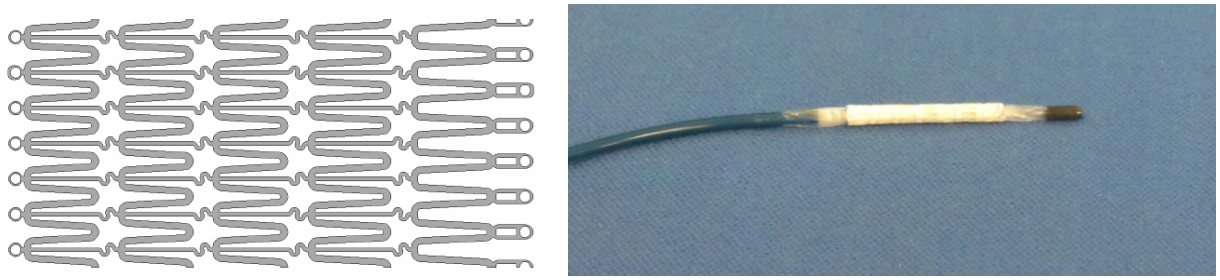
The 22Fr OD delivery system has integrated guide sheaths. The guide sheaths are preloaded through each of the fenestrations allowing for cannulation of the renal arteries prior to deployment of the stent graft. Radiopaque markers are present on the distal ends of the delivery system outer sheath, of the left sheath (one marker) and of the right sheath (two markers). The delivery system contains a hub and sideport for flushing. The catheter is compatible with a 0.035 inch guidewire.

Refer to the IFU in Attachment 1for additional information on the delivery system.

Renal Stent Grafts

Renal stent graft devices are intended for maintaining the patency of renal arteries ranging in diameter from 4 to 8mm. The stent graft (**Figure 4**) consists of a balloon-expandable CoCr alloy stent with high density ePTFE graft attached with polypropylene surgical suture to each end, and has lengths of 18, 25 or 35mm. The most proximal 5mm segment of the stent graft is intended to protrude into the aorta and undergo flaring using a 10mm balloon (not provided). Each device is premounted on a nylon balloon with diameter of 5 to 8mm. Radiopaque platinum/iridium markers are present on either end of the balloon. The delivery catheter shaft profile is 5Fr or 6Fr.

Figure 3. Renal Stent Graft. Stent design (left); stent graft crimped onto the balloon catheter (right).



7.2. INVESTIGATOR TRAINING AND EXPERIENCE

One principal investigator at each participating site will be responsible for supervision of study conduct. He/she and each any authorized sub-investigator must satisfy the following criteria prior to the enrollment of their first patient.

a) Complete review of the Investigator's Brochure, inclusive of nonclinical and clinical safety and effectiveness information regarding the marketed stent graft, nonclinical testing regarding the fenestrated stent graft system and renal stent graft, and the scientific literature review.

b) As an institutional team, have prior training and experience in the open surgical repair of JAA/PAA (≥25 cases in the prior year).

c) As an institutional team, have prior training and experience in visceral/renal artery stenting (≥25 cases in the prior year).

d) Hold a certification of completion of the physician training program for the commercially available Endologix bifurcated stent graft (inclusive of troubleshooting methods). This includes the completion of at least five clinical cases using the commercially available devices for abdominal aortic aneurysm repair.

e) Undergo didactic training on the device design, patient selection criteria, and troubleshooting methods for the Fenestrated Stent Graft System and the Renal Stent Graft as detailed in the respective Instructions for Use (IFUs).

f) Practice using the Fenestrated Stent Graft System and the Renal Stent Graft in a simulated use bench top flow model.

Completion of each criterion will be documented for each Investigator and Site prior to performance of the first clinical procedure at a given site under this protocol. Only principal investigators and authorized sub-investigators who complete all the training requirements will be authorized to operate the study device and deploy the endografts. In addition, the principal investigator must be present in the operating room with the ability to assist as needed and actively supervise each case performed by a sub-investigator.

7.3. DEVICE ACCOUNTABILITY

The Endologix bifurcated stent graft is commercially available in the US per the approved labeling (Instructions for Use). Per the FDA requirements for all endovascular stent grafts (21CFR821), device tracking forms must be completed and provided to Endologix for each patient who receives an Endologix device. Although the devices are being used in an investigational manner in this trial, they will be sourced from commercial product inventory. In the case of a device malfunction, the information will be noted in the CRFs and the device should be returned to Endologix for evaluation.

Usage of the investigational Fenestrated Stent Graft and Renal Stent Graft devices will be documented in the case report forms and on the Investigational Device Accountability Log. In the

case of a device malfunction, the information will be noted in the CRFs and the device should be returned to Endologix for evaluation in accordance with the Instructions for Use.

7.4. PATIENT AND DEVICE PREPARATION

All procedures must be performed in an operating room, or in an endovascular suite having vascular surgery and anesthesia services. The Investigator will refer to institutional protocols relating to anesthesia and monitoring of vital signs.

All institutions participating in this study must utilize fixed imaging equipment during the procedure.

The appropriate length bifurcated device (22 or 25mm diameter), the appropriate Endologix fenestrated proximal extension stent graft device, and the appropriate Endologix renal stent graft devices will be selected in accordance with the patient eligibility determination. The devices will be prepared in accordance with their respective Instructions for Use. The respective Instructions for Use, inclusive of warnings and precautions, are provided in ***Attachment 1***.[†]

All devices will be prepared and handled in accordance with their Instructions for Use.

Other ancillary devices will be selected by the physician per institutional standards.

[†]Accessories available and ancillary devices recommended for use during the procedure are listed in the respective IFU.

8. STUDY METHODS

8.1. GENERAL ENTRY PROCEDURES

Prospective patients as defined by the criteria in §5.2 and §5.3 will be considered for entry into this study. Following patient consent, complete screening documentation must be submitted to Endologix and to the Core Lab for review and evaluation.

Note: Prior to scheduling a patient for a procedure, it must be verified in writing by the sponsor that all criteria are met and the patient is accepted for enrollment.

If the patient meets all criteria, the Sponsor will fax a **CONFIRM** document to the investigator. The Investigator is required to sign and date the fax form and return to Endologix to document acknowledgement.

If the patient does not meet all criteria, the Sponsor will fax a **DENY** document to the investigator, and will identify the reason for denial. ***The patient cannot be enrolled***. The Investigator is required to sign and date the fax form and return to Endologix to document acknowledgement.

8.2. INFORMED CONSENT

Written informed consent, in accordance with applicable international standards and study center regulations, shall be obtained from each patient, or from their legal representative, prior to the study procedures. The investigator will retain a copy of the signed informed consent document in each patient's record, and provide a copy to the patient.

The Investigator must not request the written informed consent of any patient, and must not allow any patient to participate in the investigation before obtaining governing ethics committee or IRB approval.

Attachment 2 provides an example of a consent form that may be used. The example form contains the minimal consent language content that must be incorporated into the Informed Consent document. Other elements may be added or minor language changes may be made for clarity by the investigator or by the IRB, but substantial content may not be deleted.

Prior to starting the study, the investigator will provide Endologix with a copy of the sample Informed Consent document approved by the ethics committee or IRB with documented evidence that the ethics committee or IRB has approved the protocol.

8.3. METHOD FOR ASSIGNMENT TO TREATMENT GROUP

Eligible patients will be assigned a patient number to be used in all documentation. The patient identification number will use the following convention:

XXX-YYY-*ZZZ*

Where:

XXX is the designated site three-digit ID number assigned by Endologix.

YYY is a three digit sequential patient ID number beginning with 301.

ZZZ is the first letter of the patient's first, middle, and last name. For patients with the same initials at a site, the letter 'X' will be used as the middle initial for the second patient. For patients without a middle name, '---' will be used for the middle initial.

Upon satisfactory completion of all site start-up training and documentation requirements, Endologix will supply the site with written 'Go' notification that initiation of patient screening for study enrollment is authorized.

A Screening Log will be maintained by the site to document each patient who undergoes the screening process and the final determination of eligibility.

The actual procedure date will serve as the "start" date from which follow-up evaluations will be measured. After treatment, each patient will be evaluated prior to hospital discharge and will then be evaluated at one month (defined as 30 ± 14 days), at six months (defined as 180 ± 30 days), and at annual follow-ups at 1 year (defined as 365 ± 60 days), and at 2 to 5 years (± 90 days).

8.4. SCHEDULE OF MEASUREMENTS

A summary of the tests and measurements to be conducted pre-study/at baseline, operatively, prior to discharge, and during follow-up is illustrated in the following chart.

Schedule of Tests:	**Screening/ Baseline**	**Procedure (Day 0)**	**Pre-Discharge**	**1 Month***	**6 Months***	**1 to 5 Years***
Physical Exam[†]	x		x	x	x	x
Blood Labs[‡]	x		x	x	x	x
Contrast-Enhanced CT Scan[¥]	x			x	x	x
Ankle Brachial Index	x		x	x	x	x
Adverse Events		x	x	x	x	x

[†]The physical exam includes overall health and physical assessment and vital signs.

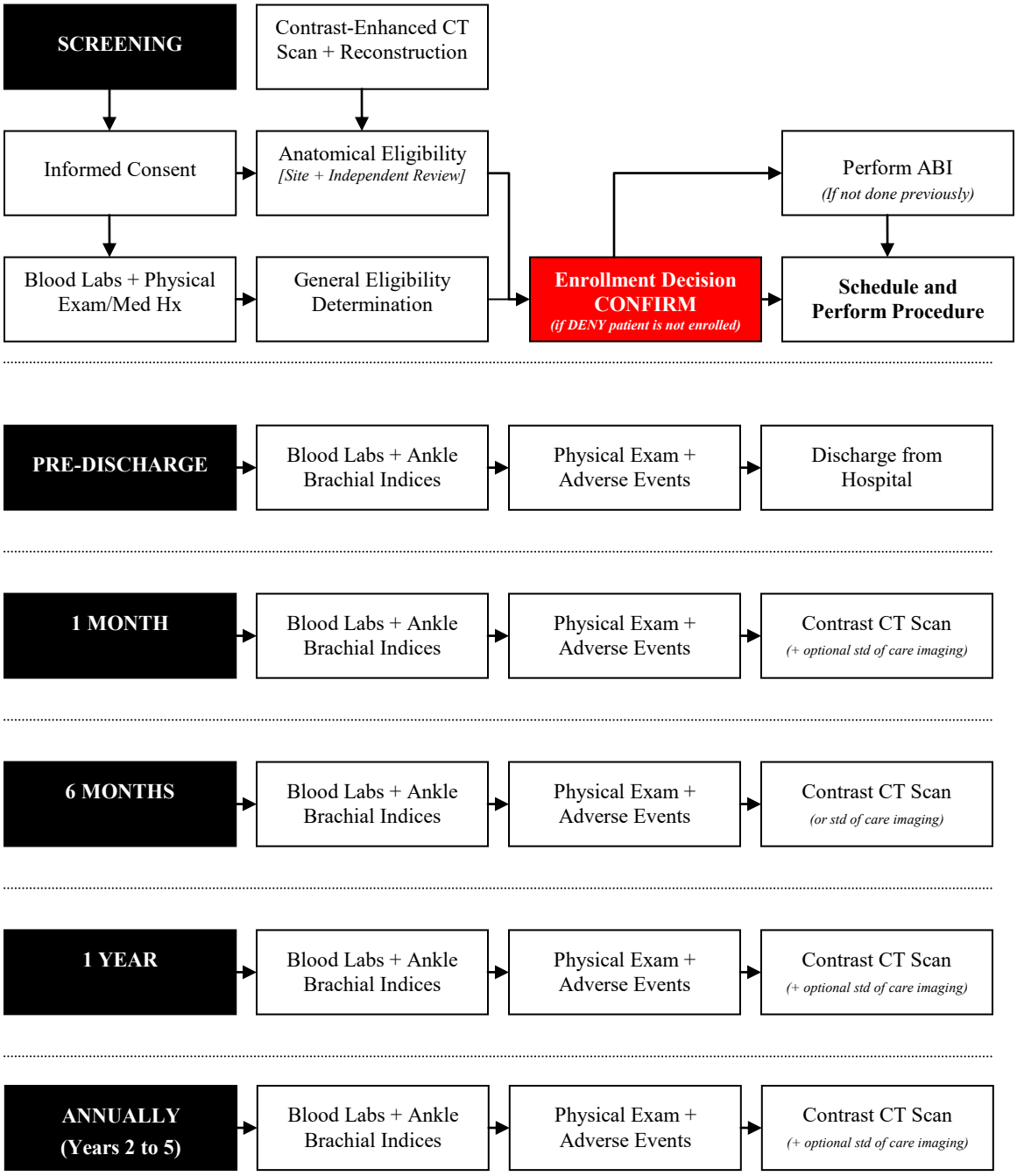
[‡]Blood labs include serum creatinine, blood urea nitrogen, hematocrit, and hemoglobin.

[¥]The baseline high resolution, contrast-enhanced CT scan (2mm or less slice spacing) performed within three months prior to enrollment will be reviewed by the independent core lab for patient eligibility determination. Evaluations of endograft performance, renal stent graft patency and integrity, and stent graft patency and integrity will be made based upon post-operative CT scan evaluations by the core laboratory.

*Follow-up windows are ±2 weeks (1 month visit); ±1 month (6 month visit); ±2 months (Year 1 visit); ±3 months (Years 2 through 5 visits)

8.5. FLOW CHART

A flow chart representing the key study methods and procedures is provided below:



8.6. STUDY PROCEDURES AND EVALUATIONS

8.6.1. Informed Consent

The patient, or his/her legal representative, is to be informed about the study and provide written consent. Confirmation of written consent will be recorded on the **SCREENING AND BASELINE** CRF for verification by the Sponsor prior to enrollment eligibility determination.

8.6.2. CT Scan Protocol

Patient enrollment into this study is based on the independent physician review and assessment of Core Lab produced three-dimensional reconstructions of high resolution, contrast-enhanced spiral CT scans. To ensure consistency, below are the requirements for acquisition of the CT Scan:

- Only high resolution, contrast-enhanced spiral CT scans are acceptable.
- Data must be uncompressed.
- Preferred maximum slice spacing is 1mm. ***In no case should it exceed 2mm***.
- The preferred protocol, shown below, is easier to attain with a multi-row scanner. If the preferred protocol cannot be used, an alternate protocol is provided.
- Instruct patient not to move during scan. Do not move table height, position, or field of view during scan. If such movement occurs, repeat scan in its entirety.
- Send data to the core lab identified in §2 via CD or per Core Lab instructions. Questions can also be forwarded to the Core Lab directly as identified in §2.

Parameter	Preferred	Alternate
Scan Mode	Helical/Spiral	
Scan Parameters	140kVp, Auto mA, 0.5sec	140kVp, 280mA (min), 1.0sec
Collimation	0.625 to 1mm	2mm
Slice Spacing	0.625 to 1mm	2mm
Superior Extent	Thoracic aorta, at least 5cm above celiac artery origin	
Inferior Extent	Lesser trochanter of femur	
Patient Instruction	Single breath hold	1st hold: 5cm above celiac to bifurcation 2nd hold: bifurcation to lesser trochanter
Contrast	Standard non-ionic	
Volume and Rate	150mL at 3 to 4 mL/sec	
Scan Delay	ROI - threshold 90Hu in aorta	ROI - threshold 90Hu in aorta or 25sec delay
Field of View	Large body	
Window Level	400/40	

8.6.3. Screening and Baseline Evaluations

Following informed consent, the patient is to be pre-screened for eligibility by the investigator. Any information provided by the patient's referring physician or from the patient's chart will be recorded on the relevant CRF. If any of this information is inadequate, procedures may be repeated / performed by the investigator to verify eligibility.

The following steps must be completed within three months prior to enrollment into the study unless otherwise indicated. All such steps that are not performed within three months of enrollment into the study must be repeated prior to the procedure.

[a] Assess eligibility criteria.

[b] Perform a physical examination, including patient height and weight, vital signs, and ASA Class determination.

[c] Review the patient's medical history.

[d] Perform blood lab analyses including serum creatinine, blood urea nitrogen, hematocrit, and hemoglobin.

[e] Perform an ankle-brachial index assessment bilaterally.

Note: The ABI test may be performed after initial screening but prior to the procedure if more convenient for the institution. ABIs may be done in the office (vascular lab is not required.)

[f] Perform diagnostic imaging per institutional standard of care.

[g] Collect a baseline high resolution, contrast-enhanced CT scan per the protocol in §8.6.2. Follow the preferred protocol to the extent possible.

[h] Document the patient's relevant concomitant medications (cardiac/circulatory medications).

Fax the SCREENING FORM as requested in [a] through [g] to the Endologix Clinical Department at +1 (949) 595-7373.

The investigator is to proceed with enrollment of the patient and procedure scheduling **ONLY after receiving written documentation from the Sponsor** that the patient meets the respective enrollment criteria, and is confirmed to meet all other inclusion and exclusion criteria. **The Sponsor will clearly CONFIRM the patient for enrollment in the ELIGIBILITY Form faxed or e-mailed to the investigator**. The investigator will sign the bottom of the CRF in the space provided to acknowledge receipt of the fax.

Any patient who is determined to be a screen failure must have clear documentation of the reason(s) for failure in the CRFs. **In such cases, the Sponsor will clearly DENY the patient for enrollment in the ELIGIBILITY Form to the investigator**. The investigator will sign the bottom of the CRF in the space provided to acknowledge receipt of the fax.

8.6.4. Enrollment

The investigator and the Sponsor will assure all **SCREENING AND BASELINE** CRFs are complete with no unresolved issues.

Only after the Sponsor notifies the investigator of the patient eligibility by fax with a **CONFIRM** designation is the patient to be scheduled for the procedure.

The date of study enrollment is the date that the procedure is performed, as documented on the **PROCEDURE REPORT** CRF. This date is also considered Day 0 for follow-up date calculation.

8.6.5. Procedural

Prepare the patient for the procedure according to §7.4 and institutional protocols. Follow the Instructions for Use to select and prepare the bifurcated device, the Fenestrated Stent Graft device, the Renal Stent Grafts, and other ancillary devices for use.

[a] Introduce the bifurcated delivery system into the designated (ipsilateral) femoral artery. Refer to the corresponding Instructions for Use for all details related to placement of the bifurcated device.

[b] Deliver and deploy the bifurcated stent graft at the target location. Refer to the corresponding Instructions for Use to prepare and deliver any accessory stent grafts as needed.

[c] Introduce the Fenestrated stent graft delivery system into the designated (ipsilateral) femoral artery.

Refer to the Fenestrated Stent Graft System Instructions for Use for all details related to placement of the device, introduction and deployment of renal stent grafts through the indwelling guide sheaths, deployment of the fenestrated stent graft, and delivery system removal.

[d] Document at the time (in 24 hour clock format) that the following procedural steps were completed.

- first breakage of skin
- bifurcated delivery system sheath entry
- bifurcated delivery system sheath removal
- fenestrated delivery system sheath entry
- cannulation of the renal arteries
- renal stent graft implant completion
- fenestrated stent graft deployment/implant
- renal stent graft flaring
- fenestrated delivery system sheath removal
- skin closure

[e] Complete the immediate post-implant evaluation section on the **PROCEDURE REPORT** Form. Fax the form to the Endologix Clinical Department at +1 (949) 595-7373

[f] Report any events that occurred during the procedure or recovery on the **ADVERSE EVENT** CRF. If an event is a serious adverse event, provide the additional event details on the **Serious Adverse Event** section of the CRF. See §8.7 for adverse event reporting requirements.

[g] A copy of the operative report is requested.

[h] A copy of the intraoperative angiography run is requested. This may be burned to CD and shipped to Endologix Clinical Research Department.

8.6.6. Pre-Discharge

Before the patient is discharged from the hospital the following steps are completed.

[a] Record the patient's weight and vital signs.

[b] Obtain a blood sample for serum creatinine, blood urea nitrogen, hematocrit, and hemoglobin measurements.

[c] Perform Ankle-Brachial Index testing bilaterally.

[d] Perform a physical examination.

[e] Perform other tests or imaging per institutional standard of care.

[f] Document any new or discontinued medications (cardiac/circulatory).

[g] A copy of the hospital discharge report or note is requested.

[h] Report any adverse finding from the diagnostic testing, or specific events that occurred since the procedure. If an event is a serious adverse event, provide the additional event details on the **Serious Adverse Event** section of the CRF. See §8.7 for adverse event reporting requirements

[i] The hospital staff should complete the *Patient Implant Card* (provided in the stent graft product packaging) and give it to the patient so that he or she can carry it at all times. The patient should be instructed to refer to the card anytime he or she visits a health practitioner, particularly for any additional diagnostic procedures (e.g., MRI).

8.6.7. Post-Discharge Follow-up Visits

The patient post-discharge follow-up visits are to occur post-procedurally at **30±14 days** (one month visit), **180±30 days** (six month visit), **365±60 days** (one year visit), **730±90 days** (two year visit), **1095±90 days** (three year visit), **1460±90 days** (four year visit), **and 1825±90 days** (five year visit).

[a] Obtain a blood sample for serum creatinine, blood urea nitrogen, hematocrit, and hemoglobin measurements.

[b] Perform a physical exam.

[c] Perform Ankle-Brachial Index testing bilaterally.

[d] Diagnostic Imaging:

- **CT Scan**: When a CT Scan is performed, collect it as a high resolution, contrast-enhanced CT scan using the same acquisition parameters required by the Core Lab as for the baseline exam. Forward the CT Scan to the Core Lab identified in §2.2. A copy of the site diagnostic report is requested.

- As per institutional standard of care, record any other imaging performed and provide a copy of the diagnostic report[s].

[e] Document any new or discontinued medications (cardiac/circulatory).

[f] Report any adverse finding from the diagnostic testing, or events that occurred since hospital discharge. If an event is a serious adverse event, provide the additional event details on the **Serious Adverse Event** section of the CRF. See §8.7 for adverse event reporting requirements.

8.6.8. Missed Patient Visits

The Investigator(s) will make every attempt to follow the patients enrolled in the study.

If a patient cannot be reached for a follow-up visit, the Investigator will document on the CRF, the efforts undertaken to contact the patient or the patient's primary health care provider. These efforts should include 2 attempts of telephone contact at separate dates and times, and a registered letter before the end of the follow-up window. If a patient cannot be reached for the follow-up visit and misses the scheduled visit, the visit will be recorded as a missed visit on the date of last attempted contact. Patients who miss a visit will not be considered withdrawn. At the next visit interval, the Investigator and/or designee will attempt to contact the patient again for follow-up. Should this attempt to contact the patient fail, a family member should be contacted in addition to the patient. Patients who miss 2 sequential follow-up visits will be considered lost to follow-up at the second missed visit and exempt from further study follow-up. After the patient is exited from the study, the Investigator will attempt to determine if the patient is alive, including searching national mortality registries as permitted by local laws.

8.6.9. Study Patient Exit

Study patients exit the study when no additional follow-up visits, procedures, or data collection are required. A Study Exit Form must be completed and full source documentation present for the reason(s). A subject may be exited from the study in the following instances:

- Patient signs a consent, surgery is scheduled, but the device is not implanted
- Patient withdraws from the study
- Patient is lost-to-follow-up
- Patient death
- Patient completes all study follow-up

8.7. ADVERSE EVENT REPORTING

Throughout the course of the study, all adverse events will be recorded on the applicable Adverse Event CRF and in the patient's medical records. The seriousness, date of onset, date of resolution, severity, action taken, relationship to the device, and relationship to the procedure will be identified by the Investigator.

8.7.1. General Definitions

An adverse event (AE) is any undesirable clinical occurrence in a patient administered a product and that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unintended sign, symptom or disease temporally associated with the use of an investigational product, whether or not related to the use of the product.

A serious adverse event (SAE) is an AE that results in death, is life threatening, requires in-patient hospitalization or that prolongs hospitalization, results in persistent or significant disability/incapacity, or that is a congenital anomaly or birth defect.

An unanticipated adverse event (UAE) 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, 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.

Severity of an AE is a clinical determination of the event intensity. The severity assessment for a clinical AE should be completed using the following definitions as guidelines:

Mild (+1): Awareness of sign or symptom, but easily tolerated.

Moderate (+2): Discomfort enough to cause interference with usual activity.

Severe (+3): Incapacitating with inability to work or do usual activity.

NOTE: An event that is fatal should be recorded as death on the **ADVERSE EVENT** CRF. The cause of death will be detailed on the **Serious Adverse Events** section of the form.

Relationship to device or procedure of an AE is a judgment determination made by the Investigator that there is a logical connection between device use (e.g., delivery system manipulation) and the occurrence of the AE.

8.7.2. Reporting of Device or Procedure Related Events

For all patients, Investigators shall submit to Endologix and to the reviewing Ethics Committee or IRB a report of any adverse device-related or procedure-related event, including, but not limited to, hospitalization or death within 10 working days after the Investigator first learns of the event. Each of these events will be investigated by Endologix. If it is determined that a UAE has occurred and presents an unreasonable risk to subjects, all investigations or parts of investigations presenting that risk will be terminated. Termination of

the investigation will occur within five (5) working days after notice of the effect is received at Endologix. The terminated investigation will not be resumed without the approval of the ethics committee/IRB.

8.7.3. Reporting of SAEs

Any SAE occurring during the study period must be recorded on the appropriate **ADVERSE EVENT** CRF and **Serious Adverse Events** section of the CRF.

For any SAE, fax the ADVERSE EVENT coversheet and supporting information within 24 hours of awareness to Paragon BioMedical and Endologix. All patients with an SAE must be followed and outcomes reported. The Investigator should supply to Endologix and the responsible ethics committee/IRB with a complete, written case history (AE forms) and any additional requested information (e.g., other diagnostic testing, discharge reports, autopsy reports, etc.).

Deaths

For any patient death, regardless of cause or timing, an autopsy should be requested. If the family has agreed to the conduct of an autopsy, a copy of the autopsy report is required.

A device explant kit will be provided to the hospital for processing and shipment to an independent pathologist per established methods. To request a kit, contact Endologix (see Section 2.1 for contact information).

Every attempt should be made to obtain as much detailed information on the events or conditions leading up to the death as possible. If the patient was hospitalized, a copy of the discharge summary source document is required.

Secondary Interventions

For patients that experience any non-diagnostic invasive secondary treatment of the groin access areas or of the abdominal aortoiliac vessels (e.g., hematoma drainage, vascular exploration for bleeding, iliac stenting, thrombectomy, additional device placement for endoleak, embolization for Type II endoleak, etc.), it is important to identify the area, region or vessel segment that is involved and the specific procedure performed on the relevant **ADVERSE EVENT** CRF. A copy of the discharge summary source document is required.

8.7.4. Anticipated Adverse Events

Adverse events that could potentially occur during this investigation are called anticipated adverse events and are listed in alphabetical order:

- Access site complications and sequelae (e.g., dehiscence, infection, pain, hematoma, pseudoaneurysm)
- Allergic reaction to contrast agent (e.g., pruritus, urticaria, bronchospasm, angioedema, hypotension or anaphylaxis that occurs during or post-procedure)
- Amputation
- Anesthetic complications and sequelae (e.g., aspiration)
- Aneurysm enlargement
- Aneurysm rupture
- Arterial damage or trauma (e.g., bleeding, perforation, dissection, rupture)
- Arterial or venous thrombosis and/or pseudoaneurysm
- Arteriovenous fistula
- Bleeding requiring transfusion and/or surgical intervention
- Bowel complications (e.g., ileus, ischemia, infarction, necrosis)
- Cardiac complications and sequelae (e.g., arrhythmia, myocardial infarction, congestive heart failure, hypotension, hypertension)
- Catheter fragmentation and sequelae (e.g., embolization, vessel trauma)
- Claudication
- Coagulopathy
- Death (due to any cause)
- Edema
- Embolization (micro and macro) with transient or permanent ischemia or infarction
- Endoleak
- Fever and localized inflammation
- Genitourinary complications and sequelae (e.g., ischemia, fistula, incontinence, hematuria, impotence, infection)
- Hepatic failure
- Infection of the aneurysm, device access site, including abscess formation, transient fever and pain.
- Local or systemic neurologic complications and sequelae, transient or permanent (e.g., stroke, transient ischemic attack, paraplegia, paraparesis, paralysis, numbness and/or tingling in legs)
- Lymphatic complications and sequelae (e.g., lymph fistula)
- Thrombosis or occlusion of stent graft or arterial vessel of the lower extremities
- Pulmonary/respiratory complications and sequelae (e.g., pneumonia, respiratory failure, prolonged intubation, pulmonary embolism)
- Renal complications and sequelae (e.g., artery occlusion, infarction, insufficiency, failure)
- Secondary procedure
- Stent graft: improper component placement; incomplete component deployment; component migration; suture break; occlusion/thrombosis; infection; stent fracture; graft material wear; dilatation; erosion; puncture and perigraft flow
- Surgical conversion to open repair

8.7.5. 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, 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.

8.7.6. Protocol Deviations

A protocol deviation is defined as an event where the Investigator or study personnel did not conduct the study according to the clinical protocol or the Clinical Study Agreement. Deviations shall be reported to the Study Sponsor regardless of whether medically justifiable or taken to protect the subject in an emergency. Reports of any deviation from the protocol conducted in an emergency situation, to protect the life or physical well-being of a patient, will be reported to Endologix and to the ethics committee as soon as possible, but no later than 24 hours from the time of the event.

Patient specific deviations and non-subject specific deviations, (e.g. unauthorized use of a study device outside the study, unauthorized use of a study device by a physician who is not listed in the Clinical Study Agreement, etc.) will be reported in writing. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB's reporting policies and procedures.

For reporting purposes, deviations may be classified as major (e.g., failure to obtain written informed consent; unauthorized use of study device by a physician who has not completed the Endologix training or who is not on the Study Signature Log) or minor.(e.g., failure to perform a hematocrit blood test; visit outside of window).

Some information collected in this study is not essential to the study endpoints and will not be considered deviation if absent.

8.7.7. Clinical Events Committee Review

Overview

The clinical events committee (CEC) identified in §2 consists of at least three physicians who will serve as independent experts responsible for evaluation and categorization of adverse events reported by the investigators in the trial. Analyses of events described in this protocol will be based on the CEC-determined categorization.

The primary purpose of these individuals is to ensure a consistent, independent review of events and their clinical significance using standardized criteria and definitions. A curriculum vita for each CEC member is maintained by Endologix, and is available for regulatory review. Due to the need for independence, these individuals may not participate in this trial as investigators, and may not hold significant material, financial or other interests which create a potential conflict with respect to this role, including but not limited to significant equity

interest in Endologix.

Process

Endologix will provide independently to the CEC the complete case report form event text that details all deaths and the events as reported by the clinical site investigators. This information will be provided without identification of the site name, and will identify patients by identification number and initials only. Non-serious events or events that are reported as clearly unrelated events will not be assessed by the CEC. The CEC will review events and any follow-up data requested from Endologix. This may include copies of such documents as progress notes, operative notes, discharge summaries, death summaries, and autopsy reports.

The CEC will document the event categorization for each event individually. Meeting notes and supporting information, requests for documentation, etc. will be maintained.

Event Definitions

The following event definitions will be applied to the Primary Endpoint Analysis during this study. Where possible, events will be categorized as being related to the endovascular procedure/bifurcated device, to the fenestrated device, or to the renal stent graft device.

- *Death*: Any death occurring during the study period, regardless of cause.

  Death will be further subcategorized as early (within 30 calendar days from the date of the procedure) or late (>30 days). It will also be subcategorized as aneurysm-related or not aneurysm-related.

  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 following any procedure intended to treat the aneurysm.

- *Procedural Technical Failure*: An event occurring procedurally or within 30 days post-procedurally that meets one or more of the following criteria:

  - *Aortic Stent Graft Failure* is defined as a failure of the bifurcated or fenestrated proximal extension stent graft to be delivered and deployed, such that the procedure is not completed, or the device failure results in a serious complication, or a residual Type I or III endoleak that cannot be resolved during the index procedure;

  - *Renal Stent Graft Failure* is defined as a failure of the renal stent graft to be delivered and deployed, such that the procedure is not completed, or the device failure results in a serious complication.

- *Major Adverse Event*: An event occurring during the trial 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*: the presence of raised levels of one or more cardiac biomarkers in comparison to laboratory reference ranges;
- *Paraplegia*: Paralysis of the lower extremities inclusive of the lower trunk.
- *Renal Failure*: the need for temporary or permanent dialysis or >0.5mg/dL increase in pre-operative serum creatinine level at two consecutive intervals;
- *Respiratory Failure*: pneumonia or 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.
- *Blood Loss >1,000cc*: Estimated blood loss during the index procedure ≥1,000cc.

- *Other Definitions*:
  - *Aneurysm Enlargement*: Core Lab reported aneurysm sac diameter increase of >5mm in late follow-up as compared to the initial post-operative measurement.
  - *Aneurysm Rupture*: internal bleeding or leaking of blood from the aneurysm subsequent to the index procedure.
  - *Conversion to Open Repair*: 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.
  - *Cardiac Morbidity*: acute myocardial infarction (diagnosed based on measured levels of one or more cardiac biomarkers in comparison to laboratory reference ranges); new onset heart failure (an acute episode or exacerbation of existing low cardiac output accompanied by distal and/or pulmonary edema); intractable or malignant arrhythmia requiring cardioversion or pacemaker placement; or coronary intervention (coronary artery bypass grafting [CABG] or percutaneous coronary intervention [PCI]).
  - *Clinically Significant Device Migration*: Core Lab reported aortic stent graft movement >10mm from the original implant location resulting in an intervention or in a serious complication.
  - *Renal Dysfunction*: a reduction in the estimated glomerular filtration rate (eGFR) of >30% from the preoperative value;
  - *Secondary Procedure*: any non-diagnostic intervention after the index procedure intended to correct or repair an endoleak, limb occlusion, migration, aneurysm sac expansion and/or a device defect;
  - *Stent Graft Occlusion*: Intervention for aortic or renal stent graft occlusion or as reported by the Core Laboratory.

- *Transient Ischemic Attack*: a sudden development of neurological deficit due to vascular lesions of *the* brain such as hemorrhage, embolism, or thrombosis that persists for <24 hours.
- *Type I/III/IV Endoleak*: Core Lab reported endoleak: between the endograft and the vessel either at the proximal attachment point (Type IA) or at the distal attachment point (Type IB); between endograft components (Type III); or transgraft (Type IV)
- *Type II Endoleak*: Core Lab reported endoleak emanating from a patent collateral vessel (e.g., inferior mesenteric artery; lumbar artery; etc.).

9. RISK ANALYSIS

The decision to repair an aortic aneurysm is generally based on the risk of rupture, the risk of complications of surgery, and patient preference. There are currently two methods used to repair aortic aneurysms. The most common and conventional method is an open surgical repair, with the implantation of a synthetic graft to replace the diseased aneurysmal vessel through a large abdominal incision. Recent technological developments have resulted in an alternative, minimally invasive, endovascular aneurysm repair, in which a stent graft is placed within the aorta through a small incision in the groin. Blood can then flow through the stent graft and is excluded from the aneurysmal portion of the aorta.

The disadvantages of open surgical repair are: general anesthesia is required, it is a major abdominal surgery (large incision), has a significant surgical complication rate, and typically requires a long hospital stay and recovery. EVAR enables local or regional anesthesia to be used, uses a minimally invasive groin incision for catheter-based access, and has been reported in US clinical studies to offer a lower operative complication rate, reduced blood loss and procedure times, and shorter hospital stay. In contrast to open repair, EVAR is a relatively new treatment, long term results have not been fully established, and life-long surveillance is recommended to verify stent graft integrity and patency and continued aneurysm exclusion. Currently, five device systems are FDA-approved and marketed in the US for endovascular infrarenal abdominal aortic aneurysm repair. All of these devices require the introduction of catheter-based treatment devices varying in outer diameter profile from 20Fr to 25Fr (ipsilateral). Standard vascular exposure is indicated for access. Prospective clinical study results support the safety and effectiveness of these stent grafts through early follow-up (to 30 days) and in late follow-up to one year and to up to five years. These and other devices are CE Marked and are available in other international regions. One custom device is available in Europe for JAA endovascular repair; however, no 'off-the-shelf' endovascular devices are currently commercially available. No device is currently approved in the US for the endovascular repair of juxtarenal or pararenal aortic aneurysm.

As with any procedure there are risks of serious complications, such as death. The inclusion and exclusion criteria for this population have been carefully established to limit the risk of mortality and morbidity in this population. The overall risk will be evaluated on an individual basis and discussed with each patient. All of the potential adverse events outlined previously could cause prolonged illness, permanent impairment of daily function or, in rare cases, death. Possible treatments could include, but are not limited to, emergency cardiac or vascular surgery.

Eligibility criteria that exclude patients who are at higher risk for experiencing an anticipated adverse event have been selected to reduce the potential risks to patients who participate in this study. In addition, the assessment of patient anatomy for enrollment by an experienced Core Laboratory is also intended to reduce the potential risks to patients who participate in this study.

Pre-procedural high resolution, contrast-enhanced CT scanning and intraprocedural arteriography will be used to identify and target the aortic anatomy to facilitate the proper introduction, delivery, and deployment of the endovascular repair devices. Physician experience, rigorous application of a common protocol, and careful performance of the procedure with close monitoring of the patient after the procedure will also help to minimize risks.

The alternative to endovascular repair of JAA/PAA is open surgical repair.

10. STATISTICAL PROCEDURES

10.1 ANALYSIS POPULATIONS

All primary analyses will be conducted on an intention to treat (ITT) basis with imputation for missing data as described in the Patient Accountability and Missing Data section below. Whereas ITT is a concept intended to be applied to randomized trials, its use in this analysis will imply that patients will be analyzed based on the attempt to implant trial devices during the procedure. Patients who complete the trial through 12 months will comprise the completed cases (CC) population. CC patients who do not have protocol violations that can affect outcome will comprise the per protocol (PP) population. Additional analyses will be conducted in the CC population.

10.2 PATIENT ACCOUNTABILITY AND MISSING DATA

The proportion of patients with documented follow-up at each interval will be presented descriptively. The number of diagnostic, laboratory, and clinical evaluations will be tabulated by follow-up interval. Also, a listing of patients who initially consent but do not undergo a procedure due to withdrawal of consent will be given. However, these patients will not be included in any analysis.

Information on missing or withdrawn patients will be tabulated presenting the number and proportion of patients eligible for and compliant with each follow-up examination. Patients who withdraw from the trial will be tabulated with the reasons for the withdrawal. Additional sensitivity analyses will be performed as described below.

The evaluation of patients with missing data presents a special concern in ITT analyses. All clinical studies analyze the results based on the completed cases (i.e., those who complete the trial). Because missing patients do not have final data, they present a problem for ITT analyses. The statistical community recommends that multiple sensitivity analyses be conducted to determine the robustness of the result in patients who complete the study.[10,11,12,13] The intention of these analyses is to demonstrate that the results obtained from the evaluable patients are not biased.

As a result, sensitivity analyses using multiple imputations will be conducted to evaluate the robustness of the study result accounting for missing observations. The primary effectiveness endpoint analysis will be based on an unbiased imputation of the determination of success or failure. It is expected that the number of patients with missing effectiveness data at one year will be approximately 15 patients (i.e., 15%). The missing value for these patients will be assigned by a simple random sample from the patients with outcomes at one year. This system is denoted the "Hot

[10]Pocock S. (1983). Clinical Trials (A Practical Approach). John Wiley and Sons, Chichester.

[11]Friedman L, Furberg C, and DeMets D. Fundamentals of Clinical Trials. 1985: Mosby Year Book, St. Louis.

[12]Guidance for Industry: E9 Statistical Principles for Clinical Trials. U. S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. International Committee on Harmonization, September 1998.

[13]Rubin D. Multiple Imputation for Nonresponse in Surveys. 1987: John Wiley and Sons, New York.

Deck by Simple Random Sampling with Replacement".[14] The number of patients to impute is small and trying to provide a more sophisticated imputation method would require modeling missingness with only approximately 15 patients or less with missing data. Additional sensitivity analyses will be done by using other imputation methods. The first shall be the last observation carried forward (LOCF). Another sensitivity analysis will entail considering the subject lost to follow-up to have failed the endpoint. A third analysis will impute the missing result as having succeeded the endpoint. A final analysis will impute the missing value by a generating a random number and comparing it to the value of the performance goal for effectiveness.

A comparison of baseline characteristics of the patients with missing data and those without missing data will be done to determine if there is evidence that the data are not missing at random (it is not possible to determine that data are missing at random). If the missing at random assumption is clearly violated by these comparisons, it is usually possible to find a sub-group that are not missing at random who have to be imputed differently, such as assigning the worst score to patients in the sub-group. For example, the proportion of patients missing an outcome may be much greater at a given study site which may also have a higher rate of failure. Those patients from that site may be assigned a failure and the baseline comparisons of the remaining patients will be rechecked to see if the imbalances are resolved. If this resolves the missing at random difficulty, the sub groups will be given special scores and the remaining patients will be imputed as described above. The resolution of the imbalance will be retested by the same methods with the patients identified above removed.

The primary imputation will be done 10 times with 10 different seeds to initiate the random selection and the combined P-value for the 10 imputations will be obtained by a method described in Rubin (1987) and in the SAS manual for PROC MIANALYZE. The seeds to be used for the 10 imputations are selected from a pseudo-random number table in Steele and Torrie (1960) and are 70303, 18191, 62404, 26558, 92804, 15415, 02865, 52449, 78509, and 43896.[15]

With regard to imputation for the primary safety endpoint, that endpoint is obtained so close to the procedure that there will be very little missing data, if any. In the control group, no patients were censored without an MAE through 30 days. If any of the test patients are lost to follow-up prior to 30 days, that patient will be assigned an MAE for primary analysis purposes.

10.3 GENERAL NOTES

Analyses of MAEs and other adverse events will be conducted at exact time points. Early events are defined as those occurring from the date of the procedure to 30 calendar days post-operatively. Late events are defined as those occurring from after 30 calendar days post-operatively (from day 31 forward). Events within six months and one year, respectively, are those occurring up to and including 183 days and 365 days following the procedure.

For categorical variables, summary statistics will include counts and proportions. Confidence limits for proportions will generally be given; for binary variables the confidence limits will be computed

[14]Little R and Rubin D. Statistical Analysis with Missing Data. 2002. John Wiley and Sons, New York.
[15]Steele R and Torrie J. Principles and Procedures of Statistics. 1960. McGraw-Hill, New York.

using the exact binomial distribution. Supportive multivariate analyses of stratified comparisons of categorical variables will be performed using appropriate logistic or Cox regression.

For continuous variables, summary statistics will include means, standard deviations, medians, and range. Groups will be compared using *t*-tests or analysis of variance, or Kruskal-Wallis tests will be used to compare more than two groups (such as trial sites). When multiple comparisons are performed after ANOVA, Scheffé's method will be used. The exact Wilcoxon test will be used to compare continuous variables where severe departures from normality are observed.

For ordinal variables, comparisons will be performed using the exact Wilcoxon rank-sum test. Unless otherwise specified, the exact form of each algorithm will be the default of SAS® Version 9.1 or later. Some preliminary descriptive analyses may be done with other software tools to be specified.

10.4 BASELINE COMPARABILITY ANALYSIS

A set of important demographic or prognostic variables will be compared across trial sites to determine homogeneity of trial sites in terms of baseline patient characteristics. Factors found to differ significantly by trial site will identify that variable or trial site as a possible covariate in subsequent analyses.

In the analysis of comparability of trial sites, it is anticipated that a small number of sites may have a patient enrollment that is too small to allow meaningful statistical analysis. To allow the inclusion of sites with this condition, small sites will be combined into one pseudo-site the size of which will not exceed the size of the largest trial site. It is not possible to determine the number of patients below which this aggregation will occur until after enrollment is completed, but generally trial sites with four or fewer patients may be combined.

10.5 POOLING

Data pooling incorporates two factors: combination of data across trial sites and the actual method of obtaining an estimate of the endpoint from combined data. Data will be combined from multiple trial sites for the trial analyses. The justification for this pooling is made on a clinical basis with three critical factors: The basis for pooling comes from: 1) The trial sites must implement one common protocol; 2) The sponsor must provide very close monitoring of study site compliance; and, 3) the trial sites must use common data collection procedures.[16]

In order to determine if there is a similar response across the sites to allow the responses to be pooled in the trial the primary safety and effectiveness proportions will be tested for homogeneity by logistic regression using a univariate model of study site within the test group. If the P-value for study site is less than 0.15, differences in study site proportions in response will be assumed to exist and the overall estimate of the proportion in the test patients will be obtained by taking a weighted average of the proportions at each site with the weight being the inverse of the variance of the proportion at that

[16]Meinert C. Clinical Trials: Design, Conduct, and Analysis. 1986; Oxford University Press. New York, NY

site.[17] The sum of these weighted proportions divided by the sum of the weights will be the overall estimate for the study. For the safety variable, the differences of the weighted proportions will form the basis of the statistical test and for the effectitveness variable, the overall weighted proportions will be the basis of the test. The test of significance in these circumstances are fully descried below.

If the heterogeneity P-value is greater than 0.15, an analysis of the primary effectiveness endpoint by the Fleiss (1993) method will be done.

10.6 PRIMARY SAFETY ANALYSIS

10.6.1 The Primary Safety Hypothesis

The primary safety research hypothesis to be tested is that the rate of Major Adverse Events (MAEs) at 30 days in the test group is less than the rate of MAE at 30 days in the control group. The null and alternative hypotheses are provided below.

$H_0: P_t \geq P_c$ vs. $H_1: P_t < P_c$, where:

P_t is the MAE rate at 30 days in the test group;

P_c is the MAE rate at 30 days in the historical surgical control group.

10.6.2 Sample Size

The primary trial safety variable is the rate of MAEs (as previously defined) at 30 days following treatment with the Fenestrated Stent Graft System. In the U.S., the alternative for these patients with juxtarenal or pararenal aortic aneurysm is open surgical repair. The open surgical concurrent control group enrolled in the original Endologix trial between 2000 and 2003 (that served as the basis for approval of the bifurcated stent graft under P040002) consisted of patients with aneurysms of these types. Of the 66 control patients enrolled in that trial, 3.0% had a suprarenal aneurysm, 21% had a pararenal aneurysm, and the remaining patients (76%) had a juxtarenal aneurysm or infrarenal aneurysm unsuitable for endovascular repair with the Endologix bifurcated device. These patients have completed full five year follow-up as documented in the Endologix PMA final report approved by FDA in 2009 (P040002/R008).

Owing to the availability of patient-level data within the Endologix PMA P040002 for this historical surgical control group with more complex aneurysms as intended to be enrolled in this trial, it is reasonable to consider it for sample size generation for the safety endpoint. The MAE incidence at 30 days in the original PMA trial for the test group and this surgical control group is tabulated below:

[17]Fleiss, J. The statistical basis of meta-analysis. *Statistical Methods in Medical Research* 1993;2:121-45.

30-Day MAE Rates in the Endologix PMA Trial (P040002)

Event	Powerlink Test (N=192)	Surgical Control (N=66)
Patients with ≥1MAE	16 (8.3%)	44 (67%)
All-Cause Mortality	2 (1.0%)	4 (6.1%)
Bowel Ischemia	0	6 (9.1%)
Myocardial Infarction	3 (1.5%)	5 (7.6%)
Paraplegia	0	0
Renal Failure	2 (1.0%)	6 (9.1%)
Respiratory Failure	2 (1.0%)	5 (7.6%)
Stroke	0	1 (1.5%)
Blood Loss ≥1,000cc	11 (5.7%)	38 (58%)

Thus, the 30-day MAE rates were 8.3% (endovascular test group) and 67% (surgical control group). To be conservative and to account for the fact that in the present trial, only more complex juxtarenal or pararenal aneurysms will be treated endovascularly, the rate for the test arm has been increased to 16.6%. It is expected that the rate of MAEs within 30 days in the treatment group in this trial will be smaller than that of the historical surgical control group as noted above. The sample size for this trial is calculated by considering this a superiority trial.

The primary hypothesis to be tested in this analysis is the following:

$H_0: P_t \geq P_c$ vs. $H_1: P_t < P_c$, where

P_t is the MAE rate at 30 days in the test group;

P_c is the MAE rate at 30 days in the historical surgical control group.

If we assume that $P_t = 0.166$, $P_c = 0.670$, one-sided alpha = 0.025, and power = 80%, a very small number of patients (<10) are required in the treatment group to test the above hypothesis, given 66 patients in the control group. If there are 97 evaluable patients in the test arm, P_t would have to be 0.434 for there to be 81% power with an alpha of 0.025.

10.6.3 Propensity Score Analysis

Because it is expected that there will be differences between the treated and control patients that might bias the comparison, a propensity score analysis will be attempted. This analysis will be done by an independent statistician (i.e., not affiliated with Endologix or with the primary study statistician, RP Chiacchierini and Associates) without knowledge of the primary safety outcomes that are adjudicated by the independent Clinical Events Committee. Furthermore, this analysis can be performed after all test patients are enrolled, and before the endpoint is reached by all patients. The independent statistician will be required to document

in his or her report the data and documentation received from the data management group for the control and test patients, with clear acknowledgement that no MAE outcomes data were provided or were available in any way.

A non-parsimonious logistic regression analysis modeling treatment assignment by baseline covariates will be done initially. Covariates for this analysis will be age, gender, ASA class, cardiac/coronary artery disease (a composite variable to include arrhythmia, CHF, prior MI, CABG/PCI, heart valve repair/replacement), histories of cancer, cerebrovascular disease, coagulopathy, COPD, diabetes, hypertension, liver disease, peripheral arterial occlusive disease, renal failure, smoking history, and aneurysm diameter. For the propensity score analysis, in covariates where missing data occurs, the missing data will be imputed by using the median by treatment group for the missing value unless the number of patients with missing data is large (greater than 10% of the sample size). In that case, the missing value will be imputed by one of two methods. If the variable is quantitative, the following steps will complete the imputation (stratified hot deck imputation):

1. A histogram will be computed;
2. A uniform random number between 0 and 1 will be chosen and compared to the relative frequency of the bars in the histogram to determine the range of the value.
3. A second uniform random number will be generated, multiplied by the range for the bar selected above; the integer portion of this product will be added to lower limit of the range to obtain the imputed value.

If the variable is categorical, the correlation of the cases with other covariates will be evaluated to determine if there is a relationship between the value of the variable with missing data and a function of other covariates used in the analysis that results in ordinal integer values (perhaps the sum of a subset of several covariates that are present could be used). If there is a significant correlation between the variable with missing values and the function, a cross tabulation of the subjects with scores for the variable with missing data and the function values will be formed. The value of the missing observation will be assigned by generating a uniform random number and comparing that random number to the relative marginal frequency of the distribution of observed values for the given score of the function. If no function can be found to be correlated with the data, the values will be assigned by simple random selection with replacement from subjects with values within treatment groups.

The model will be obtained by including all covariates in the model. The final propensity model will contain all covariates for the first evaluation of balance. The propensity score analysis will be done without knowledge of MAE results for the test group. This is made possible by the fact that test group MAEs are determined by an independent Clinical Events Committee; their adjudicated results are not part of the clinical database but are separately maintained in a dedicated CEC database.

The data will be divided into quintiles. Within the quintiles, the baseline characteristics are evaluated by comparing each characteristic between the test and control groups and observed to determine if a characteristic for which a statistically significant difference was observed

without adjustment is no longer statistically significant. An analysis of balance will be done by the method recommended by Rosenbaum and Rubin.[18] For each continuous or ordinal covariate, an analysis of variance with two treatment groups and five stratum class variables will be done. An examination of the F-tests across and within strata will be examined.

Significant main effect or interactions from this analysis will be evidence of imbalance. For categorical covariates, this analysis will be done with logistic regression. With the logistic regression analyses, the output Chi-square values will be examined. The maneuvers to be attempted if adequate balance is not achieved by the initial propensity model include reducing the model by removing non-significant covariates and adding higher order terms for significant covariates to the propensity model to see if the resulting propensity score assignments improve the balance. After each propensity adjustment, the same balance analyses will be done.

If an adequate degree of adjustment cannot be achieved using quintiles because of sparse representation of the test or control groups in a given stratum (less than two patients to allow estimation of the variance for continuous or ordinal covariates), the analysis will be attempted by using quartiles. If the data are still too sparse, tertiles will be used. While dividing the data into quintiles accounts for about 90% of the bias in measured variables, quartiles accounts for about 85% bias reduction, and tertiles account for about 80% bias reduction.[19,20]

The sole rationale for acceptability of the degree of adjustment will be based on the F-statistics for continuous or ordinal covariates or the chi-square statistics for categorical covariates.[17]

If significant imbalance remains, the analysis involving the control group will be abandoned and an alternative analysis of the performance goal discussed in §10.6.4 will be used as the primary safety analysis.

10.6.4 Analysis Plan

All patients who receive treatment will be included in the safety analysis. The number and percentage of patients in the test and control groups will be displayed in a 2x2 table. If the propensity score adjustment is adequate and there is not heterogeneity across study sites, the univariate test will be done as follows: the differences will be computed within each propensity stratum and the test will be done using the method of Mehrota and Railkar using

[18]Rosenbaum P and Rubin D. Reducing bias in observational studies using subclassification on the propensity score. J Am Statist Assoc 1984;79:516-24.
[19]Cochran W. The planning of observational studies of human populations. J Royal Statistical Society, Series A 1965;128:234-55.
[20]Cochran W. The effectiveness of adjustment by subclassification in removing bias in observational studies. Biometrics 1968;24:205-13.

the minimum risk weighting factor to obtain the z-statistic.[21] The z-statistic for this univariate test is provided in the formula below.

$$z = \frac{\hat{\delta} - (3/16)\left(\sum_{i=1}^{5} \frac{n_{ic} n_{it}}{n_{ic} + n_{ic}}\right)}{\sqrt{\sum_{i=1}^{5} w_i^2 \hat{V}_0\left(\hat{\delta}_i\right)}}$$

Where

$$\hat{\delta} = \left(\sum_{i=1}^{5} w_i \hat{\delta}_i\right),$$

$$w_i = \frac{V_i^{-1}}{\sum_{k=1}^{5} V_k^{-1}} - \left(\frac{\left(\delta_i \sum_{k=1}^{5} V_k^{-1}\right) V_i^{-1}}{\sum_{k=1}^{5} V_k^{-1}}\right)\left(\frac{\sum_{k=1}^{5} \delta_k V_k^{-1}}{\sum_{k=1}^{5} V_k^{-1}}\right),$$

$$\delta_k = p_{tk} - p_{ck},$$

$$V_k = \frac{p_{tk}(1 - p_{tk})}{n_{tk}} + \frac{p_{ck}(1 - p_{ck})}{n_{ck}},$$

$p_{ik} = x_{ik}/n_{ik}$, x_{ik} is the number of patients with MAE in treatment i in stratum k, n_{ik} is the number of patients in treatment group i and stratum k, and $V_0(\delta_i)$ is the variance of the difference in the proportions for stratum i under the null hypothesis. The formulas in Mehrota and Railkar include the theoretical δ, but for simplicity the formulas above have been presented with estimates under the null hypothesis (δ=0) which is appropriate for the test statistic to be used in this study.

If there is heterogeneity among the study sites the test will be additionally adjusted for site differences by the method of Fleiss (1993). If the data from the study sites cannot be pooled to form a common estimate of the treatment effect, the following analysis from Fleiss (1993) will be done. Within each stratum i and treatment group j, the mean proportions across study sites is given by the following formula:

$$\bar{p}_{ij} = \frac{\sum_k W_{ijk} p_{ijk}}{\sum_k W_{ijk}}$$

Where p_{ijk} is the estimated MAE proportion from stratum i and site k for treatment j, and $W_{ijk} = 1/((1/n_{ijk})p_{ijk}(1-p_{ijk})$. for i=1-5, j = T for test and C for Control and k is the site number. The

[21] Mehrotra D. and Railkar R. Minimum risk weights for comparing treatments in stratified binomial trials. Statistics in Medicine 2000;19:811-25

differences of the weighted proportions will be computed within each propensity stratum and the test will be done using the method of Mehrota and Railkar using the minimum risk weighting factor. The formula for z is the same as above except that the within stratum estimates of the difference are the given by the following,

$$\delta_k = \bar{p}_{tk} - \bar{p}_{ck}$$

Where $\bar{p}_{ik}$ is given by the formula above. The variance within the stratum of the difference is given by the following.

$$V_i = \left(\sum_{k=1}^{m_t} W_{itk} \right)^{-1} + \left(\sum_{k=1}^{m_c} W_{ick} \right)^{-1}$$

Where m_t is the number of sites in the treated sample and m_c is the number of sites in the control sample.

If the P-value from either test above is less than a one-sided 0.025, then the null hypothesis for this analysis will be rejected in favor of the alternative indicating that the new patients have a statistically significantly smaller rate of MAE than the historical surgical control group.

A descriptive analysis and a Kaplan-Meier analysis of the MAE composite at 30 days will be presented. The descriptive analysis will present the rates for the composite MAE and each individual adverse event that is part of the composite with corresponding 95% exact confidence intervals.

To determine those factors that may be associated with MAE, a supportive covariate analyses will be performed by logistic regression to determine if there are differences in the rates among groups when adjusted for other factors. Covariates for these analyses will be age, gender, ASA class, cardiac/coronary artery disease (a composite variable to include arrhythmia, CHF, prior MI, CABG/PCI, heart valve repair/replacement), histories of cancer, cerebrovascular disease, coagulopathy, COPD, diabetes, hypertension, liver disease, peripheral arterial occlusive disease, renal failure, smoking, selected aneurysm characteristics, propensity class (numerical classification of the stratum based on patient's propensity score), plus any variables found to be out of balance in the comparability analyses. Because there is no exact congruence of study sites between the test and control groups it is not possible to account for study site in this analysis. To observe the effect of study site, a multivariable analysis will be done only in the test patients to determine if the study site remains a significant influence to the rate of MAE when other covariates are included in the analysis. Often the differences in study site responses are the result of differences in baseline characteristics the patients at that site such that when a model includes both the study site effect and the covariates effect, the study site no longer retains statistical significance.

If it is not possible to break the data into classes that provide adequate coverage of both treatment groups in each stratum, an alternative primary safety test will be done against a performance goal of 56% derived from the Society for Vascular Surgery (SVS) major adverse

events outcomes for infrarenal open surgical control patients.[22] This is reasonably conservative as a performance goal. To this point, a recent publication finds that the rates of these major adverse events are similar between open infrarenal aneurysm repair and open complex aneurysm repair (juxtarenal, pararenal, suprarenal), with the exception of bleeding and renal events, which were significantly higher with open complex aneurysm repair.[23]

The null and alternative hypotheses are provided below.

H_0: $P_t \geq 0.56$

versus

H_1: $P_t < 0.56$

where P_t is the MAE rate at 30 days in the test group

If there is not heterogeneity in the study site MAE rates for the test patients, the univariate test will be done with the exact binomial distribution to determine if the frequency of MAE in the test group is statistically significantly less than 0.56. The formula for this test is provided below.

$$P(X \leq x_t | 0.56) = \sum_{k=1}^{x_t} \binom{n_t}{k} 0.56^k 0.44^{n_t - k} < 0.025$$

Where x_t is the number of test group patients experiencing an MAE and n_t is the number of patients in the test group. If the above expression holds for the observed x_t, the null hypothesis will be rejected and the alternative hypothesis will be accepted.

If there is heterogeneity among the study sites in MAE response, the analysis will be done by the method of Fleiss (1993). The test statistic will be given by the following formula.

$$z = \frac{(\bar{p}_T - 0.56)}{SE(\bar{p}_T)}$$

Where the formula for the weighted estimate of the proportion is given by the following formula.

[22]Turnbull I, Criado FJ, Sanchez L, et al. Five year results for the Talent enhanced low profile system abdominal stent graft pivotal trial including early and long term safety and efficacy. J Vasc Surg 2010; 51:537-44.

[23]Jeyabalan G, Park T, Rhee RY, et al. Comparison of modern open infrarenal and pararenal abdominal aortic aneurysm repair on early outcomes and renal dysfunction at one year. J Vasc Surg 2011;54:654-9.

$$\bar{p}_T = \frac{\sum_k W_k p_{Tk}}{\sum_k W_k}$$

And the formula for the weight in site k is given by the following

$$W_k = \frac{1}{n_k} p_k (1 - p_k)$$

And the formula for the standard error is given by the following.

$$SE(\bar{p}_T) = \left(\sum_{k=1}^{m_T} W_{Tk} \right)^{-1/2}$$

If the z has a P-value less than a one-sided alpha of 0.025, the null will be rejected and the alternative will be accepted.

Similar to the strategy employed above, to determine those factors that may be associated with MAE, a supportive covariate analyses will be performed by logistic regression to determine if there are differences in the rates among groups when adjusted for other factors in the test group only. Covariates for these analyses will be age, gender, ASA class, cardiac/coronary artery disease (a composite variable to include arrhythmia, CHF, prior MI, CABG/PCI, heart valve repair/replacement), histories of cancer, cerebrovascular disease, coagulopathy, COPD, diabetes, hypertension, liver disease, peripheral arterial occlusive disease, renal failure, smoking, maximum aneurysm diameter, and study site. The final model will be reduced by backward elimination until no covariate terms remain in the model with a P-value less than 0.05.

10.7 PRIMARY EFFECTIVENESS ANALYSIS

10.7.1 Primary Effectiveness Hypothesis

The primary effectiveness research hypothesis is that the treatment success rate at one year exceeds a performance goal of 80%. The null and alternative hypothesis is presented below.

H_0: $P \leq 0.80$ vs. H_a: $P > 0.80$

Where P is the rate of Treatment Success as defined in §10.7.2.

10.7.2 Sample Size

The primary trial effectiveness variable is the Treatment Success rate at one year post-operatively. Treatment Success is a composite of clinically-relevant outcomes, including procedural technical success and absence of: aneurysm rupture, conversion to open repair, Type I endoleak after 30 days; Type III endoleak; clinically significant migration; aneurysm enlargement; or secondary intervention for resolution of endoleak, limb occlusion, migration, aneurysm sac expansion and/or a device defect.

The sample size is obtained by using the exact binomial distribution using PASS 2008. A sample size of 82 patients at one year in the test group will have 80.58% power against a null performance goal of 80% if the proportion of Treatment Success is 90% or higher for alpha = a one-sided 0.05. It is estimated that the rate of Treatment Success will be greater than 90%.

It is anticipated that the drop-out rate of the trial will be 15% or less. Because the larger of the two sample sizes after adjustment for loss to withdrawal is the one for effectiveness, 82/0.85 = 97 patients will need to be recruited for this trial.

10.7.3 Analysis Plan

The primary effectiveness analysis will compare the Treatment Success rate as defined previously to a target rate of 80%. The null and alternative hypotheses are defined below.

H_0: $P_t \leq 0.80$

H_1: $P_t > 0.80$

Where P_t = the proportion of treated patients who meet the Treatment Success definition. The observed proportion of patients with Treatment Success at one year post-procedure will be tested with the exact binomial distribution under the null hypothesis given in the inequality above. The formula for this expression is presented below.

$$P(X > x_t | 0.80) = \sum_{k=x_t}^{n_t} \binom{n_t}{k} 0.80^k 0.20^{n_t - k} < 0.05$$

Where x_t is the number of successes at one year and n_t is the number evaluated. If the one-sided P-value is less than 0.05, the null hypothesis will be rejected and the study hypothesis will be demonstrated.

If the study site success proportions across study site are not homogeneous, then the method of Fleiss described above will be used in the Test arm only to obtain a weighted estimate of the proportion successful. The mean proportion is found the same way as the first equation above. The test statistic becomes a z-statistic with the following formula:

$$z = \frac{\left(\bar{p}_T - 0.80\right)}{SE\left(\bar{p}_T\right)}$$

Where the formula for the weighted estimate of the proportion is given by the following formula.

$$\bar{p}_T = \frac{\sum_k W_k p_{Tk}}{\sum_k W_k}$$

And the formula for the weight in site k is given by the following

$$W_k = \frac{1}{n_k} p_k \left(1 - p_k\right)$$

And the formula for the standard error is given by the following.

$$SE\left(\bar{p}_T\right) = \left(\sum_{k=1}^{m_T} W_{Tk} \right)^{-1/2}$$

If the z < 1.645 (P=0.05, one-sided), then the null hypothesis will be rejected in favor of the alternative and the primary effectiveness endpoint will be achieved.

To determine those factors that may be associated with Treatment Success, covariate analyses will be performed by logistic regression to determine if there are differences in the Treatment Success rates in the Test group when adjusted for other factors. Possible covariates eligible for these analyses will be age, gender, ASA class, cardiac/coronary artery disease (a composite variable to include arrhythmia, CHF, prior MI, CABG/PCI, heart valve repair/replacement), cancer, cerebrovascular disease, COPD, diabetes, hypertension, liver disease, peripheral arterial occlusive disease, renal failure, smoking, maximum aneurysm diameter, and study site. Because there are too many possible covariates to include in a model, screening is necessary to reduce the number of eligible covariates for consideration in the final model. Screening logistic regression models to include only the covariate, will be used. If the P-value for the screening model for the covariate is less than 0.20, the covariate will be included in the competition for the final model. The final model will be obtained by manual backward elimination to have the seven or fewer covariates with P-value less than 0.05.

10.8 ADDITIONAL EVALUATIONS

10.8.1 In the event that balance between the treated and control groups is not sufficiently close to allow direct comparison, a multivariable analysis will be done in which the MAE rates between the two groups will be compared with the treatment group, propensity score class, and the covariates for which balance was not satisfactorily achieved. This exploratory analysis will determine if treatment retains statistical significance in the presence of the propensity score class adjustment and covariate adjustment for those covariates unsatisfactorily balanced by the propensity score. Also, special interest will be directed to whether the covariates unsatisfactorily balanced have a statistically significant relationship to the MAE rate.

10.8.2 *Procedural and In-Hospital Evaluations*: The need for blood transfusion, estimated blood loss volume, contrast volume, fluoroscopy time, procedure time (and other intraprocedural times), anesthesia time and type, frequency of concomitant procedures, ICU time, and time to hospital discharge will be presented descriptively. Qualitative variables will be presented with rate. Quantitative variables will be presented with mean, standard deviation, median, minimum and maximum.

10.8.3 *Mortality*: The proportion of patients with mortality (all-cause and aneurysm-related) will be presented at 30 days and at each subsequent timepoint for which data are available (i.e., six months, and annually at years 1 through 5). A descriptive analysis and a Kaplan-Meier analysis of all-cause and aneurysm-related mortality through 30 days and for late follow-up including 30 days will be presented.

10.8.4 *Major Adverse Events (MAE) Individual Components*: The proportion of patients experiencing each category of MAE within 30 days and after 30 days at each subsequent timepoint for which data are available will be presented.

10.8.5 *Composite Late MAEs(after 30 days)*: The proportion of patients experiencing an MAE after 30 days will be presented at each subsequent timepoint for which data are available. A descriptive analysis and a Kaplan-Meier analysis of the MAE composite will be presented for follow-up through 30 days and for late follow-up including 30 days. The descriptive analysis will present the rates for the composite MAE and each individual adverse event that is part of the composite.

10.8.6 *Aneurysm Rupture*: The proportion of patients experiencing a rupture of the aneurysm will be presented at 30 days and at each subsequent timepoint for which data are available.

10.8.7 *Conversion to Open Repair*: The proportion of patients undergoing surgical conversion to open repair will be presented at 30 days and at each subsequent timepoint for which data are available.

10.8.8 *Serious Adverse Events (SAEs)*: The proportion of patients experiencing an SAE grouped in categories by body system type will be presented descriptively by timepoint. The SAEs to be studied in this way include blood and lymphatic disorders, bleeding, cardiac, gastrointestinal, genitourinary, hepatobiliary, infection,

multiorgan failure, musculoskeletal, neoplasm, neurological, renal, respiratory, secondary procedures, skin, vascular, other, and overall.

10.8.9 *Non-serious AEs*: The proportion of patients experiencing a non-serious AE grouped in categories by body system type will be presented descriptively by timepoint. The AEs to be studied in this way include blood and lymphatic disorders, bleeding, cardiac, gastrointestinal, genitourinary, hepatobiliary, infection, multiorgan failure, musculoskeletal, neoplasm, neurological, renal, respiratory, secondary procedures, skin, vascular, other, and overall.

10.8.10 *Distal Blood Flow Evaluations*: A descriptive analysis of distal blood flow and any changes at 30 days and at each subsequent timepoint for which data are available will be done based on ankle brachial index (ABI) evaluations. A determination will be made from the data as to whether the occurrence was associated with an SAE or device malfunction.

10.8.11 *Endograft Performance*: A descriptive analysis of the following will be done based on Core Lab evaluations at 30 days and at each subsequent timepoint for which data are available. A determination will be made from the data as to whether any observation was associated with an SAE or device malfunction.

Aneurysm Size Change: The changes in aneurysm size from the first post-operative evaluation will be presented descriptively at each subsequent follow-up. The maximum diameter parameter will be used for the analysis because it is the basis for comparison to other studies with endografts. For each follow-up interval, the number and percent of patients with increased sac diameter (>5 mm), stable sac diameter (≤5 mm), or decreased sac diameter (>5 mm) will be presented.

Incidence of Migration: The occurrence of migration (>10mm movement from the original implant location as determined on the first post-operative scan) will be presented descriptively at each follow-up.

Incidence of Endoleak: The occurrence of endoleak (any type or location, new and persistent) will be presented descriptively at each follow-up.

Incidence of Limb Occlusion: The occurrence of endoleak (any type or location, new and persistent) will be presented descriptively at each follow-up.

10.8.12 *Renal Function Evaluations*: A descriptive analysis of renal function will be done based on serum creatinine levels and calculated estimated glomerular filtration rate (eGFR) at 30 days and at each subsequent timepoint for which data are available. Renal dysfunction will be defined as a reduction in eGFR of >30% from the preoperative value.

10.8.13 *Renal Stent Graft Patency and Integrity*: A descriptive analysis of device patent luminal flow, absence of stent fracture, kinking, stenosis, or occlusion [>60% luminal obstruction]), absence of graft failure, and absence of renal artery infarct >30% will be determined by contrast-enhanced CT scan, as assessed by the independent core laboratory at 30 days and at each subsequent timepoint for which

data are available. A determination will be made from the data as to whether the occurrence was associated with an SAE or device malfunction.

10.8.14 *Stent Graft (fenestrated/bifurcated) Patency and Integrity*: A descriptive analysis of device patent luminal flow, absence of stent fracture, kinking, or occlusion, and absence of graft failure will be determined by contrast-enhanced CT scan, as assessed by the independent core laboratory at 30 days and at each subsequent timepoint for which data are available. A determination will be made from the data as to whether the occurrence was associated with an SAE or device malfunction.

10.8.15 *Secondary Procedures*: A descriptive analysis of secondary procedures for resolution of endoleak, limb occlusion, migration, aneurysm sac expansion, and/or a device defect will be done at 30 days and at each subsequent timepoint for which data are available.

11. ADMINISTRATIVE PROCEDURES

11.1 RESPONSIBILITIES

a) *Sponsor*: Endologix is responsible as the Sponsor is 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, and 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. Ongoing monitoring visits of the investigational center and hospital records will be conducted to verify the data recorded on the CRFs. Furthermore, the sponsor is responsible for ensuring obtaining proper regulatory approvals, and reporting to regulatory authorities per all applicable regulations.

b) *Medical Monitor*: The Medical Monitor is responsible for reviewing Serious Adverse Events to provide an independent evaluation of device relatedness, procedure relatedness, and type of SAE.

c) *Investigators*: Each investigator and study site is required to conduct the clinical investigation in accordance with the protocol, the signed investigator agreement, all applicable laws and Federal regulations and any conditions or restrictions imposed by the reviewing ethics committee. This includes compliance with requirements related to ethics committee or 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 patients under his or her care.

   Each investigator is responsible for supervising all procedures conducted under this protocol at his or her institution.

   Furthermore, the investigator is responsible for ensuring that data are completely, accurately, and promptly recorded on each patient's CRFs and related documents are available to verify the accuracy of the CRFs, and for ensuring the clinical monitor has access to all necessary records to ensure the integrity of the data.

d) *Core Lab and Independent Physician Assessor*: The Core Lab is responsible for the processing and assessment of all submitted CT scans preoperatively and imaging postoperatively and for reporting of results. The independent physician assessor is responsible for evaluating the Core Lab processed baseline CT scan to determine patient anatomical suitability for enrollment. In addition, for patients deemed anatomically eligible, the independent physician assessor is responsible for recommending the size of renal stent graft for each artery.

e) *Data Management Group*: The data management group is responsible for database development, validation, control and management of input from monitored CRFs, maintenance, and reporting for statistical analysis.

f) *Clinical Events Committee*: The independent clinical events committee will consist of at least three physician members and is responsible for review of events and complications documented on CRFs and in source documents by the study investigators during the trial, and for

categorization of these events according to the event definitions and primary endpoint criteria in this protocol. Reviews will occur on an ongoing basis throughout the trial as events are reported. The adjudicated events will be reviewed by the Data Safety Monitoring Board.

g) *Data Safety Monitoring Board (DSMB)*: Consistent with the U.S. FDA guidance document *Establishment and Operation of Clinical Trial Data Monitoring Committees*, Endologix has established a DSMB having pertinent expertise to review on a regular basis adjudicated safety data accumulated and trial progress (i.e., enrollment among groups; completeness and timeliness of data; protocol deviations; etc.) from its ongoing clinical investigations. The DSMB consists of five members, two of which must be physicians with specialty training in endovascular repair. One member of the DSMB is a statistician. The DSMB will be convened to review interim data accumulated during the trial and to render a recommendation for enrollment in the trial: continue; amend; suspend; or, terminate. All action items discussed during the meeting will be documented in the minutes, with agreed upon target completion dates for resolution. The final meeting minutes will be distributed to all DSMB members. Endologix will disclose the recommendations of the DSMB to the US FDA in its annual progress reports to the IDE.

h) *The Ventana Medical Advisory Board (VMAB):* Endologix has established the Ventana Medical Advisory Board. The purpose of the VMAB is to provide additional oversight of the Endologix Ventana Clinical Development Program to ensure appropriate monitoring, reporting and management of device related adverse events such that patient safety is optimized and investigators / investigative site health care professionals are provided direct access to necessary information, expert medical advice and timely clinical support. More specifically, the VMAB objectives are to i.) review ongoing clinical events related to device issues, ii.) assess the relatedness of such events to device or procedure, iii.) offer medical opinions on patient treatment to investigators and identify situations that may warrant early intervention, iv.) establish predictors of device related failures and v.) advise and review adjustments to protocol where warranted. The VMAB is distinct from the DSMB in membership and purpose and operates under the guidance provided by the Ventana Safety Surveillance Program document. The VMAB membership is constituted and governed by the VMAB Charter document.

i) *Biostatistician*: The independent biostatistician is responsible for the development and implementation of the data analysis plan, for conducting the data analysis, and for reporting it per the plan.

11.2 PATIENT PROTECTION

Written informed consent, in accordance with applicable international, federal, state and study center regulations, must be obtained from each patient, or from their legal representative, prior to the formal screening process as outlined in §8.6.1. The investigator will retain a copy of the signed informed consent document in each patient's record, and provide a copy to the patient. The Investigator will not request the written informed consent of any patient, and will not allow any patient to participate in the investigation before obtaining institutional review board (IRB) approval.

Attachment 2 provides an example of the consent form that may be used for the study. The example contains the minimal consent language content that must be incorporated into the Informed Consent

Document. Other elements or language may be added, or minor edits to the language may be made, but no substantial content may be deleted.

Prior to starting the study, the investigator will provide Endologix with a copy of the sample Informed Consent Document approved by the IRB with documented evidence that the IRB has approved the protocol.

j) Appropriate precautions will be taken to maintain confidentiality of patient medical records and personal information. However, the patient's name may be disclosed to the sponsor or designee, or any health authorities if they inspect the study records. A report of this study may be published; however the patient's identity will not be disclosed.

11.3 PROTOCOL CHANGES

The investigator should not implement any deviation from or changes to the protocol without approval by Endologix and prior review and documented approval from the governing ethics committee. The only exception to this is where necessary to eliminate immediate hazards to study patients, or when changes involve only administrative aspects (e.g., change in monitors, telephone numbers, etc.).

A report of withdrawal of IRB approval must be submitted to the Sponsor within five working days.

11.4 DOCUMENTATION

Clinical Investigator's Brochure: Prior to or at the time of training for the study, the investigator will be provided with a clinical investigator's brochure (CIB). This document serves as a briefing document to provide reports of prior investigations regarding nonclinical and clinical safety and effectiveness studies, as well as published and unpublished information for reference and review.

Source Documents: Source documents may include a patient's medical record, hospital charts, clinic charts, the investigator's study files, questionnaires, as well as the results of diagnostic tests such as laboratory tests, CT scans, angiograms, and the like.

The following information should be included in the patient's medical record:

- Patient's name and contact information;
- The study title, number/name, and sponsor name;
- The date the patient was enrolled into the study and the patient ID number;
- A statement that written informed consent was obtained;
- Date of procedure and implanted device information;
- Dates of all visits;
- Occurrence of any hospitalizations, any adverse events, and any medications prescribed;
- Date patient exited the study, and a notation as to whether the patient completed the study or discontinued, with the corresponding reason.

Case Report Form Completion: The investigator who signs the protocol signature page must personally approve the CRFs to ensure that the observations and findings are recorded correctly and completely. The CRFs are to be completed in a timely manner at the intervals specified by Endologix and this protocol.

All forms must be fully completed as instructed.. Guidance on proper form completion will be provided to each site for reference.

All CRFs will be reviewed and monitored for completeness and clarity. Queries for missing or unclear data will be made as necessary throughout the study.

Study Forms and Logs: Endologix will provide pre-printed forms to each study site for documentation of:

- Investigator and site training to the protocol (Training Form)
- Authorized study site personnel (Site Signature Log)
- Patient consent and screening (Screening Log)
- Monitoring visit tracking (Site Visit Log)
- Investigational Device Accountability (Investigational Device Accountability Log)

Document Retention: Study-related correspondence, patient records, consent forms, records of device implant, and associated documentation are to be maintained by the study site. Endologix requires that it be notified in writing if the investigator wishes to relinquish ownership of the data and information so that mutually agreed upon arrangements can be made for transfer of ownership to a qualified entity.

Publication: Endologix, as the sponsor of record, has a proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites, core laboratories, and Endologix. Authorship will be established prior to writing of the manuscript. No individual publications will be allowed prior to the completion of the final report for this study and as agreed in writing by Endologix.

11.5 MONITORING PLAN

Written procedures have been established by Endologix for monitoring clinical investigations, to assure the quality of the study and to assure that each person involved in the monitoring process carries out his or her duties. Standardized written procedures, sufficiently detailed to cover the general aspects of clinical investigations, will be used as a basic monitoring plan and will be supplemented by more specific or additional procedures, as required by the clinical investigation.

A pre-study monitoring visit or meeting will be conducted to ensure that the Investigator clearly understands and accepts the obligations incurred in undertaking the clinical investigation as set forth in relevant international standard, and that the facilities are acceptable. Periodic monitoring visits will be conducted with adequate frequency to ensure that the Investigator's obligations are being fulfilled and that the facilities continue to be acceptable. A study termination monitoring visit will be conducted at the completion of the clinical study to ensure that all data are properly documented and reported.

Site Termination: If a clinical monitor becomes aware that an Investigator is not complying with the signed Investigator's Agreement, the Investigational Plan, the requirements of applicable health authority regulations, or any conditions of approval imposed by the reviewing ethics committee/IRB or health authority, Endologix will immediately either secure compliance or terminate the Investigator's participation in the study. The final action will be taken with the goal of assuring the rights, safety and welfare of the patients.

Monitor Name and Address: Monitoring procedures will be performed under the direction of:

Michael Arbour Senior Manager, Clinical Affairs
11 Studebaker
Irvine, CA 92618
Tel: (949) 598-4667
Fax: (949) 598-4767
Email: marbour@endologix.com

Correspondence is to be forwarded to:

Endologix, Inc. Clinical Affairs Department
c/o Michael Arbour, Senior Manager
11 Studebaker
Irvine, CA 92618
Tel: (949) 598-4667
Fax: (949) 598-4767

11.6 REFERENCES

AbuRahma A, Campbell J, Stone PA, et al. The correlation of aortic neck length to early and late outcomes in endovascular repair patients. J Vasc Surg 2009;50:738-48.

Arko FA, Filis KA, Seidel SA, et al. How many patients with infrarenal aneurysms are candidates for endovascular repair? J Endovasc Ther 2004;11:33-40.

ASTM F1058:2002, Standard Specification for Wrought 40Cobalt-20Chromium-16Iron-15Nickel-7Molybdenum Alloy Wire and Strip for Surgical Implant Applications (UNS R30003 and UNS R30008).

Browne TF, Hartley D, Purchas S, et al. A fenestrated covered suprarenal aortic stent. Eur J Vasc Endovasc Surg 1999;18:445-9.

Carpenter JP, Baum RA, Barker CF, et al. Impact of exclusion criteria on patient selection for endovascular abdominal aortic aneurysm repair. J Vasc Surg 2001;34:1050-4.

Cochran W. The planning of observational studies of human populations. J Royal Statistical Society, Series A 1965;128:234-55.

Cochran W. The effectiveness of adjustment by subclassification in removing bias in observational studies. Biometrics 1968;24:205-13.

Fleiss, J. The statistical basis of meta-analysis. Statistical Methods in Medical Research 1993;2: 121-45.

Friedman L, Furberg C, and DeMets D. Fundamentals of Clinical Trials. 1985: Mosby Year Book, St. Louis.

Fulton JJ, Farber MA, Marston WA, et al. Endovascular stent-graft repair of pararenal and type IV thoracoabdominal aortic aneurysms with adjunctive visceral reconstruction. J Vasc Surg 2005;41:191-8.

Harrell F, Lee K, and Mark D. Multivariable prognostic models: issues in developing models, evaluating assumptions, and adequacy, and measuring and reducing errors. Statistics in Medicine 1996;15:361-87

Hoyert DL, Arias E, Smith B L, et al. Deaths: final data for 1999. Natl Vital Stat Rep 2001; 49(8):1-113.

Jeyabalan G, Park T, Rhee RY, et al. Comparison of modern open infrarenal and pararenal abdominal aortic aneurysm repair on early outcomes and renal dysfunction at one year. J Vasc Surg 2011;54:654-9.

ISO 14155:2011, Clinical Investigations of Medical Devices for Human Subjects: Good Clinical Practice

Leurs LJ, Kievit J, Dagnelie PC, et al. Influence of infrarenal neck length on outcome of endovascular abdominal aortic aneurysm repair. J Endovasc Ther 2006;13:640–8.

Little R and Rubin D. Statistical Analysis with Missing Data. 2002. John Wiley and Sons, New York.

Mehrotra D. and Railkar R. Minimum risk weights for comparing treatments in stratified binomial trials. Statistics in Medicine 2000;19:811-25.

Meinert C. Clinical Trials: Design, Conduct, and Analysis. 1986; Oxford University Press. New York, NY Park JH, Chung JW, Cho IW, et al. Fenestrated stent grafts for preserving visceral brnaches in the treatment of abdominal aortic aneurysms: preliminary results. J Vasc Interventional Radiology 1996;7:819-23.

Pocock S. Clinical Trials (A Practical Approach). 1983: John Wiley and Sons, Chichester.

Rosenbaum P and Rubin D. Reducing bias in observational studies using subclassification on the propensity score. J Am Statist Assoc 1984;79:516-524.

Rubin D. Multiple Imputation for Nonresponse in Surveys. 1987: John Wiley and Sons, New York.

Steele R and Torrie J. Principles and Procedures of Statistics. 1960. McGraw-Hill, New York.

Turnbull I, Criado FJ, Sanchez L, et al. Five year results for the Talent enhanced low profile system abdominal stent graft pivotal trial including early and long term safety and efficacy. J Vasc Surg 2010; 51:537-44.

U.S. Department of Health and Human Services, Guidance For Industry. E9 Statistical Principles for Clinical Trials, September 1998.

U.S. Department of Health and Human Services, Guidance For Industry. ICH E6, Good Clinical Practice: Consolidated Guidance, April 1996.

ATTACHMENT 1

Instructions for Use (IFUs)

ATTACHMENT 2

Informed Consent Form Template

ATTACHMENT 3

Template Case Report Forms

ATTACHMENT 4

Investigator Agreement Template