CLINICAL STUDY PROTOCOL
CP-0008 Rev. 11.6

REVISION DATE: APRIL 6, 2018

Prospective, Multicenter, Single Arm Safety and Effectiveness Study of Endovascular Abdominal Aortic Aneurysm Repair using the Nellix® System with Continued Access

EVAS I Study with Continued Access

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List of Attachments

1) **Instructions for Use (IFU)**
2) **Informed Consent Form (Template)**

Revision 02 Change Summary

Section (Page)	Change and Reason for the Change
All Pages	Changed all pages to protocol version from 01 to version 02, Date 03 July 2012 to 9 Dec 2012. Reason: Reflected revision date change in the header.
Table of Contents	Updated to reflect revision changes
1 (4)	Updated Investigator Signature page Reason: Modified first paragraph to reflect accordance with all applicable global laws.
2.1 (5)	Updated General Sponsor Contact Reason: to reflect change in Sponsor personnel.
3 (6) 5.1 (13)	Updated subject population Reason: to clarify the number of Roll-in subjects and up to 150 patients in the Intent to Treat Pivotal Cohort.
3 (6) 7.2 (18)	Updated Physician Training Reason: The training requirement has been changed to 3 required cases rather than 5 to be cleared for study enrollment.
4.1 (10)	Updated Objective: Added EndoVascular Aneurysm Sealing System Reason: To reflect updated product name
5.2 (13)	Inclusion Criteria has been updated: changed d. proximal non-aneurysmal aortic neck; length ≥ 10mm; lumen diameter 16 to 32mm; angle ≤60° to the aneurysm sac added f. Common Iliac artery lumen diameter between 8 and ≤35mm with blood lumen diameter with blood lumen diameter ≤35mm g. Ability to preserve at least one hypogastric artery Reason: to reflect Anatomic eligibility for the Nellix System per the instructions for use
6.2 (14)	Primary Effectiveness has been updated. Removed defined as migration resulting in serious adverse event or requiring secondary intervention through 12 months. Revised Secondary endovascular procedure for resolution for endoleak added (type I or type III) Reason: To clarify safety and effectiveness
6.3 (15)	Updated Additional Evaluations. Revised Secondary endovascular procedure within 30 days, at 6 months, and annually to 5 years for resolution of endoleak Type I and II. Reason: to identify the procedure and resolution of endoleak Type I and III
4.2 (11)	Updated Background to include ePTFE covered stent. Reason: To reflect the Instructions for Use
8.6 (23)	Updated Protocol Deviation Reason: to clearly define a protocol deviation
8.7.1 (24)	Updated Serious Adverse Event Definition Reason: For alignment with ISO 14155 definition.
8.7.3 (26)	Added reference to Social Security Death Index (SSD) and CDC National Death Index (NDI) to obtain patient death information. Reason: Added additional information for sites to acquire patient death information
(43)	Updated monitoring will be performed under the direction of Avi Sharma, Director, Clinical Affairs Reason: A new CRO will be contracted.
Attachment 2 (2)	Revised Informed Consent section 3. Up to 180 patients will be enrolled in the study overall. Reason: To reflect the change in the protocol.

Section (Page)	Change and Reason for the Change
Attachment 2 (3)	Revised Informed Consent section 4. The US sites will be conducted under an IDE, or Canada under an investigational test authorization.
Attachment 3	Formatting changed to DD/MMM/YY throughout all Case Report Forms Reason: To correct formatting
Attachment 3 (1)	Revised Screening and Baseline case report form inclusion criteria section 3. Patient aneurysm increase of 1.0cm. Reason: to reflect the IFU
Attachment 3 (1)	Revised Screening and Baseline case report form inclusion criteria to include in section 4. Most caudal renal artery to aortoiliac bifurcation length ≥ 70 mm Reason: to reflect the current IFU

Revision 03 changes

Note: minor punctuation or formatting changes are not included in this table.

Section (Page)	Change and Reason for the Change
All Pages	Changed all pages to protocol version from 02 to version 03, Date 09 Dec 2012 to 12 June 2013. Reason: Reflected revision date change in the header.
Table of Contents	Updated to reflect revision changes
1 (13)	'Global' changed to 'regional' Reason: PIs follow regional regulations. Protocol requirements will specify any non-regional requirements.
2 (21)	CEC and DSMB Name and Address added (Syntactx) Reason: CRO is now under contract with Endologix.
3 (22)	Regions of study populations added Reason: Clarification of enrollment sites by region.
3 (22) 3 (25)	Site enrollment maximum set to 10% Reason: To ensure a more equitable enrollment profile across sites
3(23) 7.2 (37)	Training section – changed from 3 roll-in per site to 1 roll-in. Grammatical changes. Reason: Reflect correct roll-in population as specified in Subject Population (page 10) and other sections.
3 (23) 5.3 (31)	Exclusion Criteria #3: Removed words 'enrollment or 30 day follow-up phase of' Reason: Subjects should not be involved in a competing study at any time frame, as the study population should be examining only the Nellix system as a treatment.

Section (Page)	Change and Reason for the Change
3 (24) 6.2 (32)	Primary Effectiveness Endpoint: "Endoleak type I > 30 days, and Endoleak III" changed to "Endoleak type I or Endoleak type III at 12 months " and additionally "Secondary endovascular procedure up to 12 months for resolution of Endoleak (Type I or Type III)" was added. Reason: The existence of an endoleak is, by itself, not necessarily an indication of a clinically significant leakage. Clinically, a failure of effectiveness related to endoleaks would be indicated by a re-intervention to re-exclude the aneurysm, or the existence of an endoleak sufficient to cause the aneurysm to expand. Both of those occurrences are considered failures by this endpoint. Type I or III Endoleaks at 12 months (regardless of intervention or effect) is included to conservatively allow for possible future corrective actions.
3 (24) 3(18) 10.8 (60)	Primary Effectiveness Endpoint: Added in 'device occlusion', and 'may be due to thrombus or other causes) to list of secondary procedure causes. Reason: Clarity, as requested by FDA (question 44a)
3 (24)	Primary Effectiveness Endpoint: Re-arrangement of metrics. Reason: Clarity (most of the metrics refer to secondary interventions for various device issues; these were compiled into a list).
3 (24)	Additional Evaluations: MAE Individual Components: Changed 'years 1 through 5' to 'annually to 5 years' Reason: Clarity (to match other metric descriptions in this section).
3 (24)	Additional Evaluations: Composite Major Adverse Events: added '30 days' to time frames of analysis. Reason: Error - should have been included (as in the other metrics in this section).
3 (24) 4.3 (28) 6.3 (33) 8.4 (39) 10.8 (60)	Additional Evaluations: Distal Blood Flow (ABI): Removed Reason: Per the recommendation of the study P.I., ABI (ankle brachial index) is a poor indicator of device performance. Due to the co-morbidities associated with this study population (peripheral artery disease), ABI can be permanently elevated in patients with calcified arteries, rendering ABI a poor tool for identifying future changes in blood flow. Peripheral blood flow, should of course, be examined as per physician standard of care. J Am Coll Cardiol. 2008 Apr 1;51(13):1292-8. doi: 10.1016/j.jacc.2007.11.064. doi: 10.2337/diacare.26.12.3333 *Diabetes Care December 2003 vol. 26 no. 12 3333-3341*
3 (24) 6.3 (33) 8.7.7 (46) 10.8 (60)	Additional Evaluations: Luminal Thrombus Requiring Intervention at each study timepoint: Metric and definition added Reason: Response to FDA's request concerning thrombus formation (question 46), thrombus has also been added as a separate metric for evaluation (in addition to being part of the effectiveness endpoint).
3 (25)	Statistical Considerations: Study Population: 1st paragraph changes Reason: Clarity to Intent to treat population definition, and to enrolled status.
3 (25)	Statistical Considerations: Study Population: Per Protocol population paragraph added. Reason: Clarify the Per Protocol population definition.
3 (25)	Statistical Considerations: Study Population: Completed Cases paragraph added. Reason: Clarify the Completed Cases population definition.
7 (34)	Study Materials: Single use or multiple use added to each component. Reason: Clarity (and Dispenser should have been specified multiple use).

Section (Page)	Change and Reason for the Change
7.2 (37)	Investigator Training item #2: added word 'approximately' to case number requirement Reason: Sub-investigator qualifications for implantation with regard to prior EVAR experience will be done on a case-by-case basis; however, 25 cases will be treated as a rough baseline.
7.3 (37)	Device accountability: added in 'prior to implantation' Reason: Clarity. Return of all device components can only occur if the device was not implanted.
8.1 (38) 11.2 (49)	Addition of 'independent physician review. Reason: Addition of more detail regarding patient approval process.
8.2 (38)	'global standards' changed to 'Good Clinical Practices' Reason: Clarity
8.3 (27)	Changed title of Section 8.3 to properly reflect subsequent content Reason: Error, and as noted in FDA question #49.
8.3 (27)	Removal of methodology for patient naming. Reason: Patient IDs will be automatically generated within the eDC system.
8.5.4 (40)	Addition of sentence "If, during the index procedure, the device is not implanted and/or there is conversion to open surgery, the patient will be followed until the 30 day follow-up" Reason: Clarification of follow-up process for patients that either do not receive the study device, or are converted to open surgery.
8.7.1 (46)	'…administered a product…' changed to '…enrolled in the trial…' Reason: Correction. AE reporting also applies to subjects who did not receive the product, but were enrolled.
8.7.2 (46) 8.7.3 (46)	Sections rewrite Reason: Consolidation. Many paragraphs in these two sections contained repetitious instructions. The adverse event reporting process is roughly the same regardless of the type of adverse event. AE reporting time requirements (from the site to Endologix), while mentioned, were scattered throughout text and difficult to access quickly. A table of "Adverse Events: required reporting timeframes" was generated to address this. Requirements for reporting and investigating a subject death were consolidated into one section. There were no substantive changes.
8.7.4 (46)	Removal of word 'endovascular' from section title Reason: Correction. Procedures discussed also refer to open repair.
8.7.4 (46)	Removal of fax information. Reason: reporting in this trial will be electronic via EDC.
8.7.6 (46)	Addition of Endologix reporting timeframes of UADEs. Removal of fax information Reason: Reporting will be done by the EDC system in this trial. Clarify Endologix response to such an event.
8.7.7 (46) 10.8 (60)	Revised definition for Clinically Significant Migration: Reason: Updated for consistency within the document.
8.7.7 (46)	Removal of definitions of various adverse events Reason: Consolidation. Definitions in the protocol will be limited to endpoints and device specific issues. All other clinical events will be defined by the independent CEC (Syntactx)

Section (Page)	Change and Reason for the Change
8.7.7 (46)	Revised Distal Ischemia Definition: Removed"…A reduction in ABI of 0.15 or more attributable to the index procedure and not related to natural progression of atherosclerotic disease is included in this definition. Reason: See change #17
8.7.7 (46) 10.8 (60)	Revised Migration definition: Reason: Defined per migration from the renal artery and removed intervention criteria to include all device migrations >5 mm.
8.7.7 (46)	Addition of device occlusion to secondary procedures. Reason: Treatment can also be open surgery. Obstruction and occlusion will cover any thrombus related events (FDA Question 44).
8.7.7 (46)	Removal of word 'endovascular' from Secondary Procedure definition Reason: See change#47
10.1 (53)	Removal of 'with imputation for missing data…" Reason: Removed for redundancy as this is explained in the next section.
10.1 (53)	Addition of 'or have expired prior to 12 months' Reason: Per FDA request (Question 47), provide further clarification on the Completed Cases analysis population.
10.1 (53)	Completed case (CC) changes; removal of one sentence, addition of another Reason: Clarity.
10.2 (53)	Addition 'prior to procedure' Reason: Clarity (this listing is for patients who never officially enrolled)
10.2 (53)	Change of '15 subjects' to '10% of study enrollment' (2 places in paragraph) Reason: Quantify the amount of total enrollment a given clinical site can contribute to the study.
10.2 (53)	Removal of sentence "In the control group, no subjects were…" Reason: Per FDA request (Question 51), there will be no control group comparator for this study.
10.2 (53)	Addition of paragraph beginning with "In addition to the above…" Reason: Per FDA request (Question 52), Tipping Point Analyses has been included.
10.5 (55)	Addition of sentence beginning "The estimates obtained…" Reason: Per FDA request (Question 53), provided additional clarification pertaining to heterogeneity of study sites.
10.6 (56)	For entire section: removal of word 'control'. Reason: Clarity. SVS open surgery group provides a historical OPC for this trial. The SVS group is not a direct control (i.e., patient level data) in this trial.
10.6 (41)	For entire section: change 'test group' to 'study population' Reason: Clarity. 'Test group' normally refers to one arm of a two arm trial. This trial is not designed as a two arm trial.
10.6.2 (56)	Changes to sentence beginning with 'The sample size of this trial…" Reason: Clarity. 'Test group' normally refers to one arm of a two arm trial. This trial is not designed as a two arm trial.
10.7.1 (58)	Addition of sentence beginning with "The hypothesis test will be…" Reason: Clarification of the significance level and for consistency within the document.
10.7.2 (58)	Revision of endpoint description Reason: Updated to reflect endpoint changes.

Section (Page)	Change and Reason for the Change
11.2.5 (48)	Added "An independent clinical safety review will examine all AEs and SAEs. MAEs will undergo adjudication by the CEC panel." Reason: Events that the CEC will review were clarified per FDA IDE response question #11.
11.5 (64)	Revised Study log maintenance description Reason: Updated to reflect current practices for study log maintenance.
Attachment 2 (2)	Added prior clinical studies information to informed consent Reason: This change was implemented per a request in FDA IDE Response question #13.
Attachment 2 (4)	Added information pertaining to follow-up of enrolled patients where the study device is not successfully implanted during the index procedure or patients where the device is explanted. Reason: Protocol CP-0008 Rev.03 was updated with a 30-day follow-up period for patients where the device is not successfully implanted, if the patient is converted to open surgery, or if the device is explanted with open surgical repair.
Attachment 2 (9)	Added US Clinical Trials.gov publishing requirement Reason: To inform patients that information on this study will be available on the internet.
Attachment 3 (All)	Paper CRFs were converted to electronic CRFs
Attachment 3 (5)	Revised from: "Most caudal renal artery to aorto-iliac bifurcation length >= 70 mm". To: "Most caudal renal artery to each hypogastric artery length ≥100mm" Reason: Updated to reflect current inclusion exclusion criteria per discrepancy noted in FDA IDE response question #14.
Attachment 3 (5)	Revised from: "Is there clinically significant infrarenal mural thrombus (>5mm thick over >60% circumference)" To:…(>5 mm thick over >50% circumference) Reason: Updated to reflect current inclusion exclusion criteria per discrepancy noted in FDA IDE response question #14.
Attachment 3 (17)	Removed: Nellix Extenders were removed from the CRFs Reason: Extenders are not planned to be used in this clinical study. This addresses FDA IDE response question #12

Revision 04 changes

Note: minor punctuation or formatting changes are not included in this table.

Section (Page)	Change and Reason for the Change
All Pages	Changed all pages to protocol version from 03 to version 04, Date 12 June 2013 to May 2014. Reason: Reflected revision date change in the header.
2 (13)	Added "…with conditions of the approval imposed by the reviewing Ethics Committee or Institutional Review Board….I agree to maintain adequate source documentation records throughout the clinical investigation and make them available as requested during monitioring visits. I agree to maintain the device accountability records and ensure that the investigational device is used solely by authorized users as specified by this protocol. I agree to ensure that the requirements for obtaining informed consent are met. Additionally, I agree to disclose financial interests in accordance with 21 CFR 54, and certify that such financial interests, if any, will not interfere with my responsibilities as an investigator or influence study outcomes under my supervision. Reason: These statements were added to the investigator signature page to centralize requirements from 21 CFR 812.43 (C) and ISO 14155 that were reflected across several study agreements.
3 (15)	Removal of Canada from the list of countries Reason: Canada no longer has active sites in this trial. No patients were enrolled at either site.
3 (15)	Change the site maximum enrollment from 10% to 15%. Reason: For consistency with prior EVAR trials.
3 (16)	Revised Inclusion criteria #4 for the maximum abdominal aortic aneurysm (AAA) sac diameter size from: "≥5.5cm or ≥4.5 cm which has increased by >1.0cm within the last year" to: "≥5.0cm, or ≥4.5 cm which has increased by ≥0.5cm within the last 6 months, or which exceeds 1.5 times the transverse dimension of an adjacent non-aneurysmal aortic segment". Reason: As recommended by the trial Physician Steering Committee, for alignment with SVS practice guideline recommendations and aneurysm dimensional inclusion criteria among most recently approved products/labeling, including Medtronic Endurant, Trivascular Ovation, Lombard Anaconda, and Endologix (PEVAR).
3 (16)	Revised Exclusion criteria#10 of section #3 of clinically significant mural thrombus from" Clinically significant infrarenal mural thrombus (>5mm thickness over >50% circumference)" to "Clinically significant mural thrombus within the proximal landing zone (minimum 10mm) of the infrarenal non-aneurysmal neck (>5mm thickness over >50% circumference)" Reason: Clarification of exclusion criterion. This revision clarifies that the mural thrombus exclusion applies to the infrarenal non-aneurysmal neck.
4.2 (20)	Added text beginning with "There are a number of qualifiers…" Reason: For clarification only.
5.1 (22)	Change the site maximum enrollment from 10% to 15% Reason: For consistency with prior EVAR trials.

Section (Page)	Change and Reason for the Change
5.2(22)	Revised Inclusion criteria #4 for the maximum abdominal aortic aneurysm (AAA) sac diameter size from: "≥5.5cm or ≥4.5 cm which has increased by >1.0cm within the last year" to: "≥5.0cm, or ≥4.5 cm which has increased by ≥0.5cm within the last 6 months, or which exceeds 1.5 times the transverse dimension of an adjacent non-aneurysmal aortic segment". Reason: As recommended by the trial Physician Steering Committee, for alignment with SVS practice guideline recommendations and aneurysm dimensional inclusion criteria among most recently approved products/labeling, including Medtronic Endurant, Trivascular Ovation, Lombard Anaconda, and Endologix (PEVAR).
5.3 (23)	Revised Exclusion criteria #10 of section 5.3 of clinically significant mural thrombus from" Clinically significant infrarenal mural thrombus (>5mm thickness over >50% circumference)" to "Clinically significant mural thrombus within the proximal landing zone (minimum 10mm) of the infrarenal non-aneurysmal neck (>5mm thickness over >50% circumference)" Reason: Clarification of exclusion criterion.
7.2 (28)	Revised review requirement for investigator training from" review of Investigator Brochure" to "review of prior clinical safety and effectiveness information". Reason: To reflect actual practice.
7.2 (28)	Added criteria for sub-Investigators who lead the implant procedures "For procedures led by a sub-investigator, the PI must be present to provide supervision of the case, unless the sub-Investigator has completed investigational device training and has received documented approval by Endologix." Reason: Clarification of possible sub-investigator qualifications. Some sub-investigators will receive the full PI/proctor training.
8.3 (30)	Added subject number allocation system "Subject numbers will be automatically assigned by the EDC system" Reason: Subject number allocation was inadvertently missed in the previous revision.
8.3 (30)	Clarified screening log maintenance "either on paper or electronically in the EDC" Reason: Screening log can be maintained by either method (paper or electronically).
8.5.2(30)	Clarified slice thickness criteria from "<3mm" to "<=3mm" Reason: Typographical error: CT Scan slice thickness equal to 3mm are acceptable.
8.5.4 (30)	Revised subject enrollment section to clarify screen failures. "If the device does not contact the patient, the patient will not be considered enrolled and the assigned study number will not be given to another patient and the patient is considered as a screen failure" Reason: Further clarified screen failures and patient numbers assignment in screen failures.
8.5.4 (31)	Revised conditions, when device is not implanted during index procedure. "If, during the index procedure, the device is introduced but is not implanted and/or there is conversion to open surgery, the patient will be followed until the 30 day follow-up." Reason: Further clarified situation when devices are not implanted during index procedure.
8.5.5 (32)	Removed site reference manual from instruction to complete, from "site reference manual" to "site initiation visit". Reason: The site personnel are trained during site initiation visit on how to enter data into eCRFs.

Section (Page)	Change and Reason for the Change
8.7.2 (35)	Added "If approval is obtained from the patient or a patient's authorized family member, the site should notify Endologix of the explant". Reason: Added requirement to include patient's authorization and to notify the sponsor once obtained.
8.7.7 (36)	Pulmonary related death was moved from page 35 Reason: Pulmonary related death was located in the wrong section.
8.7.7(36)	Removed definition for Migration from "death" section to "other definitions " section Reason: Editorial correction only.
8.7.7 (37)	Added "…and is still present at the 30 day CT as read by the Core Lab" to Procedural Technical Failure definition. Reason: Clarify definition of unresolved endoleak.
10.2 (41)	Removed "…and imputing the mean from all subjects with outcomes." Reason: Including this additional method is not relevant since the endpoint is dichotomous and not a continuous variable from which a mean can be calculated across patients.
10.5 (42)	Replaced Logisitic Regression using a univariate model of study site with … "extension of the Fisher's exact test (Fisher-Freeman-Halton)." Reason: This replacement is better suited for testing homogeneity across study sites.
10.5 (42)	Added "Both the safety and effectivness measures will employ weighted proportions as the basis for the statistical test." Reason: Changed for clarity, as the approach to weighing estimates of the proportions as described by the Method of Fleiss (1993) is the same for all endpoints.
10.6 (43)	Changed: "…greater…" to "…less…" Reason: This was a typographical error. The sentence was updated to reflect actual statistical test that shows significant heterogeneity when the p-value is less than 0.15.
10.6 (43)	Removed "Secondary Procedures" from the primary safety hypothesis Reason: This was inadvertently added to the primary safety hypothesis as secondary procedures are represented in the primary effectiveness analysis.
10.6.3 (44)	Updated equation: $W_k = \left(\frac{1}{n_k} p_k (1 - p_k) \right)^{-1}$ Reason: There was a typographical error in the previous version of this equation. This equation was intended to show that weight is equal to the inverse of the variance.
ICF (3)	Study Questions, #3: Changed to 'enroll up to 31 patients' Reason: to match up to maximum site enrollment
ICF (4)	Blood Pressure : removed descriptive text '… measured at your arms and ankles' Reason: protocol only specifies a normal blood pressure exam.

Section (Page)	Change and Reason for the Change
ICF (10)	Change "Endologix fenestrated device" to "Nellix system" Reason : Incorrect system title.

Revision 05 changes

Note: minor punctuation or formatting changes are not included in this table.

Section (Page)	Change and Reason for the Change
All Pages	Changed all pages to protocol version from 04 to version 05, Date Jun 2014 to Nov 2014. Reason: Reflected revision date change in the header.
Table of Contents	Updated to reflect revision changes
3 (16)	Updated protocol title, both short and long, to reflect the addition of Continued Access (as a separate cohort)
3 (16)	Clarified 'Study Devices' to include full name of device
3 (18)	Enrollment section changed to clarify the two trial phases: the Primary Investigation, and the Extended Investigation (Continued Access). Added the expected Extended Investigation enrollment and closure timeframe.
5.1 (23)	Changed title of section to 'Primary Investigation' for clarity.
5.2 (23)	New section added to explain details of the Extended Investigation. The section elucidates 1) the expected enrollment, 2) the expected time of enrollment, and 3) the sites that invited to participate.
8.7.2 (36)	Updated company clinical fax number
10.9 (49)	New section added to explain statistical treatment of the Continued Access cohort.

Revision 06 changes

Note: minor punctuation or formatting changes are not included in this table.

Section (Page)	Change and Reason for the Change
All Pages	Changed all pages to protocol version from 05 to version 06, Date Nov 2014 to Feb 2015. Reason: Reflected revision date change in the header.
Table of Contents	Updated to reflect revision changes
3 (17)	Updated Continued Access population size to 100 Reason: Reflected total population size for Continued Access
5 (24)	Updated Continued Access population size to 100 Reason: Reflected total population size for Continued Access

Revision 07 changes

Note: minor punctuation or formatting changes are not included in this table.

Section (Page)	Change and Reason for the Change
Title Page	Updated company address Reason: 2 Musick, Irvine, CA 92618 is location of new headquarters
All Pages	Changed all pages to protocol version from 06 to version 07, Date Feb 2015 to Apr 2015. Reason: Reflected revision date change in the header.
Table of Contents	Updated to reflect revision changes
2 (16)	Updated company address Reason: 2 Musick, Irvine, CA 92618 is location of new headquarters
3 (18)	Updated minimum proximal non-anuerysmal aortic neck lumen diameter from 16mm to 18mm and the minimum common iliac artery lumen diameter from 8mm to 9mm Reason: Corresponds with updated IFU. The original anatomical parameters in both the IFU and the earlier protocol versions allowed for the possible use of 8mm Nellix stent diameters. The Core Lab has already been using these more restrictive parameters to determine eligibility throughout the trial, as Nellix 8mm stents were never utilized or implanted during the study.
5 (25)	Updated minimum proximal non-anuerysmal aortic neck lumen diameter from 16mm to 18mm and the minimum common iliac artery lumen diameter from 8mm to 9mm Reason: Corresponds with updated IFU. The original anatomical parameters in both the IFU and the earlier protocol versions allowed for the possible use of 8mm Nellix stent diameters. The Core Lab has already been using these more restrictive parameters to determine eligibility throughout the trial, as Nellix 8mm stents were never utilized or implanted during the study.
11 (54)	Updated company address Reason: 2 Musick, Irvine, CA 92618 is location of new headquarters

Revision 08 changes (VERSION WAS NOT RELEASED)

Note: minor punctuation or formatting changes are not included in this table.

Section (Page)	Change and Reason for the Change
All Pages	Changed all pages to protocol version from 07 to version 08, Date May 2015 to Aug 2015. Reason: Reflected revision date change in the header.
3 (17)	Updated Continued Access population size to 270 Reason: Reflected total population size for Continued Access
5 (24)	Updated Continued Access population size to 270 Reason: Reflected total population size for Continued Access

Revision 08.1 changes

Note: minor punctuation or formatting changes are not included in this table.

Section (Page)	Change and Reason for the Change
All Pages	Changed all pages to protocol version from 08 to version 08.1, Date May 2015 to October 2015 Reason: Reflected revision date change in the header.
3 (18)	Updated Continued Access population size to 150 Reason: Reflected total population size for Continued Access
5 (25)	Updated Continued Access population size to 150 Reason: Reflected total population size for Continued Access

Revision 09 changes

Note: minor punctuation or formatting changes are not included in this table.

Section (Page)	Change and Reason for the Change
All Pages	Changed all pages to protocol version from 08.1 to version 09, Date October 2015 to April 2016 Reason: Reflected revision date change in the header.
3 (18)	Updated Continued Access population size to 250 Reason: Reflected total population size for Continued Access
5 (25)	Updated Continued Access population size to 250 Reason: Reflected total population size for Continued Access

Revision 10 changes (VERSION WAS NOT RELEASED)

Note: minor punctuation or formatting changes are not included in this table.

Section (Page)	Change and Reason for the Change
All Pages	Changed all pages to protocol version from 09 to version 10, Date April 2016 to June 2016 Reason: Reflected revision date change in the header.

Section (Page)	Change and Reason for the Change
2.1 (18)	Changed sponsor contact Reason: Updated based on current organizational structure.
3 (20)	Changed anatomical inclusion criteria of blood lumen diameter from ≤ 60 mm to ≤ 70 mm Reason: Expanded treatable blood lumen diameters in updated Instructions for Use (IFU).
5 (27)	Changed anatomical inclusion criteria of blood lumen diameter from ≤ 60 mm to ≤ 70 mm Reason: Expanded treatable blood lumen diameters in updated Instructions for Use (IFU).
7 (30)	Changed dispenser from multiple use to single use Reason: Disposable dispensers are now available to use.
7.1 (30)	Replaced "polyurethane bag (EndoBag) having a polyester reinforcement sleeve" with polyurethane EndoBag with welded seams and a lumen having an inner polyester (PET) sleeve is attached to the stent proximally and distally using polyethylene sutures Reason: Describes the changes to the the EndoBag, with the distal end now also attached to the stent.
7.1 (31)	Updated the name of the pressure monitor from Mirador Compass™ to Centurion™ Biomedical Compass™ Reason: Mirador Biomedical is now a subsidiary of Centurion Medical Products, Inc.
7.1 (32)	Replaced the picture of the console Reason: Console was updated from 4 ports to 3.
8.7 (40)	Added sentence: “These events must be reported if clinically significant.” Reason: To emphasize the importance of reporting any clinically significant AE.
11.6 (57)	Changed sponsor contact Reason: Updated based on current organizational structure.

Revision 10.1 changes

Note: minor punctuation or formatting changes are not included in this table.

Section (Page)	Change and Reason for the Change
All Pages	Changed all pages to protocol version from 09 to version 10.1, Date April 2016 to September 2016 Reason: Reflected revision date change in the header.
2.1 (18)	Changed sponsor contact Reason: Updated based on current organizational structure.
7 (30)	Changed dispenser from multiple use to single use Reason: Disposable dispensers are now available to use.
7.1 (30)	Replaced "polyurethane bag (EndoBag) having a polyester reinforcement sleeve" with polyurethane EndoBag with welded seams and a lumen having an inner polyester (PET) sleeve is attached to the stent proximally and distally using polyethylene sutures Reason: Describes the changes to the the EndoBag, with the distal end now also attached to the stent.
7.1 (31)	Updated the name of the pressure monitor from Mirador Compass™ to Centurion™ Biomedical Compass™ Reason: Mirador Biomedical is now a subsidiary of Centurion Medical Products, Inc.

Section (Page)	Change and Reason for the Change
7.1 (32)	Replaced the picture of the console Reason: Console was updated from 4 ports to 3.
8.7 (40)	Added sentence: "These events must be reported if clinically significant." Reason: To emphasize the importance of reporting any clinically significant AE.
11.6 (57)	Changed sponsor contact Reason: Updated based on current organizational structure.

Revision 11.1 changes (VERSION WAS NOT RELEASED)

Note: minor punctuation or formatting changes are not included in this table.

Section (Page)	Change and Reason for the Change
All Pages	Changed all pages to protocol version from 10.1 to version 11,0 Date September 2016 to May 2017 Reason: Reflected revision date change in the header.
3 (21)	Updated proximal non-anuerysmal aortic neck lumen diameter from 18mm-32mm to a neck diameter of 18mm-28mm and added: Distal iliac artery seal zone with length of ≥10mm, diameter range of 9 to 25mm and ratio of maximum aortic aneurysm diameter to maximum aortic blood lumen diameter <1.40. Reason: Corresponds with updated IFU.
5 (28)	Updated proximal non-anuerysmal aortic neck lumen diameter from 18mm-32mm to a neck diameter of 18mm-28mm and added: Distal iliac artery seal zone with length of ≥10mm, diameter range of 9 to 25mm and ratio of maximum aortic aneurysm diameter to maximum aortic blood lumen diameter <1.40. Reason: Corresponds with updated IFU.
8.4 (37)	Updated table to reflect enhanced follow-up visits Reason: Schedule of Measurements summarize assessments at each timepoint in the study, including enhanced follow-up. Added footnote to table to clarify population affected by the new follow-up recommendations.
8.5.6 (38)	Added section for enhanced post-operative follow-up visit. Reason: Enhanced follow-ups are recommended to monitor at-risk for migration, Type 1A endoleaks and/or AAA sac enlargement.

Revision 11.2 changes (VERSION WAS NOT RELEASED)

Note: minor punctuation or formatting changes are not included in this table.

Section (Page)	Change and Reason for the Change
All Pages	Changed all pages to protocol version from 11.1 to version 11,2 Date June 2017 to July Reason: Reflected revision date change in the header.
8.6 (38)	Added section of recommended secondary intervention treatment options. Reason: Provides options to Nellix Investigators to treat subjects who experience migration, Type 1A endoleaks and/or AAA sac enlargement.

Revision 11.3 changes

Note: minor punctuation or formatting changes are not included in this table.

Section (Page)	Change and Reason for the Change
All Pages	Changed all pages to protocol version from 11.2 to version 11.3 Date July 2017 to August Reason: Reflected revision date change in the header.
8.6.1 (40)	Updated table to reflected recommended secondary intervention treatment options for Type 1A Endoleaks Reason: When positioned correctly, with adequate seal, Onyx® can be used to treat Type 1A endoleaks.
Appendix	Added appendix of coils to be used with the Onyx Liquid Embolics System Reason: Reflects list of peripheral vascular coils available in the US, that allows physican to use preferred standard coil.

Revision 11.4 changes (VERSION WAS NOT RELEASED)

Note: minor punctuation or formatting changes are not included in this table.

Section (Page)	Change and Reason for the Change
All Pages	Changed all pages to protocol version from 11.3 to version 11.4 Date March, 2018. Reason: Reflected revision date change in the header.
2.1 (20)	Updated general sponsor contact Reason: Updated based on current organizational structure
4.3 (23)	Added enhanced follow-up reference Reason: To ensure that all types of visits are being addressed
8.5.6 (41)	Updated definition of an “at risk” subject, and added definition of an “inadequate procedure” Reason: New analysis based on current understanding of Nellix implantation best practices
8.6 (42)	Included physician training and proctoring for recommended secondary interventions. Also included “bailout procedure”, “Secondary ChEVAS”, “NiNA with Polymer, and NiNA without Polymer”, as alternative termoniology used. Reason: To provide a more clear understanding of secondary intervention treatment options

Revision 11.5 changes (VERSION WAS NOT RELEASED)

Note: minor punctuation or formatting changes are not included in this table.

Section (Page)	Change and Reason for the Change
All Pages	Changed all pages to protocol version from 11.4 to version 11.5 Date March, 2018. Reason: Reflected revision date change in the header.
8.5.6 (41)	Added punctuation to an inadequate procedure definition. Reason: Updated per FDA request

Revision 11.6 changes

Note: minor punctuation or formatting changes are not included in this table.

Section (Page)	Change and Reason for the Change
All Pages	Changed all pages to protocol version from 11.5 to version 11.6 Date April, 2018. Reason: Reflected revision date change in the header.
8.5.6 (39)	Added clarification to inadequate procedure definition Reason: Updated per FDA request

1. INVESTIGATOR SIGNATURE PAGE

I agree to conduct the study as detailed in the protocol and in accordance with conditions of the approval imposed by the reviewing Ethics Committee or Institutional Review Board, all applicable regional laws and regulations. I agree to maintain adequate source documentation records throughout the clinical investigation and make them available as requested during monitioring visits. I agree to maintain the device accountability records and ensure that the investigational device is used solely by authorized users as specified by this protocol. In addition, I agree to provide all the information requested in the electronic Case Report Forms presented to me by the Sponsor in a manner to assure completeness and accuracy.

I agree to ensure that the requirements for obtaining informed consent are met. I agree to actively enroll consecutive subjects into this study and confirm that I am not currently participating in any clinical investigations for similar types of medical devices that would inhibit my ability to participate fully in this study. Additionally, I agree to disclose financial interests in accordance with 21 CFR 54, and certify that such financial interests, if any, will not interfere with my responsibilities as an investigator or influence study outcomes under my supervision.

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, or its representatives, the Ethics Committee(s), the Institutional Review Board(s), or the core lab. Any such submission will indicate that the material is confidential.

Investigator Signature Date

Investigator Printed Name

2. STUDY CONTACT PERSONNEL

2.1. SPONSOR

GENERAL SPONSOR CONTACT
Meredith Huetter **VP, Clinical Affairs** **Endologix, Inc.** 2 Musick Irvine, CA 92618 Tel: (949) 598-4650 Fax: (949) 954-7601 Email: mhuetter@endologix.com

2.2. CONTACT NAMES AND TELEPHONE NUMBERS

CT SCAN CORE LABORATORY
Cleveland Clinic Peripheral Vascular Core Lab Contact: Paul Bishop, MSEE, RVT 3050 Science Park Drive (AC3-24) Beachwood, OH 44122 Tel : (216) 448-0539 Fax : (216) 448-0538 Email : bishopp@ccf.org

INDEPENDENT MEDICAL REVIEWER
Name on file with Sponsor

CLINICAL EVENTS COMMITTEE & DSMB
Syntactx Contact: Kenneth Ouriel, MD, MBA 7 World Trade Center, 46th Floor New York, New York 10007 Tel : (212) 266-0135 kouriel@syntactx.com

3. PROTOCOL SYNOPSIS

Title: Prospective, Multicenter, Single Arm Safety and Effectiveness Study of **E**ndo**V**ascular Abdominal Aortic **A**neurysm Repair Using the Nellix® **S**ystem with Continued Access

Short Title: **EVAS I Study with Continued Access**

Study Devices: Nellix EndoVascular Aneurysm Sealing System (Nellix System)

Study Sponsor: Endologix, Inc.

Objectives: To study the safety and effectiveness of the Nellix System for Endovascular Abdominal Aortic Aneurysm (AAA) repair. Procedures will be performed per the instructions for use, and per institutional protocols and standard of care for endovascular aneurysm repair. As such, this study will evaluate the safety and effectiveness of the device system among a wide range of physicians and in consecutively enrolled subjects to assess outcomes generalizability.

Study Design: Prospective, multicenter, single arm study with consecutive, eligible subject enrollment at each site. All subjects will undergo the Endovascular Aneurysm repair procedure with the Nellix System. Sites have been chosen with a suitable research infrastructure and physician experience in endovascular aneurysm repair to ensure adequate enrollment. Subjects will be followed procedurally to discharge, at 30 days (primary safety endpoint), six months, one year (primary effectiveness endpoint) and annually thereafter to five years (total follow-up commitment).

Investigators: Physicians (vascular surgeons or interventional cardiologists/radiologists as part of a multi-specialty team with vascular surgeons) at sites in the United States, and the European Union with well-established experience in open repair and endovascular aneurysm repair techniques (i.e., ≥25 cases in the prior year) may participate. Details of the procedural and device usage techniques are incorporated into the study protocol on the basis of prior experience with an earlier generation device system, and more recent device refinements that have been developed. In those cases where the investigator is an interventionalist, a vascular surgeon must be immediately available during the procedure to perform any necessary surgical intervention.

Subject Population: Patients diagnosed with an abdominal aortic or aortoiliac aneurysm who are considered candidates for endovascular repair and who meet the study eligibility criteria may be screened for enrollment in the study.

Enrollment: Up to 180 subjects will be enrolled at a maximum of 30 sites in the EU, and US in the Primary Investigation. This max number includes up to 30 Roll-in subjects and up to 150 patients in the Intent to Treat Pivotal Cohort. In the Primary Investigation, a single site may not enroll more than 15% of the total enrollment. At enrollment closure for the Primary Investigation, an Extended Investigation will commence at these sites to enroll up to 250 additional subjects under continued access provisions,

with the same patient selecton criteria and follow-up schedule and methods. Enrollment for this Extended Investigation cohort will occur during the Primary Investigation 1-year data collection. Enrollment closure of the Extended Investigation cohort will occur following completion of FDA review of the Pre-Market Approval (PMA) Application Submission.

Training: Initially, physicians will be directly supervised in each Nellix case by an Endologix trainer or Proctor. This training period will continue until a minimum of one case has been successfully completed and each investigator is cleared to proceed with Study enrollment without proctor supervision. This training requirement may be modified at the discretion of Endologix.

Inclusion Criteria:

1. Male or female at least 18 years old;
2. Informed consent understood and signed;
3. Patient agrees to all follow-up visits;
4. Have an infrarenal abdominal aortic aneurysm (AAA) with maximum sac diameter ≥5.0cm, or ≥ 4.5 cm which has increased by ≥0.5cm within the last 6 months., or which exceeds 1.5 times the transverse dimension of an adjacent non-aneurysmal aortic segment.
5. Anatomic eligibility for the Nellix System *per the instructions for use*:
    a. Adequate iliac/femoral access compatible with the required delivery systems (diameter ≥6 mm);
    b. Aneurysm blood lumen diameter ≤60mm;
    c. Proximal non-aneurysmal aortic neck: length ≥10mm; diameter 18 to 28mm; angle ≤60° to the aneurysm sac;
    d. Most caudal renal artery to each hypogastric artery length ≥100mm;
    e. Common iliac artery lumen diameter between 9 and 35mm;
    f. Distal iliac artery seal zone with length of ≥10mm and diameter range of 9 to 25mm;
    g. Ability to preserve at least one hypogastric artery.
    h. Ratio of maximum aortic aneurysm diameter to maximum aortic blood lumen diameter <1.40

Exclusion Criteria:

1. Life expectancy <2 years;
2. Psychiatric or other condition that may interfere with the study;
3. Participating in another clinical study
4. Known allergy to device any device component;
5. Coagulopathy or uncontrolled bleeding disorder;
6. Ruptured, leaking or mycotic aneurysm;
7. Serum creatinine level >2.0mg/dL;

8. CVA or MI within three months of enrollment/treatment;
9. Aneurysmal disease of the descending thoracic aorta;
10. Clinically significant mural thrombus within the proximal landing zone (minimum 10mm) of the infrarenal non-aneurysmal neck (>5mm thickness over >50% circumference);
11. Connective tissue diseases (e.g., Marfan Syndrome)
12. Unsuitable vascular anatomy;
13. Pregnant (females of childbearing potential only).

Primary Endpoints:

Safety: Major adverse events at 30 days.[†]

Effectiveness: Treatment Success at 1 year.

This is defined as procedural technical success and the absence of:

- Abdominal aortic aneurysm rupture;
- Conversion to open surgical repair;
- Endoleak Type I or Type III at 12 months
- Clinically significant migration[‡];
- Aneurysm enlargement; or
- Secondary endovascular procedure up to 12 months for resolution of:
    - Endoleak (Type I or Type III)
    - Device occlusion (may be due to thrombus or other causes)
    - Device migration
    - Abdominal aneurysm sac expansion
    - 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;

[†]Defined as all-cause death, bowel ischemia; myocardial infarction, paraplegia, renal failure, respiratory failure, stroke, and procedural blood loss >1,000cc. Refer to protocol §8.8.1.for detailed definitions.

[‡]Refer to protocol §8.8.1 for detailed definitions.

  - Incidence of transfusion;
  - Time in ICU;
  - Time to hospital discharge.
- Mortality (all-cause and aneurysm-related) within 30 days, at 6 months, and annually to 5 years;
- MAE Individual Components within 30 days, at 6 months, and annually to 5 years
- Composite Major Adverse Events at 30 days, 6 months, and annually to 5 years;
- Aneurysm rupture within 30 days, at 6 months, and annually to 5 years;
- Conversion to open repair within 30 days, at 6 months, and annually to 5 years;
- Adverse Events: All serious and non-serious events within 30 days, at 6 months, and annually to 5 years;
- Device performance (aneurysm sac diameter change from the first post-operative CT scan; device migration; incidence of endoleak) at 30 days, 6 months, and annually to 5 years;
- Renal function as assessed by estimated glomerular filtration rate (eGFR) pre-discharge and at 30 days, 6 months, and annually to 5 years;
- Device Patency and Integrity at 30 days, 6 months, and annually to 5 years;
- Luminal Thrombus Requiring Intervention at 30 days, 6 months, and annually to 5 years
- Secondary endovascular procedure or open surgery within 30 days, at 6 months, and annually to 5 years for resolution of endoleak (Type I or III), device 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 study procedure. Following EC/IRB approval of the study and the written informed consent form, patients will be screened for eligibility. Following informed consent, a physical exam and laboratory testing will be performed prior to the procedure. Subjects will be followed procedurally and to hospital discharge, and will then be followed at intervals: 30 days; 6 months; 1 year; and annually to 5 years.

Statistical Considerations: ***Study Population***: The Intent To Treat (ITT) population in this study consists of all subjects who are enrolled with an attempt to implant the Study Device. All roll-in subjects will be evaluated as a separate group. The subject is considered enrolled when the study device enters the access vessel.

The Per Protocol (PP) population in this study consists of all ITT subjects that have a device implanted and are alive when exiting the procedural room.

The Completed Cases (CC) population consists of all PP subjects that have completed 12 month follow-up visit.

Study Success, Safety: The primary safety analysis is ***Major Adverse Events (MAE)***, as previously defined. The primary endpoint is to show that the percentage of subjects with an MAE is statistically superior to that in the Society for Vascular Surgery (SVS) open surgical control group at 30 days (56%). 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 success.

Study Success, Effectiveness: The primary effectiveness analysis is ***Treatment Success***, as previously defined. The primary endpoint is to show that the proportion of subjects 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 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 Nellix® EndoVascular Aneurysm Sealing System for the endovascular repair of infrarenal abdominal aortic aneurysms (AAA). Procedures will be performed per the Nellix Instructions For Use (IFU) and per institutional protocols and standard of care for endovascular aneurysm repair. As such, this study will evaluate the safety and effectiveness of this device system among a wide range of physicians and in consecutively enrolled subjects to assess outcomes generalizability.

4.2. BACKGROUND

Mortality due to AAA rupture ranks 13th in the United States and 10th in Canada among men older than 65 years.* In addition, several authors have suggested an increase in the mortality rate due to rupture of AAA in the past decades in both the United Stated and England, with more than 14,000 and 7,259 deaths/year in those respective countries.†,‡ Despite being significant, such figures are probably underestimated, because many deaths resulting from ruptured aneurysms are not verified by autopsy, and are consequently not documented.§ Some researchers have reported that the overall lethality associated with rupture of AAA approaches 80%, including dead on arrival subjects or those who die before the diagnosis is made.**

*Semenciew R, Morrison H, Wigle D, et al. Recent trends in morbidity and mortality rates for abdominal aortic aneurysms. Rev Canadien Santé Publique 1992;83:274-6.

†Lelienfeld DE, Gurdenson PD, Sprafka JM, et al. Epidemiology of aortic aneurysms: Mortality trends in the United States 1951-1981**.** Atherosclerosis 1987;**7**:637-43.

‡Fowkes FRG, Macintyre CCA, Rucjerley CV. Increasing incidence of aortic aneurysms in England and Wales. Brit Med J 1989;298:33-5.

§Quil DS, Colgan MP, Summer DS. Ultrasonic screening for the detection of abdominal aortic aneurysms. Surg Clin North Am 1989;69:713-20.

**Bengtsson H, Bergqvist D. Ruptured abdominal aortic aneurysm: a population-based study. J Vasc Surg 1993; 18:74-80.

AAA is defined clinically as a focal dilatation of the aorta causing a diameter increase of >50% of the expected normal diameter.[*] Although any artery may develop an aneurysm, they are most commonly observed in the infrarenal abdominal aorta, thoracic aorta, popliteal artery and common iliac artery.

The principal risks related to aneurysms are rupture and thrombus migration. Aneurysms slowly and continually increase in size leading to the aneurysm rupture. The larger an aneurysm becomes, the likelihood of eventual rupture increases. The natural history of aortic aneurysms is to enlarge and rupture. Other potential complications of the aneurysm include compression of adjacent organs which may result in aortoenteric fistula, or aortocaval fistula. If the thrombus embolizes and flows down the blood stream, this can induce acute or chronic arterial obliteration of the lower limbs.

The risk of rupture is weighed against the risk of perioperative morbidity. The United Kingdom Small Aneurysm trial (UKSAT) reported 103 aneurysm ruptures in 2,257 subjects over a period of seven years, with an annual rupture rate of 2.2%.[†] The decision to treat a patient that presents with an asymptomatic aneurysm is primarily dependent upon the size of the aneurysm. Current Society for Vascular Surgery (SVS) practice guidelines recommend surveillance for most subjects with a fusiform AAA in the range of 4.0 to 5.4cm in maximum diameter; therefore, surgical repair of abdominal aneurysms of 5.5 cm or greater in diameter is recommended in healthy subjects, as is repair of saccular aneurysms. There are a number of qualifiers within the SVS guidelines that recommend AAA repair at 5.0cm, such as rapidly expanding aneurysms, and women.

It is estimated that approximately 25% to 40% of infrarenal AAA are not suitable for endovascular aneurysm repair (EVAR) due to unfavorable proximal neck anatomy (e.g., highly angulated, dilated, short, or encroaching on or involving the renal arteries.[‡,§] In most studies of endovascular AAA repair, the infrarenal non-aneurysmal neck length and angulation to the aneurysm sac requirements are ≥15mm and ≤60°, respectively; shorter lengths or greater angulation have been reported to increase the risk of migration and type 1A endoleak and associated need for intervention.[**,††]

When selecting the specific stent graft to be used for EVAR, the characteristics of the graft must be considered in light of the patient's anatomic and physiologic characteristics. Endovascular devices vary in the type of stent design. For example, most of the currently available devices seal aneurysm by proximal and distal fixation of the stent graft by either active fixation (anchoring pins) or oversizing the stent diameter for increased radial force thereby achieving seal and excluding the aneurysm sac

[*]Hallett JW Jr. Diseases of the aorta and its branches – aneurysms. Merck Manual, Online Medical Manual (2008). Retrieved on 19March2010 from http://www.merck.com/mmpe/sec07/ch079/ch079b.html.

[†]Mortality results for randomized controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms Lancet 1998; 352:1649-55.

[‡]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.

[§]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.

[**]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.

[††]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.

lumen. Greater than 25% of subjects develop an endoleak (mostly type II endoleaks due to back-bleeding of lumbar or visceral arteries within the aneurysm sac) within the first two years following endoluminal stent-graft repair,[*] and approximately 15-20% of the endoleaks persist at five years.[8] Endoleaks may lead to sac enlargement and migration and may require reintervention, using either catheter-based techniques or conversion to open repair. These secondary procedures increase the risk to the patient and increase the cost of treatment.[†] Accordingly, EVAR subjects are routinely monitored annually by contrast-enhanced CT scan after treatment contributing further to treatment costs and increasing patient exposure to nephrotoxic contrast agents and radiation. Recent reports suggest contrast nephrotoxicity affects 7 to 12% of subjects after CT angiography.[‡]

The Nellix System was designed to withstand the migration and lateral displacement forces acting on endografts, while at the same time excluding the aneurysm sac lumen and minimizing endoleaks of any kind. The system is comprised of two independent flow channels, one to each iliac artery. Each flow channel consists of a balloon-expanded ePTFE covered stent surrounded by a Polymer-filled EndoBag which fills the blood lumen within the aorta, thus providing positional stability of the endograft and sealing the aneurysm completely from side-branch flow.[§] A clinical trial has been performed to assess the safety and effectiveness of the first generation Nellix system for endovascular AAA repair and results serve as the basis for CE Mark approval (October 2012); initial results to one year have been reported.[**] Results of this trial demonstrate the versatility of the Nellix System in treating a variety of AAA anatomies, including those that have common iliac artery involvement bilaterally.

Continued clinical evaluation of the Nellix System in a broader group of institutions and physicians is therefore appropriate to assess the safety and effectiveness of the device for AAA repair and the generalizability of the approach.

4.3. STUDY DESIGN

This is a multicenter, prospective, single arm clinical study. Subjects with infrarenal AAA who are suitable candidates for endovascular repair using the Nellix System, based on protocol Inclusion/Exclusion criteria, will be considered for enrollment.

After this protocol and the patient informed consent form are reviewed and approved by the local Ethics Committee/Institutional Review Board (EC/IRB), patients having infrarenal AAA 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 Principal Investigator (PI) and site personnel. Agreement to participate and to attend all follow-up visits

[*] Stavropoulos SW and Charagundla SR. Imaging techniques for detection and management of endoleaks after endovascular aortic aneurysm repair. Radiology 2007; 243(3):641-55.

[†] Vogel TR, Symons RG, Flum DR. Longitudinal outcomes after endovascular repair of abdominal aortic aneurysms. J Vasc Endovasc Surg 2008;47(2):264-9.

[‡] Chaer RA, Gushchin A, Rhee R, et al. Duplex ultrasound as the sole long-term surveillance method post-endovascular aneurysm repair: a safe alternative for stable aneurysms. J Vasc Surg 2009; 49:845-9.

[§] Donayre CE, Zarins CK, Krievins DK, et al. Initial clinical experience with a sac anchoring endoprosthesis for abdominal aortic aneurysm repair. J Vasc Surg 2011;53:574-82.

[**] Krievins DK, Holden A, Savlovskis J, et al. EVAR using the Nellix sac anchoring endoprosthesis: treatment of favorable and adverse anatomy. Eur J Vasc Endovasc Surg 2011;42:38-46.

will be documented with the patient's signature on the informed consent form, with appropriate signatures of the site PI and an impartial witness.

After providing written informed consent, screening and eligibility determinations will be performed by the site, Core Lab, Independent Anatomical Evaluation and Endologix. Subjects 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 PI and by an independent core laboratory and will undergo independent medical evaluation. Other tests include a physical examination, review of medical history for exclusionary conditions, and selected blood laboratory analyses. Endologix will notify, in writing, each potential patients final eligibility status before a case may be scheduled.

Following discharge from the hospital, the first follow-up visit will be made at 30 days (±2 weeks). A CT scan will be performed to assess aneurysm morphology and device integrity and patency, as well as the status of the implanted devices. Subsequent follow-up visits will be made at six months, one year, and annually to five years per institutional standard of care for subjects with endovascular stent grafts. Enhanced post-operative follow-up visits are discussed in protocol §8.5.6. Continued subject follow-up beyond five years is outside of the scope of this study. Nonetheless, all subjects should be monitored and evaluated per the institutional standards of care for patients with an implanted endovascular stent graft.

5. STUDY POPULATION

5.1. PRIMARY INVESTIGATION

Up to 30 sites in the EU, Canada, and the United States will enroll up to 180 subjects including 30 Roll-in subjects and up to 150 patients in the Intention to Treat Pivotal Cohort for endpoint analysis. Total enrollment at a single site is restricted to 15% of the Pivotal Cohort. Following investigator training, each PI will commence patient screening and enrollment under approval per applicable national and local clinical trial requirements* and complete a minimum of one (1) successful Nellix case (Roll-in) in their training phase. This training period may be modified at the discretion of Endologix. Physicians will be directly supervised in each case by designated Endologix staff.

Pivotal Cohort: Up to 150 subjects will be enrolled at a maximum of 30 sites in the US and the EU. This includes the statistically justified sample size of 132 plus an allowance for deviations from assumptions.

Roll-In Cohort: One (1) roll-in subject may be enrolled per site, therefore a maximum of 30 enrolled in the study, to allow for Investigator(s) to receive additional training on the Nellix System. Any roll-in subjects will be screened, consented, treated and followed identically to the main study cohort. However, the roll-in cohort of this study will be evaluated separately.

* Commercially approved clinical trial requirements in the EU (CE Mark), IDE approval in the US, and ITA approval in CA

5.2. EXTENDED INVESTIGATION

Sites that participated in the Primary Investigation will be invited to participate in an Extended Investigation after enrollment closure of the primary investigation. This Extended Investigation will permit study site continued access to the Nellix System through the Primary Investigation's completion of the primary safety and effectiveness endpoint, and FDA review of the premarket approval (PMA) Submission. It is estimated that this Extended Investigation (Continued Access) phase will enroll an additional 150 patients.

Continued Access Cohort: Up to 250 patients will be enrolled into the Extended Investigation based on an enrollment rate of 0.5 patients per site per month and an estimated 20 months from the close of enrollment in the Primary Investigation. Enrollment in Extended Investigation (continued access) phase will be limited to the 27 US sites only as the Nellix System is commercially available to the three participating European sites.

5.3. INCLUSION CRITERIA

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

1. Male or female at least 18 years old;
2. Informed consent form understood and signed and patient agrees to all follow-up visits;
3. Abdominal aortic aneurysm with sac diameter ≥5.0cm, or ≥4.5cm which has increased by ≥0.5cm within the last 6 months, or or which exceeds 1.5 times the transverse dimension of an adjacent non-aneurysmal aortic segment.
4. Anatomically eligible for the Nellix System (per Instructions For Use):
    a. Adequate iliac/femoral access compatible with the required delivery systems (diameter ≥6 mm);
    b. Aneurysm blood lumen diameter ≤60mm;
    c. Proximal non-aneurysmal aortic neck:
        i. length ≥10mm;
        ii. diameter 18 to 28mm;
        iii. angle ≤60° to the aneurysm sac;
    d. Most caudal renal artery to each hypogastric artery length ≥100mm;
    e. Common iliac artery lumen diameter between 9 and 35mm;
    f. Distal iliac artery seal zone with length of ≥10mm and diameter range of 9 to 25mm;
    g. Ability to preserve at least one hypogastric artery.
    h. Ratio of maximum aortic aneurysm diameter to maximum aortic blood lumen diameter <1.40

5.4. EXCLUSION CRITERIA

A patient who meets ***none of the following*** criteria potentially ***may be included*** in the study:

1. Life expectancy <2 years as judged by the Investigator;
2. Psychiatric or other condition that may interfere with the study;
3. Participating in another clinical study;
4. Known allergy or contraindication to any device material;
5. Coagulopathy or uncontrolled bleeding disorder;
6. Ruptured, leaking or mycotic aneurysm;
7. Serum creatinine (S-Cr) level >2.0 mg/dL;†
8. CVA or MI within three months of enrollment/treatment;
9. Aneurysmal disease of the descending thoracic aorta;
10. Clinically significant mural thrombus within the proximal landing zone (minimum 10mm) of the infrarenal non-aneurysmal neck (>5mm thickness over >50% circumference);
11. Connective tissue diseases (e.g., Marfan Syndrome);
12. Unsuitable vascular anatomy that may interfere with device introduction or deployment;
13. Pregnant (female of childbearing potential only).

6. RESPONSE MEASURES

6.1. PRIMARY SAFETY

The safety endpoint is defined as the incidence of Major Adverse Events (MAE) at 30 days, defined as the composite of the following. Event definitions are provided in §8.8.7

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

Refer to §10.6 for primary safety endpoint analysis details.

†This criterion does not apply to patients on dialysis prior to study screening/enrollment.

6.2. PRIMARY 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 infrarenal AAA as follows. Event and related definitions are provided in §8.8.7.

Treatment Success: Procedural technical success [¥] and absence of:

- Abdominal aortic aneurysm rupture;
- Conversion to open surgical repair;
- Endoleak Type I or III at 12 months;
- Clinically significant migration[‡];
- Aneurysm enlargement; or
- Secondary endovascular procedure up to 12 months for resolution of
    - Endoleak (Type I or Type III)
    - Device obstruction or occlusion
    - Device migration
    - Abdominal aneurysm sac expansion
    - Device defect.[‡]

Refer to §10.7 for primary effectiveness endpoint analysis details.

[¥] Procedural technical success is deployment of the Nellix System in the planned location and without unintentional coverage of both internal iliac arteries or any visceral aortic branches and with the removal of the delivery system.

[‡]Refer to protocol §8.8.1 for detailed definitions.

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 6 months, and annually to 5 years;
- **MAE Individual Components** within 30 days, at 6 months, and annually to 5 years;
- **Composite MAEs** after 30 days, at 6 months, and annually to 5 years;
- **Aneurysm Rupture** within 30 days, at 6 months, and annually to 5 years;
- **Conversion to Open Surgical Repair** within 30 days, at 6 months, and annually to 5 years;
- **Adverse Events** (serious and non-serious) within 30 days, at 6 months, and annually to 5 years;
- **Device Performance** (aneurysm sac diameter change from the first post-operative visit; device migration; clinically significant device migration, incidence of endoleak) at 30 days, 6 months, and annually to 5 years;
- **Renal Function** pre-discharge and at 30 days, 6 months, and annually to 5 years, as assessed by the estimated glomerular filtration rate (eGFR) and changes over time;
- **Device Patency and Integrity** within 30 days, at 6 months, and annually to 5 years, 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 device failure
- **Luminal Thrombus Requiring Intervention** within 30 days, at 6 months, and annually to 5 years;
- **Secondary Procedure** within 30 days, at 6 months, and annually to 5 years for resolution of endoleak, device occlusion, migration, aneurysm sac expansion and/or a device defect.

[‡]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.

7. STUDY MATERIALS

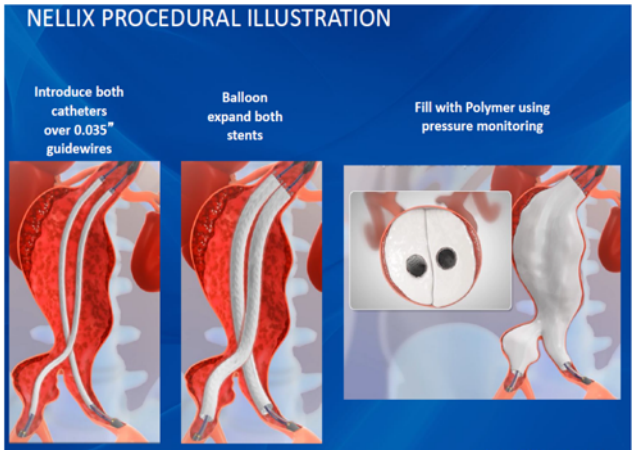
The Nellix System is comprised of four components as further described below:

1. Nellix Catheters (single use);
2. Nellix Accessory kit (single use);
3. Nellix Dispenser (single-use);
4. Nellix Polymer (single-use).

7.1. DEVICE DESCRIPTION

Implanted Devices. The Nellix implant consists of two devices, each advanced from the respective femoral artery via a catheter-based delivery system over a standard .035" guidewire. Each implanted device has the following main components: an expanded polytetrafluouroethylene (ePTFE) covered balloon expandable cobalt chromium alloy stent surrounded by a polyurethane EndoBag with welded seams and a lumen having an inner polyester (PET) sleeve is attached to the stent proximally and distally using polyethylene sutures, and a biostable Polymer formulation which is introduced through the catheter system to the EndoBag and cures in situ.

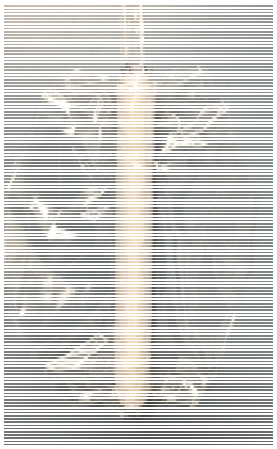
An illustration of the implant procedure is shown below. Images of the stent (with and without ePTFE graft), EndoBag, and the final implant in a silicone model are shown subsequently.



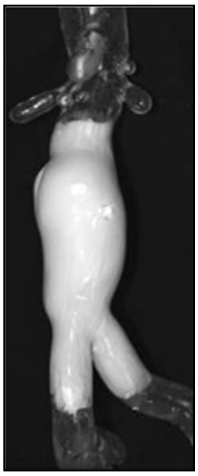
Stent

ePTFE Covered Stent

Stent



EndoBag



Final Implant

The mechanism of action is as follows. The ePTFE covered stents form lumens through which blood flows to the distal limbs and vasculature. The EndoBags with cured polymer exclude the aneurysm from blood flow, preventing aneurysm pressurization and rupture. This seals the entire anatomy from the infrarenal segment to the origin of the hypogastric arteries.

Delivery Systems. The 17Fr profile (OD) delivery systems are sterile, single use, catheter-based systems used to deploy the stents with EndoBags and are compatible with standard 0.035-inch guidewires. All delivery systems are of the same design regardless of stent/EndoBag model.

Three other single use components complete the Nellix System:

- Sterile Polymer dual chamber cartridges requiring storage at or below -20°C until use. Immediately prior to use (1-2 hours), the required Polymer cartridge(s) are thawed per the Instructions For Use (IFU).
    - Sterile accessory kit including a console with dual sets of tubing and quick connects for simultaneous attachment to two delivery catheters; two mixers, and a Centurion™ Biomedical Compass™.[†] The mixer attaches to the end of the Polymer cartridge and mixes the two chamber solutions during transfer into the EndoBags. A second mixer is provided as a back-up if needed.
- Polymer dispenser

The pre-operative high resolution, contrast enhanced CT scan serves to determine anatomical measures for subject eligibility and device initial sizing determinations. Arteriography with the aid of a marker

[†]The pressure monitoring device is marketed by Mirador Biomedical, a subsidiary of Centurion Medical Products, Inc. (Williamston, MI, USA) and is CE Marked through LNE G-MED.

catheter bilaterally serves to verify the specific device length needed on each side to ensure full coverage of the Nellix device from the infrarenal segment to the supra-hypogastric segments.

After selected delivery system is introduced through femoral arteriotomy under fluoroscopic guidance, each is advanced and positioned across the aneurysm sac at the desired location to place the stents below the most caudal renal artery and aligned at their proximal edge. The outer sheath of each delivery system is retracted to expose each constrained stent/EndoBag. (Note: A tether wire attaches each EndoBag to the catheter. The catheter can be removed only after disengaging the tether wire. This is a safety mechanism designed to hold the implant in place during deployment.)

At this time, the console is attached to both delivery systems using the mating, color-coded quick connects as depicted in the image below. White connectors denote the EndoBag evacuation and Polymer fill line; black connectors denote the stent balloon expansion line; luer connectors denote the angiographic media injection line (exiting the ports in the delivery system tip). The .035" guidewire lumens are on the outermost ends of the delivery catheter handles.

EndoBag evacuation, balloon expansion, Polymer introduction, and angiographic media injection are all performed through the console:

- A vacuum is applied via console port 1 with the switch in the 'open' position to simultaneously evacuate air from both EndoBags. After evacuation, the switch is placed in the 'closed' position.
- An inflation device is attached to control console port 2 to simultaneously balloon expand both ePTFE covered stents with contrast enhanced saline per the IFU. The stents expand from each end toward the center. The balloons are then simultaneously deflated per standard technique.
- The EndoBags are then filled by dispensing Polymer through console port 3 with the pressure transducer placed between the mixer and the port 3 luer. Polymer filling of the EndoBags occurs simultaneously, and is to continue until the pressure transducer displays a reading of 180mmHg. In the case of a patient with systolic blood pressure exceeding 180mmHg, Polymer filling continues to a pressure that is 20mmHg above the patient's systolic pressure. Once Polymer is completely injected into the EndoBags, the physician will allow the polymer to cure for approximately 3 to 5

minutes. Polymer curing is visually observable through the window on console port 3, which will change in color from red to white when cured.

A final angiographic run is done to confirm the complete seal of the aneurysm sac and absence of endoleaks. If deemed appropriate by the physician, a secondary fill may be performed to add additional Polymer to each EndoBag independently. The delivery systems are then detached from the implant by releasing the tether wires, and are removed from the patient and discarded per hospital standard practice.

7.2. INVESTIGATOR TRAINING AND EXPERIENCE

Investigators will be directly supervised in each case by an Endologix trainer or a certified Proctor until a minimum of one Nellix case have been successfully completed. One Principal Investigator (PI) at each participating site will be responsible for supervision of study conduct. He/she and any authorized sub-investigator must satisfy the following criteria prior to the enrollment of their first patient.

1. Complete review of prior clinical safety and effectiveness information regarding the earlier generation device, as well as design qualification testing regarding the Nellix System under study, and the scientific literature review.
2. Have prior training and experience in the open surgical or endovascular repair of AAA (approximately ≥25 cases as an institutional team, in the prior year).
3. Undergo didactic training on the device anatomy and design, Instructions for Use (IFU) including patient selection criteria, contraindications, warnings, precautions, and proper device use, and troubleshooting methods.
4. Practice using the Nellix System in a simulated use bench top model. Completion of each criterion will be documented for each PI and site *prior* to performance of the first clinical procedure at a given site under this protocol. Sub-Investigators will also be required to meet training requirements. This may be completed at a later date per Endologix discretion.

For procedures lead by a sub-investigator, the PI is expected to be present to provide proper supervision of the case, unless the sub-Investigator has been through investigational device training and approval by Endologix.

Roll-In Subjects:
Once the study formally initiates one (1) roll-in subject per site may be enrolled to allow for Investigator(s) to receive additional training on the Nellix System. This requirement may be waived at the discretion of Endologix for sites that have prior experience with the Nellix System. Any roll-in subjects will be screened, consented, treated and followed identically to the main study cohort. However, the roll-in cohort of this study will be evaluated as a separate feasibility group.

7.3. DEVICE ACCOUNTABILITY

Usage of the Nellix System will be documented in the electronic Case Report Forms (eCRF) and within an Investigational Device Accountability Log.

In the case of a device malfunction prior to implantation, the information will be noted in the eCRFs and all device components must be returned to Endologix. Should the device be removed from the body, the device should be returned to Endologix for evaluation per the IFU. Usage of the devices will be documented in the eCRFs and on the site's inventory log.

7.4. PATIENT AND DEVICE PREPARATION

All procedures must be performed in an operating room, or in an endovascular suite having full imaging capabilities, vascular surgery and anesthesia services. The PI will refer to institutional protocols relating to anesthesia and monitoring of vital signs. The appropriate devices will be selected in accordance with the patient eligibility determination. The devices will be prepared and handled in accordance with the IFU, which is provided in *Attachment 1*.[†] Other ancillary devices will be selected by the physician per institutional standards.

8. STUDY METHODS

8.1. GENERAL ENTRY PROCEDURES

Prospective subjects as defined by the criteria in §5.2 will be considered for entry into this study.

All site personnel involved in patient screening and data collection procedures will be trained on this protocol and the electronic remote data capture (eDC) system. Following patient consent, inclusion/exclusion criteria information will be entered into the eDC system. This action will notify Endologix that a patient has been consented and is being considered for enrollment. In parallel, the pre-operative CT scan will be uploaded to Core Lab by the site. The Core Lab will subsequently provide the anatomical measurements for confirming eligibility. Endologix will then facilitate an independent clinician review of anatomical and medical information for final sign off. Sites will be notified of individual study subject eligibility via the EDC system.

8.2. INFORMED CONSENT

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

The PI must not request the written informed consent of any patient, and must not allow any potential patient to participate in the investigation before obtaining governing EC/IRB approval.

Attachment 2 provides a template of the consent form that may be used. The sample 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 PI or by the EC/IRB, but substantial content may not be deleted.

[†]Ancillary devices recommended for use during the procedure are listed in the IFU.

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

8.3. SUBJECT IDENTIFICATION

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

Subject numbers will be automatically assigned by the EDC system.

A Screening Log will be maintained by the site, either on paper or electronically in the EDC, to document each subject who undergoes the screening process and the 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 Mo.** ± 14 days	**6 Mo.** ± 30 days	**Every 6 months (Enhanced Follow-up)[£]**	**1 Yr.** ± 60 days	**2 to 5 Yrs.** ± 90 days
Inclusion/Exclusion	x							
Demographics/Medical History	x							
Physical Exam[†]	x		x	x	x	x	x	x
Blood Labs[‡]	x		x	x	x		x	x
Contrast-enhanced CT scan[¥]	x			x	x	x	x	x
Procedural Information		x						
Adverse Events		x	x	x	x	x	x	x

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

[‡]Blood labs include serum creatinine and hemoglobin.

[¥]The baseline high resolution, contrast-enhanced CT scan performed within the prior three months will be performed to determine anatomical eligibility.

[£]Subjects who experience migration, AAA sac enlargement and/or a Type 1A or 1B endoleak or subjects who are considered at risk are recommended to be followed every 6 months.

8.5. STUDY PROCEDURES AND EVALUATIONS

8.5.1. 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 entered in the eCRF for verification by the Sponsor prior to enrollment eligibility determination. Please see attachments of the informed consent template and the study eCRFs.

8.5.2. CT Scan Protocol

Patient enrollment into this study is based on the site evaluation of patient conformance with the protocol-specified selection criteria (§5.2), including anatomical requirements for the device based on the high resolution (slice thickness *minimum* ≤3mm; axial, coronary, sagittal views), contrast-enhanced CT scans. To ensure consistency, below are the requirements for CT acquisition:

- Only high resolution, contrast-enhanced spiral CT scans are acceptable.
- Data must be uncompressed.
- **Preferred maximum slice spacing is 2mm.** ***In no case should it exceed 3mm.***
- 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.

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

8.5.3. Pre-Operative Activities

Following informed consent, the **SCREENING AND BASELINE** eCRFs are to be completed. The PI is to proceed with procedure scheduling **only** after receiving acknowledgement from Endologix that the patient meets the enrollment criteria. This determination is based on the documented responses and data provided by the PI, the Core Lab CT assessment and the independent medical review.

8.5.4. Subject Enrollment

Enrollment in the study only occurs upon advancement of the study device into the subject's vasculature. Therefore, the date of study enrollment is the date of the Nellix System implant, as documented in the Visit Date field in the Index Procedure eCRF. If the device does not contact the patient, the patient will be considered as screen failure and the assigned study number will not be given to another patient. If, during the index procedure, the device is introduced but is not implanted and/or there is conversion to open surgery, the patient will be followed until the 30 day follow-up.

8.5.5. Post-Operative Follow-up Visits

The eCRFs are to be entered for each subject at the post-operative follow-up visits. These visits should be scheduled 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).

8.5.6. Enhanced Post-Operative Follow-up Visits

Subjects who experience migration, AAA sac enlargement and/or a Type 1A or 1B endoleak or who are at risk of experiencing any of these events are recommended to be followed every 6 months. *"At risk" is defined as those subjects who would not meet the new inclusion/exclusion criteria, or those subjects with an inadequate procedure, based on current understanding of Nellix implantation best practices. Specifically, procedures resulting in low placement of the device, or lack of adequate proximal or distal seal, are now considered an inadequate procedure. An inadequate procedure is defined as <u>not</u> meeting any one of the following:*

1. *(CoreLab Proximal Seal – 4 mm) ≥ 10 mm*
2. *Acquired distal seal ≥ 10 mm*
3. *Lowest stent within 10 mm of the lowest renal artery*

Please reference the **Schedule of Measurements** §8.4 for a summary of tests and measurements to be performed at the enhanced follow-up visit

Please note: notification of at-risk subjects provided to each site Principal Investigator.

Instructions for eCRF completion and the study-required evaluations for each visit will be provided at the site initiation visit.

8.6. RECOMMENDED SECONDARY INTERVENTION TREATMENT OPTIONS (ALSO KNOWN AS BAILOUT PROCEDURES)

Endologix submitted an Unanticipated Adverse Device Effect (UADE) report to the FDA on October 14, 2016 to report higher than anticipated rates of migration, endoleak (Type IA), and AAA sac enlargement, based on the 2-year follow-up data from the Nellix US IDE trial. As part of the investigation of the higher than anticipated rates of Type 1A endoleaks, migration and AAA sac enlargement, Endologix, in consultation with physicians, reviewed alternative treatment options from clinical studies, commercial use, literature, physician experience and use in similar technologies (e.g., EVAR) to develop a list of recommended treatment options. For many of the treatment options, the clinical data to support the safety and effectiveness of the treatment is limited.

The treating physician should consider multiple factors such as subject anatomy, subject risk profile, hospital standard of care and physician preference when determining the appropriate treatment option. Endologix's treatment recommendation is based on a subset of those factors, and as such, should be used as a reference for physicians and not a requirement. Each secondary intervention case requiring an additional Nellix device will undergo an internal review process. Implanting physicians in such cases will go through device training prior to their first bailout procedure and a proctor will be provided for secondary ChEVAS procedures. The recommended treatment options are provided below.

It should be noted conversion to open repair should be used if a less invasive option is not feasible for the subject, based on the physician's clinical judgment. Even with the other recommended treatment options available, conversion to open repair can be performed at any time, per the physician's discretion.

8.6.1. Treament Options for Type 1 Endoleaks

8.6.1.1. Type 1A Endoleaks

The recommendation for treatment of Type 1A endoleaks is based on evaluation of the implant position and proximal seal zone. The Nellix implant is correctly aligned if the bottom of the first stent cell element is aligned with the distal origin of the most caudal renal artery and the second stent not more than one stent strut higher on the opposite side. The Nellix implant has an adequate proximal seal zone if at least 10mm of the Nellix Endobags are in contact with healthy (i.e. minimal tortuosity, occlusive disease, and/or calcification) aortic proximal neck vessel wall. The length of the aortic proximal seal is measured from the lower margin of the most caudal renal artery to the point distally where the lumen diameter change is 10%. Based on evaluation of these factors, two potential treatment options for the treatment of Type 1A endoleaks have been identified:

- Coils (see Appendix A on **page 68** for list of recommended coils) and liquid embolics (Onyx®) with or without proximal covered stent extenders (balloon-expandable or self-expanding)
- Nellix proximal extenders with or without commercially available stent grafts in the visceral arteries (NiNA with polymer/ Secondary ChEVAS)
    - Covered stents are placed in the visceral arteries to allow blood flow and the Nellix implant is placed in a sufficient length of healthy supra-renal aortic neck to enable aneurysm sealing.

The table below summarizes these options, aligning each with evaluation criteria:

Implant and Anatomic Evaluation Criteria	Potential Treatment Options for Type IA Endoleaks
Implant positioned correctly with adequate sealing zone	- Coils* and liquid embolics (Onyx®) -
Implant positioned incorrectly with adequate sealing zone	- Coils* and liquid embolics (Onyx) with proximal covered stent extenders (iCAST)
Implant positioned correctly with inadequate sealing zone	- Nellix Proximal Extenders with commercially available stent grafts in the visceral arteries (iCAST) (Secondary ChEVAS)
Implant positioned incorrectly with inadequate sealing zone	- Nellix Proximal Extenders (NiNA with Polymer) - Nellix Proximal Extenders with commercially available stent grafts in the visceral arteries (iCAST) (Secondary ChEVAS)

***** See Appendix A on **page 68** for a list of recommended coils

8.6.1.2. Type 1B Endoleaks

A potential treatment option for Type 1B endoleaks have been identified, which can be used based on the physician's preference:

- Distal Covered Stents

The table below summarizes this options, aligning each with evaluation criteria:

Implant and Anatomic Evaluation Criteria	Potential Treatment Options for Type IB Endoleaks
Inadequate sealing in the between the Nellix Endobags and the iliac vessel wall	- Distal Covered Stent Extenders (Ovation iX Iliac Stent Graft)

8.6.2. Treatment Options for Migration

The recommendation for treatment of migration is based on evaluation of the distance the implant has migrated, presence of endoleak and comparison between proximal and distal migration distances. Based on evaluation of these factors, three potential treatment options for the treatment of migration have been identified:

- CT Surveillance
- Nellix proximal extenders with or without commercially available stent grafts in the visceral arteries (NiNA with polymer/ Secondary ChEVAS)
- Nellix Stent Relining (NiNA without Polymer)
    - For subjects in which the proximal migration is more significant than the distal migration of the Nellix implant, stent relining should prevent or slow the rate of migration. Relining the stent will increase the stiffness and column strength of the Nellix implant which may increase its resistance to the hemodynamic forces acting upon it.

The table below summarizes these options, aligning each with evaluation criteria:

Implant and Anatomic Evaluation Criteria	Potential Treatment Options for Migration
Nellix implant has migrated <10mm, in the absence of Type 1A endoleak and a proximal seal zone of at least 10mm remains	- CT Surveillance (Enhanced Follow-up)
Nellix implant has migrated ≥10mm, in the absence of Type 1A endoleak and a proximal seal zone of at least 10mm remains	- Nellix Relining (NiNA without Polymer)
Implant migration associated with Type 1A endoleak and a proximal neck of at least 30mm is available	- Nellix Proximal Extenders (NiNA with Polymer)
Implant migration associated with Type 1A endoleak and a proximal neck of less than 30mm is available	- Nellix Proximal Extenders with commercially available stent grafts (iCAST) in the visceral arteries (Secondary ChEVAS)

8.6.3. Treatment Options for Aneurysm Expansion

The recommendation for treatment of aneurysm expansion is based on the presence of Type 1A/B endoleaks. Based on evaluation of these factors, two potential treatment options for the treatment of aneurysm expansion have been identified:

- Type 1A Endoleak Treatments
- Distal Extension (Ovation iX Iliac Stent Graft)

The table below summarizes these options, aligning each with evaluation criteria:

Implant and Anatomic Evaluation Criteria	Potential Treatment Options for Aneurysm Expansion
Aneurysm expansion is associated with Type 1A endoleak	Refer to treatment option for Type IA endoleak for further detail
Aneurysm expansion is associated with Type 1B endoleak	- Distal Covered Stent Extenders (Ovation iX Iliac Stent Graft)
Aneurysm expansion in the absence of endoleak	- Distal Covered Stent Extenders (Ovation iX Iliac Stent Graft)

8.7. PROTOCOL DEVIATIONS

A protocol deviation occurs when a clinical investigator and/or study site personnel do not conduct the study according to the clinical investigational plan. All deviations are recorded on a Protocol Deviation Form. United States regulations (21 CFR 812.140) require that investigators maintain accurate, complete, and current records relating to the clinical study. This includes documents showing the dates and reasons for each deviation from the clinical investigational plan. Depending upon the nature of the protocol deviation, expedited reporting and prior approval from Endologix may be required. All deviations will be summarized and submitted in IDE progress reports, annual reports, and the final study report to FDA.

If Endologix finds that an investigator is not complying with the executed study agreements, the investigational plan, FDA regulations, or the requirements of the reviewing IRB, prompt action will be taken to secure compliance. In addition, shipment of the device may be stopped or the participation of the investigator may be terminated.

8.7.1. Deviations with Expedited Reporting Requirements

For the following types of protocol deviations (per 21 CFR 812.150), an investigator is required to notify Endologix and the IRB within 5 business days of the deviation.

- Emergency Deviation from the Investigational Plan (a deviation to protect the life or physical well-being of a subject in an emergency).
- Failure to obtain Informed Consent

Notification to Endologix and/or the IRB should be documented and maintained in the clinical study file at the site and at Endologix.

8.7.2. Deviations Requiring Prior Approval

An investigator is required to obtain prior approval from clinical study management at Endologix and the IRB before initiating deviations from the Investigational Plan that affect the scientific soundness of the plan, or the rights, safety, and welfare of the subjects (non-emergent situation). However, prior approval is not required in situations where unforeseen circumstances are beyond the investigator's control, e.g., subject did not attend scheduled follow-up visit, laboratory test was performed incorrectly, and test equipment did not operate properly.

8.7.3. Non-Urgent Deviations

Protocol deviations which do not have the urgency associated with expedited notification or prior Endologix/ IRB approval (as discussed in the above paragraphs)

will be reported upon discovery, such as during completion of eCRFs or a monitoring visit.

8.8. ADVERSE EVENT REPORTING

Adverse events will be entered on the applicable eCRF and in the patient's medical records. The date of onset, severity, and action taken are requested to be identified by the PI.

8.8.1. General Definitions

An adverse event (AE) is any undesirable clinical occurrence in a patient enrolled in the trial 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 adverse event that:

- Led to a death.
- Led to a serious deterioration in the health of the subject that:

  a. Resulted in life threatening illness or injury.
  b. Resulted in a permanent impairment of a body structure or a body function.
  c. Required in-patient hospitalization or prolongation of existing hospitalization.

- Resulted in medical or surgical endovascular procedure to prevent permanent impairment to a body structure or a body function.
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, degree of incidence. Additionally, an unanticipated adverse device effect 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** eCRF. The cause of death will be detailed on the **Serious Adverse Events** section of the form.

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

occurrence of the AE.

8.8.2. Reporting of Adverse Events

For all adverse events occurring during the study period, data must be entered in the Adverse Event eCRF in the EDC system. For serious adverse events (SAEs), the section of the eCRF describing the serious nature of the AE must also be completed.

All device and procedure related adverse events will be investigated by Endologix.

The PI should supply to Endologix and the responsible EC/IRB with a complete, written case history (AE forms) and any additional redacted source documentation and information (e.g., other diagnostic testing, discharge reports, autopsy reports, etc.) as it is available.

Deaths

For any death, regardless of cause or timing, it is recommended that the site notify the Endologix Clinical Department via the EDC system within 1 working day of awareness. The PI should supply to Endologix and the responsible EC/IRB with a complete, written case history (AE forms) and any additional redacted source documentation and information (e.g., other diagnostic testing, discharge reports, autopsy reports, etc.).

In all cases, the death certificate is to be uploaded to the EDC system. 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. Also sites can search Social Security Death Index (SSDI) or CDC National Death Index (NDI) to obtain more information.

If approval is obtained from the patient or a patient's authorized family member, the site should notify Endologix for submission of the explant to Endologix. 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, send a fax to Endologix at +1 949-954-7601, or contact Endologix by telephone at +1 (949) 595-7200.

8.8.3. Adverse Events: required reporting timeframes

Note: Site reporting times to Endologix only; responsible IRB/EC reporting requirements must still be followed by the site, in addition to those recommended below.

AE Type	Reporting Recommendations
Non-device or procedure related AE	Recommended monthly at minimum
Device or procedure related AE	Within 10 working days
Non-device or procedure related SAE	Within 10 working days
Device or Procedure related SAE	Within 1 working day
Death as outcome (regardless of cause)	Within 1 working day
Unanticipated Adverse Device Effect	Within 1 working day

8.8.4. Secondary procedures

For subjects 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, conversion to open repair, etc.), it is important to identify the specific procedure performed on the relevant **ADVERSE EVENT** eCRF. A copy of the discharge summary source document should be uploaded to the EDC system.

8.8.5. Anticipated Adverse Events

Adverse events that could potentially occur during this investigation are called anticipated adverse events. These events must be reported if clinically significant. A list of anticipated AEs 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 or implant component 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)
- Nellix implant: improper component placement; incomplete component deployment; component migration; occlusion/thrombosis; infection; stent fracture; EndoBag material wear; dilatation; erosion; puncture and perigraft flow

- 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 Intervention
- Surgical conversion to open repair

8.8.6. Unanticipated Adverse Device Effect

The investigator shall submit to Endologix and to the reviewing EC/IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 24 hours after the PI first learns of the effect. PIs must submit to Endologix documentation of the report made to the EC/IRB via the EDC system. Endologix will report a UADE to the FDA within 5 working days of becoming aware of the event, as required by regulations.

8.8.7. Adverse Event Definitions

The following event definitions will be applied during this study.

- *Death*: Any death occurring during the study period, regardless of cause.
  - *Aneurysm-related death* is defined as any death occurring within 30 days from the date of the procedure, regardless of cause, and death due to aneurysm rupture or following any procedure intended to treat the aneurysm.
  - *Cardiac-related death* is defined as death due to arrhythmia, heart failure (including cardiogenic shock), or myocardial infarction.
  - *Pulmonary-related death* is defined as death due to due to pulmonary edema, respiratory failure, or pulmonary embolism.
  - *Vascular-related death* is defined as death due to stroke, cerebral hemorrhage, or other clear vascular event that is not categorized as cardiac-related or pulmonary-related.
  - *Other* is to be used to identify a death due to any event that cannot be clearly categorized as above, but where some information is available.
  - *Unknown* is to be used to identify a death where no information is available.
- *Procedural Technical Failure* is defined as a failure of the Nellix system to be delivered and deployed, such that the procedure is not completed, or the device failure results in a serious complication, or a residual endoleak occurs that cannot be resolved during the index procedure and is still present at the 30 day CT as read by the Core Lab.
- *Major Adverse Event*: An event occurring during the study that meets one of the following criteria:
  - *All-Cause Death* (see above);
  - *Bowel Ischemia*: the lack of adequate blood flow to the intestines that requires intensification of medical therapy or surgical/endovascular intervention;

- *Myocardial Infarction*: the presence of raised levels of one or more cardiac biomarkers in comparison to local 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;
- *Procedural Blood Loss >1,000mL*: Estimated blood loss during the index procedure ≥1,000mL.

- *Other Definitions:*
  - *Aneurysm Sac Enlargement*: Aneurysm sac diameter increase of >5mm in late follow-up as compared to the initial post-operative measurement.
  - *Aneurysm Rupture*: bleeding or leaking of blood from the aneurysm subsequent to the index procedure.
  - *Clinically significant migration***:** Core Lab reported stent distal movement >10mm from the original implant location relative to the center of the distal renal artery resulting in an intervention or in a serious complication.
  - *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.
  - *Device Positional Stability*: Core Lab reported position of each stent relative to the center of the L3 vertebrae. Stable positioning is defined as within 5mm of the positioning on the first post-operative CT scan.
  - *Luminal Thrombus Requiring Intervention*: any endovascular surgical intervention after completion of the Nellix System implantation for resolution of endograft thrombosis.
  - *Distal Ischemia*: New onset of compromised peripheral blood flow resulting in femoral or peripheral arterial occlusion or stenosis (attributable to the index procedure and not related to natural progression of atherosclerotic disease) causing a threat to the viability of the limb and requiring surgical or percutaneous intervention; or stent graft occlusion requiring any intervention..
  - *Endoleak*: Clear evidence of contrast outside of one or both EndoBags which communicates with the aneurysm sac originating proximally at the infrarenal segment (Type IA), distally (Type IB); between components, if an extender is used (Type III); trans-device (Type IV); or from a patent collateral vessel (Type II: e.g., lumbar artery; inferior mesenteric artery). Contrast outside of an EndoBag that does not communicate with the aneurysm sac is not to be reported as an endoleak.

- *Migration*: Core Lab reported stent distal movement >5mm from the original implant location relative to the center of the distal renal artery.
- *Clinically significant migration:* Core Lab reported stent distal movement >10mm from the original implant location relative to the center of the distal renal artery resulting in an intervention or in a serious complication.
- *Occlusion*: Intervention for stent occlusion or as reported by the Core Lab.
- *Secondary procedure*: any non-diagnostic intervention after the index procedure intended to correct or repair an endoleak, device occlusion, migration, aneurysm sac expansion and/or a device defect (including infection).

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 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. More recent technological developments have resulted in an alternative, minimally invasive, endovascular aneurysm repair, in which a prosthesis is placed within the aorta through a small incision in the groin. Blood can then flow through the implanted device 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/EVAS enables local or regional anesthesia to be used, uses a minimally invasive groin incision for catheter-based access, and has been reported in multiple studies to offer a lower perioperative complication rate, reduced blood loss and procedure times, and shorter hospital stay. In contrast to open repair, EVAR/EVAS is a relatively new treatment, long term results have not been fully established, and life-long surveillance is recommended to verify implant integrity and patency and continued aneurysm exclusion. Multiple device systems are CE Marked and marketed in the European Community for endovascular abdominal aortic aneurysm repair. All of these devices require the introduction of catheter-based treatment devices varying in outer diameter profile. Standard vascular exposure is indicated for access. Prospective clinical study results support the safety and effectiveness of these devices through early follow-up (to 30 days) and for some in late follow-up to one year and beyond to up to five years.

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 subjects who are at higher risk for experiencing an anticipated adverse event have been selected to reduce the potential risks to subjects who participate in this study. In addition, the assessment of patient computed tomography angiography imaging by an experienced Core Laboratory is also intended to reduce the potential risks to subjects 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 AAA is open surgical repair.

10. STATISTICAL PROCEDURES

10.1 ANALYSIS POPULATIONS

All primary analyses will be conducted on an intention to treat (ITT) basis. Whereas ITT is a concept intended to be applied to randomized trials, its use in this analysis will imply that subjects will be analyzed based on the attempt to implant trial devices during the procedure. Subjects who complete the trial through 12 month follow-up, or have expired prior to 12 month follow-up, will comprise the Completed Cases (CC) population. Additional analyses will be conducted in the CC population. Completed Cases subjects who have an implanted device and are alive upon exit from the procedure room will be considered per protocol (PP) population. All roll-in subjects treated will be evaluated as a separate feasibility group.

10.2 PATIENT ACCOUNTABILITY AND MISSING DATA

The proportion of subjects 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 prior to procedure will be given. However, these subjects will not be included in any analysis.

Information on missing or withdrawn subjects will be tabulated presenting the number and proportion of subjects eligible for and compliant with each follow-up examination. Subjects 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 subjects 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 subjects 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 subjects who complete the study.[*,†,‡,§] The intention of these analyses is to demonstrate that the results obtained from the evaluable subjects 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 analyses will be recalculated using an unbiased imputation of the determination of success or failure. It is expected that the number of subjects with missing effectiveness data at one year will be approximately 10% of study enrollment. The first method of imputation will be to assign values using a simple random sample from the subjects with outcomes at one year. This system is denoted the "Hot Deck by Simple Random Sampling with Replacement".[**] The number of subjects to impute is small and trying to

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

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

[‡]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.

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

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

provide a more sophisticated imputation method would require modeling missingness with only approximately 10% of enrolling subjects or less with missing data. Additional sensitivity analyses will be done by using other imputation methods; Last Observation Carried Forward (LOCF); subjects lost to follow-up considered an endpoint failure; impute the missing result as having succeeded the endpoint; and 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 subjects 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 subjects in the sub-group. For example, the proportion of subjects missing an outcome may be much greater at a given study site which may also have a higher rate of failure. Those subjects from that site may be assigned a failure and the baseline comparisons of the remaining subjects 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 subjects will be imputed as described above. The resolution of the imbalance will be retested by the same methods with the subjects 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.[*]

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 of the test subjects are lost to follow-up prior to 30 days, that patient will be assigned an MAE for primary analysis purposes.

In addition to the above missing data analyses, Tipping Point analyses will also be performed. For each imputed data set, one MAE will be added and the exact binomial test will be done. The number of steps required to achieve non-significance of the MAE endpoint will be reported for each imputation. The supportive tipping point analysis will be repeated for the completed cases and will be done in the same way by adding one MAE and doing an exact binomial test of the result. The number of steps required to achieve non-significance will be reported for this analysis as well.

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

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

180 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 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 study sites to determine homogeneity of sites in terms of baseline patient characteristics. Factors found to differ significantly by site will identify that variable or 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 subjects below which this aggregation will occur until after enrollment is completed, but generally trial sites with four or fewer subjects may be combined.

10.5 POOLING

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

In order to determine if there is a similar response across the study sites for each response, the primary safety and effectiveness will be tested for homogeneity by extension of the Fisher's exact test (Fisher-Freeman-Halton).. If the P-value for study site is less than 0.15 for any response, differences between study site will be assumed to exist and the overall estimate of the proportion in the test subjects will be obtained by taking a weighted average of the proportions at each site with the weight being the inverse

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

of the variance of the proportion at that site.[*] The sum of these weighted proportions divided by the sum of the weights will be the overall estimate for the study. Both the safety and effectivness measures will employ weighted proportions as the basis for the statistical test. The test of significance in these circumstances are fully described below in Sections 10.6 and 10.7.

If the heterogeneity P-value is less than 0.15, an analysis of the primary effectiveness endpoint by the Fleiss (1993) method will be done. The estimates obtained from this method provide a mechanism to test homogeneity and to adjust the value of the overall estimate if heterogeneity exists.

10.6 PRIMARY SAFETY ANALYSIS

10.6.1 Primary Safety Hypothesis

The primary safety hypothesis to be tested is that the rate of Major Adverse Events (MAEs) at 30 days in the study population is less than 56%, which is the rate of MAE at 30 days in the Society for Vascular Surgery (SVS) open surgery group. MAEs include all-cause death, bowel ischemia, myocardial infarction, paraplegia, renal failure, respiratory failure, stroke, and procedural blood loss ≥1,000mL. 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 success. The null and alternative hypotheses are provided below.

$$H_0: P_t \geq 0.56 \text{ vs. } H_1: P_t < 0.56,$$

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

10.6.2 Sample Size

The primary trial safety variable is the rate of MAEs (as defined previously) at 30 days following treatment with the Nellix System. The SVS open surgical group has been characterized.[†]

Owing to the availability of data within the SVS database for this surgical group, it is reasonable to consider it for sample size generation for the safety endpoint. The MAE rate in the SVS surgical control group at 30 days is 56%. 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 repair of juxtarenal aneurysms and those involving the renal arteries), with the exception of bleeding and renal events, which were significantly higher with open more complex aneurysm repair.[‡] To be further conservative and to account for the fact that in the present study, shorter necked infrarenal aneurysms will be treated endovascularly with the Nellix System, the rate for the test arm has been increased to 16.6%. It is expected that the rate of MAEs within 30 days in in this study will be smaller than

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

[†]Zwolak RM, Sidawy AN, Greenberg RK, et al. Lifeline registry of endovascular aneurysm repair: open repair surgical controls in clinical trials. J Vasc Surg 2008;48:511-8. The SVS surgical control group results are detailed in the FDA Summary of Safety and Effectiveness Data (SSED) for the Medtronic Talent™ Device.

[‡]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.

that of the SVS historical surgical control group as noted above. The sample size for this trial is calculated to demonstrate a difference between the observed MAE rate and the performance goal established using SVS historical surgical data.

If we assume that $P_t = 0.166$, $P_c = 0.560$, one-sided alpha = 0.025, and power = 80%, a very small number of subjects are required in the treatment group to test the above hypothesis. Should the Nellix rate be as high as 31%, then 50 subjects would provide approximately 81% power to test the primary safety endpoint at the one-sided 2.5% significance level.

10.6.3 Analysis Plan

All subjects who receive treatment will be included in the safety analysis.

A univariate test will be done with the exact binomial distribution to determine if the frequency of MAE in the study population is statistically significantly less than 0.56. The formula for this test is provided below.

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

Where x_t is the number of study subjects experiencing an MAE and n_t is the number of subjects in the study. 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.

$$z = \frac{\left(\overline{p}_T - 0.56\right)}{SE\left(\overline{p}_T\right)}$$

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

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

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

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

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

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

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

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 study population 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 accident, 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.

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 MAEs and each individual adverse event that is part of the composite with corresponding 95% exact confidence intervals.

10.7 PRIMARY EFFECTIVENESS ANALYSIS

10.7.1 Primary Effectiveness Hypothesis

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

H_0: $P \leq 0.80$ vs. H_1: $P > 0.80$

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 freedom from: aneurysm rupture; conversion to open repair; Type I endoleak at 12 months; Type III endoleak at 12 months; clinically significant migration; aneurysm sac enlargement; or secondary endovascular procedure up to 12 months for resolution of Type I or III endoleak, device 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 132 subjects at one year in the study population will have 80% power against a null performance goal of 80% if the proportion of Treatment Success is 88% or higher. It is estimated that the rate of Treatment Success will be greater than 88%.

It is anticipated that the drop-out rate of the trial will be 12% or less. Because the larger of the two sample sizes after adjustment for loss to withdrawal is the one for effectiveness, a minimum

of 132/0.88 = 150 subjects will need to be recruited for this study. Thus to allow for deviations from assumptions, 150 subjects will need to be recruited for this study.

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 subjects who meet the Treatment Success definition. The observed proportion of subjects 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:

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

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

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

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 < 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 study population 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 accident, 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

- *Procedural and In-Hospital Evaluations*: The estimated blood loss volume, % of subjects receiving a blood transfusion, contrast volume, fluoroscopy time, endovascular device time, Polymer volume used, procedure time, anesthesia time and type, frequency of concomitant procedures, ICU time, time to hospital discharge, and % of subjects discharged to skilled nursing facilities or assisted living facilities who were not prior residents will be presented descriptively. Qualitative variables will be presented with rate. Quantitative variables will be presented with mean, standard deviation, median, minimum and maximum.
- *Mortality*: The proportion of subjects with mortality (all-cause and aneurysm-related) will be presented at 30 days and at each subsequent time point 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.
- *Major Adverse Events (MAE) Individual Components*: The proportion of subjects experiencing each category of MAE within 30 days and after 30 days at each subsequent time point for which data are available will be presented.
- *Composite Late MAEs (after 30 days)*: The proportion of subjects experiencing an MAE after 30 days will be presented at each subsequent time point 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.

- *Aneurysm Rupture*: The proportion of subjects experiencing a rupture of the aneurysm will be presented at 30 days and at each subsequent time point for which data are available.
- *Conversion to Open Repair*: The proportion of subjects undergoing surgical conversion to open repair will be presented at 30 days and at each subsequent time point for which data are available.
- *Serious Adverse Events (SAEs)*: The proportion of subjects experiencing an SAE will be presented descriptively by time point.
- *Non-serious AEs*: The proportion of subjects experiencing a non-serious AE will be presented descriptively by time point.
- *Device Performance*: A descriptive analysis of the following will be done based on Core Lab evaluations at 30 days and at each subsequent time point 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.
- *Luminal Thrombus Requiring Intervention***:** any endovascular surgical intervention after completion of the Nellix System implant for resolution of endograft thrombosis**.**
- *Aneurysm Sac Changes*: The changes in aneurysm sac (vessel) diameter from the first post-operative CT evaluation will be presented 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 subjects with increased sac diameter (>5mm), stable sac diameter (≤5mm), or decreased sac diameter (>5mm) will be presented.
- *Incidence of Migration*: Core Lab reported stent distal movement >5mm from the original implant location relative to the center of the distal renal artery.
- *Incidence of Clinically Significant Migration*: Core Lab reported stent distal movement >10mm from the original implant location relative to the center of the distal renal artery resulting in an intervention or in a serious complication.
- *Incidence of Endoleak*: The occurrence of endoleak (any type or location, new and persistent) will be presented descriptively at each follow-up.
- *Incidence of Stent Occlusion*: The occurrence of stent occlusion will be presented descriptively at each follow-up. 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.
- *Nellix Implant Patency and Integrity*: A descriptive analysis of stent patent luminal flow, absence of stent fracture, kinking, or occlusion, and absence of device failure will be determined by contrast-enhanced CT scan, as assessed by the independent core laboratory at 30 days and at each subsequent time point 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.

- *Secondary Endovascular procedures*: A descriptive analysis of secondary endovascular procedures for resolution of endoleak (Type I or III), device occlusion, migration, aneurysm sac expansion, and/or a device defect (including infection) will be done at 30 days and at each subsequent time point for which data are available.

10.9 CONTINUED ACCESS

Data collected from patients enrolled in the Extended Investigation (continued access) phase will be evaluated separately from that of the Primary Investigation. No formal hypothesis testing will be performed in this separate continued access cohort. Only descriptive statistics will be presented on this cohort.

11. ADMINISTRATIVE PROCEDURES

11.1 STATEMENT OF COMPLIANCE

This clinical investigation will follow the international standard for Clinical Investigation of Medical Devices for Human Subjects -- Good Clinical Practice (ISO 14155:2011). The Sponsor and Investigator(s) will comply with their responsibilities as defined in 21 CFR 812.

11.2 RESPONSIBILITIES

1. *Sponsor*: Endologix is responsible as the Sponsor to ensure proper site and investigator selection, availability of signed investigator agreements prior to study initiation, availability of regulatory and EC/IRB approval prior to the initiation of the study at any site, obtaining and maintaining appropriate insurance policies for the study, 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. Furthermore, the sponsor is responsible for ensuring proper regulatory approvals are obtained, and reporting to regulatory authorities per applicable regulations.
2. *Investigators*: Each investigator and study site is required to conduct the clinical investigation in accordance with the protocol, the signed investigator agreement, Good Clinical Practices (GCP), all applicable laws and regulations and any conditions or restrictions imposed by the reviewing EC/IRB. This includes compliance with requirements related to EC/IRB approval and reporting, and proper patient informed consent prior to participation in the study. The investigator is also responsible for protecting the rights, safety, and welfare of the subjects under his or her care.
    a. Each investigator is responsible for supervising all procedures conducted under this protocol at his or her institution.
    b. Furthermore, the investigator is responsible for ensuring that data are completely, accurately, and promptly entered in each patient's eCRFs and related documents are

available to verify the accuracy of the eCRFs, and for ensuring the clinical monitor has access to all necessary records to ensure the integrity of the data.

3. *CT Scan Core Laboratory*: The CT Scan Core Laboratory is a contract supplier having validated processes that is responsible for receipt, de-identification, handling, processing, and assessment of all submitted CT scans preoperatively and postoperatively and for reporting of results per a written, approved protocol.

4. *Data Management Group*: The data management group is responsible for electronic data capture database development, validation, control and management of input from study sites/monitored data, maintenance, and reporting for statistical analysis.

5. *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 the eCRFs and in source documents by the study PIs during the trial, and for categorization of these events according to the event definitions and primary endpoint criteria in this protocol. An independent clinical safety review will examine all AEs and SAEs. MAEs will undergo adjudication by the CEC panel. 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.

6. *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.

7. *Independent Reviewer*: The Independent Reviewer will be an expert in endovascular therapy for repair of abdominal aortic and aortoiliac aneurysms. The Independent Reviewer will review all aneurysm-related images prior to subject enrollment into the study. Approval by the Independent Reviewer will include assessing vascular suitability for treatment with the study device and review of anatomic measurements provided by the Core Lab to determine each patient's eligibility. More than one Independent Reviewer may be required for case selection decision adjudication.

8. *Biostatistician*: The 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.

11.3 PATIENT PROTECTION

This clinical investigation will be conducted in accordance with the ethical principles that have their

origin in the Declaration of Helsinki. Written informed consent, in accordance with applicable international and local study center regulations, must be obtained from each patient, or from their legal representative, prior to the formal screening process as outlined in this protocol. The PI will retain a copy of the signed informed consent document in each subject's record, and provide a copy to the subject. The PI will not request the written informed consent of any patient, and will not allow any patient to participate in the investigation before obtaining EC/IRB approval.

Attachment 2 provides a sample of the consent form that may be used for the study. The sample 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 PI will provide Endologix with a copy of the sample Informed Consent Document approved by the EC/IRB with documented evidence that the EC/IRB has approved the protocol.

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.

11.4 PROTOCOL CHANGES

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

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

11.5 DOCUMENTATION

Clinical Investigator's Brochure: Prior to or at the time of training for the study, the PI 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. Source document worksheets will be provided by Endologix for use by study personnel.

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 patient ID number;
- A statement that written informed consent was obtained;
- Date of procedure and implanted device information;
- Dates of all visits;
- Occurrence of complication and adverse events, hospitalizations, or adverse events;
- Date patient exited the study, and a notation as to whether the patient completed the study or discontinued, with the corresponding reason.

Electronic Case Report Form Completion: The PI who signs the protocol signature page must personally electronically sign the eCRFs to ensure that the observations and findings are entered correctly and completely. The eCRFs are to be entered in a timely manner at the intervals specified by Endologix and this protocol.

All eCRFs must be entered as instructed. An explanation must be provided for any missing data points. Completion instructions and training will be provided to each site for reference.

All eCRFs will be reviewed and monitored for completeness and clarity. Queries for missing or unclear data will be made as necessary throughout the study. Timely resolution of queries is required by institutional staff and the PI.

Study Logs: The following logs will be maintained for the study:

- Investigator and site training to the protocol (Training Log)
- Authorized study site personnel (Site Signature Log)
- Patient consent and screening (Enrollment Log)
- Monitoring visit tracking (Site Visit Log)
- Nellix Inventory eTracking Log (Device Accountability Log)

Document Retention: Study-related correspondence, patient records, consent forms, records of device implant, and source documents are to be maintained by the study site. Endologix requires that it be notified in writing if the PI 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.

11.6 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 (SIV/SAV) will be conducted to ensure that the PI 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 PI's obligations are being fulfilled and that the facilities continue to be acceptable.

Site Termination: If the Sponsor or a clinical monitor becomes aware that a PI 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 EC/IRB or health authority, Endologix will immediately either secure compliance or terminate the PI's participation in the study. The final action will be taken with the goal of assuring the rights, safety and welfare of the subjects.

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

Shari O'Quinn
VP, Clinical & Regulatory Affairs
Endologix, Inc.2 Musick, Irvine, CA 92618
Tel: (949) 598-4650

CRFs, AE reports, source documents as required, invoices for payments per executed agreements, and all correspondence are to be forwarded to:

Endologix, Inc.
Clinical Affairs Department
2 Musick, Irvine, CA 92618
Tel: (949) 595-7200
Fax: (949) 595-7373

12. REFERENCES

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13. APPENDIX A: LIST OF COILS INVESTIGATORS MAY USE ADJUNCTIVELY WITH ONYX®

Coil Name	Manufacturer
Interlock	Boston Scientific
Nester	Cook Medical
Concerto	Medtronic
POD	Penumbra
Ruby	Penumbra
Azur	Terumo