POST-APPROVAL STUDY PLAN

Zenith® TX2® TAA Endovascular Graft Post-Approval Study

Global Clinical Number 08-005

Version: 08-005-05
Version Date: 14 March 2018

Global Sponsor: Cook Research Incorporated

STUDY PLAN SIGNATURE PAGE

Global Sponsor Contact:

I hereby acknowledge that the content presented in this Study Plan has been reviewed and agreed upon.

X _____ .:Jt?i 7 7 ~ ::MI/tf
Signature Date (DD Mon **YYYY)**

Jennifer L. Kerr - President, Cook Research Incorporated
Printed Name

STUDY PLAN SIGNATURE PAGE

Principal Investigator:

I hereby acknowledge that the content presented in this Study Plan has been reviewed and agreed upon.

X _____ _____
Signature Date (DD Mon YYYY)

_____
Printed Name

Post-Approval Study Investigational Plan

The following is a proposed investigational plan for a post-approval study to evaluate long-term safety and performance of the Zenith® TX2® TAA Endovascular Graft through 5 years.

1. Purpose

The purpose of the post-approval study is to evaluate the long-term safety and performance of the Zenith® TX2® TAA Endovascular Graft in the elective treatment of patients with descending thoracic aortic aneurysms or ulcers.

2. Name and Intended Use of the Device

The Zenith® TX2® TAA Endovascular Graft (proximal and distal components) is indicated for endovascular treatment of patients with aneurysms/ulcers of the descending thoracic aorta having morphology suitable for endovascular repair, including:

- Adequate iliac/femoral access compatible with the required introduction systems
- Non-aneurysmal aortic segments (fixation sites) proximal and distal to the aneurysm:
  - with a length of at least 25 mm,
  - with a diameter measured outer-wall to outer-wall of no less than 24 mm and no greater than 38 mm,
  - with a radius of curvature greater than 35 mm for aortic arch landing zones, and
  - with an angle less than 45 degrees (any angle in the arch or distal aorta).

Note: A diagram of these parameters is presented in Figure 2-1.

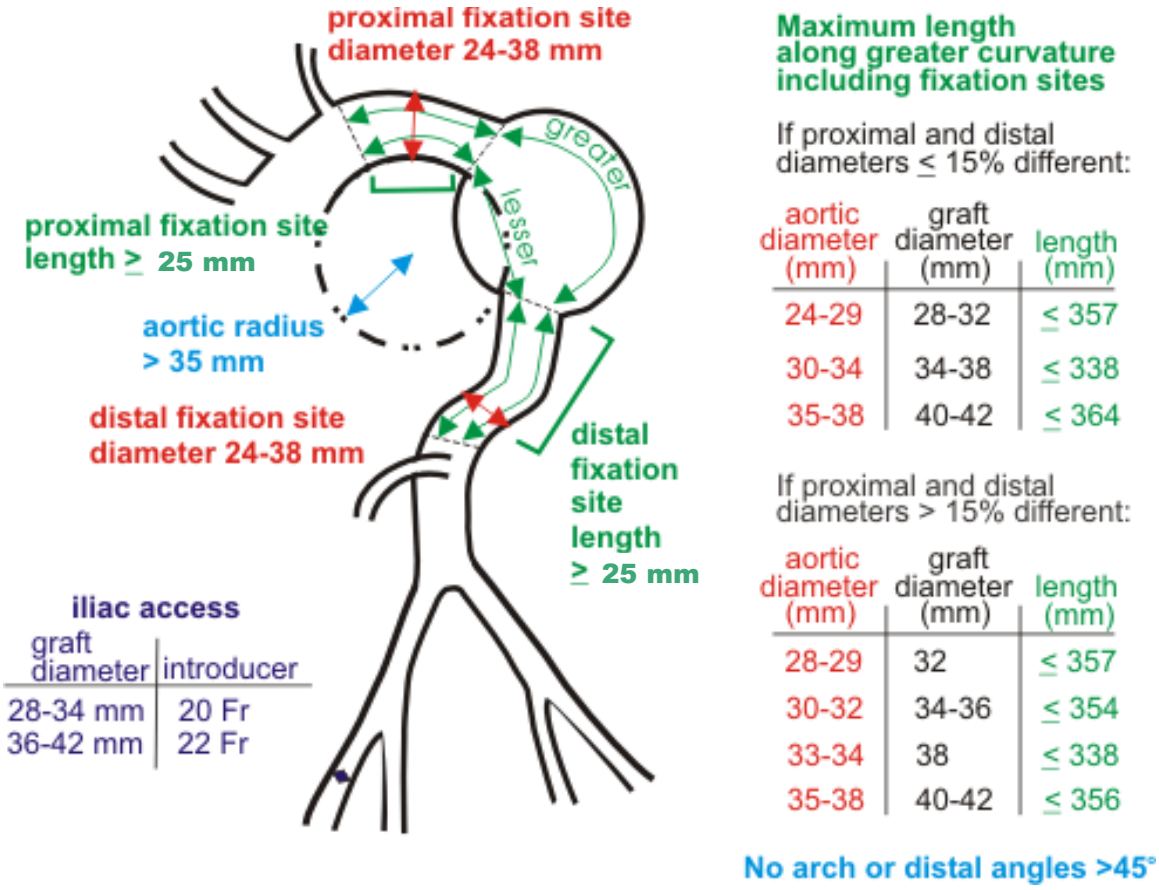


Figure 2-1. Anatomical inclusion criteria

3. Specific Aims

The specific aims of the study include assessment of:

1) long-term safety of the device, as measured by the freedom from aneurysm-related mortality through 5 years [Information redacted due to confidential content.]

4. Duration of the Investigation

Patient recruitment should be completed within 72 months of initiating the study. All subjects will be evaluated at pre-procedure, pre-discharge (within 7 days), 1, 6, and 12 months, and yearly thereafter through 5 years. Informed consent will allow for following of patients through 5 years post-procedure.

5. Study Design

5.1. Hypothesis to be Tested

The primary endpoint will be evaluated according to the hypothesis that patients treated with the Zenith® TX2® TAA Endovascular Graft will have a rate of aneurysm-related mortality at 5 years that meets an objective performance criterion of 7.7% with a margin of $\delta = 7\%$. With regards to delta, it should be noted that this would require an allowable mortality in the endovascular treatment group at 5 years that is lower than the mortality reported in some prior surgical studies at 30 days, setting a standard for endovascular repair that some surgical studies do not meet.

The hypothesis is formulated as follows:

Null Hypothesis: the 5-year TAA-related mortality rate, γ, is greater than or equal to 7.7% + 7%. (Interpretation: the TAA-related mortality rate does not meet the OPC.)

$H_o: \gamma \geq 7.7\% + \delta$

Alternative Hypothesis: the 5-year TAA-related mortality rate, γ, is less than 7.7% + 7%. (Interpretation: the TAA-related mortality rate does meet the OPC.)

$H_a: \gamma < 7.7\% + \delta$

The hypothesis will be tested by using an exact binomial test (StatXact 8.0) where the test statistic is defined as follows:

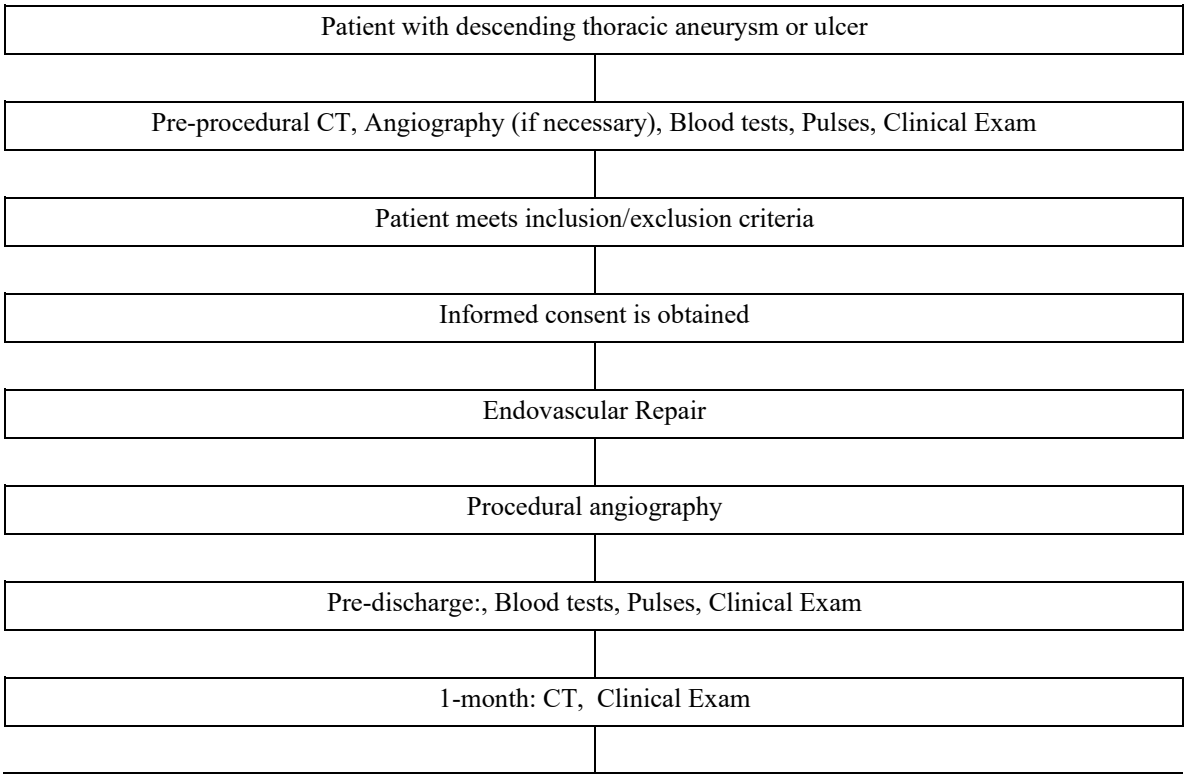
$$\hat{\gamma} = \frac{n_{TAA}}{N}$$

where n_{TAA} is the number of patients with TAA-related death within 5 years, and N is the total number of patients with 5 year follow-up or death (any cause) within 5 years.

5.2. Design of the Study

This study will be conducted as a post-approval registry, where the 5-year aneurysm-related mortality following endovascular treatment will be compared to an objective performance criterion (OPC) of 5-year aneurysm-related mortality following open surgical repair. The OPC of 5-year survival from aneurysm-related mortality will be established based on results from a meta-analysis of published reports on open thoracic aneurysm repair in combination with survival rates from the open surgical control patients that were enrolled in the multi-center pivotal clinical study (development of the OPC is discussed further in Section 10).

The study will be conducted at up to 50 multi-national investigative sites, with the minimum expected number of participating centers being 15, and the maximum number of patients to be enrolled at any one center will be 25. Patients may be enrolled prospectively or retrospectively, if they received the Zenith® TX2® TAA Endovascular Graft on or after May 21, 2008. **All subjects, if found to be eligible for study participation, will be invited to participate in the study**. The entry criteria for the endovascular treatment group are listed in Section 6.



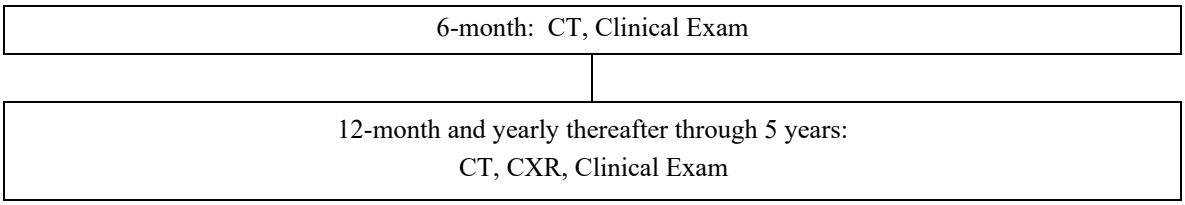


Figure 5-1. Study flow diagram

5.3. Sample Size Determination

As directed by the Division of Postmarket Surveillance within FDA, the sample size for the study can be calculated using EpiInfo (available through the Centers for Disease Control and Prevention) by assuming a 9.5% rate of TAA-related mortality in the endovascular treatment group at 5 years (2 year estimate is currently 7.1% in the pivotal clinical trial). $\alpha = 0.05$ and power = 0.80. The resultant sample size is 273 endovascular treatment patients. A total of 300 patients will be included in the study (273 + 27 for possible lost to follow-up), consisting of the 185 endovascular treatment patients from the IDE clinical trial (160 pivotal + 25 continued access) plus an additional 115 endovascular patients to be enrolled in the post-approval study.

5.4. Participation Endpoints of the Study

A patient's follow-up in the study will end after any of the following:

1) Explant of the prosthesis + 30 days
2) Patient withdrawal
3) Patient death
4) Closure of the post-approval study
5) Completion of all scheduled clinical and imaging visits, through 5 years

5.5. Limitations of the Study

This study is inherently limited by the small number of patients with descending thoracic aortic aneurysms. The estimated incidence of thoracic aortic aneurysms is 6 per 100,000 person years. However, this incidence rate is inclusive of all etiologies and conditions [e.g., atherosclerotic aneurysm, degenerative aneurysm, mycotic aneurysm, inflammatory aneurysm, symptomatic aneurysm, chronic dissection, acute dissection, traumatic injury,

leaking/ruptured aneurysm, impending rupture, aortobronchial fistula, aortoesophogeal fistula, diagnosed or suspected congenital degenerative collagen disease (Marfan's syndrome or Ehlers-Danlos syndrome)]. Recognizing that different etiologies may respond differently to endovascular repair with the Zenith® TX2® TAA Endovascular Graft, etiology and condition must be considered when selecting patients.

Based on indications for use of the device gained through experience to date, this study will include only those patients who have undergone or will undergo elective repair of degenerative/atherosclerotic aneurysms, including degenerative/atherosclerotic ulcers ≥ 10 mm in depth and 20 mm in diameter, inflammatory aneurysms, and symptomatic aneurysms; but not including mycotic aneurysm, chronic dissection, acute dissection, traumatic injury, leaking/ruptured aneurysm, impending rupture, aortobronchial fistula, aortoesophogeal fistula, or diagnosed or suspected congenital degenerative collagen disease (no Marfan's or Ehlers-Danlos syndrome).

The proportion of eligible patients is further confounded by anatomic considerations. Performance and safety of the Zenith® TX2® TAA Endovascular Graft can be compromised by use in unsuitable endovascular anatomy. Therefore, inclusion in the study requires that a patient's anatomy be amenable to endovascular repair. Specific anatomical characteristics (vessel diameters and lengths) are often different between patients, and although the device is designed to treat a wide range of anatomy, a number of patients with descending thoracic aortic aneurysms are expected to be ineligible due to unsuitable endovascular anatomy. In light of the influence of etiology and anatomy on patient selection, the proportion of patients with descending thoracic aortic aneurysms eligible for study enrollment is expected to be small.

The limitations imposed on this study by the target patient population dictate the choice of study design. Although a randomized controlled study is a preferred study design due to its academic appeal, randomization is not feasible given the small target patient population. In addition, eligible patients would need to meet both the endovascular and open surgical inclusion/exclusion criteria, further lowering the potential study population. Lastly, it is expected that patients would be less likely to participate in the study if randomized to the surgical control group. Together, these factors would result in untenable enrollment rates with a randomized design.

A non-randomized study with a concurrent open surgical control has strengths and was chosen for the pivotal study, supplemented with retrospective cases. Despite substantial efforts to complete enrollment in a reasonable timeframe, patient accrual was slow. It

took roughly 2.5 years to enroll 70 open surgical control patients from over 40 eligible institutions. Importantly, commercial availability of a thoracic endograft had a profound effect on enrollment of surgical controls, with a 50% decrease in enrollment rate following approval of the Gore TAG device. The decreased surgical enrollment rate has persisted through the continued access phase of the pivotal study; only a single patient has been enrolled since July 2006. Reduced availability of surgical control patients is expected, given that endografts are often considered a viable treatment alternative for surgical candidates who are also reasonable controls (i.e., have similar extent of disease). The confounding effect of commercially available endografts will only be exacerbated with the impending approval of additional endografts that will expand the range of anatomies amenable to endovascular treatment. Cook has evaluated the multiple confounding factors and concluded that use of concurrent surgical controls is not a viable option for a post-approval study.

Consequently, in the setting of a post-approval study, a registry design with comparison to an OPC is the only good option for comparing the long-term safety and performance of endovascular treatment to open surgery.

This study is also limited by the anticipated comorbidities likely to be found in these patients, which may confound data analysis.

5.6. Safety Monitoring

The post-approval study will be monitored by a Data Safety Monitoring Board (DSMB) according to a written safety monitoring plan. Safety monitoring will include collecting and reviewing data on major and other adverse events. Section 11 (Risk Analysis) lists the possible adverse events associated with this study. A DSMB consisting of independent physicians, who are not investigators in the study, nor have a perceived conflict of interest with the conduct and administration of the study, will be convened as applicable to review adverse events according to standardized procedures.

An independent Clinical Events Committee (CEC) consisting of physicians, who are not investigators in the study, nor have a perceived conflict of interest with the conduct and administration of the study, will be established to adjudicate death, rupture, and conversion reported during the study. This adjudication will be performed according to standard operating procedures to assess whether the events were due to a pre-existing or unrelated condition, procedure-related, technique-related, and/or device-related.

A central core lab will be used for image analysis to provide uniformly defined morphological and morphometric analysis of images.

Bioresearch monitoring including on-site visits will be conducted, in part, for identification of adverse events and assurance they are correctly reported to the DSMB and CEC.

Study Administration

This study is based on the STARZ TX2 pivotal trial, the design of which had been counseled by a National Principal Investigator and Steering Committee consisting of physicians with endovascular device and clinical study experience. These consisted of Jon Matsumura, MD and Richard Cambria, MD; Michael Dake, MD; Roy Greenberg, MD; and Lars Svensson, MD, PhD.

6. Specific Protocol

6.1. Definitions

Please see Appendix A.

6.2. Inclusion and Exclusion Criteria

Consecutive patients who are willing to participate and who meet the inclusion/exclusion criteria will be selected for the study. All patients eligible for aneurysm repair or who have been treated with the Zenith® TX2® TAA Endovascular Graft will be evaluated for enrollment in this study according to the inclusion/exclusion criteria. All patients eligible for entry into the study will have the potential risks and benefits of the procedures and the overall study protocol explained to them. Each patient who wishes to participate in this study will provide written informed consent prior to his or her enrollment into the study.

All patients must meet at least one of the general inclusion criteria to be enrolled in the study. **No** patients may be enrolled in the study if any of the general exclusion or medical exclusion criteria is true. Patients **may not** be enrolled if any of the anatomical exclusion criteria are true.

The general exclusion criteria will be assessed during the initial patient evaluation by conducting a history and physical examination. Anatomical criteria will be assessed using a variety of imaging techniques that are routinely performed during the evaluation

of descending thoracic aortic aneurysms. Sectional imaging will be performed by CT scan. Angiography and intravascular ultrasound will be performed selectively.

Assessment of inclusion and exclusion criteria will be based upon data available prior to enrollment. Data obtained peri-operatively and post-operatively may contradict pre-enrollment assessment, and such is anticipated in several cases. However, such contradiction should not be construed as evidence of inadequate or inaccurate pre-enrollment assessment with respect to the enrollment criteria or evidence of inappropriate enrollment. Enrollment is to be based upon the best available pre-enrollment data. Therefore, some criteria relate to subjective assessment while other criteria are considered absolute and able to be determined definitively. Variability in assessment between centers, investigators and observers is expected with several criteria.

General Inclusion Criteria:

A patient may be suitable for inclusion if treatment is clinically indicated and the patient has at least one the following:

1) Descending thoracic aneurysm with diameter ≥ 5.0 cm
2) Descending thoracic aneurysm with a history of growth ≥ 0.5 cm within the previous 12 months
3) Descending thoracic degenerative or atherosclerotic ulcers ≥ 10 mm in depth and 20 mm in diameter

General Exclusion Criteria:

Patients must be excluded if any of the following are true:

1) Age < 18 years
2) Other medical condition (e.g., cancer, congestive heart failure) that may cause the patient to be non-compliant with the protocol, confound the results, or is associated with limited life expectancy (i.e., less than 2 years)
3) Pregnant, breast-feeding, or planning on becoming pregnant within 24 months
4) Unwilling or unable to comply with the follow-up schedule
5) Inability or refusal to give informed consent
6) Simultaneously participating in another investigative device or drug study.

(The patient must have completed the primary endpoint of any previous study at least 30 days prior to enrollment in this study.)

Medical Exclusion Criteria:

Patients must be excluded if any of the following are true:

1) Receiving home oxygen therapy
2) $FEV_1 < 1$ liter
3) Left ventricular ejection fraction < 20%
4) New York Heart Association Classification 4
5) Myocardial infarction within the last 3 months
6) Stroke within the last 3 months
7) Diagnosed or suspected congenital degenerative collagen disease (no Marfan's or Ehlers-Danlos syndrome)
8) Systemic infection (e.g., sepsis)
9) Bleeding diathesis, uncorrectable coagulopathy or refuses blood transfusion
10) Allergy to stainless steel, polyester, solder (tin, silver), polypropylene, nitinol, or gold
11) Untreatable reaction to contrast, which in the opinion of the investigator, cannot be adequately premedicated
12) Symptomatic carotid disease warranting intervention, which will not be performed prior to TAA repair
13) Mycotic aneurysm, leaking/ruptured aneurysm, impending rupture, aortobronchial fistula, aortoesophogeal fistula, dissection or traumatic injury
14) Surgical or endovascular AAA repair within 30 days before or after TAA repair
15) Previous placement of a thoracic endovascular graft
16) Aortic dissection
17) Prior open repair involving descending thoracic aorta including supra-renal aorta and/or arch (except prior elephant trunk procedure is acceptable if > 30 days post-procedure)

18) Interventional and/or open surgical procedures (unrelated to TAA repair) within 30 days before or after TAA repair

Anatomical Endovascular Exclusion Criteria:

Patients must be excluded if any of the following are true:

1) Treatment length (i.e., aneurysm/ulcer length including fixation sites) along greater curvature is:
   a) > 357 mm (for 28 to 32 mm diameter straight graft or 32 mm diameter tapered graft)
   b) > 354 mm (for 34 to 36 mm diameter tapered graft)
   c) > 338 mm (for 34 to 38 mm diameter straight graft or 38 mm diameter tapered graft)
   d) > 364 mm (for 40 to 42 mm diameter straight graft)
   e) > 356 mm (for 40 to 42 mm diameter tapered graft)
2) Proximal neck length measuring < 25 mm between the left common carotid and aneurysm (covering subclavian is acceptable except in patients with anomalous vertebral off of the arch in the region of the subclavian or a dominant vertebral off of the subclavian)
3) Distal neck length measuring < 25 mm between celiac and aneurysm
4) Aortic arch radius ≤ 35 mm (if device deployed in arch)
5) Proximal neck diameter, measured outer-wall to outer-wall on a sectional image or multiplanar reconstruction (CT), < 24 mm or > 38 mm
6) Distal neck diameter, measured outer-wall to outer-wall on a sectional image or multiplanar reconstruction (CT), < 24 mm or > 38 mm (estimate from more proximal segment if diaphragm makes identification of the outer-wall difficult)
7) Tortuosity, calcification or arterial diameter, measured inner-wall to inner-wall on a sectional image, that are not conducive to placement of the introducer sheath (20 Fr. for 28 to 34 mm diameter graft or 22 Fr. for 36 to 42 mm diameter grafts)
8) Prohibitive calcification, occlusive disease or tortuosity of intended access vessels

9) Prohibitive calcification, occlusive disease, or tortuosity of intended fixation sites

10) Circumferential thrombus in region of intended fixation sites

11) Inverted funnel-shaped proximal neck with ≥ 3 mm increase in diameter from proximal fixation site to the aneurysm (over the 25 mm fixation site)

12) Funnel-shaped distal neck with ≥ 3 mm increase in diameter from distal fixation site to the aneurysm (over the 25 mm intended fixation site)

13) Inability to preserve the left common carotid artery and celiac artery

14) Aneurysm or angulation in the distal thoracic aorta that would preclude advancement of the introduction system

6.3. Registration

Patient registration will be accomplished by a telephone call to a centralized computer system that tracks patient enrollment. The central computer system is located at Cook Research Incorporated, in West Lafayette, Indiana. The system can be contacted 24 hours a day via a toll-free number. A valid password must be entered to access the system. The caller is asked to say their name, which is digitally recorded. The caller is asked to enter the patient's initials and date of birth. A check is made to ensure that a patient with identical initials and date of birth has not already been enrolled at that investigative site. If so, the caller is requested to contact Cook Research Incorporated for clarification. Otherwise, the system then provides the caller with an enrollment number to be used for identification on all subsequent paperwork (e.g., Case Report Forms, Follow-up Forms, Complication Forms) related to this patient.

Upon completing the registration procedure, the computer automatically faxes a confirming document to the investigative site indicating that a patient with the specific initials and birth date was enrolled on the specified date and assigned the indicated enrollment number.

7. Methods

For information related to endovascular graft planning and sizing, choosing and measuring proximal and distal fixation sites, determining anatomical lengths,

endovascular graft placement procedure, peri-operative care, and treatment of endoleaks, please refer to the device Instructions for Use (IFU).

8. Measurements and Data Collection

A dedicated study coordinating nurse and physician team will complete standardized, preprinted, electronically scanable data collection forms, which may serve as source documents. The original data forms, pertinent procedural and follow-up imaging data will be sent to Cook Research Incorporated, which will coordinate shipment to the core lab for independent analysis. Data will be reviewed, processed and entered into electronic databases by the data coordinating center (Cook Research Incorporated) according to validated standardized procedures.

The results of the endovascular repair will be assessed by radiological and clinical follow-up through five years, as outlined in Table 8-1.

Table 8-1. Study exam schedule

				Month		
	Pre-op	Intra-op	Pre-discharge	1	6	12[3]
CT Scan	X[1]			X[1,2]	X[1,2]	X[1,2]
4-view device X-ray						X
Angiography	X[4]	X				
Pulses	X		X			
Blood tests	X	X	X			
Clinical Exam	X		X	X	X	X

[1]CT scan must be able to support electronic submission, or have the ability to reproduce 3-D reconstruction, multi-planar, or trans-axial images.
[2]Physician's discretion as to additional imaging modalities necessary to evaluate patients experiencing renal failure or who are otherwise unable to undergo contrast-enhanced CT scan.
[3]Endovascular patients will be followed at yearly intervals through five years
[4]Pre-procedure angiography to be performed electively, or as needed depending on adequacy of 3-D reconstruction and complexity of patient anatomy.

8.1. Pre-operative Assessment Data

Detailed pre-procedural examination data will be collected for patients meeting the selection criteria who have provided informed consent. Data will be collected and stored in a database. For specific data included, please refer to case report forms attached in Appendix B.

8.2. Intra-operative Data Collection

The endovascular aneurysm procedure will be documented in such a way to permit analysis of any untoward occurrences in terms of cause and effect. Data will be collected and stored in a database. For specific data included, please refer to case report forms attached in Appendix B.

8.3. Post-operative Data Collection

The interval between graft deployment and discharge will be documented. For specific data included, please refer to case report forms attached in Appendix B.

8.4. Follow-up

The results of the endovascular repair will be assessed by radiological and clinical evaluation, as described in Table 8-1.

For specific data included, please refer to case report forms attached in Appendix B.

8.5. Deaths

Details of any deaths occurring during the study will be stored in a database. Along with the death form, copies of the death certificate (if available) and autopsy report (if applicable) will be maintained. For specific data included, please refer to case report form attached in Appendix B.

8.6. Explants

An autopsy will be requested in all patients who die with a prosthesis in place. At the autopsy, the entire thoracic aorta will be excised from the aortic arch, proximal to the graft, down to and including the celiac artery. Both the excised aorta and the endovascular graft will be fixed in 4% formaldehyde and sent for subsequent examination.

If the prosthesis is excised in the course of conversion to open repair, the position, and attachment of the prosthesis within the arterial tree will be recorded. In addition, every care should be taken to ensure that the prosthesis is removed intact, as long as patient

safety is not compromised. For example, if possible vascular clamps should be applied at remote sites from stent attachments. The prosthesis will then be washed with saline to remove surface thrombus. The graft components will be fixed in 4% formaldehyde and sent for subsequent examination. Do not soak in bleach since bleach affects the evaluation of explant corrosion.

Explanted devices will be examined radiographically while still within the aorta (if applicable) before destructive studies are initiated. Explanted devices will undergo gross and microscopic examination to assess structural integrity of the graft material and stent components. Gross photography and/or scanning electron microscopy will be used to examine the structural integrity of the z-stent components and the attachment barbs as well as the overlap joint. Any device-related gross pathology will also be documented.

Histopathologic studies will be conducted on the aortic tissues in the near vicinity of the endovascular graft as well as in the regions of the attachment sites, the mid-graft region and the main body/leg extension docking sites.

Sites that are unable to comply with the explant protocol will be instructed to contact Cook Research Incorporated for instructions. Data will be collected and stored in a database. For specific data included, please refer to case report form attached in Appendix B.

Fixed explanted device will be sent to:

Cook Research Incorporated

1 Geddes Way

West Lafayette, IN 47906

8.7. Lost to Follow-up

For specific data included, please refer to case report form attached in Appendix B. To ensure maximum follow-up, sites will be expected to attempt contacting a patient for follow-up via telephone, mail, and through the last known contact for the patient. Only when each attempt has been unsuccessful should a patient be considered lost to follow-up.

9. Assessing Outcome

The primary assessment of outcome will be based on long-term survival and device performance (change in aneurysm size, endoleak, migration, device integrity, and secondary interventions). [Information redacted due to confidential content.]

The prevalence of morbidity events in a defined index, occurring within 30 days post-procedure will be assessed. Adverse events comprising the morbidity index are classified into 7 categories. These categories are cardiovascular, pulmonary, renal, gastrointestinal, neurologic, vascular, and wound. Events known to be related to pre-existing conditions or existing at admission are not considered adverse events in the index (e.g., prior medically-treated cardiac arrhythmia with no change in status during the endovascular procedure). Additionally, common standard of care practices are excluded as adverse events (e.g., centers located at high geographical altitudes that discharge all patients on home oxygen therapy regardless of procedure). For specific events to be recorded, please refer to case report form attached in Appendix B.

The events within a category are not of equal severity, but are equally weighted in the index. Because events are equally weighted in the index, an assessment of outcome based on events considered to be severe (disabling) will also be performed. Adverse events comprising the severe (disabling) morbidities were identified consistent with the reporting standards for endovascular repair.[2] The severe morbidities were categorized as cardiovascular, pulmonary, renal, gastrointestinal, neurologic, vascular, and wound. Also included is related death within the same hospitalization or within 30 days of the adverse

event.

Cardiovascular:

1) Q-wave myocardial infarction
2) Cardiac event involving arrest, resuscitation, or balloon pump

Pulmonary:

1) Ventilation >72 hours or re-intubation
2) Pulmonary event requiring tracheostomy or chest tube

Renal:

1) Permanent dialysis, hemofiltration or kidney transplant in a patient with a normal pre-procedure serum creatinine level

Gastrointestinal:

1) Bowel resection

Neurologic:

1) Stroke or severe impairment

Vascular:

1) Amputation involving more than the toes
2) Aneurysm or vessel leak requiring re-operation
3) Deep vein thrombosis requiring surgical or lytic therapy
4) Pulmonary embolism involving hemodynamic instability or surgery
5) Coagulopathy requiring surgery

Wound:

1) Wound complication requiring return to the operating room

Quantitative and qualitative analysis will be performed on the pre-procedural, procedural and follow-up films for all patients. Independent analysis of the images, following standardized protocols and procedures will be conducted by a centralized imaging core laboratory.

10. Statistical Methods

10.1. OPC Development

The OPC is determined from a standard meta-analysis (mixed model approach) of appropriate literature-based control data (in combination with surgical control data from the pivotal study). The reported operative/30-day/in-hospital mortality rates from the selected literature (range 3.0% - 14.3%) were combined with the 365-day mortality rate for open surgery in the pivotal study (11.8%) to generate an OPC for aneurysm-related mortality. Development of the OPC utilized a mixed model approach using SAS's PROC GENMOD (binomial distribution with logit link) with the study as the subject factor in the REPEATED statement. This resulted in an estimate of the overall probability of an aneurysm-related death (7.7%) and corresponding 95% confidence interval (6.6%, 9.0%). It should be noted that assuming a 5-year TAA-related mortality based on the early mortality rate for the population establishes a rigorous comparison for endovascular treatment, as late TAA-related deaths following open repair, which are known to occur to a limited extent (such as due to rupture at the surgical anastomosis), are not captured in the OPC, but are captured in the endovascular treatment arm.

10.2. Analysis Plan [Information redacted due to confidential content.]

The analysis plan for this study will encompass the analyses necessary to perform summary statistics as well as statistical comparisons to an objective performance criterion (OPC). Demographic data, co-morbidities and procedural data will be summarized to provide an overall picture of the endovascular treatment patients prospectively enrolled in the post-approval study. These data will be accompanied by the available literature-derived data, in cases where it is possible to interpret the literature data accurately.

Aneurysm-related mortality is the primary study endpoint, and the primary hypothesis for the post-approval study is non-inferior 5-year aneurysm-related mortality in the

endovascular treatment group compared to open surgery (as derived from literature and the open surgical control patients enrolled in the pivotal study). The hypothesis will be tested by using an exact binomial test (StatXact 8.0) where the test statistic is defined as follows:

$$\hat{\gamma} = \frac{n_{TAA}}{N}$$

where n_{TAA} is the number of patients with aneurysm-related death within 5 years, and N is the total number of patients with 5 year follow-up or death (any cause) within 5 years. This statistic excludes patients that are withdrawn or lost to follow-up, and is consistent in its construction with the formulation and assumptions of the derived OPC.

Other sensitivity analyses may be performed to assess the influence of missing data and cases where the available demographic and co-morbid data suggest imbalances between the control and endovascular treatment data.

11. Risk Analysis

This will be a study of an approved device for which the risks and benefits are described in the labeling. There are no known additional risks from participation in the study. Oversight by the DSMB will allow for detection and assessment of any new information that may affect the known risk/benefit profile.

12. Description of Device

[Information redacted due to confidential content. Refer to the IFU for further information.]

13. Monitoring Procedures

The study will be monitored in accordance with written standard operating procedures consistent with 21 CFR 812 and other applicable regulations.

Name and Address of the Monitor

Cook Research Incorporated

1 Geddes Way

West Lafayette, IN 47906

Telephone: 765-463-7537

Written Procedures for Monitoring the Investigation

Written procedures for monitoring the investigation are maintained by the monitor.

APPENDIX A
Contact Information

Global Sponsor and Monitor

Cook Research Incorporated
1 Geddes Way
West Lafayette, IN 47906
USA

Manufacturer

William Cook Europe
Sandet 6
Bjaeverskov, 4632, DK

APPENDIX B
Definitions

DEFINITIONS

Aneurysm-related Mortality:		Death from any cause occurring within 30 days of the initial procedure or a secondary intervention; or any death determined by the independent clinical events committee to be causally related to the initial implant procedure, secondary intervention, or rupture of the treated aneurysm.
Barb Separation:		Radiographic evidence of detachment of barbs from the stent strut as confirmed by the independent angiographic core laboratory
Calcification:		Calcification will be graded based upon the following:
	None:	Lack of calcification
	Mild:	Less than 40% circumferential calcification;
	Moderate:	40-70% circumferential calcification; or
	Severe:	Greater than 70% circumferential.
Disabling COPD:		Forced expiratory volume (FEV_1) < 1.0 liter or receiving home oxygen therapy.
Embolization:		Clinical evidence of ischemic tissue remote from the operative field, caused by air, thrombus dislodged from the aneurysmal sac and/or aortic neck, including those tissues supplied by vessels in the head, renal arteries, superior mesenteric artery (SMA), pelvic (IIA) vessels and vessels of the lower limbs. This is, of course, distinct from pre-operative, operative or post-operative intentional embolization procedures.
Endoleak:		Contrast-enhanced blood entering the aneurysm sac from around the proximal or distal end of the graft system (Type I), between joints of the graft and extension (if applicable) or through defects in the graft material (Type III), via collateral vessels (Type II), or graft fabric porosity (Type IV).[1]

Endoleak Type Classification:

Type I endoleak:	A peri-prosthetic leak occurring at the proximal and/or distal attachment zones.
Type II endoleak:	A leak caused by retrograde flow from patent vessels. (Requires imaging documentation of Type II source. To classify an endoleak as Type II, documentation with a selective angiogram clearly showing the source is required. Type IIa include significant subclavian, celiac or anomalous vertebral arteries. Type IIb include bronchial and intercostals artery involvement or minor leaks.)
Type III endoleak:	A leak caused by a defect in the graft fabric, inadequate seal (between graft components only), or disconnection of graft ancillary components.
Type IV endoleak:	A leak caused by graft fabric porosity, often resulting in a generalized blush of contrast within the aneurysm sac.
Unknown endoleak:	Continuing blood flow into the aneurysmal sac with undefined origin.
Endoleak (early):	Endoleak within 30 days of device deployment.[1]
Endoleak (late):	Endoleak occurring after 30 days from device deployment, which was not documented during the first 30 days post-deployment.
Left Ventricular Ejection Fraction:	The measurement of the left ventricular function in the resting state. The normal LVEF lies between 55% and 80% (mean = 67%).
Major Complications:	Cardiac events requiring surgical management, prolonged ventilation requiring tracheostomy, renal failure requiring dialysis where not previously needed, aortic fistula, mesenteric ischemia (interruption in blood flow to all or part of the small or large bowel), paralysis or paraperesis unresolved after 30 days of therapy, pulmonary embolism, stroke, and multi-system organ failure.

MI (Non-Q-Wave): Clinical evidence of a myocardial infarction with elevated peak CK values greater than or equal to three times the upper limit of normal with elevated CK-MB (above the institution's upper limit of normal) in the absence of new pathological Q-waves or clinical evidence of a myocardial infarction with troponin greater than three times the upper limit of normal, as determined by the investigator.

MI (Q-Wave): Requires one of the following criteria:

- Post-procedure chest pain or other acute symptoms consistent with myocardial ischemia and the presence of new pathological Q-waves in two or more contiguous ECG leads in the absence of timely cardiac enzyme data.
- New, post-procedure pathological Q-waves in two or more contiguous ECG leads as determined by independent review of the CEC and elevation of cardiac enzymes.

Migration (radiographic): Core laboratory determination of antegrade or retrograde movement of the proximal or distal components of the endoprosthesis > 10 mm relative to anatomical landmarks identified on the first post-operative CT scan.

Migration (clinical): Antegrade or retrograde movement of the proximal or distal components of the endoprosthesis resulting in the need for a secondary intervention.

New York Heart Association Classification:

1. Patient with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea.
2. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest, ordinary physical activity results in fatigue, palpitation or dyspnea.
3. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest, less than ordinary physical activity causes fatigue, palpitation or dyspnea.
4. Patients with cardiac disease resulting in inability to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Occlusive Disease of Iliacs:	Occlusive disease will be graded based upon the following:	
	None:	Lack of occlusive disease
	Mild:	Some disease, focal with less than 30% narrowing
	Moderate:	Between 30-50% narrowing not requiring interventional techniques to meet inclusion criteria
	Severe:	Greater than 50% or any patient requiring angioplasty prior to endograft delivery.
Refractory Hypertension:	Systolic arterial pressure > 160 mmHg despite receiving medication.	
Renal Failure:	Acute or progressive renal insufficiency leading to the need for dialysis or hemofiltration.	
Reversible Ischemic Neurologic Deficit (RIND):	Clinically significant central nervous system deficit lasting > 24 hours and < 72 hours.	
Renal Insufficiency:	A rise in serum creatinine of more than 30% above the pre-procedure level, resulting in a serum creatinine level > 2.0 mg/dl that does not spontaneously resolve (does not include those patients with a pre-procedure serum creatinine > 2.0 mg/dl).	

Serious Adverse Events: Conversion to open repair, aneurysm leak or rupture (blood external to the aneurysm sac as evidenced by contrast enhancement on CT scan, or open visual observation), or death.

Stent/Attachment System Fracture/Break: Fracture or breakage of any portion of the stent or attachment system including metallic fracture or breakage of any suture material used to construct the stent or secure the stent or attachment system to the graft material.

Stroke: Permanent clinically significant central nervous system deficit lasting > 24 hours.

Tortuosity of Iliac Arteries: Tortuosity will be graded based upon the following:

None: Lack of tortuosity

Mild: Fairly straight arteries

Moderate: Angulation manageable with stiff wires, < 70 degrees

Severe: Angulation difficult, may require surgical exposure for straightening, not straightened entirely with wires

Transient Ischemic Attack: Clinically significant central nervous system deficit lasting ≤ 24 hours.