# CLINICAL INVESTIGATION PLAN

Zenith® Fenestrated AAA Endovascular Graft Post-Approval Study
(Long-Term Study)

**Global Clinical Number 11-005**

Sponsor:

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

**Summary of Revisions**

| Version # | Description | Date |
|---|---|---|
| 11-005-01 | Original version | 12 December 2012 |
| 11-005-02 | Provision for retrospective enrollment | 13 March 2013 |
| 11-005-03 | Sponsor change | 04 Apr 2018 |

# CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

## Sponsor Contact

This clinical investigation will be conducted in compliance with the clinical investigation plan (CIP), GCP, ISO 14155, 21CFR812, JGCP and other applicable requirements as appropriate.

Jennifer L. Kerr
Jennifer L. Kerr (Apr 5, 2018)

Signature

05-Apr-2018

Date (DD Mon YYYY)

Jennifer L. Kerr

Printed Name

# CLINICAL INVESTIGATION PLAN SIGNATURE PAGE, CON'T

## Principal Clinical Investigator

I hereby confirm that I approve of this Clinical Investigation Plan and agree to comply with its terms as laid out in this document.

_____ _____

Signature Date (DD Mon YYYY)

_____

Printed Name

# CONFIDENTIALITY STATEMENT

**This document shall be treated as a confidential document for the sole information and use of the clinical investigation team and the Ethics Committee/IRB.**

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## Appendices

## 1.0 Clinical Investigation Plan Overview

The purpose of this post-approval study is to evaluate the long-term safety and performance of the Zenith® Fenestrated AAA Endovascular Graft to treat aortic or aorto-iliac aneurysms in patients with short aortic infrarenal necks by evaluating primarily aneurysm-related mortality.

This study will enroll 88 total patients (including patients enrolled in the pivotal and continued/expanded access phases of the pre-approval study) with 21 new patients to be enrolled (prospectively or retrospectively) from a minimum of 5 sites that will be randomly selected from the pool of institutions that use the standard (non-fenestrated) Zenith AAA Endovascular Graft, did not enroll in the pre-approval study, have completed the commercial training program, and have the necessary research infrastructure and staff to support the study, thus providing for a secondary assessment of commercial training program effectiveness.

Patients with anatomy amenable to endovascular repair and meet other enrollment criteria will be included in the study. Patients who do not meet the criteria will be excluded. A patient will be considered enrolled in the study once the delivery system of the study device has been inserted under the skin.

At the physician's discretion, the Zenith® Alignment Stent may be used to stent visceral vessels targeted by a fenestration. Clinical and imaging follow-up will be performed in accordance with standard of care through 5 years. The primary endpoint is aneurysm-related mortality; additional endpoints to be assessed include morbidity, device integrity, device patency, change in aneurysm size, endoleak, migration, conversion, rupture, and secondary interventions.

## 2.0 Product Description and Intended Use

### 2.1 General Product Description

The Zenith® Fenestrated AAA Endovascular Graft is a modular system consisting of three components, a proximal body graft, a distal bifurcated body graft and one iliac leg. Additional ancillary components (main body extensions, iliac leg extensions, converters, and occluders) are available. The Zenith® Alignment Stent is a balloon-expandable stent that can be deployed through scallops or fenestrations in a Zenith® Fenestrated AAA Endovascular Graft into branch vessels of the aorta.

A more complete product description, discussion of the principle of operation, installation, storage and handling requirements, preparation for use and any intended re-use, pre-use checks for safety and performance, precautions to be taken after use, summary of necessary training and experience, description of procedures required for use, and results from previous clinical experience with the Zenith® Fenestrated AAA Endovascular Graft and Zenith® Alignment Stent, are found in their respective Instructions for Use (IFU).

2.2 Intended Use

The Zenith® Fenestrated AAA Endovascular Graft with the H&L-B One-Shot™ Introduction System is indicated for the endovascular treatment of patients with abdominal aortic or aortoiliac aneurysms having morphology suitable for endovascular repair including:

- Adequate iliac/femoral access compatible with the required introduction systems.
- Non-aneurysmal infrarenal aortic segment (neck) proximal to the aneurysm:
    - with a length of at least 4 mm and unsuitable for a non-fenestrated endograft,
    - with a diameter measured outer wall to outer wall of no greater than 31 mm and no less than 19 mm,
    - with an angle less than 45 degrees relative to the long axis of the aneurysm, and
    - with an angle less than 45 degrees relative to the axis of the suprarenal aorta.
- Ipsilateral iliac artery distal fixation site greater than 30 mm in length and 9-21 mm in diameter (measured outer wall to outer wall).
- Contralateral iliac artery distal fixation site greater than 30 mm in length and 7-21 mm in diameter (measured outer wall to outer wall).

The Zenith® Alignment Stent is indicated for use as an adjunct to the Zenith® Fenestrated AAA Endovascular Graft to assist alignment and patency at the orifice of aortic branch vessels with diameters ranging from 3 to 8 mm.

## 3.0 Objectives of the Clinical Investigation

The purpose of the study is to evaluate the long-term safety and performance of the Zenith® Fenestrated AAA Endovascular Graft to treat aortic or aorto-iliac aneurysms in patients with short aortic infrarenal necks in the US.

3.1 Primary Objectives

The primary objectives of the study is to assess the long-term safety and performance of the Zenith® Fenestrated AAA Endovascular Graft and determine if the 5-year aneurysm-related mortality is reasonable considering the treatment alternatives.

3.2 Secondary Objectives

The secondary objectives of the study are to:

- perform additional assessments of rupture, conversion, morbidity, device integrity, device patency, change in aneurysm size, endoleak, migration, and secondary interventions.
- evaluate commercial training program effectiveness as measured by the composite freedom from the following events at 30 days in up to 3 patients from each site: technical failure, loss of patency (by core lab analysis), rupture, secondary intervention, conversion, Type I or III endoleak (by core lab analysis). Results for patients enrolled by physicians that completed the commercial training

program (i.e., un-proctored cases) will be compared to results for patients treated by physicians that did not complete the training program (i.e., physicians that enrolled patients in the pre-approval study).

3.3 Specific Hypothesis to be Accepted or Rejected by Statistical Data

Long-term safety and performance of the Zenith® Fenestrated AAA Endovascular Graft will be evaluated by testing a primary hypothesis related to the rate of AAA-related mortality.

The primary endpoint will be evaluated according to the hypothesis that patients treated with the Zenith® Fenestrated AAA Endovascular Graft will have a rate of aneurysm-related mortality at 5 years that meets a performance goal of 18% (see Section 6.0), and is expressed as follows:

*Null Hypothesis*: the 5-year AAA-related mortality rate, $\gamma$, is greater than or equal to 18%. (Interpretation: the AAA-related mortality rate does not meet the performance goal.)
$H_0$: $\gamma \geq 18\%$

*Alternative Hypothesis*: the 5-year AAA-related mortality rate, $\gamma$, is less than 18%. (Interpretation: the AAA-related mortality rate does meet the performance goal.)
$H_a$: $\gamma < 18\%$

Same as the agreed upon post-approval study for P070016, which similarly had a 5-year aneurysm-related mortality endpoint, the hypothesis for this study will be tested by using an exact binomial test where the test statistic is defined as follows:

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

where $n_{AAA}$ is the number of patients with AAA-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.

Per FDA request, the primary endpoint will also be assessed through Kaplan-Meier analysis. For this purpose, the primary endpoint (expressed in terms of freedom from aneurysm-related mortality) will be assessed using a Z-statistic against the performance goal of 82%. The Z-statistic is given by:

$$Z = (ARM_{FEN} - 0.82)/SE$$

where

$ARM_{FEN}$ = Kaplan-Meier estimated freedom from AAA-related mortality at 5 years post-procedure.

$SE$ = Standard Error = $\sqrt{V(ARM_{FEN})}$

where $V(ARM_{FEN})$ is the estimate of the variance of the Kaplan-Meier estimate

using the Greenwood formula.

The primary null hypothesis will be rejected in favor of the alternative if $ARM_{FEN} > Z_{\alpha}$*SE-0.082, for $\alpha$=0.05. In testing this hypothesis, all available patients will be used. Patients will be censored based on death, withdrawal, or lost to follow-up dates.

The secondary endpoints of this study will be analyzed using only descriptive statistics, and will not be analyzed for the purpose of statistical inference.

Refer to section 6.0 Statistical Considerations for additional details.

## 4.0 Design of the Clinical Investigation

### 4.1 Type of Investigation

This is a non-randomized, multi-center cohort study consisting of a combination of extended follow-up of subjects included in the pre-approval study (n=67) and newly enrolled subjects (21 patients from a minimum of 5 sites), providing a total enrollment of 88 patients. The newly enrolled patients (to be enrolled either prospectively or retrospectively) will be from centers that were randomly selected from the pool of institutions that use the standard (non-fenestrated) Zenith AAA Endovascular Graft, did not enroll in the pre-approval study, have completed the commercial training program, and have the necessary research infrastructure and staff to support the study. All patients, if found to be eligible for study participation, will be invited to participate in the study. All patients that meet the inclusion criteria/exclusion criteria at participating sites and who are willing to provide consent will be enrolled.

### 4.2 Endpoints

The primary endpoint of the study is to assess the long-term safety of the Zenith® Fenestrated AAA Endovascular Graft as measured by aneurysm-related mortality (AAA-related mortality) through 5 years.

The secondary endpoints of the study are to:

- perform additional assessments of rupture, conversion, morbidity, device integrity, device patency, change in aneurysm size, endoleak, migration, and secondary interventions.
- evaluate training program effectiveness as measured by the composite freedom from the following events at 30 days in up to the first 3 patients from each site: technical failure, loss of patency (by core lab analysis), rupture, secondary intervention, conversion; Type I or III endoleak (by core lab analysis).

### 4.3 Variables to be Measured to Demonstrate Achievement of Endpoints

To evaluate AAA-related mortality, information regarding each patient death (e.g., date of death, cause of death) will be captured on the applicable case report form.

Secondary objectives will be evaluated through the following:

- Complications (e.g., those comprising the morbidity index) and secondary interventions, if any, will be captured throughout the course of the study on

applicable case report forms.

- Assessment of device outcome (e.g., integrity, patency, aneurysm size, endoleak, and migration) will be captured from available intra-operative and follow-up imaging.

4.4 Inclusion Criteria

Patients must meet at least one of the inclusion criteria below to be enrolled in the study. General and medical exclusion criteria will be assessed during the initial patient evaluation by collecting medical history and performing a physical examination. Anatomical exclusion criteria will be assessed using a variety of imaging techniques that are routinely performed during the evaluation of abdominal aortic aneurysms. Sectional imaging will be performed by CT scan. Angiography and intravascular ultrasound will be performed selectively.

Assessment of entry criteria will be based upon data available prior to enrollment. Data obtained peri-operatively and post-operatively may contradict pre-enrollment assessment, and 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 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.

*Inclusion Criteria:*

A patient may be suitable for inclusion in the study if the patient has at least one of the following (and in the opinion of the investigator, is not a good candidate for open surgical repair and also does not have proximal neck anatomy suitable for treatment with a non-fenestrated graft):

1) Aortic or aortoiliac aneurysm with diameter $\geq$ 5 cm
2) Aortic or aortoiliac aneurysm with a history of growth $\geq$ 0.5 cm per year, or clinical indication for AAA repair

*Exclusion Criteria:*

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

General Exclusion Criteria

1) Less than 18 years of age
2) Life expectancy less than 2 years
3) Pregnant or breastfeeding
4) Unwilling to comply with the follow-up schedule
5) Inability or refusal to give informed consent

Medical Exclusion Criteria

1) Baseline creatinine > 2.0 mg/dl
2) Cultural objection to receipt of blood or blood products
3) Allergy to stainless steel, polyester, solder, gold, or nitinol
4) Anaphylactic reaction to contrast that cannot be adequately pre-medicated
5) Leaking/ruptured or symptomatic aneurysm
6) Uncorrectable coagulopathy
7) Previous stent at the ostium of any renal or visceral artery to be accommodated with a small fenestration

Anatomical Exclusion Criteria

1) Prohibitive occlusive disease, tortuosity, or calcification of intended access vessels
2) Prohibitive occlusive disease, tortuosity, or calcification of intended fixation sites
3) Proximal neck < 4 mm, or ≥ 15 mm in length unless otherwise compromised to preclude seal
4) Proximal neck, measured outer wall to outer wall on a sectional image (CT), > 31 mm in diameter or < 19 mm in diameter
5) Proximal neck angulated more than 45 degrees relative to the long axis of the aneurysm
6) Immediate suprarenal neck angulated more than 45 degrees relative to the immediate infrarenal neck
7) Proximal neck diameter change over the length of the proximal seal zone ≥ 4 mm
8) Proximal seal site with circumferential thrombus/atheroma above the renal arteries
9) Tortuosity, calcification, or arterial diameter, measured inner wall to inner wall on a sectional image (CT), that is not conducive to placement of the 20 Fr introducer sheath
10) Ipsilateral iliac artery fixation site diameter, measured outer wall to outer wall on a sectional image (CT), < 9.0 mm (prior to deployment) unless an additional iliac leg graft is to be deployed
11) Iliac artery diameter, measured outer wall to outer wall on a sectional image (CT), < 7.0 mm or > 21 mm at distal fixation site
12) Iliac artery distal fixation site < 30 mm in length
13) Inability to maintain at least one patent hypogastric artery
14) Renal artery stenosis > 50% (prior to deployment)
15) Non-bifurcated segment of any artery to be stented < 15 mm in length, unless an uncovered stent is intended to be deployed.
16) Artery to be stented with a maximum diameter < 3 mm or > 8 mm at the vessel ostium
17) Unsuitable arterial anatomy

## 4.5 Point of Enrollment

Point of enrollment will be based on the intent-to-treat population, and is defined to include any patient for which informed consent has been obtained and the treatment procedure is initiated. More specifically, once the delivery system of the study device (Zenith® Fenestrated AAA Endovascular Graft) has been inserted under the patient's skin, this patient would be included in the intent-to-treat population. Primary statistical analyses will be based on this set of patients.

### 4.6 Enrollment Objective and Study Timeline

The training requirements, anticipated rate of enrollment (based on that from the pre-approval study, which averaged 0.79 patients/site/year during the final year prior to approval), and length of follow-up dictate the overall timeline for the study. Each physician will first need to complete the training program and case proctoring before becoming eligible to enroll cases in the post-approval study. Based on this, and given that at least 5 sites will participate in this long-term study, a training period (including proctoring) and study start-up period (with IRB review, which cannot initiate until the protocol is formally approved by FDA) of approximately 1.25 years (beginning in June 2012) is anticipated prior to the sites being eligible to enroll (by September 2013), following which it is estimated to take approximately 5 years to complete enrollment of 21 new patients (for an approximate enrollment completion date of September 2018). Follow-up data will continue to be collected for 5 years after graft deployment (completing by September 2023), with a final report projected to be submitted approximately 3 months after patient follow-up is completed (December 2023).

## 5.0 Methods

For information related to endovascular graft planning and sizing, choosing and measuring proximal and distal fixation sites, determining anatomical lengths, endovascular graft and fenestration stent placement procedures, follow-up care, and treatment of endoleaks, please refer to the device IFU.

Informed consent will allow for follow-up data to be collected according to standard of care for five years after graft deployment for each patient in the study.

### 5.1 Measurements and Data Collection

Clinical data and imaging measurements will be collected on standardized forms. Clinical and imaging follow-up will be performed in accordance with standard of care at each institution through 5 years. An example of the expected standard of care follow-up for the Zenith® Fenestrated AAA Endovascular Graft is provided in the table below (Table 5.1-1).

Table 5.1-1. Expected standard of care follow-up schedule

| **Example of Expected Follow-up Schedule** | | | | | |
|---|---|---|---|---|---|
| | Pre-procedure | Procedure | 30 Day | 6 Month (optional) | 12 Month[3] |
| Clinical exam | X | | X | X | X |
| CT | X | | X[1] | X[1] | X[1] |
| Device x-ray | | | X | X | X |
| Angiography | X[2] | X | | | |
| Renal duplex ultrasound | X | | X | X | X |
| Blood tests to assess renal function (e.g., serum creatinine, BUN) | X | | X | X | X |

[1] Duplex ultrasound along with a non-contrast CT may be used to assess the aneurysm for those patients experiencing renal failure or who are otherwise unable to undergo contrast enhanced CT scan.
[2] Pre-procedure angiography may be required at the discretion of the implanting physician or film reviewer.
[3] Patients will be followed at yearly intervals through five years.

## 5.2 Subject Consent

Patients who meet the inclusion/exclusion criteria will be invited to participate in this investigation. All patients eligible for entry into the investigation will have the clinical investigation plan explained to them, as well as potential risks and benefits of their participation in the investigation. Each patient who agrees to participate will be required to sign an informed consent document prior to his or her enrollment into the study.

## 5.3 Pre-procedure

Detailed pre-procedural examination data will be collected for patients meeting the selection criteria who have provided informed consent. Information collected will include a patient history as well as anatomical information from available imaging.

## 5.4 Procedure

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. Data collected will include the number of arteries stented and the types of stents used.

## 5.5 Follow-up

The results of the endovascular repair will be assessed by radiologic and/or clinical criteria in accordance with standard of care through 5 years. An example of the expected standard of care for patients implanted with the Zenith® Fenestrated AAA Endovascular Graft is described in Table 5.1-1. Data collected will include the results of available clinical and imaging assessments as well as the available details of any deaths, conversions, ruptures, adverse events, explants, or cases of patients who are lost to follow-up or withdraw from the study.

Information on clinical outcomes is expected to be collected annually through 5 years post-procedure on at least 80% of patients enrolled (excluding those discontinued due to death).

To ensure maximum follow-up, each patient's nominal anniversary date for follow-up will be calculated upon enrollment and provided to both the patient and the site. Sites will be notified if follow-up data have not been received for patients who are eligible, and sites will be expected to attempt to contact 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 (LTF). The investigator is also expected to remind the patient about the importance of adhering to the study follow-up schedule.

## 5.6 Imaging Protocols

Imaging will be performed according to the standard of care at each institution. Available imaging will be reviewed by an independent imaging core laboratory to ensure uniform and independent interpretation of the data.

## 5.7 Assessing Outcome

The primary assessment of outcome will be based on long-term freedom from AAA-related death at 5 years. Additional assessments include rupture, conversion, morbidity, device integrity, device patency, change in aneurysm size, endoleak, migration, and secondary interventions.

The morbidity index will be calculated as a composite rate of adverse events. This index is defined as the proportion (percentage) of patients who have one or more of the listed events within a category (see Appendix C). Adverse events comprising the morbidity index are classified into 7 categories. These categories are cardiovascular, pulmonary, renal, gastrointestinal, wound, neurologic, and vascular. While the events within a category are not of equal severity, they are weighted equally in the index. Pre-existing conditions at admission are not considered adverse events in the index (e.g., home oxygen therapy prior to admission). 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).

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

## 6.0 Statistical Considerations

### 6.1 Performance Goal Development

The target population for the Zenith Fenestrated AAA Endovascular Graft is composed of patients who are generally not good candidates for open surgery, have unsuitable anatomy for standard (non-fenestrated) endografts, and thus have medical management as the only option for preventing aneurysm rupture. The outcome associated with patients who refuse or are unfit for surgery therefore provides an appropriate comparison for Zenith Fenestrated. The rate of death due to rupture in such patients can range from 18 to 36%.[1,2,3] Based on the limited treatment options otherwise available for patients requiring a Fenestrated Graft and the associated outcomes, a performance goal of 18% for 5-year aneurysm-related mortality is justified.

### 6.2 Sample Size Calculation

Evaluation of the primary hypothesis, 5-year AAA-related mortality rate, requires 70 patients to determine if the performance goal of 18% has been met. Cook will enroll a total of 88 patients, allowing for an additional 14% for patients who may withdraw or be lost to follow-up (based on the rate from the pre-approval study) plus 6 additional patients to compensate for a one-time loss of 6 patients who refused to consent for long-term follow-up in the pre-approval study.

Sample size calculation for the primary hypothesis can be performed with the following assumptions. Using a performance goal of 18%, an expected mortality rate of 8%, a one-sided test with exact binomial calculation, a type I error rate of 0.05 and power of 0.8, 70 patients are required to demonstrate that the Zenith® Fenestrated AAA Endovascular Graft meets the stated performance goal. The calculation was performed with the SAS UnifyPow macro.

Information on clinical outcomes is expected to be collected annually through 5 years post-procedure on at least 80% of patients enrolled (excluding those discontinued due to death).

### 6.3 General Statistical Analyses

Descriptive summaries will be provided where appropriate for each of the primary and secondary variables. In general, summaries will be complete over the total population. Continuous variable summaries will include the number of subjects (N), mean, standard

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[1] Lederle FA, Johnson GR, Wilson SE, et al. Rupture rate of large abdominal aortic aneurysm in patients refusing or unfit for elective repair. JAMA 2002; 287: 2968-2972.

[2] Aziz M, Hill AA, Bourchier R. Four-year follow up of patients with untreated abdominal aortic aneurysms. ANZ J Surg 2004; 74: 935-40.

[3] Conway, KP, Byrne J, Townsend M, Lane IF. Prognosis of patients turned down for conventional abdominal aortic aneurysm repair in the endovascular and sonographic era: Szilagyi revisited? J Vasc Surg 2001; 33: 752-7.

deviation. Categorical variable summaries will include the frequency and percentage of subjects who are in the particular category. In general the denominator for the percentage calculation will be based upon the total number of subjects with the measurement, unless otherwise specified. Patients with missing variables will not be included in percentage calculations, unless otherwise specified.

## 7.0 Risk Analysis and Risk Assessment

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. Please refer to the IFU for a complete list of the risks associated with the use of this device.

## 8.0 Safety Monitoring and Event Reporting

### 8.1 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) consisting of independent physicians, who are not investigators in the investigation, nor have a perceived conflict of interest with the conduct and administration of the investigation, may be convened on a regular basis to evaluate investigation progress and review adverse events.

### 8.2 Clinical Events Committee

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

Regularly scheduled review/monitoring of all patient data will be conducted at the Data Coordinating Center, in part, for identification of adverse events and assurance that they are correctly reported to the DSMB and CEC.

### 8.3 Adverse Event Reporting

Adverse events will be captured on an Event form and reported to the Data Coordinating Center. Event forms should be submitted to the Data Coordinating Center immediately upon knowledge of the event.

Sites will be responsible for following their normal reporting process (e.g., to manufacturer, to investigational review board/ethics committee) for any problems with the devices. The Data Coordinating Center will also review the information submitted within the clinical study for possible vigilance reporting to the manufacturer.

## 9.0 Administrative

### 9.1 Data Collection

Data will be collected on case report forms (CRFs) as described herein. Patient data will

be collected and provided by the investigative site to the sponsor by qualified personnel.

9.2 Data Management and Quality Assurance

Patient demographics, procedural information and follow-up data will be collected on standardized CRFs. Data are verified for accuracy and consistency, and all data edits are tracked with a verifiable audit trail.

9.3 Data Reporting

Progress reports every six months during the first two years and annually thereafter, and a final report at the conclusion of the clinical investigation will be submitted by the investigators and sponsor to the regulatory bodies and IRBs as required by local regulations.

9.4 Criteria and Procedures for Withdrawal

The reasons for withdrawal and discontinuation of any patient from the investigation shall be recorded. If such discontinuation is because of problems with safety or lack of effectiveness, that patient shall still be followed in the investigation, if possible.

9.5 Publication Policy

Publication policy, rights and obligations for this investigation have been negotiated, detailed and defined in the Investigation Contractual Documents and Agreements with the Investigation Site and Investigators.

9.6 Approvals and Agreements

The sponsor and the principal clinical investigators for each site shall agree to this document and any modifications. A justification for any modifications will be documented. Approval and agreement will be indicated by signing and dating the appropriate document.

9.7 General Information

9.7.1 Sponsor

The Sponsor for this investigation is Cook Research Incorporated. See Appendix A for contact information.

9.7.2 Manufacturer

The Manufacturer for this investigation is William A. Cook Australia Pty. Ltd. for the Zenith® Fenestrated AAA Endovascular Graft and Cook Incorporated for the Zenith® Alignment Stent. See Appendix A for contact information.

9.7.3 Data Coordinating Center/Monitor

The Data Coordinating Center for this study is Cook Research Incorporated. See Appendix A for contact information.

9.7.4 Investigation Compliance

This clinical investigation shall not begin until the required approval from the IRB and

regulatory authority has been obtained.

Additional requirements imposed by an IRB or regulatory authority shall be followed, if appropriate.

9.7.5 Investigators
A complete list of the principal clinical investigators, clinical investigators, and core lab, along with their contact information and respective site information, will be updated and maintained by the Data Coordinating Center and updates will be sent to sites periodically, as needed.

9.7.6 Monitoring Arrangements
The monitor for this investigation is Cook Research Incorporated. See Appendix A for contact information.

The investigation will be monitored in accordance with written standard operating procedures consistent with applicable regulations. Written procedures for monitoring the investigation are maintained by the monitor and can be found in Appendix B.

## 10.0 Bibliography

A review of the available literature on the Zenith® Fenestrated AAA Endovascular Graft for treatment of juxtarenal aortic aneurysms has been performed. A list of the significant references regarding this technology is provided below.

1) Nordon IM, Hinchliffe RJ, Holt PJ, Loftus IM, Thompson MM. Modern treatment of juxtarenal abdominal aortic aneurysms with fenestrated endografting and open repair--a systematic review. Eur J Vasc Endovasc Surg. 2009;38:35-41.

2) Amiot S, Haulon S, Becquemin JP, Magnan PE, Lermusiaux P, Goueffic Y, et al. Fenestrated endovascular grafting: the French multicentre experience. Eur J Vasc Endovasc Surg. 2010;39:537-44.

3) Haulon S, Amiot S, Magnan PE, Becquemin JP, Lermusiaux P, Koussa M, et al. An analysis of the French multicentre experience of fenestrated aortic endografts: medium-term outcomes. Ann Surg. 2010;251:357-62.

4) Kristmundsson T, Sonesson B, Malina M, Björses K, Dias N, Resch T. Fenestrated endovascular repair for juxtarenal aortic pathology. J Vasc Surg. 2009;49:568-74.

5) Chisci E, Kristmundsson T, de Donato G, Resch T, Setacci F, Sonesson B, et al. The AAA with a challenging neck: outcome of open versus endovascular repair with standard and fenestrated stent-grafts. J Endovasc Ther. 2009;16:137-46.

6) Verhoeven EL, Vourliotakis G, Bos WT, Tielliu IF, Zeebregts CJ, Prins TR, et al. Fenestrated stent grafting for short-necked and juxtarenal abdominal aortic aneurysm: an 8-year single-centre experience. Eur J Vasc Endovasc Surg. 2010;39:529-36.

7) Verhoeven EL, Prins TR, Tielliu IF, van den Dungen JJ, Zeebregts CJ, Hulsebos RG, et al. Treatment of short-necked infrarenal aortic aneurysms with fenestrated stent-grafts: short-term results. Eur J Vasc Endovasc Surg. 2004;27:477-83.

8) Beck AW, Bos WT, Vourliotakis G, Zeebregts CJ, Tielliu IF, Verhoeven EL. Fenestrated and branched endograft repair of juxtarenal aneurysms after previous open aortic reconstruction. J Vasc Surg. 2009;49:1387-94.

9) Greenberg RK, Haulon S, Lyden SP, Srivastava SD, Turc A, Eagleton MJ, et al. Endovascular management of juxtarenal aneurysms with fenestrated endovascular grafting. J Vasc Surg. 2004;39:279-87.

# APPENDIX A
Contact Information

## Contact Information

**Sponsor, Monitor, and Data Coordinating Center**
Cook Research Incorporated
1 Geddes Way
West Lafayette, IN 47906
USA

| | |
|---|---|
| Contact: | Jennifer L. Kerr, President, Cook Research Incorporated |
| Telephone: | (765) 463-7537 |
| Fax: | (765) 497-0641 |
| E-mail: | Jennifer.Kerr@CookMedical.com |

**Manufacturer (Zenith® Fenestrated AAA Endovascular Graft)**
William A. Cook Australia Lty. Ptd.
95 Brandl Street
Eight Mile Plains
Brisbane, QLD 4113, Australia

**Manufacturer (Zenith® Alignment Stent)**
Cook Incorporated
750 Daniels Way
Bloomington, IN 47404
USA

# APPENDIX B

Written Procedures for Monitoring Investigations

## Written Procedures for Monitoring Clinical Investigations

A. Selection of the monitor.

Designated by the sponsor to oversee the investigation, the monitor may be an employee of Cook, an employee of a monitoring organization (CRO) or an independent contractor or consultant. The monitor shall be qualified by training and experience to monitor the investigation in accordance with all applicable regulations and standards for conducting clinical investigations.

B. General duties of the monitor.

The monitor must ensure that the investigation is conducted in accordance with:

1. The signed investigator agreement.
2. The Clinical Investigation Plan (CIP)/protocol.
3. Any conditions imposed by the IRB/EC or regulatory authority.
4. The requirements of the applicable regulations and standards.

C. Reports by the monitor to the sponsor.

1. Any noncompliance with the items listed above. In the event that the investigator is not complying with the requirements outlined above, it is the sponsor's responsibility to secure compliance.
2. Any adverse events or effects that are potentially reportable to a regulatory authority.

D. Initiating the investigation.

Prior to initiating any clinical use of the device, the monitor will participate in a pre-investigation or initiation visit with each investigative site.

At a minimum, the following items shall be addressed during the site initiation visit:

- Provide training to investigator on his/her responsibilities per the investigator agreement, applicable laws, regulations and standards; and
- Provide training to investigator that the IRB/EC approval letter and informed consent/patient information is on file before initiation of the clinical investigation.

Additionally, training may be provided to the investigator on:

- The regulatory status of the device/product(s) and the requirements for the accountability of same;
- The nature of the clinical investigation plan (CIP);
- The requirements for an adequate and well-controlled clinical investigation;
- His or her obligation to obtain informed consent in accordance with applicable regulations;
- His or her obligation to ensure continuing review of the clinical investigation by the IRB/EC in accordance with conditions of approval and applicable regulations and to keep the sponsor informed of such IRB/EC approval and subsequent IRB/EC actions concerning the investigation;
- The importance of access to an adequate number of suitable subjects to conduct the investigation;
- The importance of adequate facilities for conducting the clinical investigation; and
- The importance of sufficient time from other obligations to carry out the responsibilities to which the investigator is committed by applicable regulations.

E. During the course of the investigation, at the direction of the Project Manager, the monitor should visit the site frequently enough to ensure that:

- The facilities and research staff used by the investigator continue to be acceptable for purposes of the clinical investigation;
- The applicable version of the CIP and agreements are being followed;
- Changes to the CIP, informed consent/patient information have been approved by the IRB/EC and/or reported to the sponsor and the IRB/EC;
- Accurate, complete, and current records are being maintained;
- Accurate, complete, and timely reports are being made to the sponsor and IRB/EC; and
- The investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff.

As appropriate, the following tasks could be performed during periodic visits:

- Device/product accountability review;
- Adverse event review to ensure that events are appropriately reported within the time periods required by the sponsor, CIP, IRB/EC, and applicable regulatory requirements; and
- Source data verification per the monitoring plan to determine that :

- Informed consent/patient information has been documented in accordance with applicable regulations and expectations of local IRB/EC;
- The information recorded in the case report forms (paper or electronic) is complete, accurate, and legible;
- There are no omissions in the CRFs of specific data elements, such as the administration to any patient of concomitant test articles or the development of an intercurrent illness;
- Missing visits or examinations are noted; and
- Subjects failing to complete the clinical investigation and the reason for each failure are noted.

F. Records of the monitor.

The monitor shall prepare and maintain records of each initiation visit and each periodic visit, general site contact, or discussion. These will include:

1. Date, name and address of the investigator, and names of other staff members present at each meeting.
2. A summary of the findings of the visit.
3. A statement of any action taken by the monitor or investigator to correct any deficiencies noted.
4. The monitor shall immediately notify the sponsor of any conditions of non-compliance with the protocol, Clinical Investigation Plan, conditions of IRB/EC or regulatory authority approval, or the applicable regulations.

## APPENDIX C
Definitions

## Definitions

*Aneurysm-related mortality:* Death from aneurysm rupture through 5 years; death from any cause occurring within 30 days of the initial procedure or a secondary intervention; or any death determined to be related to the aneurysm or its treatment.

*Proximal neck:* Infrarenal aortic segment from the lowest level of the distal-most renal artery intended to remain patent, to the proximal end of the aneurysmal aorta.

*Calcification:* Calcification will be graded based upon the following:

None: Lack of calcification
Mild: Less than 40% circumferential calcification
Moderate: 40-70% circumferential calcification
Severe: Greater than 70% circumferential

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

*Occlusive disease of iliac arteries:* 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 and 50% narrowing not requiring interventional techniques to meet entry criteria
Severe: Greater than 50% or any patient requiring angioplasty prior to endograft delivery

*MI (Non-Q-Wave)*: Clinical evidence of a myocardial infarction with elevated peak CK values greater than 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):* Post-procedure presence of new Q-waves greater than 0.04 seconds in at least two EKG leads.

*Renal failure*: Acute or progressive renal insufficiency leading to the need for dialysis or hemofiltration.

*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).

*Embolization:* Clinical evidence of ischemic tissue remote from the operative field, presumably caused by thrombus dislodged from the aneurysmal sac, aortic neck, or adjacent vessels, including ischemia of the kidneys, pelvis (IIA), or lower limbs. This is, of course, distinct from intentional pre-operative, operative, or post-operative embolization procedures.

*Limb occlusion:* The presence of thrombus within one, or both, of the graft limbs (including any legs and extensions) creating occlusion.

*Type I endoleak:* A peri-prosthetic leak occurring at the proximal and/or distal fixation zones, including leakage around fenestrations.

*Type II endoleak:* A leak caused by retrograde flow from patent lumbar or inferior mesenteric arteries.

*Type III endoleak:* A leak caused by a defect in the graft fabric, or inadequate seal of modular graft components.

*Type IV endoleak:* A leak caused by graft fabric porosity, often resulting in a generalized blush of contrast within the aneurysm sac.

*Endoleak (early):* Any endoleak observed within 30 days of device deployment.

*Endoleak (late):* Any endoleak observed later than 30 days after device deployment that was not documented during the first 30 days post-deployment.

*Radiographic migration (stent-graft):* Antegrade or retrograde movement of the stent-graft $\geq$ 10 mm at the level of the renal arteries as compared to the position on the first post-operative CT scan.

*Radiographic migration (fenestration stent):* Antegrade or retrograde movement of a fenestration stent $\geq$ 10 mm within the stented artery as compared to the position on the first post-operative CT scan.

*Clinically significant migration (stent-graft):* Antegrade or retrograde movement of the stent-graft requiring surgical or endovascular intervention.

*Clinically significant migration (fenestration stent):* Antegrade or retrograde movement of any fenestration stent requiring surgical or endovascular intervention.

*Barb separation*: Radiographic evidence of detachment of barbs from the stent strut as confirmed by the independent imaging core laboratory.

*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 as confirmed by the independent imaging core laboratory.
*Technical success:* Successful access of the aneurysm site and deployment of the Zenith® Fenestrated AAA Endovascular Graft in the intended location. The endovascular graft and all vessels targeted with fenestrations must be patent at the time of deployment completion as evidenced by intraoperative angiography.

*Procedural success:* Technical success, with all of the following at 30 days:

- No Type I or Type III endoleaks;
- No procedure related serious adverse events or major complications; and
- Patency of the endovascular graft and all vessels targeted with fenestrations as evidenced by CT scan, angiography, or duplex ultrasound.

*Treatment success:* Technical success, with all of the following at 6 months:

- No Type I or Type III endoleaks;
- No AAA-related serious adverse events or AAA-related major complications; and
- No aneurysm enlargement greater than 0.5 cm.

*Serious adverse event:* Occurrence of any of the following:

- Death;
- Aneurysm rupture; or
- Conversion to open surgical repair.

*Major complication:* Occurrence of a serious adverse event, or any of the following:

- Q-wave myocardial infarction;
- New onset of congestive heart failure occurring within 30 days of procedure;
- Cardiac ischemia requiring intervention;
- Renal failure requiring permanent dialysis;
- Bowel obstruction, ischemia, or fistula;
- Stroke with permanent deficit; or
- Paralysis.

*Adverse events included in the Morbidity Index*:

Cardiovascular

1) Q-wave myocardial infarction;
2) Non-Q-wave myocardial infarction;
3) Congestive heart failure;
4) Arrhythmias which require intervention or treatment;

5) Cardiac ischemia requiring intervention;
6) Inotropic support; and
7) Medically intractable hypertension
(excludes patients with these conditions pre-procedure).

Pulmonary

1) Reintubation;
2) Ventilation >24 hours;
3) Pneumonia requiring antibiotics; and
4) Patient receiving supplemental oxygen at discharge
(excludes patients with these conditions pre-procedure).

Renal

1) Dialysis in patients with normal pre-operative renal function;
2) Creatinine rise >2 mg/dl and >30% from baseline on two or more follow-up tests;
3) Occlusion of a fenestrated renal vessel; and
4) Renal infarct.

Creatinine levels will be assessed regularly based on standard of care. Two successive values on scheduled follow-ups (e.g., post-discharge and 30 days) greater than 2 mg/dl which also represent a 30% increase from baseline will be considered definitive for renal impairment. Transient creatinine elevations due to contrast loading without clinical consequences (normal renal function) are not expected to be reflected in sustained creatinine elevations and are not considered adverse clinical events for the purpose of this study.

GI

1) Bowel obstruction;
2) Bowel ischemia/infarct;
3) Aorto-enteric fistula; and
4) Paralytic ileus > 4 days
(excludes patients with these conditions pre-procedure)

Wound

1) Wound infection requiring antibiotic treatment;
2) Incisional hernia;
3) Lymph fistula;
4) Seroma requiring treatment;
5) Wound breakdown requiring debridement; and
6) Wound complication requiring return to operating room
(excludes patients with these conditions pre-procedure)

Neurologic

1) Stroke;

2) TIA/RIND; and
3) Spinal cord ischemia/paralysis
(excludes patients with these conditions pre-procedure)

Vascular

1) Limb thrombosis;
2) Embolization resulting in tissue loss or requiring intervention;
3) Transfusion post-procedure (resulting from pseudoaneurysm, vascular injury, aneurysm leak, or other procedure related causes;
4) Pseudoaneurysm;
5) Vascular injury (such as inadvertent occlusion, dissection, or other procedure related causes);
6) Aneurysm leak or rupture;
7) Increase in aneurysm size by more than 0.5 cm relative to the smallest of any prior measurement; and
8) Occlusion of a fenestrated SMA or celiac artery.
(excludes patients with these conditions pre-procedure)