CLINICAL INVESTIGATION PLAN

Study Assessing Safety and Effectiveness of Perivisceral Aortic Aneurysm Treatment with the Zenith® Fenestrated AAA Endovascular Graft or the Zenith® p-Branch® and the Effects on Organ and Extremity Perfusion

Global Clinical Number 07-003

Sponsor: Cook Research Incorporated
1 Geddes Way
West Lafayette, IN 47906

Summary of Changes:

Version	Description	Date
07-003-01	Orignal version	26 February 2007
07-003-02	Clarified that the DSMB will be independent and that each Fenestrated graft will be specifically designed for each patient	13 April 2007
07-003-03	Added the Zenith® Alignment Stent, increased the maximum number of fenestrations (3 to 4), allowed large fenestrations on the proximal component	14 May 2010
07-003-04	Added the Zenith® p-Branch® device	28 February 2012
07-003-05	Combined the pre-discharge and 30-day follow-up visits	3 October 2014
07-003-06	Figures 1.5.2-1, 1.5.2.1-1, 1.5.2.1-2, and 1.5.2.2-1 were updated to reflect device and delivery system changes. Proximal neck	10 December 2014

	diameter exclusion criterion was updated to align with the current IFU	
07-003-07	Removed Duplex Ultrasound after 12 months and ABIs/Pulse assesments after 30 days. Removed X-ray and Renal Scintigraphy imaging requirements. Removed PT, APTT, INR, pH, ESR, CBC, and urine eosinophil tests. Removed core temperature assessments. Modified pre-procedure though follow-up data collection requirements. Added written monitoring procedures.	19-Nov-2015
07-003-08	Changed Sponsor from Cook Incorporated to Cook Research Incorporated. Removed designee and added the title, email, address and fax number to the Name and Address of the Monitor.	26-Mar-2018

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

Sponsor Contact:

This clinical study will be conducted in accordance with the Clinical Investigation Plan (CIP), 21 CFR 812, and other applicable requirements as appropriate. The CIP will be revised, as appropriate, based on new information.

X _____ _____

Signature Date (DD Mon YYYY)

_____ _____

Printed Name Title

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE
Continued

Principal 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.

X _____ _____

Signature Date (DD Mon YYYY)

_____ _____

Printed Name Title

CONFIDENTIALITY STATEMENT

This document shall be treated as a confidential document for the sole information and use of the clinical study team and the Institutional Review Board (IRB).

Table of Contents

1. INVESTIGATIONAL PLAN

1.1. Purpose

The purpose of this study is to assess safety and effectiveness and examine in detail the effect of fenestrated stent-graft technology on organ and extremity perfusion, using the Zenith® Fenestrated AAA Endovascular Graft or the Zenith® p-Branch®.

1.1.1. Name and Intended Use of the Device

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. In some instances, the physician may also choose to use a Zenith® Alignment Stent, which 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 mm to 8 mm.

The Zenith® p-Branch® with the Zenith® preloaded delivery system is indicated for the endovascular treatment of patients with abdominal aortic aneurysms having morphology suitable for endovascular repair. The Zenith® p-Branch® may require adjunctive placement of a balloon-expandable covered stent to assist with alignment and patency at the renal and visceral vessels incorporated by the Zenith® p-Branch® endovascular graft fenestrations.

1.1.2. Specific Aims

This study is intended to:

1. Assess safety and effectiveness of the Zenith® Fenestrated AAA Endovascular Graft to exclude AAA;
2. Assess safety and effectiveness of the Zenith® p-Branch® to exclude AAA;
3. Monitor highly sensitive indicators of end organ and extremity perfusion;
4. Provide additional refinement of the patient population that can potentially benefit from fenestrated stent-grafts.

1.1.3. Duration of the Investigation

It is anticipated that patient recruitment could be completed within 84 months of initiating the study. Follow-up data will continue to be collected for five years after graft deployment for each patient in the study, making the study duration approximately 12 years.

1.2. Study Design

The design will be a prospective non-randomized study enrolling up to 40 patients to receive either the Zenith® Fenestrated AAA Endovascular Graft or the Zenith® p-Branch® at two clinical sites. No comparison groups will be included within this study, although study results may be compared with those from other similar patient groups.

1.2.1. Limitations of the Study

Due to the overall diminished life-expectancy of the predominantly high risk patient population to be enrolled, it is anticipated that there will be a number of unrelated deaths that will reduce the number of patients surviving to the end of study follow-up. This study is designed to assess short, medium, and long-term outcomes related specifically to organ and extremity perfusion.

1.2.2. Safety Monitoring

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, will be convened on a regular basis to evaluate investigation progress and review adverse events.

Clinical Events Committee

An independent clinical events committee (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 events were due to a pre-existing or unrelated condition, procedure-related, technique-related, and/or device-related.

1.3. Specific Protocol

1.3.1. Definitions

Proximal neck for treatment with the Zenith® Fenestrated AAA Endovascular Graft:

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.

Proximal sealing zone for treatment with the Zenith® p-Branch®:

Aortic segment from the distal-most aspect of the celiac artery to the proximal end of the aneurysmal aorta.

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.

Tortuosity of iliac arteries 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 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 entry criteria
- Severe: Greater than 50% or any patient requiring angioplasty prior to endograft delivery.

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.

Disabling chronic obstructive pulmonary Disease (COPD):

Having a forced expiratory volume (FEV_1) <1.0 liter or receiving home oxygen therapy.

Medically intractable Hypertension:

Having a systolic arterial pressure >160 mmHg despite receiving medication.

MI (Non-Q-Wave):

Investigator identified patients having 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 institutions 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 in the case of bare stents in visceral vessels incorporated by 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 including leakage around fenestrations in the case of covered stents in visceral vessels incorporated by the fenestrations.

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 relative to anatomical landmarks identified on the first post-operative CT scan.

Radiographic migration (stent):

Antegrade or retrograde movement of a fenestration stent ≥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 (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.

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.

Technical Success:

Successful access of the aneurysm site and deployment of the Zenith® Fenestrated AAA Endovascular Graft or the Zenith® p-Branch™ 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 post-procedure (within 30 days):

- No type I or type III endoleaks;
- No procedure related serious adverse events or major complications;

- Patency of the endovascular graft and all vessels targeted with fenestrations as evidenced by CT scan, angiography or by duplex ultrasound in those patients experiencing renal failure or otherwise unable to undergo contrast enhanced CT scan.

Treatment Success:

Procedural Success, with all of the following at 12 months:

- No type I or type III endoleaks;
- No serious adverse events or major complications;
- No aneurysm enlargement greater than 0.5 cm;
- Patency of the endovascular graft and all vessels targeted with fenestrations as evidenced by CT scan, angiography or by duplex ultrasound in those patients experiencing renal failure or otherwise unable to undergo contrast enhanced CT scan.

Serious adverse event:

Occurrence of any of the following:

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

Major complication:

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

- Q-wave myocardial infarction;
- Congestive heart failure;
- Cardiac ischemia requiring intervention;
- Renal failure requiring dialysis;
- Bowel obstruction, ischemia, or fistula;
- Stroke;

- Paralysis.

1.3.2. Entry Criteria

Patients must meet at least one of the inclusion criteria to be enrolled in the study. General and medical exclusion criteria will be assessed during the initial patient evaluation by conducting a history and 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 as needed to further assess inclusion/exclusion criteria.

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

General inclusion criteria

A patient may be suitable for inclusion in the study if the patient has at least one of the following:

1. Abdominal aortic aneurysm $\geq$5.0 cm or 2 times the normal aortic diameter;
2. Abdominal aortic aneurysm with history of growth $\geq$0.5 cm in 6 months;
3. Penetrating juxtarenal aortic ulcer $\geq$10 mm in depth and 20 mm in diameter.

General exclusion criteria (all must be no):

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

1. Age <18 years;

2. Life expectancy <2 years;
3. Pregnant or breast feeding;
4. Inability or refusal to give informed consent;
5. Unwilling or unable to comply with the follow-up schedule.

Medical exclusion criteria (all must be no):

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

1. Allergy to stainless steel, polyester, solder, gold, or nitinol;
2. Anaphylactic reaction to contrast that cannot be adequately pre-medicated;
3. Leaking/ruptured or symptomatic aneurysm;
4. Uncorrectable coagulopathy;
5. Previous orificial stent in any vessel to be accommodated with a small fenestration that protrudes into the aorta (for the Zenith® Fenestrated AAA Endovascular Graft);
6. Previous orificial stent in any vessel to be accommodated with the SMA fenestration or pivot fenestrations that protrudes into the aorta (for the Zenith® p-Branch®).

Anatomical exclusion criteria (all must be no):

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

1. Prohibitive occlusive disease, tortuosity, calcification, or thrombus;
2. Unsuitable proximal neck/sealing zone length:
    a. For Zenith® Fenestrated AAA Endovascular Graft, proximal neck length <4 mm or ≥15 mm (unless otherwise unsuitable for standard endograft) between start of aneurysm and lowest renal artery;
    b. For Zenith® p-Branch®, proximal sealing zone length <15 mm (unless otherwise unsuitable for standard endograft) between start of aneurysm and the distal-most aspect of the celiac artery;
3. Unsuitable proximal neck diameter:

a. For Zenith® Fenestrated AAA Endovascular Graft, aortic neck diameter >31 mm or <19 mm (measurements based on outer diameter unless evidence of vessel thickening);

b. For Zenith® p-Branch®, aortic neck diameter >32 mm or <21 mm (measurements based on outer diameter unless evidence of vessel thickening);

4. Unsuitable aortic neck morphology precluding fixation or seal;
5. Aortic neck angulation precluding ability to cannulate fenestrations;
6. Tortuosity, calcification, or arterial diameter not conducive to placement of the introducer with use of a conduit;
7. Unsuitable ipsilateral iliac artery fixation site diameter for the abdominal device:

    a. For Zenith® Fenestrated AAA Endovascular Graft, ipsilateral iliac artery fixation site diameter <9.0 mm (measured outer wall to outer wall on a sectional image prior to deployment);

    b. For Zenith® p-Branch®, ipsilateral iliac artery fixation site diameter <8.0 mm (measured outer wall to outer wall on a sectional image prior to deployment);

8. For Zenith® Fenestrated AAA Endovascular Graft, iliac artery diameter >21 mm (measured outer wall to outer wall on a sectional image);
9. For Zenith® Fenestrated AAA Endovascular Graft, iliac artery distal fixation site <15 mm in length;
10. Inability to maintain at least one patent hypogastric artery with abdominal device;
11. Non-bifurcated segment of any artery to be stented <10 mm in length if use of covered stent is planned;
12. For Zenith® p-Branch®, renal and visceral vessel anatomy incompatible with the graft (see Section 1.5.2.1. for more details on the renal and visceral vessel criteria).

1.3.3. Methods

1.3.3.1. Endovascular Graft Sizing

Refer to the IFU for endovascular graft sizing.

1.3.3.2. Endovascular Graft Deployment

Refer to the IFU for endovascular graft deployment.

1.3.3.3. Completion

Following graft deployment, the delivery system is removed leaving the sheath in place. Aortography is then performed to confirm perfusion of the celiac artery, SMA, and renal arteries, and to visualize exclusion of the aneurysm sac. The presence of contrast material in the aneurysm sac is indicative of an endoleak. Type I or III endoleaks should be treated at the time of implantation by modifications of the proximal or distal fixation points. Definite Type II endoleaks can be treated at the physician's discretion.

1.3.3.4. Peri-operative Care

Treatment with the Zenith® Fenestrated AAA Endovascular Graft or the Zenith® p-Branch® calls for no departure from the usual peri-operative management of patients undergoing endovascular repair with the standard infrarenal Zenith® AAA Endovascular Graft.

1.3.3.5. Post-operative Treatment of Endoleaks

Type I and III endoleaks warrant immediate treatment. Type II endoleaks should be treated at the physician's discretion, depending on aneurysm behavior and size, endoleak source, and time from implantation. If the aneurysm is enlarging, treatment by embolization or ligation should be considered. Type III endoleaks should be treated with additional ballooning or prostheses.

1.3.4. Measurements and Data Collection

Clinical data and imaging measurements will be collected on standardized forms. The results of the endovascular repair will be assessed by radiologic and/or clinical criteria at the time of graft insertion and according to the schedule listed in Table 1.3.4-1.

Table 1.3.4-1. Study schedule

	Pre-op	Intra-op	Post-procedure[1]	6 Month	12 Month[11]
CT	X		X[2]	X[2]	X[2]
Device x-ray			X[3]	X[3]	X[3]
Angiography	X[4]	X			
Duplex Ultrasound[5]	X		X	X	X[6]
Clinical Exam	X		X	X	X
Pulses/ABI	X		X		
Blood Test[7]	X		X	X	X
CSF Analysis[8]					
Endoscopy			X[9]	X[9]	X[9]
Colonoscopy			X[10]	X[10]	X[10]

1. Post-procedure follow-up should be completed within 30 days of the index procedure.
2. 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.
3. Device x-ray performed as needed.
4. Pre-procedure angiography performed as needed.
5. Duplex ultrasound will be specific to vessels targeted by a fenestration.
6. Duplex ultrasound not required after 12-month follow up.
7. The following will be tested to establish baseline: AST, ALT, AP, LDH, Cr, BUN, LA, and CPK with follow-up testing only of those that are specific to vessels targeted by a fenestration.
8. Cerebrospinal fluid will be evaluated for markers of spinal cord ischemia (i.e., neuronal-specific enolase, glial fibrillary acidic protein, lactate, and S100B) in any patients who require placement of an intrathecal catheter.
9. Endoscopy and gastric tonometry will be used at follow-up to determine gastric and duodenal mucosal pH only if there is an indication of gastric perfusion alteration.
10. Colonoscopy using narrow band imaging to visualize submucosal vessels for an assessment of perfusion will be performed on follow-up only if there is an indication of colon perfusion abnormalities.
11. Patients will be followed up at yearly intervals through five years.

If there is evidence of compromise in organ or extremity perfusion as a result of the Zenith® Fenestrated AAA Endovascular Graft or the Zenith® p-Branch®, additional tests

may be performed to assess highly sensitive indicators of end organ and extremity perfusion, as applicable to the vessels targeted by a fenestration.

Mesenteric Perfusion

Perfusion to the liver, spleen, stomach, duodenum and colon will be monitored as follows:

1. Patency of the celiac, superior mesenteric and inferior mesenteric arteries will be assessed with duplex ultrasound through 12 months and CTA through 5 years;
2. Perfusion to the liver and spleen will be evaluated using CT scanning;
3. Liver function test battery to determine hepatic perfusion (AST, ALT, Alkaline Phosphatase, LDH [1,2,3].

If either of these tests are significantly abnormal, then more invasive testing, if clinically indicated, will be performed to include the following tests:

1. Endoscopy with gastric tonometry will be used to determine gastric and duodenal mucosal pH if there is an indication of gastric perfusion alteration;
2. Colonic perfusion will be assessed via flexible colonoscopy using narrow band imaging to visualize submucosal vessels allowing an assessment of perfusion if there are indications of colon perfusion abnormalities [4].

Renal Perfusion

A wide range of renal function can fall within the boundaries of a “normal” creatinine, thus assessment of renal perfusion using serum creatinine is notoriously inaccurate. As indicated, renal perfusion will be assessed by more precise measurements of renal function, including:

1. Renal artery patency will be assessed with duplex ultrasound and CTA;
2. Creatinine clearance will be determined by calculating glomerular filtration rate using the Cockcroft-Gault equation [5];

3. Renal perfusion and embolization will be assessed by CT scanning to evaluate for wedge infarcts and evidence of microembolization.

Systemic Perfusion

Systemic indicators of organ and/or extremity perfusion to be evaluated include:

1. Serum lactate levels;
2. Creatinine phosphokinase (CPK);
3. Cerebrospinal fluid will be evaluated for markers of spinal cord ischemia, including neuronal-specific enolase, glial fibrillary acidic protein, lactate, and S100B [6] in any patients who require placement of an intrathecal catheter.

1.3.4.1. Pre-operative Assessment Data Collection

Patients meeting the selection criteria who have provided informed consent will undergo a detailed pre-procedural examination. Data will be collected and stored in a database. Data points include:

1. Date of examination;
2. Age, gender, weight, and height;
3. Past medical history;
4. Lower extremity pulse and ABI evaluation;
5. Radiographic results listed on case report forms including:
    a. Aortic diameters;
    b. Aortic lengths;
    c. Common iliac artery measurements;
    d. Extent of iliac artery occlusive disease, calcification, tortuosity;
    e. Renal and visceral artery measurements;
6. Baseline laboratory data including:
    a. BUN;
    b. Creatinine;

c. Alkaline phosphatase;

d. AST;

e. ALT;

f. Lactate;

g. LDH.

h. CPK

1.3.4.2. 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. Data points include:

1. Date of procedure;
2. Procedure time (skin to skin);
3. Endoprosthesis time (from insertion of initial catheter to removal of final angiographic catheter);
4. Contrast volume:
5. Total fluoroscopy time;
6. Estimated blood loss;
7. Exogenous blood transfused and cell saver blood transfused;
8. Diameter, length and configuration of the prosthesis (derived from product label);
9. Assessment of system performance including: ease of insertion, visualization, and ease of removal;
10. Assessment of ability to successfully place peripheral stents;
11. Make, model, diameter, and length of each renal or visceral vessel stent;
12. Ancillary equipment needed;
13. Adjunctive maneuvers including: balloon dilation of iliac arteries, additional stents required, additional surgical procedures, maneuvers to move or re-align stents, the need for thrombectomy;

14. Nature of completion assessment (angiogram or IVUS);
15. Findings of completion assessment: patency, endoleak, kinks.

1.3.4.3. Post-operative Data Collection

The interval between deployment of the endoprosthesis and within 30 days post-procedure will be documented. Data points include:

1. Date of discharge;
2. Survival or death; if the patient has died, a study exit form should be filled out;
3. Complications (if any);
4. Patient withdrawal;
5. Post-operative imaging information including:
    a) Device integrity (kink, separation, stent fracture, barb separation);
    b) Aortic diameters;
    c) Iliac diameters;
    d) Endoleak;
    e) Graft patency;
    f) Branch vessel status;
6. Duration of ICU stay;
7. Time to resumption of fluid intake;
8. Condition of incision;
9. Lower extremity pulse and ABI evaluation;
10. Laboratory data at time of discharge (to include the assessments listed under #65 in Section 1.3.4.1);

1.3.4.4. Follow-up

The results of the endovascular repair will be assessed by radiologic and/or clinical criteria at the time of graft insertion and according to the schedule given in Table 1.3.4-1.

Data points to be obtained during follow-up include:

1. Date of examination;
2. Survival or death;
3. Complications (if any);
4. Patient withdrawal;
5. Follow-up imaging information (to include the assessments listed under #5 in Section 1.3.4.3 and migration assessment);
6. Clinical exam;
7. Laboratory data at follow-up (to include the assessments listed under #10 in Section 1.3.4.1);
8. Evaluation of patency of visceral vessels targeted by a fenestration by duplex ultrasound (post-procedure to 12-months).

1.3.4.5. Deaths

Details of any deaths occurring during the evaluation will be stored in a database. Data points include:

1. Date of death;
2. Whether an autopsy was performed;
3. Underlying cause of the fatal condition:
    a. Related to the prosthesis;
    b. Related to the procedure;
    c. Related to a previous condition.

1.3.4.6. Explants

An autopsy may be requested for patients who die with a prosthesis in place. At the autopsy, the entire abdominal aorta (over the extent of the endograft) will be excised down to and including both common iliac arteries. Both the excised aorta and the endovascular graft will undergo examination. If the family does not wish for a full

autopsy to be performed, a limited autopsy to remove the involved vasculature and graft will be requested.

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 precaution will be taken to ensure that the prosthesis is removed intact. For example, vascular clamps will be applied at remote sites from stent attachments. The prosthesis will then be washed with saline to remove surface thrombus. The graft components should be fixed in 4% formaldehyde for subsequent examination.

Explanted devices will be examined radiographically while still within the aorta 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 both be used to examine the structural integrity of the z-stent components, the attachment barbs, and any renal or visceral vessel stents. Any device-related gross pathology will also be documented.

Histopathologic studies will be conducted on the aorta and iliac artery 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.

Data will be collected and stored in a database.

Data points include:

1. Date of explant;
2. Patient's status at explant;
3. Reason for explant;
4. Degree of attachment/ingrowth.

1.3.4.7. Lost to Follow-up

Efforts will be taken to avoid patients becoming lost to follow-up. Prior to enrollment in the trial, the requirement for timely and complete follow-up will be discussed with the patient and their primary physician. .

If a patient is lost to follow-up, the following information will be recorded:

1. Date of last contact with patient;

2. Reasons for patient's unavailability: withdrawal, moved away, unreachable, etc.;
3. Summary of attempts to contact patient;

1.3.5. Assessing Outcome

In addition to assessing the indicators of perfusion described in Section 1.3.4, the study will provide an assessment of serious adverse events, major complications, endoleak, migration, change in aneurysm size, clinical utility measures (ICU stay, days to resumption of oral fluid intake, days to hospital discharge, and blood replacement requirements), device integrity, technical success, procedural success, treatment success, and secondary interventions.

1.4. Risk Analysis

The Zenith® Fenestrated AAA Endovascular Graft and the Zenith® p-Branch® are implantable endoprosthetic devices intended to prevent aneurysm rupture. The hazards associated can be categorized as procedure-related, performance-related, or technical or material-related. The consequent risks to the patient depend on the incidence and effects of each hazard, which have been explored in a large number of experimental and clinical insertions. These risks of endovascular aneurysm repair must be weighed against the risks associated with the current alternative forms of management.

1.4.1. Procedure-related Risks

The complications considered to be deployment-related hazards are those that occur during the insertion procedure. Previous clinical experience has provided extensive information on the incidence, avoidance, treatment, and consequences of many of these risks. These include possible failure to traverse the iliac arteries, inaccurate deployment of the proximal or distal aortic component or fenestration stent, failure to deploy the endovascular graft or fenestration stent, inadvertent internal iliac artery occlusion and ischemic colitis, stent-graft or fenestration stent displacement, injury to access arteries, aortic injury, damage to the visceral vessels or visceral organs, embolism, systemic effects, and local effects.

1.4.1.1. Failure to Traverse the Iliac Arteries

Failure to traverse the iliac arteries is unlikely because the delivery systems have a long, tapered tip for trackability, and a central cannula for uniform stiffness. The gradient stiffness of the nose of the device greatly facilitates insertion through tortuous iliacs. The soft, flexible end of the tip follows a wire guide around almost any bend, and in so doing, exerts force on the next segment of the tip to pass into the bend in the artery. This segment is less flexible, but with the help of the preceding segment, it too can bend. This effect is repeated as the rest of the tip passes through the bend, with the segments becoming progressively stiffer. Eventually, the iliac artery is sufficiently straight to allow the remainder of the central carrier and sheath to pass. The stiffer central carrier of the Zenith® delivery system actually facilitates insertion through the tortuous iliac artery by preventing kinking of the sheath. Tortuosity is rarely a serious impediment to device insertion, in the absence of severe calcification, which limits iliac artery straightening, or severe atherosclerosis, which diffusely narrows the iliac artery lumen.

1.4.1.2. Inaccurate Deployment of the Fenestrated Aortic Component

The Zenith® Fenestrated AAA Endovascular Graft and the Zenith® p-Branch® aortic components have a staged deployment with multiple points of control. Independent mechanisms for partial deployment, markers around the fenestrations, and the use of catheter alignment between fenestrations and the visceral arteries afford additional control of position and orientation.

Both ends of the stent-graft are attached to the delivery system by trigger wires. The bare stent with barbs remains contained within the topcap of the delivery system following sheath withdrawal to allow for fine adjustments in position and orientation. For the Zenith® Fenestrated AAA Endovascular Graft, the insertion of a bridging catheter between each fenestration and the corresponding visceral artery is sometimes facilitated by further adjustments in stent-graft position or orientation. These catheters then guide the last stages of stent-graft expansion. The result is a precise alignment of fenestrations and visceral vessel orifices. Only then is the bare stent with barbs deployed, fixing the Zenith® Fenestrated AAA Endovascular Graft in position. This position can be further secured by replacing the bridging catheters with stents (Zenith® Alignment Stent, JOSTENT, iCAST™).

The Zenith® p-Branch® uses a preloaded delivery system which features preloaded wires that are placed through both renal fenestrations to eliminate the need to cannulate the fenestrations and to facilitate cannulation of the target vessels (see Section 1.4.1.5).

At each step stent-graft position is assessed by reference to serial visceral vessel angiograms. Experience with the standard Zenith® system showed that the aorta can move as caudally directed force is applied to the iliac arteries during sheath withdrawal. Precise control over stent-graft position is of no value unless angiographic visceral vessel localization is equally precise. All participants in this study are experienced users of the standard Zenith® device, and all are familiar with these lessons of the Zenith® study.

Exact placement of fenestrations is more a function of stent-graft design than implantation technique. The risk of inadvertent visceral vessel artery occlusion is minimized by: the large combined experience of the imaging team and product specialists who will review all pre-operative imaging and order forms; a strict protocol for pre-operative imaging; conservative selection criteria to eliminate sources of variability in stent-graft orientation, such as neck angulation, and sources of difficult visceral vessel catheterization, such as orificial stenosis; and a high level of skill and experience in both Zenith® implantation and visceral vessel intervention, which will be required of all participants in this study.

1.4.1.3. Inaccurate Deployment of the Non-Fenestrated Aortic Component

The modularity of the Zenith® Fenestrated AAA Endovascular Graft and Zenith® p-Branch® allows the operator to focus independently on precise deployment of the two ends of the stent-grafts. The goals in placing the non-fenestrated aortic component are to ensure an adequate seal to the aneurysm is achieved, any vessel intended to remain patent is not covered, and an adequate overlap with the fenestrated aortic component is achieved. These goals should be readily achieved in each case by referring to angiographic and stent-graft landmarks before deployment.

1.4.1.4. Inaccurate Deployment of the Fenestration Stent

The risk of inaccurate deployment of the Zenith® Alignment Stent is minimized by the presence of radiopaque markers on both the balloon catheter and on the stent itself. The platinum marker bands on the balloon catheter are located proximal and distal to the undeployed stent. The gold markers on the stent indicate the distal end of the flarable segment of the device and should be aligned with the gold markers around the

fenestration or scallop of the Zenith® Fenestrated AAA Endovascular Graft prior to stent deployment. If unable to accurately deploy the Zenith® Alignment Stent, the stent and delivery system can be removed as one unit, leaving the wire guide in place. Available balloon-expandable covered stents (JOSTENT and/or iCAST™) may also be used.

If a Zenith® Alignment Stent is inadvertently deployed too proximal or too distal to the intended location, an additional stent can be deployed. Given the presence of the radiopaque markers and the lack of significant stent foreshortening, inaccurate deployment of the Zenith® Alignment Stent is expected to be a rare occurrence.

The primary risk of the Zenith® p-Branch® over other fenestrated/branched devices is the ability to cannulate the vessels if a misalignment between the pivot fenestrations and the target vessels occurs. This risk is mitigated by the ability of the implant positioning to be manipulated, double diameter reducing ties, and the preloaded system (where the renal fenestrations are preloaded with wires). Adjusting tension of the preloaded wire guide may facilitate cannulation of the renal arteries by changing the angle of the preloaded sheath relative to the fenestration. Pushing on the preloaded wire just distal to the valve of the sheath will increase the angle of the sheath relative to the fenestration. Additional tension may be placed on both ends of the preloaded wire guide to apply additional compression to the graft at the level of the pivot fenestrations. This may provide extra space to allow cannulation of the renal arteries.

1.4.1.5. Failure to Deploy the Endovascular Graft

The most difficult aspect of modular endovascular graft deployment is often catheterization of the short limb of the non-fenestrated AAA component. The Zenith® Fenestrated AAA Endovascular Graft and the Zenith® p-Branch® incorporate features designed to minimize this problem. First, the independent deployment of the distal body permits one to access the short limb while maintaining the capability to reorient the graft body. Second, the long trunk of the endovascular graft brings the orifice of the short limb close to the contralateral common iliac artery. Finally, if one is still unable to obtain access to the main endovascular graft body through the short limb using the brachial or contralateral femoral arteries, the device can be converted into an aortouni-iliac device quite easily.

1.4.1.6. Failure to Deploy the Fenestration Stent

The most difficult aspect of stenting visceral vessels is gaining and maintaining wire guide access. If extensive manipulations are required, time may be added to the procedure, radiation exposure may be increased, and the risk of embolization to the kidney may be increased. These risks are reduced by a high level of operator skill and exclusion of patients with high risk pathology such as severe renal artery stenosis.

If unable to deploy the fenestration stent accurately, the stent and delivery system can be removed as one unit while leaving the wire guide in place. Another fenestration stent can then be implanted.

When balloon-expandable stents are used as the fenestration stent, flaring of the stent is expected to minimize the length of stent protruding into the lumen of the endovascular graft. This is expected to reduce the risk of stent displacement during reinstrumentation during the implant procedure or during a secondary intervention, if required.

1.4.1.7. Inadvertent Internal Iliac Artery Occlusion and Ischemic Colitis

The short leg/long leg configuration of the non-fenestrated AAA component is the same as the distal half of early versions of the Zenith® AAA Endovascular Graft, which was used extensively in Europe and Australia with a low rate of inadvertent internal iliac artery occlusion. The sole case of ischemic colitis in the Zenith® AAA Endovascular Graft clinical study followed inadvertent internal iliac artery occlusion. We expect the rate to be as low, or lower, in the current study. Strict adherence to the guidelines regarding the preservation of hypogastric patency should minimize this risk.

1.4.1.8. Stent-graft Displacement

Displacement through re-instrumentation during deployment is very rare with the Zenith® family of endovascular grafts. The Zenith® Fenestrated AAA Endovascular Graft and the Zenith® p-Branch® are expected to behave in the same way.

1.4.1.9. Dislodgement of the Fenestration Stent

An insertion tool is provided with the Zenith® Alignment Stent to minimize the risk of stent dislodgement during insertion through a hemostatic valve.

If dislodgement of the stent from the balloon catheter occurs prior to deployment of the

stent, the stent and guiding catheter/sheath should be removed as one unit, leaving the wire guide in place. Another fenestration stent can then be implanted.

1.4.1.10. Displacement of the Fenestration Stent

The Instructions for Use for the Zenith® Alignment Stent recommend flaring of the proximal segment of the stent.

Flaring of the stent is expected to minimize the length of stent protruding into the lumen of the endovascular graft, thereby reducing the risk of stent displacement during re-instrumentation and/or during secondary interventions.

1.4.1.11. Injury to Anatomy

Injury to access arteries

The risks of femoral or external iliac artery injury have been very low with the Zenith® family of endovascular grafts. Any likelihood for injury to access arteries will be minimized through the use of access conduits when necessary.

Aortic injury

The presence of stiff wire guides in the descending thoracic aorta, and even the arch, raises the possibility of perforation or dissection. Very few such injuries have been observed in studying the Zenith® family of endovascular grafts, and we expect an even lower incidence in this study. All the investigators in this study are experienced enough to pay careful attention to wire guide position, and to use interventional techniques which minimize unobserved, uncontrolled movements of wire guides, catheters, and sheaths.

Damage to the visceral vessels

Perforation and dissection are possible risks from any visceral vessel instrumentation and stenting. The risks are reduced by: a high level of operator skill; selection criteria that

eliminate cases of high risk anatomy, such as early bifurcation, and high risk pathology, such as severe renal artery stenosis.

1.4.1.12. Embolism

Deployment of non-fenestrated Zenith® components produces a very low rate of embolism, despite femoral artery flow throughout the procedure. Fenestrated stent-graft deployment increases risk somewhat, due to the additional perigraft instrumentation involved in visceral vessel catheterization and stenting, particularly if there is extensive (circumferential) thrombus in this area. These factors will be considered during patient selection, and only those investigators experienced in visceral interventions will participate.

1.4.1.13. Stroke

The risk of stroke increases as the aneurysm approaches the origins of the cerebral vessels. The lack of aortic cross-clamp placement with endovascular repair may diminish the risk of stroke. The necessity of wire placement within the ascending aorta demands instrumentation on the arch, which is believed to be associated with a risk of embolic stroke. These factors will be considered during patient selection.

1.4.1.14. Paraplegia

While the absence of aortic cross-clamping may reduce the risk for paraplegia, this may be counterbalanced by the inability to re-implant intercostal arteries. Consequently, as the length of aneurysm increases, so does the risk for paraplegia with repair. Patients requiring extensive aneurysm repair (e.g., concurrent thoracic and abdominal aneurysm repair) are believed to be at greater risk than those with less extensive repairs. These factors will be considered during patient selection.

1.4.1.15. Systemic Effects

The incidence of cardiopulmonary complications following any surgical procedure likely reflects the severity of the pre-existing disease and the physiologic stress induced by surgery. The main advantage of an endovascular approach to aneurysm exclusion is the avoidance of many of the pathologic stresses associated with abdominal operation, aortic cross-clamping, and prolonged lower extremity ischemia. Lower rates of complications such as myocardial infarction, pneumonia, venous thrombosis, and prolonged mechanical ventilation are expected for the endovascular approach to aneurysm treatment as compared to open surgical procedures due to the limited femoral dissection, lower blood loss, and diminished amount of fluid sequestration resulting from this approach.

1.4.1.16. Local Effects

Local effects, such as wound infection and hematoma at the insertion site, are expected to be low due to the limited access required for the procedure. In addition, the absence of graft material in the femoral region decreases the anticipated severity of these complications markedly.

1.4.2. Performance-Related Risks

The properly functioning endovascular graft and fenestration stent (if applicable) carries blood freely to the visceral vessels, the pelvis and the legs, and prevents blood from entering the aneurysm cavity. To accomplish this, the endovascular graft must have a patent lumen, targeted visceral vessel arteries must remain patent, and the ends of the device must remain affixed in the vessel to the arteries proximal and distal to the aneurysm. Performance-related risks include the potential for migration, component separation, graft limb occlusion, occlusion of stented visceral vessels, endoleak and endotension, and graft infection.

1.4.2.1. Migration of the Endovascular Graft

The fenestrated components are very sensitive to migration, as small disturbances in position of a fenestration relative to its corresponding visceral vessel would cause stenosis, thrombus deposition, and complete occlusion. However, the likelihood for migration is expected to be low, as the Zenith® Fenestrated AAA Endovascular Graft and the Zenith® p-Branch® incorporate several design features intended to prevent migration.

Both fenestrated aortic components utilize an uncovered stent with anchoring barbs for fixation. Additionally, the system features a two-piece main body, which reduces the forces applied to the fenestrated portion of the graft, enhancing placement and reducing risk of disturbing position of the fenestrations. Although the barbed suprarenal fixation stent is the primary source for resistance to migration, the radial force exerted by the proximal sealing stent is also a contributor to graft fixation.

1.4.2.2. Component Separation

As the Zenith® Fenestrated AAA Endovascular Graft and the Zenith® p-Branch® are part of modular systems, there exists the potential for component separation. In designing the endovascular grafts, it was determined that the benefits of a modular system outweighed the risks of component separation, which can be readily managed through regular follow-up and early intervention with use of ancillary stent-graft components to increase the length of overlap between separating modular components. To mitigate the risk of component separation, the endovascular grafts were designed to include z-stents of sufficient radial force for ensuring apposition and friction between the components within the overlap region. Additionally, the z-stents within the overlap region have been positioned so as to maximize graft-to-graft contact between the proximal and distal components in the main body overlap; this not only augments the frictional forces between components within the overlap, but also promotes sealing within the overlap in order to minimize the likelihood for Type III endoleak. Furthermore, proctor overview of planning and sizing may be provided to review the length of overlap between components. The connection between the contralateral iliac extension and its docking site on the distal aortic component of the endovascular grafts is not as stable as the connection between aortic components. The overlap is not as long, the surface area is not as high, and the iliac extension is more flexible than the aortic components. Nevertheless, the rate of component separation at this site was very low in the standard Zenith® AAA Endovascular Graft clinical study, and we would expect it to be even less in the current study, because the recommended overlap is longer.

1.4.2.3. Migration of the Fenestration Stent

Stent migration occurs primarily because of undersizing with respect to the target vessel or underexpansion of the stent.

The risk of undersizing is mitigated for the Zenith® Alignment Stent through the sizing recommendations (1.0 to 1.1 times the reference vessel diameter) and physician experience with renal and visceral vessel stenting. Labeling also includes the stent diameter at balloon nominal inflation pressure, reducing the risk of underexpansion during stent deployment.

The Zenith® p-Branch® may be used with the JOSTENT and/or iCAST™ balloon-expandable covered stents, where manufacturer instructions for vessel sizing should be followed.

1.4.2.4. Graft Limb Occlusion

The iliac limbs of the Zenith® Fenestrated AAA Endovascular Graft and the Zenith® p-Branch® are essentially the same as those of the standard Zenith® AAA Endovascular Graft and have the same risk of thrombosis. In the U.S. pivotal study, the cumulative rate of limb thrombosis was 0.3% at 1 year. There appear to be three circumstances that predispose to limb thrombosis: narrowing of the distal aorta, acute angulation of the common iliac artery, and external iliac implantation combined with oversizing, orificial stenosis or angulation. These factors will be considered during patient selection.

1.4.2.5. Occlusion of Visceral Vessels

The presence of fenestrations in the graft targeting visceral vessels may lead to thrombosis or neointimal hyperplasia in the stented segment. Placement of a stent (Zenith® Alignment Stent, JOSTENT, and iCAST™) with a history of clinical use for similar applications is expected to minimize this risk.

1.4.2.6. Endoleak and Endotension

Endoleak represents incomplete aneurysm isolation from arterial flow, and endotension represents incomplete aneurysm isolation from arterial pressure. Both are associated with aneurysm dilatation and persistent risk of rupture. However, prevailing opinion is that the indirect forms of endoleak (Type II), generally through patent lumbar vessels or the inferior mesenteric artery, are more benign than direct endoleak around the ends of the stent-graft (Type I), from modular joints or through defects in the stent-graft (Type III). Therefore, the study protocol mandates intervention for direct endoleak, while

intervention for Type II endoleak is performed at the physician's discretion, depending on factors such as aneurysm diameter, aneurysm diameter change, and endoleak duration.

Although a fenestrated stent graft does allow the proximal sealing stent to be deployed in a healthier, more cylindrical segment of the aorta, it does nothing to lengthen the critical interface between the stent-graft and non-dilated infrarenal neck. Poor apposition in this area will likely cause endoleak through the fenestration into the aneurysm. We anticipate a higher rate of adjunctive maneuvers, such as balloon dilatation, or additional stent implantation to enhance apposition, optimize the seal, and eliminate endoleak. All the investigators in this study have experience with these types of maneuvers. The risk of endoleak is somewhat reduced by excluding patients with a very tortuous aorta.

1.4.2.7. Graft Infection

All endovascular grafts and the Zenith® Alignment Stent will be sterilized with ethylene oxide. The effectiveness of this sterilization procedure is validated prior to initiating this study. These devices will be opened in the operating room under the same conditions as traditional open resection vascular graft material.

1.4.3. Technical or Material-related Risks

Technical or material-related risks include the potential for stent breakage, barb separation, proximal stent separation, fabric erosion, and biocompatibility for the endovascular grafts and the potential for stent breakage, stent crush, and biocompatibility for the fenestration stent.

1.4.3.1. Stent Breakage

The Zenith® Fenestrated AAA Endovascular Graft and the Zenith® p-Branch® utilize the same time-proven z-stent technology as is used by all other products in the Zenith® family of endovascular grafts. These self-expanding stainless steel and nitinol z-stents have a long history of use and proven structural integrity. Use of the z-stent design is expected to minimize the likelihood of stent fracture.

The Zenith® Fenestrated AAA Endovascular Graft and the Zenith® p-Branch® may use additional fenestration stents within the renal and visceral vessels. A variety of balloon-expanded and self-expanding stents have been used in these locations. None are known to have led to clinical problems due to stent breakage. *In vitro* testing appropriate to fenestration stents has shown comparable results between the Zenith® Alignment Stent and representative balloon-expandable stents.

1.4.3.2. Fenestration Stent Crush

A fenestration stent may become crushed due to: longitudinal movement of the endovascular graft, rotational movement of the endovascular graft, inaccurate deployment of the endovascular graft, and incorrect planning and sizing of the endovascular graft.

Although the rate of graft migration is low (see Section 1.4.2.1.), some initial longitudinal movement (<5 mm) of the proximal endovascular component is possible before the bare, barbed stent becomes seated in the aorta. In most instances, the radial force of the proximal sealing stent is able to withstand physiologic forces (i.e., downward blood flow) contributing to longitudinal movement during barb seating; however, longitudinal movement with subsequent stent crush is possible. In addition, stent crush due to longitudinal movement is mitigated by planning the location of the vessel/stent at the distal end of a small fenestration when possible.

The risk of rotational movement is mitigated by several factors. During deployment of the Zenith® Fenestrated AAA Endovascular Graft and the Zenith® p-Branch®, diameter reducing ties are used on one side of the device to keep the grafts from fully expanding, allowing for rotational control of the device during alignment with and cannulation of the visceral vessels. Once access has been gained to the targeted vessels, a trigger-wire connected to these diameter reducing ties is removed, allowing expansion of the graft to aortic diameter. The bare, barbed stent is then deployed by releasing the top cap. Excessive oversizing of the graft may lead to uneven expansion and rotational forces on the fenestration stent.

Should stent crush occur, kidney/bowel function should be assessed by the physician and a secondary surgical or endovascular intervention may be necessary.

The Zenith® Alignment Stent is available for use as a fenestration stent. To mitigate the effects of uneven expansion and rotational forces due to excessive oversizing, the Zenith®

Alignment Stent features additional crush resistance in the location of the fenestration. The risk of incorrect planning and sizing and inaccurate deployment (see Section 1.4.1.2.) is minimized by: the large combined experience of the imaging team and product specialists who may review pre-operative imaging and graft order forms and may be present at cases with new investigators; a strict protocol for pre-operative imaging; conservative selection criteria to eliminate sources of variability in stent-graft orientation, such as neck angulation, and sources of difficult renal catheterization, such as orificial stenosis; and a high level of skill and experience in both Zenith® implantation and renal intervention, which will be required of all investigators in this study.

The risk of fenestration stent crush in the Zenith® p-Branch® is mitigated by the pivot nature of the fenestrations. The pivot fenestrations may be manipulated during deployment to accommodate a range of renal anatomies. As the pivot fenestrations are designed to be manipulated, they may allow limited longitudinal movement of the proximal endovascular graft to occur without crushing the fenestration stent. Additionally, use of the JOSTENT and/or iCAST™ balloon-expandable covered stents, which have a history of clinical use for similar applications, should mitigate the risk.

1.4.3.3. Barb Separation

The Zenith® Fenestrated AAA Endovascular Graft and the Zenith® p-Branch® utilize the same barb design (including barb wire diameter and barb number) as with other grafts in the Zenith® family, which have a time-proven history of durable performance (i.e., Zenith® AAA Endovascular Graft and Zenith® TX2® TAA Endovascular Graft).

1.4.3.4. Bare Stent Separation

Early experience using predicate designs of the standard Zenith® AAA Endovascular Graft showed a few rare cases of proximal stent separation and catastrophic caudal migration of the covered portion of the stent-graft. These observations resulted in a doubling of the sutures between the proximal stent and the proximal margin of the graft. The result was a significant increase in the durability of the attachment, based on the findings of accelerated durability testing. The Zenith® Fenestrated AAA Endovascular Graft and the Zenith® p-Branch® incorporate the double suture attachment technique.

1.4.3.5. Fabric Erosion

All current stent-grafts combine a soft, flexible fabric with relatively stiff, unyielding stents. These widely differing mechanical properties are a potential source of late failure, particularly if there exists any potential for movement of one element relative to the other. The Zenith® design addresses these issues in two ways. First, the stent and fabric are securely attached to one another by many continuous sutures. Second, the fabric of the Zenith® endovascular grafts is relatively thick and tightly woven. Very similar fabrics are available for conventional surgical use; a role in which they have demonstrated long-term durability. In this regard, the Zenith® Fenestrated AAA Endovascular Graft, Zenith® p-Branch®, and standard Zenith® stent-grafts are identical. Fenestrations in the fabric are heat sealed to prevent fraying. The interface between the fenestration and the visceral vessel stent is a potential source of injury to the graft, if repetitive movement were to occur at this site. However, when properly deployed the stent acts as a sort of rivet, preventing movement and protecting the graft from injury.

1.4.3.6. Biocompatibility

Biocompatibility risks include a lack of sterility, toxicity, or biodegradation of the device. The devices will be packaged and sterilized by exposure to ethylene oxide using sterilization cycles validated to industry standards. The endovascular grafts and stents will be opened in the operating room under the same conditions of sterility used for routine surgical procedures. Component materials of construction for the Zenith® Fenestrated AAA Endovascular Graft and Zenith® p-Branch® include stents made of 304 stainless steel or nitinol, graft material woven from polyester yarn, mono-filament sutures composed of polypropylene, braided sutures composed of polyester, gold radiopaque markers, and small fenestration support rings composed of nitinol. The Zenith® Alignment Stent materials of construction include stents made of 316L stainless steel with radiopaque gold markers. All of these materials have known biocompatibility and implant histories. The specified balloon-expandable covered stents (JOSTENT and iCAST™) also have an established history with respect to biocompatibility.

1.4.4. Protection Against Risks

As described above, the design of the devices and the Instructions for Use, along with a physicians' training program, are intended to minimize the risks associated with endovascular procedures.

Previous clinical and animal experience has been used to:

1. Improve the delivery system;
2. Improve endovascular graft fixation;
3. Develop an adequate insertion and deployment technique;
4. Determine methods to treat complications;
5. Improve patient selection.

1.4.5. Potential Benefits to the Subjects and Alternative Treatments

Although this procedure is being performed worldwide for both high and standard risk patients, the benefits offered to high risk patients are straightforward. The best method to evaluate these benefits is to compare the potential alternative treatment modalities to that of endovascular repair.

International clinical experience with the Zenith® Fenestrated AAA Endovascular Graft has shown this to be an effective method of treatment of AAA in those patients who meet the anatomic criteria. Implantation of the Zenith® Fenestrated AAA Endovascular Graft is a much less invasive surgical procedure than open surgical repair, therefore the procedure provides a treatment option for those high medical risk patients who are not candidates for open surgery. Standard risk patients who are enrolled are likely to have suitable AAA repair with less risk and fewer complications than patients treated by traditional open resection.

The Zenith® Fenestrated AAA Endovascular Graft is custom-designed for each patient with an abdominal aortic aneurysm. The sizing and manufacturing process for customization requires 4-8 weeks; consequently, this device cannot be implanted in patients requiring urgent repair. In contrast, the Zenith® p-Branch® is intended to be an "off-the-shelf" device, with 2 configurations that may be used in immediate treatment of up to 70-80% of patients with juxtarenal or pararenal aneurysms. The ability to have immediate access to this device has the potential to benefit many patients, especially those with very large aneurysms and those with symptoms attributable to aneurysms that currently cannot be treated using endovascular means.

1.4.5.1. Observation

A patient who is not treated is at risk for aneurysm rupture at an overall rate that depends on the aneurysm's size and the patient's longevity. All patients eligible for inclusion in this study have a risk of rupture, the degree of risk being based primarily on aneurysm size.

1.4.5.2. Conventional Surgery

Conventional repair of peri-visceral aneurysms is highly effective at preventing aneurysm rupture. However, it is associated with a significant risk of cardiopulmonary complications as a result of a prolonged abdominal operation, significant blood loss and aortic cross-clamping. As such, conventional surgery is not an option for many of the patients who will be eligible for this study. For those patients who survive open surgical repair the long-term risks are small, despite the potential for the development of bowel obstructions, graft infections, occlusions and para-anastomotic aneurysms.

1.4.5.3. Endovascular Repair

Endovascular repair minimizes the pathologic stress of surgery by avoiding aortic cross-clamping and celiotomy or thoracotomy. The reported lower incidence of cardiopulmonary complications noted with endovascular repairs has the potential to significantly benefit patient care. There is an accumulating body of evidence to support the assumption that aneurysm exclusion documented by CT, angiographic or ultrasound criteria indicates freedom from the risk of rupture. Aneurysm rupture following endovascular repair occurs in the presence of endoleak. Therefore, a patient without evidence of endoleak can be considered effectively treated. However, endoleaks are present in approximately 10-20 percent of patients following endovascular aneurysm repair. Based on worldwide experience, it appears that most of these can be treated by a secondary endovascular procedure.

The long-term benefits and risks of endovascular aneurysm repair are less clear. Conventional surgery has few problems, while the long-term results of endovascular repairs give cause for concern on many counts. The most serious problem is stent-graft migration leading to late endoleak formation followed by aneurysm rupture. The Zenith® Fenestrated AAA Endovascular Graft and the Zenith® p-Branch® design features are intended to reduce the risk of these problems. The implantation of a barbed stent and balloon-assisted seating of sealing zones is an approach calculated to maximize secure

stent-graft attachment. Coupled with proper stent-graft sizing and reliable materials, the incidence of this problem is expected to be reduced.

1.5. Device Description

1.5.1. Zenith® Fenestrated AAA Endovascular Graft

The Zenith® Fenestrated AAA Endovascular Graft shares many attributes of the Zenith® AAA Endovascular Graft, being a modular system constructed of full-thickness woven polyester fabric sewn to self-expanding stainless steel z-stents with braided polyester and monofilament polypropylene sutures (Figure 1.5.1-1). As with the approved standard AAA device, the modules are fully stented to provide stability and expansile force during deployment, and attachment and seal of the graft to the vessel wall after deployment. Identical to the standard AAA device, the bare suprarenal stent at the proximal end of the graft contains barbs that are placed at 3 mm increments for additional fixation of the device. Refer to the IFU for planning and sizing information.

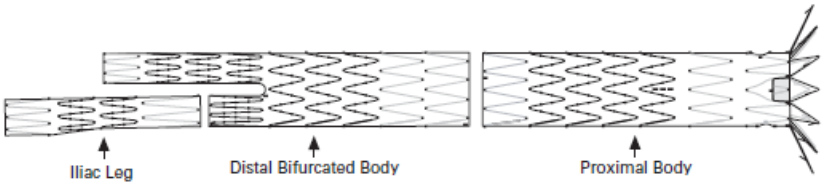

Figure 1.5.1-1. The Zenith® Fenestrated AAA Endovascular Graft is a modular system that includes a proximal fenestrated body, a distal bifurcated body, and iliac leg component(s).

1.5.1.1. Proximal Body Graft

The bare suprarenal stent at the proximal end of the proximal body graft (Figure 1.5.1.1-1) is identical to that of the Zenith® AAA Endovascular Graft, containing barbs that are placed at 3 mm increments for additional fixation of the device. This graft component includes up to four precisely located holes (fenestrations) at or near the proximal margin of the graft material. The fenestrations may be a combination of small fenestrations, large fenestrations, and scallop fenestrations, and allow the proximal margin of the device to sit higher in the abdominal aorta than the standard AAA device. This design permits uninterrupted blood flow to branch vessels of the aorta such as the renal and superior mesenteric arteries after device deployment.

In order to facilitate cannulation of small fenestrations, the perimeter of each small fenestration is supported by an open loop nitinol wire ring. The nitinol rings are secured to the graft material surrounding the fenestration with braided polyester sutures.

To facilitate fluoroscopic visualization of the stent graft, four gold radiopaque markers are positioned in a circumferential orientation within 1 mm of the most superior aspect of the graft material and one gold marker on the lateral aspect of the most distal stent. To facilitate orientation and alignment of fenestrations, gold markers are also positioned as follows: three vertically-aligned gold markers on the anterior aspect of the graft and three horizontally-aligned gold markers on the posterior aspect of the graft for anterior/posterior orientation, four gold markers around the perimeter of each large and small fenestration, and three gold markers around each scalloped fenestration.

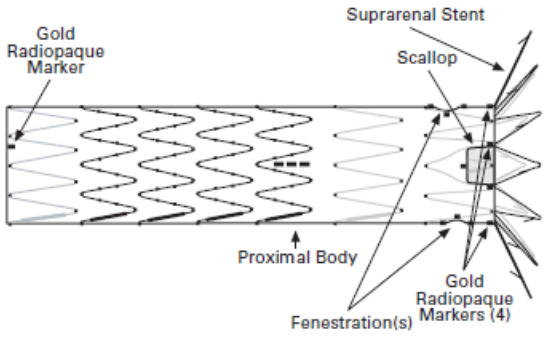

Figure 1.5.1.1-1. Zenith® Fenestrated AAA Endovascular Graft proximal body graft.

1.5.1.2. Proximal Body Graft Introduction System

The Zenith® Fenestrated AAA Endovascular Graft proximal graft is shipped preloaded onto the H&L-B One-Shot™ Introduction System (Figure 1.5.1.2-1). It has a sequential deployment method with built-in features to provide continuous control of the endovascular graft throughout the deployment procedure. During manufacture the graft is reduced in diameter by an independent wire tied to removable diameter reducing ties. This feature allows the partially constrained graft to be manipulated within the aorta to allow accurate positioning of the graft so that the fenestrations can line up with the desired arteries before complete device deployment. The bare suprarenal stent is constrained within a top cap and held there by a trigger-wire. The distal end of the graft

is also attached to the delivery system and held by an independent wire. The H&L-B One-Shot™ Introduction System enables precise positioning and allows readjustment of the final graft position before deployment of the bare barbed suprarenal stent. The delivery system uses a 20 French H&L-B One-Shot™ Introduction System. All systems are compatible with a 0.035 inch wire guide.

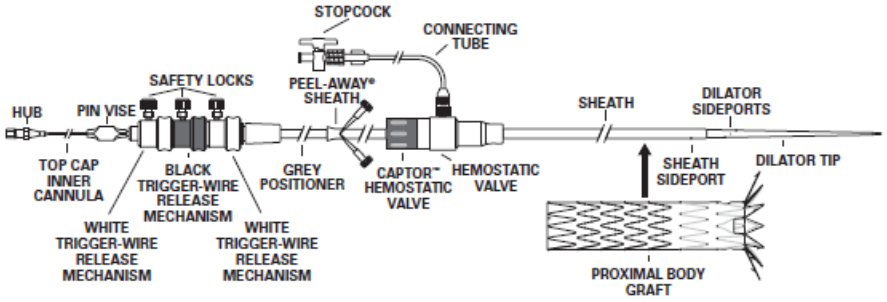

Figure 1.5.1.2-1. H&L-B One-Shot™ Introduction System used to deliver the proximal components of the Zenith® Fenestrated AAA Endovascular Graft.

1.5.1.3. Distal Body Graft

The Zenith® Fenestrated AAA Endovascular Graft distal body graft is bifurcated with one long limb with iliac cuff and one short limb on the contralateral side (Figure 1.5.1.3-1). To facilitate fluoroscopic visualization of the stent graft, there is a radiopaque marker at the graft bifurcation and a radiopaque checkmark at the distal end of the contralateral limb.

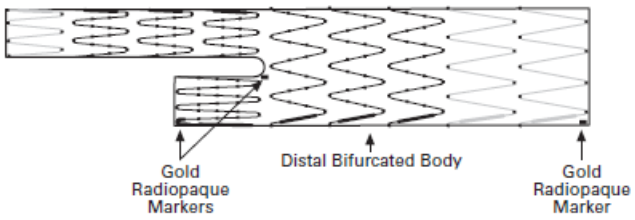

Figure 1.5.1.3-1. Zenith® Fenestrated AAA Endovascular Graft distal body graft.

1.5.1.4. Distal Body Graft Introduction System

The Zenith® Fenestrated AAA Endovascular Graft distal body graft is shipped preloaded onto the H&L-B One-Shot™ Introduction System. It has a sequential deployment method with built-in features to provide continuous control of the endovascular graft throughout the deployment procedure. Both the proximal and distal ends of the graft are attached to the delivery system and held by independent wires. The H&L-B One-Shot™ Introduction System enables precise positioning and allows readjustment of the final graft position before deployment of the stent-graft. The delivery system uses a 20 French H&L-B One-Shot™ Introduction System. All systems are compatible with a 0.035 inch wire guide.

1.5.1.5. Iliac Leg Graft

The Zenith® Fenestrated AAA Endovascular Graft uses the same iliac legs as the standard Zenith® graft. The iliac legs are tubular grafts which are used to extend the fenestrated graft into the iliac arteries. An iliac leg must be placed into the short limb from the contralateral side.

1.5.1.6. Iliac Leg Graft Introduction System

The Zenith® AAA Endovascular Graft iliac legs are shipped preloaded onto the H&L-B One-Shot™ Introduction System. The delivery system is designed for ease of use with minimal preparation. The iliac leg delivery system uses a 14 French or 16 French H&L-B One-Shot™ Introduction System. All systems are compatible with a 0.035 inch wire guide.

1.5.1.7. Fenestration Stent

Stenting of all small fenestrations is recommended. At the physician's discretion, the Zenith® Alignment Stent may be chosen as the fenestration stent and can be deployed through scallops or fenestrations in a Zenith® Fenestrated AAA Endovascular Graft into branch vessels of the aorta. The stent is constructed of 316L stainless steel. The distal segment of the stent (non-flared segment) is designed to be expanded across the target

lesion. The proximal segment of the stent (flared segment) is designed to extend into the lumen of a Zenith® Fenestrated AAA Endovascular Graft already deployed in the aorta. This proximal segment of the stent is denoted by circumferentially arranged gold eyelets to facilitate alignment with the fenestration and can be flared (allowing for easier access of the branch vessel if a secondary intervention is required) using a standard non-compliant balloon. The remainder of the stent is not intended to be flared. The region of the stent that is intended to be aligned with the fenestrations of a Zenith® Fenestrated AAA Endovascular Graft has been reinforced with wider struts. The Zenith® Alignment Stent is available in lengths of 18 and 26 mm, and nominal expanded diameters of 3, 4, 5, 6, 7, and 8 mm.

1.5.1.8. Zenith® Alignment Stent Introduction System

The Zenith® Alignment Stent is pre-mounted between two radiopaque (platinum) marker bands on a balloon catheter, which serves as the delivery system. The Zenith® Alignment Stent balloon catheter is offered in an 80 cm length and has a low outside diameter profile, which permits vascular access via 6.0 or 7.0 Fr introducer sheaths. The balloon catheter design is consistent with other commercially available non-compliant balloon catheters.

1.5.1.9. Ancillary Components

The Zenith® Fenestrated AAA Endovascular Graft is compatible with the same ancillary components as the standard Zenith® graft. The following ancillary endovascular components are available:

1. Main body extensions;
2. Leg extensions;
3. Converters;
4. Iliac occluders/plugs.

1.5.2. Zenith® p-Branch®

The Zenith® p-Branch® is a modular system constructed of full-thickness woven polyester fabric sewn to self-expanding stainless steel and nitinol z-stents with braided

polyester and monofilament polypropylene sutures (Figure 1.5.2-1). [redacted]

The Zenith® p-Branch® endovascular graft features three holes (fenestrations) and a cut-out from the proximal margin (scallop) of the graft material through which a balloon-expandable covered stent (JOSTENT and/or iCAST™) may be placed to preserve blood flow to the visceral vessels. Two of the fenestrations are conical shaped pivot fenestrations, aimed to accommodate a range of renal anatomies with a single design. The graft is available in 2 fenestration/scallop configurations to provide an optimal fit for individual patient anatomies (see Section 1.5.2.1). Refer to the IFU for planning and sizing information.

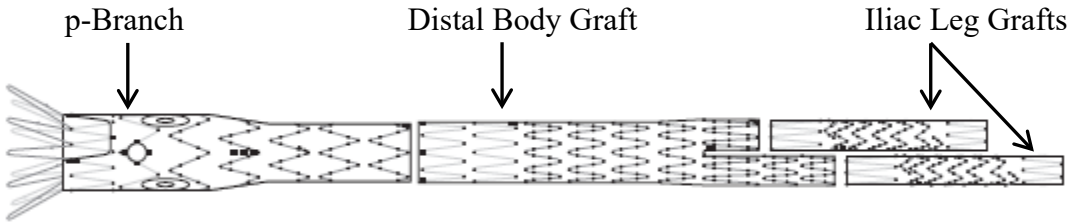

Figure 1.5.2-1. The Zenith® p-Branch® is part of a modular system that may include bifurcated devices (e.g., Zenith® Universal Bifurcated Body Endovascular Graft) and commercially avalible iliac leg devices.

1.5.2.1. Proximal Body Graft

[redacted] The device includes three holes (fenestrations) and a cut-out from the proximal margin (scallop) of the graft material to preserve blood flow to renal and visceral vessels. Two of the fenestrations are pivot fenestrations used to cannulate the renal arteries, and the third fenestration is used to cannulate the SMA. [redacted]

Two device configurations (A and B) accommodate a range of patient anatomies with a single design (see Figures 1.5.2.1-1 and 1.5.2.1-2). All radial measurements are calculated assuming the SMA position is 12:00 o'clock (0°).

Configuration A:

- Celiac scallop: 20 mm wide, centered at 12:30 (15°), 11 mm proximal to SMA;
- SMA fenestration: 8 mm in diameter, centered at 12:00 (0°);
- Right pivot (renal) fenestration: 6 mm inner diameter and 15 mm outer diameter, 5 mm deep, centered at 9:30 (285°), 12 mm distal to SMA (center-to-center);
- Left pivot (renal) fenestration: 6 mm inner diameter and 15 mm outer diameter, 5 mm deep, centered at 2:30 (75°), 12 mm distal to SMA (center-to-center).

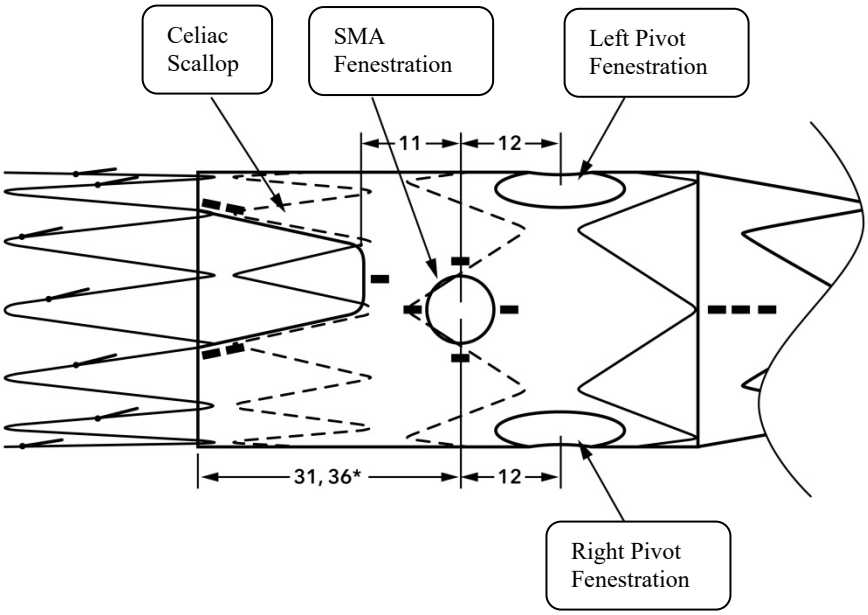

Figure 1.5.2.1-1. Zenith® p-Branch® endovascular graft configuration A.
* For 36 mm diameter grafts only

Configuration B:

- Celiac scallop: 30 mm wide, centered at 12:30 (15°), 9 mm proximal to SMA;
- SMA fenestration: 8 mm diameter, centered at 12:00 (0°);
- Right pivot (renal) fenestration: 6 mm inner diameter and 15 mm outer diameter, 5 mm deep, centered at 9:30 (285°), 16 mm distal to SMA (center-to-center);
- Left pivot (renal) fenestration: 6 mm inner and 15 mm outer diameter, 5 mm deep, centered at 2:30 (75°), 20 mm distal to SMA (center-to-center).

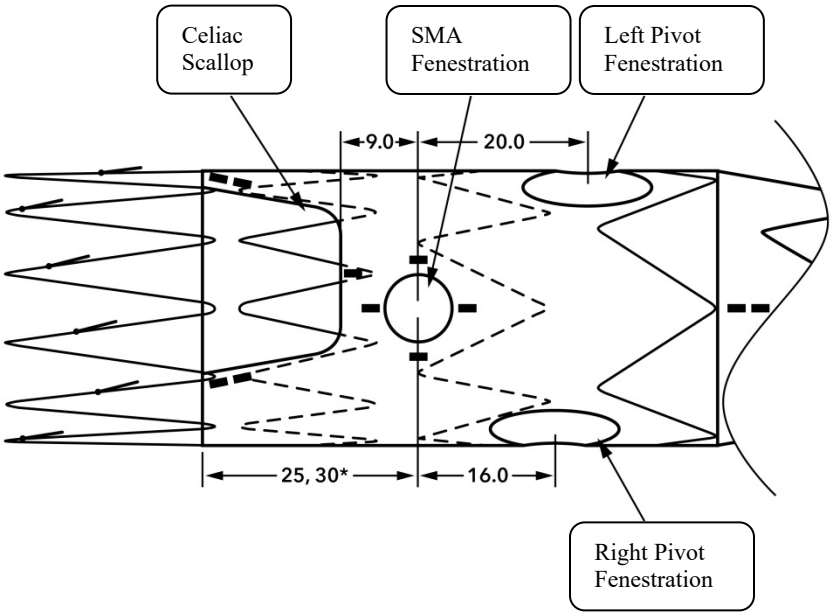

Figure 1.5.2.1-2. Zenith® p-Branch® endovascular graft configuration B.
* For 36 mm diameter grafts only

Anatomic Criteria for Zenith® p-Branch®

Standard Zenith® p-Branch® endovascular graft configuration A or B will be chosen in accordance with the following criteria. All radial measurements are calculated assuming the SMA position is 12:00 o'clock (0°).

1. Criteria for configuration A (renal fenestrations at same longitudinal level):
    a. The celiac artery arises from the aorta between 11:30 and 1:30 (345° and 45°);
    b. The SMA is ≥11 mm distal to the celiac artery (unless the celiac artery is occluded or expendable);
    c. Longitudinal positions of renal arteries arise 4.5 mm – 19.5 mm distal to the SMA;
    d. The circumferential location of the right renal artery can range between 8:30 and 10:30 (255° and 315°) and the circumferential location of the left renal artery can range between 1:30 and 3:30 (45° and 105°) (assuming the endovascular graft diameter is approximately 30 mm);
2. Criteria for configuration B (left renal fenestration lower longitudinally than right renal fenestration):
    a. The celiac artery arises from the aorta between 11:00 and 2:00 (330° and 60°);
    b. The SMA is ≥9 mm distal to the celiac artery (unless the celiac artery is occluded or expendable);
    c. Longitudinal position of the right renal artery arises 8.5 mm – 23.5 mm distal to the SMA;
    d. Longitudinal position of the left renal artery arises 12.5 mm – 27.5 mm distal to the SMA;
    e. The circumferential location of the right renal artery can range between 8:30 and 10:30 (255° and 315°) and the circumferential location of the left renal artery can range from 1:30 and 3:30 (45° and 105°) (assuming the endovascular graft diameter is approximately 30 mm).

1.5.2.2. Proximal Body Graft Introduction System

The Zenith® p-Branch® endovascular graft is shipped loaded onto a 20 Fr or 22 Fr (dependent on graft diameter) Zenith® preloaded delivery system. The delivery system uses a sequential deployment method with built-in features to provide continuous control of the graft throughout deployment. During manufacture, the graft is reduced in diameter by two independent wires tied to diameter reducing ties. This feature allows the partially constrained graft to be manipulated within the aorta to accurately position the fenestrations with the corresponding visceral vessels before complete deployment. The bare, barbed supraceliac stent is constrained within a top cap and held by a trigger-wire. A preloaded wire is placed through each renal fenestration to eliminate the need to cannulate the fenestrations and to facilitate cannulation of the target vessels. The distal end of the graft is attached to the delivery system and held by an independent wire. Trigger-wire release mechanisms lock the endovascular graft onto the delivery system until released by the physician (Figure 1.5.2.2-1). The delivery system enables precise positioning of the graft and allows readjustment of the final graft position before deployment of the supraceliac stent. The delivery system is compatible with a 0.035 inch wire guide to enable it to track through the aorta into position. The delivery system features a Flexor® introducer sheath with a Captor® Hemostatic Valve. For added hemostasis, the Captor® Hemostatic Valve can be opened or closed for the introduction and/or removal of ancillary devices. The Flexor® introducer sheath resists kinking and is hydrophilically coated. Both features are intended to enhance trackability.

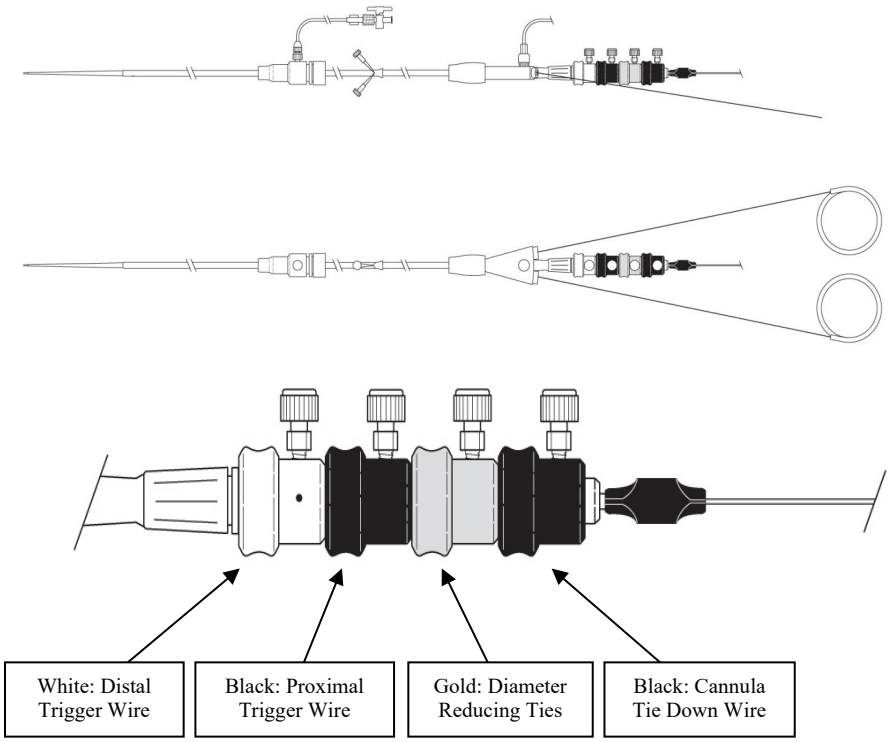

Figure 1.5.2.2-1. Top: Zenith® preloaded delivery system showing preloaded nitinol wire. Bottom: Detail of the release handles.

1.5.2.3. Distal Body Graft

The distal component of the Zenith® p-Branch® endovascular graft is the Zenith® Universal Distal Body Endovascular Device. The distal body graft is constructed of woven polyester fabric sewn to self-expanding stainless steel z-stents with braided polyester and monofilament polypropylene sutures. The graft is fully stented to provide stability and the expansile force necessary to open the lumen of the graft during deployment. The graft is bifurcated with one long ipsilateral iliac limb and one short contralateral limb. Gold radiopaque markers are sewn into the graft material to aid in alignment with the visceral vessels during deployment. Refer to the IFU for device sizes and planning and sizing information.

1.5.2.4. Distal Body Graft Introduction System

The Zenith® Universal Distal Body Endovascular Device is shipped preloaded onto a 20 French H&L-B One-Shot™ Introduction System. The delivery system uses a sequential deployment method with built-in features to provide continuous control of the graft throughout deployment. Both the proximal and distal ends of the graft are attached to the delivery system and held by independent wires. The delivery system enables precise positioning and allows for readjustment of the final graft position before deployment. The delivery system is compatible with a 0.035 inch wire guide.

1.5.2.5. Ancillary Components

The following ancillary endovascular components are available for the Zenith® p-Branch®:

1. Main body extensions;
2. Iliac leg grafts and extensions;
3. Converters;
4. Iliac occluders/plugs.

1.5.3. Fenestration Stents

iCAST™ and/or JOSTENT balloon-expandable covered stents will be used in the renal and visceral vessels incorporated by the Zenith® p-Branch® endovascular graft fenestrations. The manufacturers' instructions for use should be referred to for additional information.

1.5.4. Description of Each Important Component, Ingredient, and Property

Each component and its associated properties have been described.

1.5.5. The Principle of Operation of the Device

The Zenith® Fenestrated AAA Endovascular Graft and Zenith® p-Branch® are implantable endoprosthetic devices intended to prevent aneurysm rupture. The principle

of operation of the Zenith® Fenestrated AAA Endovascular Graft and the Zenith® p-Branch® is described in the Methods section of this protocol and further description and device illustrations are included in the respective Instructions for Use. If applicable, the principle of operation of the Zenith® Alignment Stent is described in the Methods section of this protocol and further description and device illustrations are included in the Instructions for Use.

1.5.6. Description of Anticipated Changes in the Device During the Investigation

The purpose of this study is to examine safety and effectiveness of fenestrated stent-graft technology and the effects on perfusion, namely the effects of perivisceral aortic fenestrated stent-grafting on organ perfusion. The need for use of a fenestrated stent-graft to achieve aneurysm exclusion may arise not only from proximal extension of abdominal aortic aneurysmal disease to the perivisceral segment, but also distal extension of descending thoracic aortic aneurysmal disease to the perivisceral segment. Therefore, incorporation of a distal fenestrated thoracic stent-graft for treatment of descending thoracic aortic aneurysms not treatable with current thoracic stent-grafts is anticipated to allow for further evaluation of the effects of perivisceral aortic fenestrated stent-grafting on organ perfusion.

1.6. Monitoring Procedures

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

[redacted]

[redacted]

APPENDIX A
Written Procedures for Monitoring Studies

A. Selection of the monitor.

Designated by the sponsor to oversee the clinical study, 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 study in accordance with all applicable regulations and standards for conducting clinical studies.

B. General duties of the monitor.

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

1. The signed investigator agreement.
2. The Clinical Investigation Plan (CIP).
3. Any conditions imposed by the IRB 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 which are potentially reportable to a regulatory authority.

D. Initiating the study.

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

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

1. Provide training to investigator on his/her responsibilities per the investigator agreement, applicable laws, regulations and standards; and
2. Provide training to investigator that the IRB approval letter and informed consent/patient information should be on file before initiation of the clinical study.

Additionally, training may be provided to the investigator on:

1. The regulatory status of the device and the requirements for the accountability of same;
2. The nature of the CIP;
3. The requirements for an adequate and well-controlled clinical study;
4. His or her obligation to obtain informed consent in accordance with applicable regulations;
5. His or her obligation to ensure continuing review of the clinical study by the IRB in accordance with conditions of approval and applicable regulations and to keep the sponsor informed of such IRB approval and subsequent IRB actions concerning the study;
6. The importance of access to an adequate number of suitable patients to conduct the study;
7. The importance of adequate facilities for conducting the clinical study; and
8. 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 study, at the direction of the Project Manager, the monitor should visit the site frequently enough to ensure that:

1. The facilities and research staff used by the investigator continue to be acceptable for purposes of the clinical study;
2. The applicable version of the CIP and agreements are being followed;
3. Changes to the CIP, informed consent/patient information have been approved by the IRB and/or reported to the sponsor and the IRB;
4. Accurate, complete, and current records are being maintained;
5. Accurate, complete, and timely reports are being made to the sponsor and IRB; and

6. 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:

1. Device accountability review;
2. Adverse event review to ensure that events are appropriately reported within the time periods required by the sponsor, CIP, IRB, and applicable regulatory requirements; and
3. Source data verification per the monitoring plan to determine that :
   a. Informed consent/patient information has been documented in accordance with applicable regulations and expectations of local IRB;
   b. The information recorded in the CRFs (paper or electronic) is complete, accurate, and legible;
   c. 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;
   d. Missing visits or examinations are noted; and
   e. Patients failing to complete the clinical study 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.

   The monitor shall immediately notify the sponsor of any conditions of non-compliance with the CIP, conditions of IRB or regulatory authority approval, or the applicable regulations.