CLINICAL INVESTIGATION PLAN

Use of the Zenith® Dissection Endovascular System in the Treatment of Patients with Acute, Complicated Type B Aortic Dissection

Global Clinical Number 11-007

Sponsor: **Cook Research Incorporated**

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West Lafayette, IN 47906
USA

Summary of Revisions

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11-007-01	Original version	4 Nov 2011
11-007-02	Updated data analysis plan	30 Mar 2012
11-007-03	Updates regarding adjunctive device use	23 Jan 2013
11-007-04	Updates to exclusion criteria and updates to follow-up schedule	9 July 2013
11-007-05	Updated enrollment total and data analysis plan	8 Jan 2014
11-007-08	Updated sponsor name, address, and contact information	19 Mar 2018

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

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.

Signatures:

Global Sponsor Contact

Jennifer L. Kerr
Signature

28 March 2018
DD/MM/YYYY

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PRESIDENT
Title

In-country Sponsor Contact

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Title

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE, CON'T

Coordinating Clinical Investigator

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

Signature	5/30/18 DD/MM/YYYY
Joseph V. Lombardi Printed Name	Global Principal Investigator Title

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	DD/MM/YYYY
Printed Name	Title

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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1.0 Clinical Investigation Plan Overview

This clinical investigation is designed as a prospective, non-randomized study enrolling 73 patients (67 patients for hypothesis testing) to receive the Zenith® Dissection Endovascular System at up to 30 global clinical sites with a maximum enrollment of up to 14 patients per individual site. The primary safety and effectiveness endpoints, as described in Section 3.1, will be compared to the performance goals derived from the combined physician-sponsored studies reported by the Society for Vascular Surgery Outcomes Committee.[1]

Any patient with an acute, complicated, type B aortic dissection with either aortic rupture or branch vessel obstruction/compromise that results in malperfusion (see Appendix C, Definitions) is eligible for enrollment in the study. The study flow diagram is presented in Figure 1.

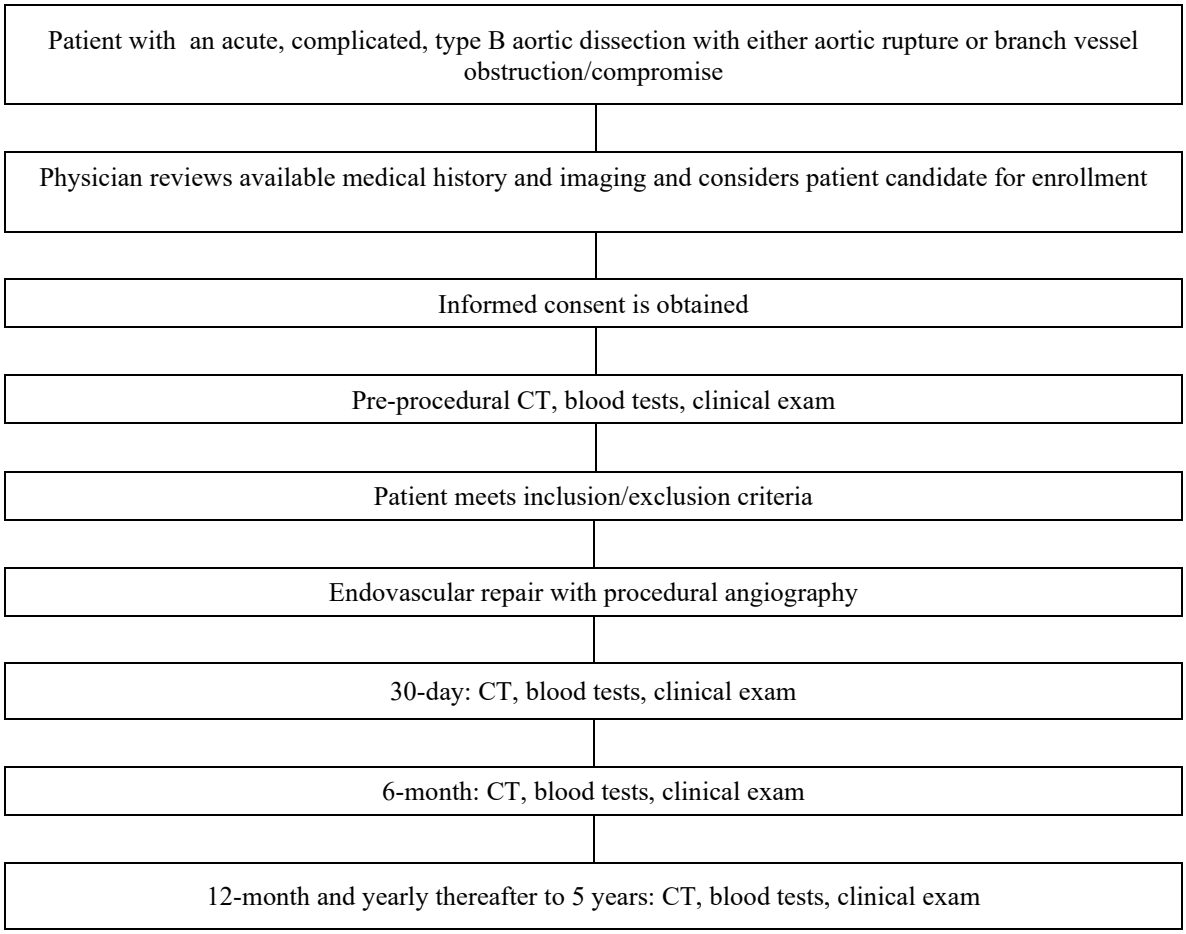

Figure 1. Study flow diagram

2.0 Summary of Preliminary Investigations

2.1 Preclinical Testing

Non-clinical tests were conducted in accordance with Good Laboratory Practice requirements, or performed in compliance with verified methods and Standard Operating Procedures to maintain the integrity of the results. *In vitro* testing has established reasonable safety of the device for the expected duration of the study and in the trial population to be studied. Please refer to the Clinical Investigator Brochure for a summary of non-clinical testing.

2.2 Previous Clinical Experience

Refer to the Clinical Investigator Brochure for a complete description of the previous clinical experience with similar devices.

2.3 Justification for the Investigation

This study design and the performance goal are justified given there are no other treatment alternatives that are being commonly practiced at present for patients with acute, complicated Type B aortic dissection. Open surgical repair is rarely performed in these patients due to the very high rate of mortality associated with the procedure. Likewise, medical therapy is not practical as the definitive treatment for these patients, who often require a more aggressive therapy in the form of endovascular/surgical intervention to relieve symptoms and prevent any further adverse clinical sequelae.

3.0 Objectives of the Clinical Investigation

3.1 Primary Objectives

The objective of the study is to evaluate the safety and effectiveness of the Zenith® Dissection Endovascular System in the treatment of patients with complicated, type B aortic dissection. The primary safety endpoint will be rate of freedom from major adverse events (see Appendix C, Definitions) at 30 days. The primary effectiveness endpoint will be the survival rate at 30 days.

3.2 Secondary Objectives

Information redacted

3.3 Specific Hypothesis to be Accepted or Rejected by Statistical Data

3.3.1 Primary Safety Hypothesis

The primary safety endpoint is the rate of freedom from 30-day major adverse events (see Appendix C, Definitions). The published rate of freedom from 30-day MAE from the combined physician-sponsored studies is 61.2%.[1] With a clinically relevant non-inferiority margin of 10%, a performance goal of 51.2% has been established for the primary safety endpoint. The performance goal will be said to have been met provided that the null hypothesis is rejected in favor of the alternative with a one-tailed exact binomial test at the 0.025 level. Given that $\pi_{noMAE(30)}$ is the probability that a randomly selected patient did not experience any MAE at 30 days, the null and alternative hypotheses are as follows.

Null Hypothesis: The rate of freedom from 30-day MAE, $\pi_{noMAE(30)}$, does not meet the performance goal (51.2%).

H_0: $\pi_{noMAE(30)} \leq 51.2\%$

Alternate Hypothesis: The rate of freedom from 30-day MAE, $\pi_{noMAE(30)}$, meets the performance goal (51.2%).

H_a: $\pi_{noMAE(30)} > 51.2\%$

3.3.2 Primary Effectiveness Hypothesis

The primary effectiveness endpoint is the survival rate at 30 days. The published survival rate at 30 days from the combined physician-sponsored studies is 89.4%.[1] With a clinically relevant non-inferiority margin of 10%, a performance goal of 79.4% has been established for the primary effectiveness endpoint. The performance goal will be said to have been met provided that the null hypothesis is rejected in favor of the alternative with a one-tailed exact binomial test at the 0.025 level. Given that $\pi_{s(30)}$ is the probability that

a randomly selected patient is alive at 30 days, the null and alternative hypotheses are as follows.

Null Hypothesis: The survival rate at 30 days, $\pi_{s(30)}$, does not meet the performance goal (79.4%).

H_0: $\pi_{s(30)} \leq 79.4\%$

Alternate Hypothesis: The survival rate at 30 days, $\pi_{s(30)}$, meets the performance goal (79.4%).

H_a: $\pi_{s(30)} > 79.4\%$

For each endpoint, the hypothesis will be assessed by a one-sided exact binomial test, at a type I error rate of 0.025 and a power of 0.8. The safety and effectiveness of the device will be established if both null hypotheses are rejected in favor of the alternatives at the above mentioned error rates.

4.0 Product Description and Intended Use

The Zenith® Dissection Endovascular System is a disease-specific family of components intended for the treatment of patients with Type B aortic dissection.

4.1 General Product Description

As depicted in Figure 2, the system is comprised of a covered proximal component (Zenith® TX2® Dissection Endovascular Graft) and an uncovered distal component (Zenith® Dissection Endovascular Stent).

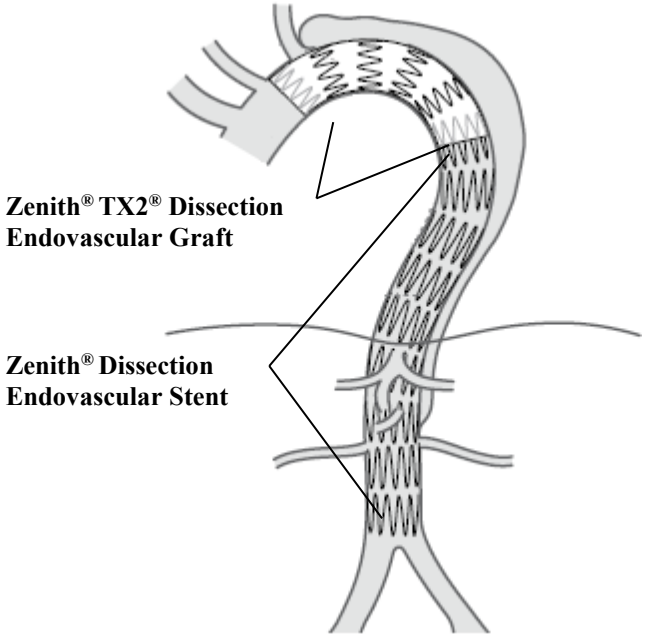

Figure 2. Zenith® Dissection Endovascular System

Zenith® TX2® Dissection Endovascular Graft

The Zenith® TX2® Dissection Endovascular Graft is predicated on the Zenith® TX2® TAA Endovascular Graft, which is commercially-available in the United States for the treatment of patients with descending thoracic aortic aneurysms and ulcers, and in many countries outside the U.S. for the treatment of patients with aneurysms, dissections, or contained ruptures. The design of the Zenith® TX2® Dissection Endovascular Graft is identical to the Zenith® TX2® TAA Endovascular Graft, except for the removal of fixation barbs in order to provide a disease-specific covered component (Figure 3).

Figure 3. Zenith® TX2® Dissection Endovascular Graft

As shown in Table 1, the Zenith® TX2® Dissection Endovascular Graft is available in multiple sizes ranging from 22 to 42 mm in diameter and 79 to 218 mm in length and is also available in both straight and tapered configurations. Tapered components with diameter changes of 4 mm or 8 mm are available.

Table 1. Zenith® TX2® Dissection Endovascular Graft sizes

Graft Diameter (mm)	Length of Straight Component (mm)	Length of Tapered Component – 4 mm Taper (mm)	Length of Tapered Component – 8 mm Taper (mm)
22	79 / 117	n/a	n/a
24	79 / 117	n/a	n/a
26	79 / 136	n/a	n/a
28	82 / 142 / 202	n/a	n/a
30	82 / 142 / 202	n/a	n/a
32	82 / 142 / 202	162 / 202	158 / 196
34	79 / 154 / 204	159 / 199	156 / 194
36	79 / 154 / 204	159 / 199	159 / 199
38	79 / 154 / 204	154 / 204	159 / 199
40	83 / 164 / 218	160 / 210	165 / 205
42	83 / 164 / 218	160 / 210	160 / 210

Zenith® Dissection Endovascular Stent

The Zenith® Dissection Endovascular Stent consists of multiple z-stent segments, made of nitinol, sewn together end-to-end with polyester sutures (Figure 4).

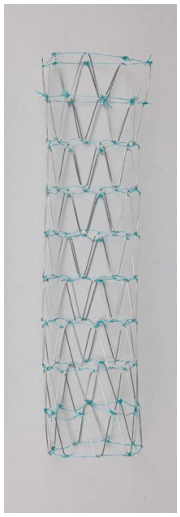

Figure 4. Zenith® Dissection Endovascular Stent

As shown in Table 2, the Zenith® Dissection Endovascular Stent is available in multiple sizes.

Table 2. Zenith® Dissection Endovascular Stent sizes

Stent Diameter (mm)	Stent Length (mm)
36	80 / 120 / 180
46	80 / 120 / 185

4.2 Intended Use

The Zenith® Dissection Endovascular System is intended for the endovascular treatment of patients with symptomatic aortic dissection of the descending thoracic aorta having morphology suitable for endovascular repair. Refer to the Instructions for Use (IFU) for further details.

4.3 Product Identification and Tracking

Products under investigation will have a unique lot number and will be tracked throughout the course of the study through use of a Product Log, upon which lot numbers, quantity and disposition of product will be recorded. Product Logs will be maintained in the site's Investigator File. Additionally, the quantity(s), size(s) and lot number of products used in subjects will be recorded on the case report forms.

4.4 Instructions for Use

Please reference the manufacturer's Instructions for Use for complete instructions including installation, storage and handling requirements, preparation for use and precautions to be taken after use.

4.5 Summary of Necessary Training and Experience

Please reference the manufacturer's Instructions for Use for a summary of the necessary training and experience required for use of this product.

4.6 Description of the Necessary Medical or Surgical Procedures

Please reference the manufacturer's Instructions for Use for a description of the procedures involved in the use of this product.

4.7 Adjunctive Devices

At physician discretion, adjunctive devices may be used on an individual basis during either the initial implant procedure or secondary intervention and may include the following (as discussed in Section 6, Methods): aneurysm stent-graft components (for coverage of reentry tears), coils/occluders (for embolization of sources for false lumen flow), uncovered balloon-expandable or self-expanding stents (for branch vessel obstruction), and covered balloon-expandable or self-expanding stents (for coverage of reentry tears involving branch vessels). If adjunctive devices are used, it is recommended that the Instructions for Use (IFU) of that device be reviewed, and the risks of using that device be considered. The specific type/make/model of any adjunctive device implanted during either the initial implant procedure or secondary intervention should be recorded on the case report forms. Additionally, the performance of any adjunctive device placed should be monitored during follow-up.

5.0 Design of the Clinical Investigation

5.1 Type of Investigation

The current investigation is a prospective, non-randomized, non-blinded study.

5.2 Endpoints

The primary safety endpoint will be rate of freedom from major adverse events (see Appendix C, Definitions) at 30 days. The primary effectiveness endpoint will be the survival rate at 30 days. Mortality is the greatest procedural risk associated with alternative treatments and is also the principal outcome any treatment is intended to prevent (up to 50% of patients are at risk for mortality within 48 hours if untreated[2]).

5.3 Variables to be Measured to Demonstrate Achievement of Endpoints

To evaluate deployment characteristics, procedural outcome and follow-up, the following data points will be collected:

1) Assessment of system performance including: deployment issues, ease of insertion, visualization, and ease of removal;
2) Clinical utility measures such as days to discharge from hospital;
3) Ancillary equipment needed;
4) Adjunctive maneuvers including: balloon dilation of iliac arteries, additional stents required, and additional surgical procedures;
5) Complications including major adverse events during procedure and at follow-up;
6) Device integrity findings at completion of procedure and follow-up: device patency, stent fracture, and graft kinks;
7) Type and sources of entry-flow at procedure and follow-up;
8) Dimensions of the true and false lumen over the course of follow-up; and
9) Secondary interventions performed.

5.4 Measures to be Taken to Avoid or Minimize Bias

This study is not randomized or blinded. It is intended to prospectively collect information regarding the safety and effectiveness of the Zenith® Dissection Endovascular System. The study will utilize uniform definitions for study endpoints, event adjudication by an independent clinical events committee, and imaging data analysis by a centralized core laboratory. Study results will be analyzed in accordance with a prospectively defined analysis plan.

5.5 Study Criteria

Assessment of entry criteria will be based upon data available pre-operatively. Data obtained peri-operatively and post-operatively (including the results from core lab analysis of pre-procedure imaging) may contradict pre-operative assessment. However, such contradiction is not considered a violation of the Clinical Investigation Plan and 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. 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.

5.5.1 Inclusion Criteria

A patient is deemed suitable for inclusion in the study if the patient has an acute, complicated, Type B aortic dissection with at least one of the following characteristics (see Appendix C, Definitions):

1) Aortic rupture; or
2) Branch vessel obstruction/compromise resulting in malperfusion

5.5.2 Exclusion Criteria

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

General Exclusion Criteria

1) Age < 18 years;
2) Other medical condition (e.g., cancer, congestive heart failure) that may cause the patient to be non-compliant with the Clinical Investigation Plan, confound the results, or is associated with limited life expectancy (i.e., less than 2 years);
3) Pregnant, breast-feeding, or planning on becoming pregnant within 60 months;
4) Unwilling or unable to comply with the follow-up schedule;
5) Inability or refusal to give informed consent; or
6) Simultaneously participating in another investigative device or drug study. (The patient must have completed the primary endpoint of any previous study at least 30 days prior to enrollment in this study.)

Medical Exclusion Criteria

7) Suspicion of bowel necrosis (as determined by the implanting physician based on imaging observations, peritoneal signs, surgical exploration, elevated serum lactate levels, and/or acidosis)
8) ASA risk class V (i.e., moribund patient not expected to live 24 hours with or without operation)
9) Embolic stroke within the last 14 days prior to potential enrollment in the study or

hemorrhagic stroke within 30 days prior to potential enrollment in the study;
10) Diagnosed or suspected congenital degenerative connective tissue disease (e.g., no Marfan's or Ehler-Danlos syndrome);
11) Systemic infection (e.g., sepsis);
12) Bleeding diathesis, uncorrectable coagulopathy, or refuses blood transfusion;
13) Allergy to stainless steel, polyester, solder (tin, silver), polypropylene, nitinol, or gold;
14) Untreatable reaction to contrast, which, in the opinion of the investigator, cannot be adequately pre-medicated;
15) Surgical or endovascular AAA repair within 30 days before or after dissection repair;
16) Previous placement of a thoracic endovascular graft;
17) Prior open repair involving descending thoracic aorta including suprarenal aorta and/or arch; or
18) Interventional and/or open surgical procedures (unrelated to dissection) within 30 days before or after dissection repair.

Anatomical Exclusion Criteria

19) Dissection of aorta proximal to left subclavian artery (either primary entry tear or most proximal extent of dissection);
20) Proximal landing zone length measuring < 20 mm between the left common carotid artery and most proximal extent of dissection (covering left subclavian artery is acceptable, except in patients with a dominant vertebral artery off of the arch in the region of the subclavian or a dominant vertebral off of the subclavian);
21) Proximal landing zone diameter for proximal stent-graft component < 20 mm or > 38 mm, measured outer-wall to outer-wall on a sectional image or multiplanar reconstruction;
22) Aortic arch radius of curvature < 35 mm (if device deployed in the arch);
23) Distal landing zone diameter for proximal stent-graft component < 20 mm (estimate based on transaortic diameter) or > 38 mm (estimate based on true lumen diameter), measured outer-wall to outer-wall on a sectional image or multiplanar reconstruction;
24) Diameter < 20 mm (estimate based on transaortic diameter) or > 38 mm (estimate based on true lumen diameter) for any segment of vessel into which deployment of bare stent device is intended, measured outer-wall to outer-wall on a sectional image or multiplanar reconstruction;
25) Prohibitive angulation in segments of vessel into which deployment of bare stent

device is intended (e.g., radius of curvature < 35 mm, or localized angle > 45 degrees);

26) Both iliac arteries having prohibitive tortuosity, calcification, occlusive disease or arterial diameter, measured inner-wall to inner-wall on a sectional image, that are not conducive to placement of the introducer sheath (use of access conduit permitted);
27) Prohibitive calcification, occlusive disease, or angulation in intended proximal landing zone;
28) Circumferential thrombus in region of intended proximal landing zone;
29) Inability to preserve the native left common carotid artery and celiac artery origins; or
30) Aneurysm or angulation in the distal thoracic aorta that would preclude advancement of the introduction system.

5.6 Point of Enrollment

Point of enrollment will be based on the intent-to-treat population, and is defined to include any patient for whom the treatment procedure is initiated. More specifically, once a procedure has begun (i.e., cutdown or percutaneous access initiated), the patient would be included in the intent-to-treat population. The patient's informed consent will be obtained and assessment of the patient's conformance to the inclusion/exclusion criteria will occur prior to the procedure.

Study results will also be analyzed with respect to the consented patient population (i.e., all patients who gave consent to participate in the study, regardless of treatment).

5.7 Enrollment Objective

67 patients will be enrolled in accordance with Version 4 of the CIP at up to 30 global clinical sites with a maximum enrollment of up to 14 patients per individual site. In order to account for patients who would not be eligible for enrollment based on the clarifications reflected in Version 4 of the CIP, the total enrollment for the study has increased to provide for six additional patients (73 patients total).

6.0 Methods

6.1 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 the procedure.

6.2 Pre-procedure

Stent-grafts and dissection stents are sized based on the findings from pre-operative computerized tomography (CT) in conjunction, if necessary, with other imaging modalities such as angiograms and intravascular ultrasound (IVUS). Refer to the Instructions for Use for details regarding the suggested sizing guidelines.

6.3 Procedure

Standard techniques for placement of arterial access sheaths, guiding catheters, angiographic catheters, and wire guides should be employed during use of the Zenith® Dissection Endovascular System. Care must be exercised in placing of sheaths and wireguides, and in advancing the delivery system of the devices. Molding balloon angioplasty in the dissected region of the aorta must be avoided.

Precautions should be taken to minimize the risk of stroke. All air should be flushed from sheaths and lumens before insertion using elevated tip technique. Wire placement and manipulation in the ascending thoracic aorta and aortic arch should be minimized.

Fluoroscopic guidance and angiography should be used throughout the procedure to verify positioning of the device with respect to the patient's anatomy.

Refer to institutional protocols relating to anesthesia, anticoagulation, access technique, spinal drainage and monitoring of vital signs. Coverage of the left subclavian artery is acceptable; however, revascularization of the left subclavian artery should be considered.[3]

Refer to the Instructions for Use for complete details regarding use of the Zenith® Dissection Endovascular System. In general, placement of a bare stent following

coverage of the primary tear with a stent-graft is recommended to support the distal, delaminated segments of the aorta. However, bare stent placement following stent-graft coverage of the primary entry tear may not be necessary in patients for whom all of the following are applicable:

- No continued signs or symptoms of obstructed/compromised branch vessel (if patient was included in the study for obstructed/compromised branch vessel) after placement of the proximal component

- Systolic pressure gradient ≤ 20 mm Hg between the aortic root and a distal obstructed aortic segment/vessel (if patient was included in the study for obstructed/compromised branch vessel)

- No false lumen flow through secondary re-entry tears

Bare stent deployment within regions of tortuosity or acute angulation should be avoided. It might be necessary to use multiple Zenith® Dissection Endovascular Stents of shorter length, so as to avoid deployment of the bare stents within tortuous or acutely angled segments.

6.4 Peri-operative Care

Refer to institutional protocols for peri-operative management of patients undergoing treatment for aortic dissection.

6.5 Post-operative Treatment of Entry-flow

All instances of entry-flow should be evaluated promptly with an angiogram, and if necessary a selective angiogram, to determine the origin of the flow. The completion angiogram should be examined carefully for entry-flow.

Type I entry-flow should be promptly considered for treatment using additional balloon seating or if necessary, placement of additional stent-graft prostheses (use of Zenith main body extensions is recommended). Placement of embolization coils may be needed to occlude sources of Type II entry-flow and collateral flow if the leak is believed to be significant and/or in the presence of an enlarging false lumen. Use of occluder devices (e.g., Amplatzer) to embolize the left subclavian artery has also been reported. Type III entry-flow represents graft or junctional defects and should be promptly considered for treatment with additional ballooning or prostheses. Type IV entry-flow is generally

associated with grafts with a high porosity and is unlikely with the graft component of this system. Secondary/reentry tears may also require coverage with placement of additional stent-graft prostheses in the aorta or covered balloon-expandable and/or self-expanding stents in branch vessels if flow through the tear is significant and/or in the presence of an enlarging false lumen.

6.6 Follow-up Treatment of Entry-flow and Flow Through Secondary Tears

Perfusion of the false lumen should be carefully monitored over the course of the follow-up exams. Treatment for significant entry-flow and flow through secondary tears should be considered especially in the presence of enlarging false lumen (as described in Section 6.5).

6.7 Treatment of Obstruction

Obstruction of the aortic true lumen resulting in end-organ ischemia/malperfusion may require placement of additional stent-graft prostheses or Dissection stents. Obstruction within a branch vessel true lumen resulting in end-organ ischemia/malperfusion may require placement of uncovered balloon-expandable and/or self-expanding stents.

6.8 Secondary Interventions

Some patients may need secondary intervention(s) for treatment of entry-flow, flow through secondary tears, obstruction/compromise of branch vessels, device migration, etc. The use of Zenith stent-graft components is recommended when additional stent-graft placement in the aorta is necessary to extend the length of primary graft coverage or to selectively cover secondary/reentry tears. The placement of uncovered balloon-expandable and/or self-expanding stents may be necessary to assist with true lumen patency in obstructed/malperfused branch vessels. Similarly, the placement of balloon-expandable and/or self-expanding covered stents may be necessary to assist with sealing secondary tears involving branch vessels. The timing and method of such interventions are based on the judgment of the treating physician. If ancillary devices (such as balloons, stents, etc.) are used during these interventions, it is recommended that the Instructions for Use (IFU) of that device be reviewed, and the risks of using that device be considered.

6.9 Follow-up

The study follow-up schedule is provided in Table 3. The suggested guidelines for scheduling the clinical and/or imaging evaluation is as follows: at the time of graft insertion, within 7 days post-procedure, at 30 days (± 10 days), 6 months (180 ± 30 days), 12 months (365 ± 45 days), 2 years (730 ± 60 days), 3 years (1095 ± 60 days), 4 years (1460 ± 90 days), and 5 years (1825 ± 90 days).

Table 3. Study follow-up schedule

	Pre-operative	Intra-operative	Post-procedure	30-day	6-month	12-month	24-month to 5-year[5]
Clinical Exam	X		X	X	X	X	X
Blood Tests[1]	X		X	X	X	X	X[6]
Contrast CT Scan	X		X[3,4]		X[3]	X[3]	X[3]
Angiography	X[2]	X					

1. Including tests to evaluate kidney and liver function.
2. Required only to resolve any uncertainties in anatomical measurements necessary for graft sizing.
3. TEE or non-contrast CT imaging may be used for those patients experiencing documented renal failure (eGFR < 30) or who are otherwise unable to undergo contrast enhanced CT scan.
4. CT must be performed prior to hospital discharge. In case of impaired renal function at the time of discharge, CT may be performed at 30 days.
5. Yearly through 5 years.
6. Required only for patients with malperfusion that has not stabilized.

6.10 Criteria and Procedures for Study Termination

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

1) Failure to deploy the device + 30 days;
2) Conversion to open surgical repair + 30 days;
3) Patient withdrawal;
4) Patient death;
5) Closure of the investigation; or
6) Completion of all scheduled clinical and imaging visits through 5 years.

7.0 Statistical Considerations

7.1 Sample Size Calculations

The study is designed to enroll 67 patients to evaluate the safety and effectiveness hypotheses (Section 3.3).

For the primary safety endpoint, based on the data from the combined physician-sponsored studies[1], the rate of freedom from 30-day major adverse events (see Appendix

C, Definitions) was estimated to be 61.2%. With a clinically relevant non-inferiority margin of 10%, a performance goal of freedom from 30-day MAE was established to be 51.2%. Sixty patients will be necessary to assess the primary safety hypothesis, under an expected rate of freedom from 30-day MAE at 69.2% (estimated from an on-going clinical trial with the Zenith® Dissection Endovascular System in patients with complicated, type B aortic dissection), with a one-sided exact binomial test, at a type I error rate of 0.025 and a power of 0.8.

For the primary effectiveness endpoint, based on the data from the combined physician-sponsored studies, the survival rate at 30 days was estimated to be 89.4%. With a clinically relevant non-inferiority margin of 10%, a performance goal for 30-day survival was established to be 79.4%. Forty patients will be necessary to assess the primary effectiveness hypothesis, under an expected 30-day survival rate of 94.9% (estimated from an on-going clinical trial with the Zenith® Dissection Endovascular System in patients with complicated, type B aortic dissection), with a one-sided exact binomial test, at a type I error rate of 0.025 and a power of 0.8.

Cook intends to enroll 73 patients, to allow for additional patients who may withdraw or be lost to follow-up, and to account for six previously enrolled patients that would not be eligible for enrollment based on the clarifications provided in Version 4 of the CIP (i.e., patients who were ASA class V or who were without confirmed absence of bowel necrosis at the time of enrollment). While the data from all 73 patients enrolled in the study will be reported, the primary safety and effectiveness hypotheses will be assessed based on the 67 patients enrolled according to the inclusion/exclusion criteria specified in Version 4 of the CIP.

7.2 Performance Goals

The performance goals used in the hypotheses of section 3.3 and the sample size calculations in section 9.1 were derived from the combined physician-sponsored studies. Using those data, the performance goal for the 30-day freedom from major adverse events was 61.2%, while the performance goal for the 30-day survival rate was 89.4%. With a clinically relevant margin of 10%, the performance goals are established as 51.2% and 79.4%, respectively.

7.3 Site-level Poolability

Poolability of data from multiple sites will be verified by examining the primary and secondary safety and effectiveness measures among sites as well as important patient baseline characteristics. Site-level poolability will be considered appropriate provided that these measures are similar among sites.

It is expected that many sites will have too few patients to provide reasonable site-level estimates of primary, secondary, and baseline measures. Each investigative site will be allowed to enroll no more than 14 patients (20% of the total enrollment) to ensure the overall result is not biased by the results from a single site. Pooling of this information will be explored based on hospital size (large versus small), site enrollment (large versus small), type of hospital (community versus teaching), and other group-wise strategies.

It is recognized that patient baseline characteristics may differ among sites, with some sites routinely treating patients with more severe disease progression. It is anticipated that the primary and secondary endpoint measures may be related to covariates that reflect this disease progression, which are in turn related to outcome. Thus, any observed site-specific differences among the primary or secondary endpoints will be checked for confounding with other measured covariates. This can be accomplished using regression models (linear and logistic where appropriate) that include site and other measured covariates as independent variables.

Should one or more sites significantly differ from the rest, then all subsequent analyses will include the discriminating covariate or a covariate to distinguish between the unusual site(s) and those sites that are considered poolable.

7.4 Missing Data

Missing data will be addressed using three primary strategies: 1) estimating missing data with the best available data, 2) case deletion, and 3) multiple imputation.

The first strategy may be used for missing imaging data. Previous clinical trial experience suggests that some portion of the imaging data may not meet the criteria for accurate measurements by the core laboratory. However, it is recognized that the treating physician uses this information to provide the best possible care for the patient. Therefore, it is reasonable to substitute any missing core laboratory measurements with the corresponding measurements made by the treating physician (or their staff). In addition, the absence or presence of clinical sequelae may provide the required missing

core laboratory assessment of device performance. Furthermore, imaging at subsequent time points may be available, making it possible to infer patient status at the time point of interest. This strategy is a best approximation of the missing data value.

The second strategy is case deletion. If the amount of missing data does not result in a reduction of analyzable patients to a number that is below that required for sufficient statistical power of the primary endpoints, then case deletion will be the method of choice for that analysis.

The third method is multiple imputation. This method will be used to predict missing endpoint or covariate data. It may be that the primary study endpoints may depend upon certain covariates. Therefore, it may be possible to model study endpoints, given a series of related covariates. This model-based imputation exercise may provide estimates of the missing data that can be utilized in estimating event rates and confidence bounds.

Strategies originating from Schafer[4] will be used, supplemented with notes provided by Schafer.[5] The computations will be performed using PROC MI and PROC MIANALYZE in SAS version 9.1 or later, or WinBUGS 1.4 or later.

Additional analyses of missing data may be performed as appropriate, including a tipping point analysis and a worst-case analysis.

7.5 Future Use of Study Data

Information redacted due to confidential content

8.0 Risk Analysis and Risk Assessment

8.1 Risks and Foreseeable Adverse Device Effects

Information redacted. Please refer to the Instructions for Use

8.2 Methods to Minimize Risks

The device design, non-clinical testing, clinical study design, and the Instructions for Use are intended to minimize the risks associated with the endovascular procedures.

9.0 Safety Monitoring and Event Reporting

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

9.2 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.

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.

9.3 Adverse Event Reporting

Events known to be related to pre-existing conditions or existing at admission are not considered adverse events (e.g., prior medically-treated cardiac arrhythmia with no change in status during the endovascular procedure). Additionally, common standard of care practices are not considered adverse events (e.g., centers located at high geographical altitudes that discharge all patients on home oxygen therapy regardless of procedure).

All adverse events (i.e., device-related and non-device-related) are to be reported using the appropriate case report form (Adverse Event/Complication form). In cases of adverse device effects (adverse event with relation to the study device) or serious adverse events, completed forms should be submitted to the Data Coordinating Center immediately upon knowledge of the event.

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The Data Coordinating Center will notify the sponsor accordingly. In accordance with applicable requirements, the investigator will notify the local Ethics Committee/IRB, while the sponsor will notify the regulatory authority. Furthermore, if the sponsor determines that the device presents a potential risk to the study patients, all investigators in the study will be notified. Refer to section 8.1 for a list of potential adverse events related to this study.

10.0 Administrative

10.1 Data Collection

Patient data will be collected and entered by the investigative site into an electronic case report form (eCRF) system. This is a secure, web-based system, allowing those with permission to access data from any location at any time. Data will be entered by qualified site personnel. Site personnel are required to have unique login names and passwords in order to enter patient data, and, in accordance with 21 CFR Part 11, the eCRF system creates a secure, computer-generated, time stamped audit trail to record the date and time of operator entries and actions that create, modify, or delete electronic records.

10.1.1 Data Archiving

Patient data and documents pertaining to the study are to be kept for the longest time required by the regulatory bodies overseeing the study. Archiving will be done in such a way that the data are not lost during this period. Both investigators and sponsor are obliged to keep the documents.

10.1.2 Data Protection

Each patient will be assigned a unique enrollment number, and will be identified to the sponsor only by this unique enrollment number and patient initials. While monitors necessarily will have access to protected health information, all monitors will have

appropriate training and follow procedures for proper handling of patient-identified information. Furthermore, whenever feasible, de-identified health information will be used by researchers involved in the study. "Researchers" include the patient's physician and the staff of collaborators, investigators in other locations studying this device, the sponsor, and the companies or individuals with research responsibilities delegated by the sponsor.

These data may be used to gain additional experience with this device and to advance medical knowledge through presentations and articles regarding the study. These data may also be reviewed by government agencies that oversee research and may approve medical devices for commercial use.

These data may also be combined with health information about other patients. The sponsor or their designee will keep the data in an ongoing database of information about the Zenith® Dissection Endovascular System, so that information can be studied and analyzed. When the follow-up period is complete, no new information about individual patients will be added, but review of the data may continue. Presentations, reports, and articles about this investigation will contain only de-identified information.

10.1.3 Data Protection Agency

If applicable, the Danish Data Protection Agency will be notified about this investigation to conform with The European Act on Processing of Personal Data (Act No 429 of May 31, 2000) which entered into force on July 1, 2000, and which implements the Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

10.2 Data Reporting

Progress reports and a final report at the conclusion of the clinical investigation will be submitted by the investigators and sponsor to the Ethics Committees and regulatory bodies as required by local regulations.

10.3 Emergency Situations and Vulnerable Subjects

Patients will not be treated with the Zenith® Dissection Endovascular System in emergency situations where prior consent of the patient or the patient's legally-authorized representative in accordance with 21 CFR Part 50 is not possible.

10.4 Criteria and Procedures for Withdrawal

The investigator must make a reasonable effort to ascertain and record the reason for withdrawal or discontinuation for each patient while fully respecting the subject's rights. 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-up in the investigation, if possible.

10.5 Deviations from Clinical Investigation Plan

Deviations or non-compliances will be recorded together with an explanation. Deviations shall be reported to the sponsor, regulatory authorities, and Ethics Committee/IRB as required.

10.6 Early Termination or Suspension of the Investigation

The sponsor reserves the right to terminate/suspend the study at any point should they believe that important harmful events might result from its continuation. Subjects may withdraw from the study at any time without penalty or loss of benefits. The investigator may also decide to withdraw a subject from the study at any time on the basis of medical judgement. In any case, the reasons for withdrawal will be documented, when available.

10.7 Limitations of the Investigation

This study is inherently limited by the number of patients who will be excluded due to general, medical, and anatomical exclusion criteria. Additional challenges to the study include the anticipated comorbidities, which may confound data analysis.

10.8 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.

10.9 Approvals and Agreements

The sponsor, coordinating investigator (if applicable), 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.

10.10 General Information

10.10.1 Sponsor

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

10.10.2 Manufacturer

The Manufacturer for this investigation is William Cook Europe, ApS. See Appendix A for contact information.

10.10.3 Data Coordinating Center

The Data Coordinating Center for this investigation will be Cook Research Incorporated . See Appendix A for contact information.

10.10.4 Investigation Compliance

The investigation shall be performed according to the Declaration of Helsinki**.**

The investigator is responsible for obtaining approval of this clinical investigation by the relevant Ethics Committee/IRB. The sponsor must be provided with a copy of this approval before delivery of any study device. Furthermore, the investigator will ensure that local regulations concerning data protection are followed.

Cook Research Incorporated is certified with the U.S. Department of Commerce's Safe Harbor Privacy program for the transfer of clinical study data pertaining to residents of the European Union. The Safe Harbor Privacy Program, which is jointly sponsored by the Department of Commerce and the EU Commission, allows organizations to self-certify to privacy standards that are higher than those currently required in the United States.

The U.S. companies that participate in the Safe Harbor Privacy Program voluntarily agree to uphold seven Safe Harbor Privacy Principles: Notice, Choice/Consent, Onward Transfer, Access and Correction, Data Integrity, Security, and Enforcement.

Adherence to these Safe Harbor Privacy Principles may be limited to the extent required by any legal, governmental, national security or public interest obligation.

10.10.5 Investigators

A complete list of the coordinating clinical investigator, principal clinical investigators, and clinical investigators will be updated and maintained by the Data Coordinating Center. Updates will be sent to sites periodically.

10.10.6 Monitoring Arrangements

The monitor for this investigation will be 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 monitors and can be found in Appendix B.

10.10.7 Insurance

The devices are covered by sponsor’s product liability insurance with Chubb Group of Insurance Companies, and a clinical study insurance policy will be taken out according to local requirements. A copy of the insurance certificate(s) will be included in the investigator file. By signing the Clinical Investigation Plan, all the investigators and co-investigators involved declare to be covered by liability insurance in case of an adverse event due to medical error occur during the Zenith® Dissection investigation.

10.10.8 Exposition of the Clinical Investigation Plan

In case of translation of the Clinical Investigation Plan into the language of the participating countries, the English version is to be considered as the original; i.e., when expounding the contents of the Clinical Investigation Plan in these languages, the English version is definitive in case of doubt.

11.0 Bibliography

Please reference the Clinical Investigator Brochure for a complete literature review and evaluation.

APPENDIX A
Contact Information

Contact Information

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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).
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 case report forms (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 Clinical Investigations Plan, conditions of IRB/EC or regulatory authority approval, or the applicable regulations.

APPENDIX C
Definitions

Calcification: Landing zone and iliac 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.

Clinical Utility Measures: Number of blood transfusions; Ventilator days*;* Days to resumption of oral fluids; Days to resumption of normal diet; Days to resumption of normal bowel function; Duration of ICU stay; Days to discharge.

Disabling Chronic Obstructive Pulmonary Disease: Forced expiratory volume (FEV_1) < 1.0 liter or receiving home oxygen therapy.

Dissection Grade:

Acute:	Within 14 days of onset;
Subacute:	Between 15 days and 30 days of onset; or
Chronic:	Between 31 days and 90 days of onset.

Embolization: Clinical evidence of ischemic tissue remote from the operative field, caused by air, thrombus dislodged from the aneurysmal sac, aortic neck, and/or false lumen, including those tissues supplied by vessels in the head, renal arteries, aortic visceral branches, pelvic vessels, and vessels of the upper and lower limbs. This is, of course, distinct from pre-operative, operative or post-operative intentional embolization procedures (e.g., to treat Type II entry-flow).

Entry-flow: Contrast-enhanced blood entering the false lumen for one or more of the following reasons:

Type I entry-flow: Entry-flow caused by peri-prosthetic flow at the proximal and/or distal seal zones;

Type II entry-flow: Entry-flow caused by retrograde flow from patent collateral vessels into the false lumen through the primary tear;

Collateral entry-flow: Entry-flow caused by retrograde flow from collateral vessels directly into the false lumen;

Type III entry-flow: Entry-flow caused by a defect in the graft fabric, inadequate seal (between covered graft components only), or disconnection of covered graft ancillary components;

Type IV entry-flow: Entry- flow caused by graft fabric porosity, often resulting in a generalized blush of contrast within the false lumen; or

Unknown entry-flow: Entry-flow through undefined origin.

Left Ventricular Ejection Fraction: The measurement of the left ventricular function in the resting state. The normal LVEF ranges between 55% and 80% (mean = 67%).

Major Adverse Events: - Myocardial infarction, chronic renal insufficiency/chronic renal failure requiring dialysis, bowel ischemia, stroke, paraplegia or paraparesis, and prolonged (> 72 hours) ventilatory support.

Malperfusion: Malperfusion in the setting of an aortic dissection is defined as one or more of the following[1]:

1. Visceral hypoperfusion by an acute abdomen, abdominal pain out of proportion to physical examination findings in setting of radiographic hypoperfusion of mesenteric bed, lactic acidosis attributed to visceral malperfusion, or need for bowel resection.
2. Renal hypoperfusion including oliguria or aneuria in setting of rising rnalfunction tests (creatinine or blood urea nitrogen) or radiographic evidence of impaired renal artery blood flow.
3. Lower extremity hypoperfusion indicated by abnormal pulse examinations in conjunction with leg pain, pallor, paresthesias or paralysis.
4. Spinal cord hypoperfusion as noted by altered motor function of one or both of legs attributed to a possible spinal cord source.

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 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 chest pain or other acute symptoms consistent with myocardial ischemia and the presence of new pathological Q-waves in two or more contiguous ECG leads.

Migration (radiographic): Antegrade or retrograde movement of the proximal or distal components of the endoprosthesis > 10 mm relative to anatomical landmarks identified on the first post-operative CT scan as evaluated by core laboratory.

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

New York Heart Association Classification:

1. Patient with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.

2. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest; ordinary physical activity results in fatigue, palpitation or dyspnea.

3. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest; less than ordinary physical activity causes fatigue, palpitation or dyspnea.

4. Patients with cardiac disease resulting in inability to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Occlusive Disease of iliacs: Occlusive disease will be graded based upon the following:

None:	Lack of occlusive disease;
Mild:	Some disease, focal with less than 30% narrowing;
Moderate:	Between 30-50% narrowing not requiring interventional techniques to meet inclusion criteria; or
Severe:	Greater than 50% or any patient requiring angioplasty prior to endograft delivery.

Pain/Symptoms rating:

None:	No pain/symptoms;
Mild:	Nagging, annoying, interfering little with activities of daily living (ADLs);
Moderate:	Interferes significantly with ADLs; or
Severe:	Disabling; unable to perform ADLs.

Resistant Hypertension: arterial pressure > 140/90 mm Hg despite use of three antihypertensive medications. (Kaplan NM. Resistant hypertension. Journal of Hypertension 2005; 23: 1441-1444.)

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

Reversible ischemic neurologic deficit (RIND): Clinically significant central nervous system deficit lasting > 24 hours and < 72 hours.

Renal Insufficiency: A rise in serum creatinine of more than 30% above the pre-procedure level, resulting in a serum creatinine level > 2.0 mg/dl that does not spontaneously resolve (does not include those patients with a pre-procedure serum creatinine > 2.0 mg/dl).

Rupture: Rupture in the setting of aortic dissection is defined by the presence of hemorrhage outside the aortic boundaries, which is noted on CT scans.[1]

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

Stroke: Permanent, clinically significant central nervous system deficit.

Tortuosity of iliac arteries: Tortuosity will be graded based upon the following:

None:	Lack of tortuosity;
Mild:	Fairly straight arteries;
Moderate:	Angulation manageable with stiff wires, < 70 degrees; or
Severe:	Angulation difficult, may require surgical exposure for straightening, not straightened entirely with wires.

Transient Ischemic Attack (TIA): Central nervous system deficit lasting ≤ 24 hours.

Type B Aortic Dissection: Thoracic aortic dissection with the most proximal extent of dissection distal to the left subclavian artery.

APPENDIX D
References

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3. Matsumura et al., The Society for Vascular Surgery practice guidelines: management of the left subclavian artery with thoracic endovascular aortic repair. J Vasc Surg 2009; Nov; 50(5):1155-8.

4. Schafer, JL. Analysis of Incomplete Multivariate Data. London: Chapman & Hall; 1997.

5. Schafer, JL. Missing Data: A Review. A seminar sponsored by the Cleveland Chapter of the American Statistical Association; October 14, 2002; Cleveland, OH.