CLINICAL INVESTIGATION PLAN

Zenith® TX2® Low Profile Endovascular Graft for Blunt Thoracic Aortic Injury Clinical Study

Global Clinical Number 11-004

Manufacturer:	William Cook Europe, ApS Sandet 6 DK 4632 Bjaeverskov, Denmark
Sponsor:	Cook Incorporated 750 Daniels Way Bloomington, IN 47404 USA

Summary of Revisions

Version #	Description	Date
11-004-01	Original version	14 June 2012

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

This clinical investigation will be conducted in compliance with the clinical investigation plan (CIP), GCP, ISO 14155, 21 CFR 812, and other applicable requirements as appropriate.

Signatures:

Sponsor Contact

[signature]	27/06/2012
Signature	DD/MM/YYYY
Scott Williams	Director Regulatory Affairs
Printed Name	Title

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

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

09/07/2012
DD/MM/YYYY

STARNES
Printed Name

CHIEF, Professor
Title

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

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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Appendices

1.0 Clinical Investigation Plan Overview

This study will be conducted as a prospective, nonrandomized, noncomparative, single-arm study enrolling a total of 50 patients at up to 30 global centers. The purpose of this study is to assess the safety and effectiveness of the Zenith® TX2® Low Profile Endovascular Graft in the treatment of patients with blunt thoracic aortic injury (BTAI).

A patient is deemed suitable for inclusion in the study if the patient has blunt thoracic aortic injury of the descending thoracic aorta and is suitable for treatment with the Zenith® TX2® Low Profile Endovascular Graft and 16 Fr, 18 Fr, or 20 Fr Z-Trak Plus® Introduction System. The study flow diagram is presented in Figure 1.

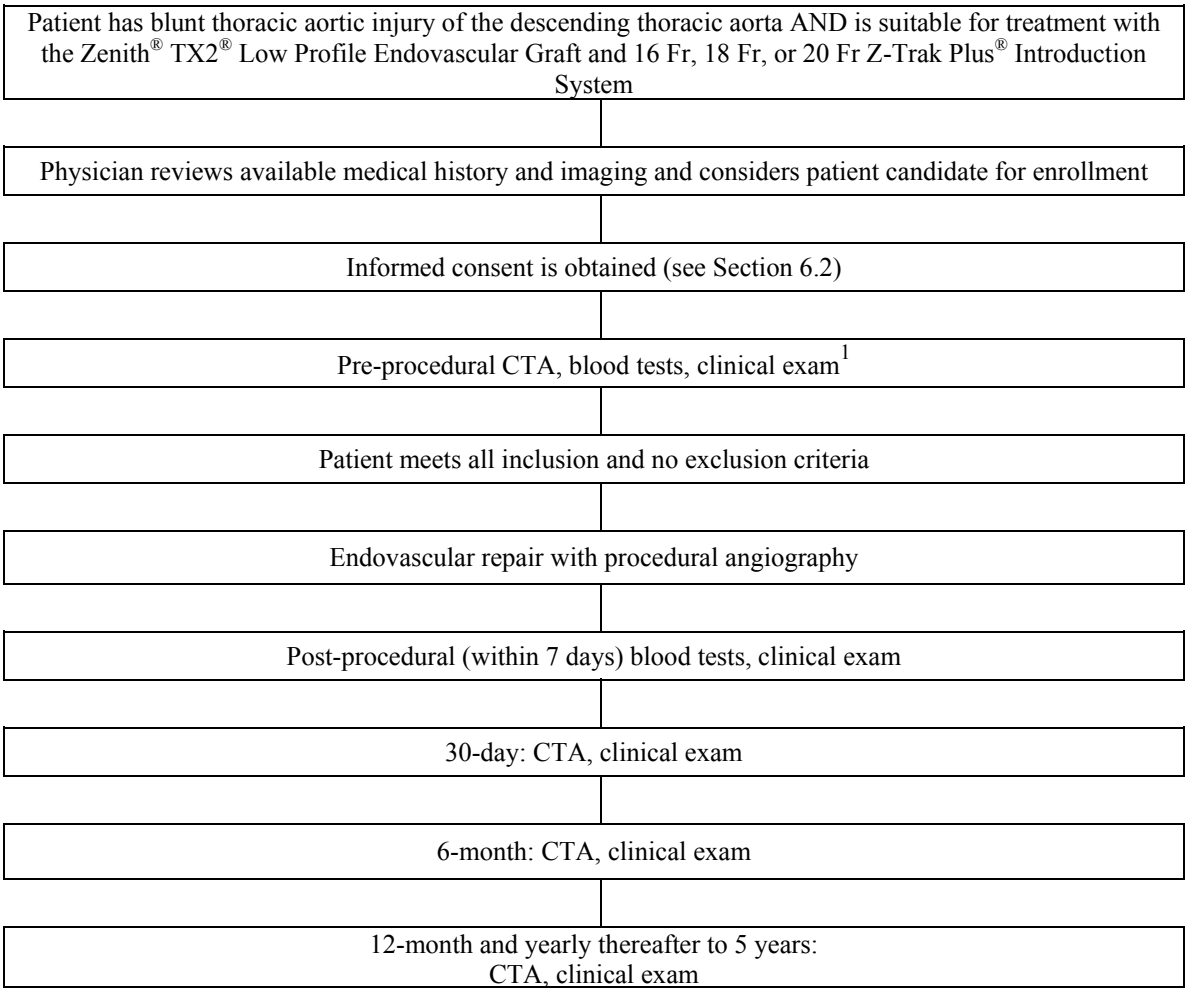


Figure 1. Study flow diagram

[1] Data collected prior to the patient's signing of an Informed Consent are acceptable if they are standard of care at the investigative site.

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 reference the Clinical Investigator Brochure for a summary of non-clinical testing.

2.2 Previous Clinical Experience

Please reference the Clinical Investigator Brochure for a complete description of the previous clinical experiences with the device or other similar devices, if applicable.

2.3 Justification for the Investigation

Endovascular repair has been reported as an independent predictor of survival for patients with blunt thoracic aortic injury (BTAI).[1] A meta-analysis performed by the Society for Vascular Surgery (SVS) showed a mortality rate of 9% with endovascular treatment as compared to 19% with open surgical repair. These findings led the SVS committee to preferentially recommend endovascular repair of traumatic thoracic aortic injuries over open surgical repair or nonoperative management.[2,3]

However, limited endovascular treatment options are available for patients with blunt thoracic aortic injury. Furthermore, several publications have noted the need for devices with better arch conformability to accommodate the steep curvature of the aortic arch.[3,4] Device infolding and collapse were also noted to be issues, often resulting from excessive oversizing at the site of fixation.[3,4,5] As patients with BTAI are on average much younger[6] than those treated for thoracic aortic diseases such as aneurysms,[7] smaller diameter endovascular grafts with better arch conformability are needed to treat this patient population.

The Zenith® TX2® Low Profile Endovascular Graft has multiple design features that address the challenges of treating BTAI. The availability of the Zenith® TX2® Low Profile Endovascular Graft in smaller sizes and in smaller profile delivery systems will allow physicians to treat patients with smaller aortic anatomy and therefore eliminate the need to treat patients with larger endografts that are not suitable for their anatomy. Furthermore, the Zenith® TX2® Low Profile Endovascular Graft features a bare alignment stent in combination with a curved cannula on the introduction system to help ensure adequate proximal conformability. The Zenith® TX2® Low Profile Endovascular Graft device has been designed to accommodate a radius of curvature of 20 mm, whereas the currently available Zenith® TX2® TAA Endovascular Graft accommodates a radius of curvature of 35 mm. Based on these device design features and the clinical need for devices to treat BTAI, the clinical study to evaluate the safety and performance of the Zenith® TX2® Low Profile Endovascular Graft in patients with BTAI is justified.

3.0 Objectives of the Clinical Investigation

3.1 Primary Objectives

The objectives of the study are to evaluate the safety and effectiveness of the Zenith® TX2® Low Profile Endovascular Graft for the treatment of patients with BTAI. The primary safety endpoint will be all-cause and aortic-injury-related mortality (see Appendix C, Definitions) at 30 days. The primary effectiveness endpoint will be device success (see Appendix C, Definitions) at 30 days.

3.2 Secondary Objectives

Additional objectives for descriptive purposes include assessment of the following: procedural time and clinical utility measures at the intra-operative and post-procedure time points (see Appendix C, Definitions); major adverse events (see Appendix C, Definitions), injury healing (as determined by maximum transverse diameter at the site of injury), secondary interventions, endoleak, device migration, device patency, device integrity, and device collapse through the 5-year time point.

3.3 Specific Hypothesis to be Accepted or Rejected by Statistical Data

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

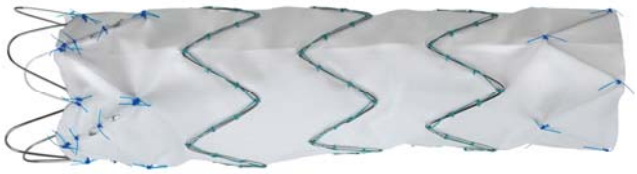
4.0 Product Description and Intended Use

The Zenith® TX2® Low Profile Endovascular Graft is currently under clinical investigation for the treatment of patients with descending thoracic aortic aneurysms/ulcers. The treatment of BTAI uses the same proximal main body component as that intended for the treatment of aneurysms/ulcers. While the system that is available for the treatment of aneurysms/ulcers also has an overlapping distal component in order to provide the added coverage often needed, the available system for the treatment of BTAI will include only a proximal component, as the aortic segment requiring coverage is expected to be much more focal than that for an aneurysm/ulcer.

4.1 General Product Description

As depicted in Figure 2, the proximal component is constructed of self-expanding nitinol stents sewn to polyester graft material with braided polyester and monofilament polypropylene sutures. At the proximal end there is an uncovered stent and an internal sealing stent with fixation barbs that protrude through the graft material. All other stents are external to the graft material, except for the distal-most stent, which is located internal to the graft material. There are radiopaque markers at the proximal and distal edges of the graft. The proximal component will be available in multiple diameters and lengths and can be either straight or tapered, as shown in Table 1.

Proximal component (straight)



Proximal component (tapered)

Figure 2. Zenith® TX2® Low Profile Endovascular Graft proximal component

Table 1. Available Zenith® TX2® Low Profile Endovascular Grafts: diameter and length

Diameter (mm)*	Length of Straight Proximal Component (mm)	Length of Tapered Proximal Component (mm)
18	105	N/A
20	105	N/A
22	105	105
24	105	N/A
26	105	105
28	109	N/A
30	109	108
32	109	N/A
34	113	N/A
36	113	N/A
38	117	N/A
40	117	N/A
42	121	N/A
44	125	N/A
46	125	N/A

* For tapered components the proximal diameter is listed; taper is 4 mm

4.1.1 Delivery System

Each Zenith® TX2® Low Profile Endovascular Graft component will be shipped preloaded onto a 16 Fr, 18 Fr, or 20 Fr Z-Trak Plus® Introduction System (Figure 3), which has a sequential deployment method with built-in features to provide control of the endovascular graft throughout the deployment procedure. All delivery systems feature Flexor® introducer sheaths, which resist kinking and are hydrophilically coated, and use the Captor® Hemostatic Valve for added hemostasis. The proximal component is deployed from a delivery system

with a precurved inner cannula and a single trigger-wire release mechanism, which attaches the proximal and distal ends of the stent-graft to the delivery system following withdrawal of the sheath, until released by the operator.

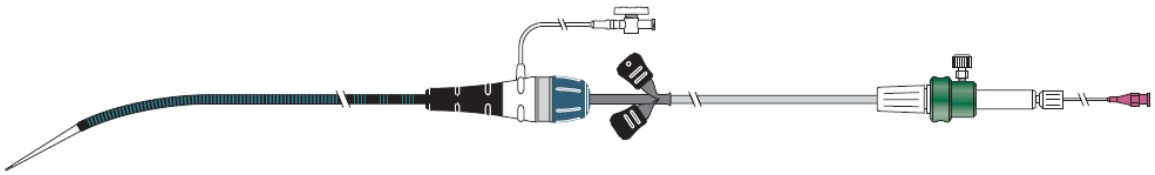


Figure 3. Zenith® TX2® Low Profile Endovascular Graft proximal component Z-Trak Plus® Introduction System

4.2 Intended Use

The Zenith® TX2® Low Profile Endovascular Graft with the Z-Trak Plus® Introduction System is indicated for the endovascular treatment of patients with blunt thoracic aortic injury of the descending thoracic aorta having vascular morphology suitable for endovascular repair, including:

- Adequate iliac/femoral access compatible with the required delivery systems,
- Aortic segments (fixation sites) proximal and distal to the blunt thoracic aortic injury:
  - with a length of at least 20 mm and
  - with a diameter measured outer-wall to outer-wall of no greater than 42 mm and no less than 15 mm.

Please reference the Instructions for Use (IFU) for details regarding intended use.

4.3 Product Identification and Tracking

The identification and labeling of the products under investigation are outlined in the Clinical Investigator Brochure and Instructions for Use.

Products under investigation 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 by the sites. Additionally, the quantity(s), size(s), and lot number(s) of products used in patients 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 implantation, storage and handling requirements, preparation for use, pre-use checks for safety and performance, 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 complete 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 complete description of the procedures involved in the use of this product.

5.0 Design of the Clinical Investigation

5.1 Type of Investigation

The current investigation is a prospective, nonrandomized, noncomparative, single-arm clinical study. Enrollment is expected to be completed within 24 months of initiating the study.

5.2 Endpoints

The primary safety endpoint will be all-cause and aortic-injury-related mortality at 30 days.

The primary effectiveness endpoint will be device success, defined as technical success (i.e., successful access of the injury site and deployment of the Zenith® TX2® Low Profile Endovascular Graft in the intended location, and endovascular graft patency upon completion of deployment) with none of the following at 30 days:

- Device collapse;
- Type I or type III endoleak requiring reintervention; or
- Conversion to open surgical repair.

The secondary endpoints include an assessment of the following:

- At the intra-operative and post-procedure time points:
  - Procedural time and clinical utility measures (see Appendix C, Definitions);
- Through the 5-year time point:
  - Major adverse events (see Appendix C, Definitions),
  - Injury healing (as determined by maximum transverse diameter at the site of injury),
  - Secondary interventions,
  - Endoleak,
  - Device migration,
  - Device patency,
  - Device integrity, and
  - Device collapse.

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) Complications including major adverse events during procedure and at follow-up;
4) Device integrity findings at completion of procedure and follow-up: device migration, patency, stent fracture, and graft kinks;
5) Type and sources of endoleaks at procedure and follow-up; and
6) 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® TX2® Low Profile Endovascular Graft. 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 laboratory 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

All patients must meet all of the following inclusion criteria to be eligible for enrollment into this study:

1) Blunt thoracic aortic injury of the descending thoracic aorta
2) Suitable for treatment with the Zenith® TX2® Low Profile Endovascular Graft and 16 Fr, 18 Fr, or 20 Fr Z-Trak Plus® Introduction System
3) Treatment with the Zenith® TX2® Low Profile Endovascular Graft can be performed within 14 days of the blunt thoracic aortic injury
4) Age ≥ 16 years
5) Proximal fixation site length measuring ≥ 20 mm between the left common carotid artery and most proximal extent of the injury site (covering left subclavian artery is acceptable)
6) Distal fixation site length measuring ≥ 20 mm between the distal-most aspect of aortic injury and most distal extent of graft
7) No previous placement of a thoracic endovascular graft
8) No prior open surgical repair involving the descending thoracic aorta including suprarenal aorta and/or arch
9) Proximal neck diameter, measured outer-wall to outer-wall on a sectional image or multiplanar reconstruction (CT), ≥ 15 mm and ≤ 42 mm
10) Distal neck diameter, measured outer-wall to outer-wall on a sectional image or multiplanar reconstruction (CT), ≥ 15 mm and ≤ 42 mm
11) Ability to preserve the left common carotid artery and celiac artery
12) Willing and able to comply with the follow-up schedule

13) Informed consent given by the patient or a legally authorized representative [Note: For pediatric patients, in addition to obtaining permission from their parents or guardians, assent from the patients may need to be obtained based on IRB requirements. See Section 6.2 for further information.]

5.5.2 Exclusion Criteria

Patients must be excluded if any of the following general, medical, or anatomical exclusion criteria are true:

General Exclusion Criteria

1) Injury severity score (see Appendix C, Definitions) at the time of initial hospital admission is 75
2) Aortic injuries classified as grade 1[8] (see Appendix C, Definition of Traumatic Aortic Injury)

Medical Exclusion Criteria

1) Pregnancy
2) Known allergy to polyester, polypropylene, nitinol, or gold
3) Allergic reaction to contrast, which in the opinion of the investigator, cannot be adequately premedicated
4) Aortic dissection
5) Systemic infection (e.g., sepsis)
6) Degenerative connective tissue disorder (e.g., Marfan's disease)
7) Bleeding diathesis, uncorrectable coagulopathy, or refusal of blood transfusion
8) 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 and not enroll in another study until 30 days after blunt thoracic aortic injury repair in this study)

Anatomical Exclusion Criteria

1) Treatment length (i.e., length of aortic injury including proximal and distal fixation sites) along greater curvature:
   > 105 mm for 18 mm to 26 mm diameter grafts
   > 109 mm for 28 mm to 32 mm diameter grafts
   > 113 mm for 34 mm to 36 mm diameter grafts
   > 117 mm for 38 mm to 40 mm diameter grafts
   > 121 mm for 42 mm diameter grafts
   > 125 mm for 44 mm to 46 mm diameter grafts
2) Aortic arch radius of curvature < 20 mm (only if the device is intended to be deployed in the aortic arch)
3) Tortuosity, calcification, occlusive disease, or arterial diameter of the intended access vessels (e.g., iliac and/or femoral arteries), measured inner-wall to inner-wall on a sectional image, that are not conducive to placement of the introducer sheath (16 Fr for 18 mm to 30 mm diameter grafts, 18 Fr for 32 mm to 38 mm diameter grafts, 20 Fr for 40 mm to 46 mm diameter grafts) – use of an access conduit is acceptable
4) Prohibitive calcification, occlusive disease, or tortuosity of intended fixation sites
5) Circumferential thrombus in region of intended fixation sites
6) 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 in whom the treatment procedure is initiated. More specifically, once a procedure has begun (i.e., cutdown or percutaneous access initiated), the patient will 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.

5.7 Enrollment Objective

Fifty patients will be enrolled to provide greater assurance of the study results and to also account for possible loss to follow-up or withdrawal from the study. Up to 30 centers in the US and outside the US may participate.

6.0 Methods

6.1 Subject Assessment and Screening

Patients will be screened prior to the procedure to ensure they meet all of the inclusion and none of the exclusion criteria.

6.2 Subject Consent

Patients who meet all of the inclusion and none of the 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.

Informed consent from the patient or a legally-authorized representative will be obtained (in accordance with 21 CFR 50) prior to the procedure or any study-specific testing.

A short-form consent document, in accordance with 21 CFR 50.27, may be developed, to allow for oral presentation of the elements of the informed consent to the patient. Because in many instances the patient may not be able to provide consent and the legally-authorized representative may not be able to be present at the hospital immediately, approval for telephone consent (wherein treatment options are discussed with the legally-authorized representative over the phone, and a consent form is then either faxed or emailed to the individual so the individual can sign and return the consent form via fax or email) may be sought from the IRBs/ECs (see Appendix D for short-form and telephone consent templates).

For pediatric patients, in addition to obtaining permission from the parents or guardians of the patient, assent from the patient may be necessary based on the requirements of the IRB.

Patients will not be treated with the Zenith® TX2® Low Profile Endovascular Graft in emergency situations where prior consent of the patient or the patient's legally-authorized representative in accordance with 21 CFR Part 50.24 is not possible.

This study will not be conducted as emergency research under 21 CFR 50.24. Use of study devices in an emergent situation, wherein a patient or a legally-authorized representative is unable to provide consent, must be reported according to applicable FDA and IRB/EC requirements.

6.3 Medications

The hospital's standard protocol should be followed with respect to medications.

6.4 Pre-procedure

Grafts are sized based on pre-operative radiologic findings, using computerized tomography (CT). Please reference the Instructions for Use for details regarding the suggested imaging studies to be obtained and sizing guidelines.

Because patients with traumatic aortic injury most often have other serious concomitant non-aortic injuries, endovascular repair of the aortic injury may be postponed until other injuries have been treated.

6.5 Procedure

Standard techniques for placement of arterial access sheaths, guiding catheters, angiographic catheters, and wire guides should be employed during use of the Zenith® TX2® Low Profile Endovascular Graft. The Zenith® TX2® Low Profile Endovascular Graft is compatible with 0.035 inch diameter wire guides.

Reference the institutional protocols and SVS guidelines 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]

Reference the Instructions for Use for complete details regarding use of the Zenith® TX2® Low Profile Endovascular Graft. Fluoroscopic guidance and angiography should be used throughout the procedure to verify positioning of the device with respect to the patient's anatomy.

6.6 Peri-operative

Reference the institutional protocols for peri-operative management of patients undergoing treatment for BTAI.

6.7 Post-operative Treatment of Endoleaks

Type I and type III endoleaks warrant immediate treatment. Type II endoleaks should be treated at the physician's discretion, depending on endoleak source and time from implantation. Type III endoleaks should be treated with additional ballooning or prostheses.

6.8 Secondary Interventions

Some patients may need secondary intervention(s) for treatment of endoleaks, device migration, etc. The timing and method of such interventions are based on the judgment of the treating physician. If ancillary devices (balloons, stents, etc.) are used during these interventions, it is recommended that Instructions for Use (IFU) of that device be reviewed, and the risks of using that device be considered.

6.9 Follow-up

The results of the endovascular repair will be assessed by clinical and/or imaging evaluation intra-operatively and post-operatively, including within 7 days post-procedure, at 30 days (± 10 days) post-procedure, and at 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) post-procedure as summarized in Table 2. Follow-up windows are intended as guidelines only. They are not absolute and are not intended to limit data collection due to scheduling conflicts.

Table 2. Study follow-up schedule

	Pre-op	Intra-op	Post-procedure	30-day	6-month	12-month[3]
Clinical exam	X		X	X	X	X
Blood tests	X		X			
CTA	X[1]			X[2]	X[2]	X[2]
Angiography		X				

[1]The CTA must be obtained as close as possible to the study procedure.
[2]MR or non-contrast CT imaging may be used for those patients experiencing renal failure or who are otherwise unable to undergo contrast-enhanced CT scan, with TEE being an additional option in the event of suboptimal MR imaging.
[3]Performed yearly for 5 years.

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 or lost to follow-up;
4) Patient death;
5) Closure of the investigation; or
6) Completion of all scheduled clinical and imaging visits through 5 years.

An autopsy, including explant of the study device, may be requested for patients who die with a study device in place. Both the excised aorta and the study device should be sent to the Data Coordinating Center for subsequent examination. Any study device excised in the course of conversion to open repair should also be sent to the Data Coordinating Center. Further instructions will be provided as needed. Data will be collected and stored in a database.

7.0 Statistical Considerations

7.1 Sample Size Calculations

The 30-day mortality rate is estimated to be 7.6%[2,6,9-14] based on a literature review of patients treated with endovascular repair for BTAI. The data used to calculate the mortality rate are provided in Appendix E. Forty-three patients are required to construct a 95% confidence interval with a margin of error of 8%. A total of 50 patients will be enrolled to account for possible loss to follow-up or withdrawal from the study. Up to 30 centers in the US and outside the US may participate.

The following formula is used to calculate the sample size: $n = \frac{z^2_{0.975} p(1-p)}{\Delta^2}$, where $z_{0.975}$ is the 97.5th quantile, p is the performance goal, and Δ is the margin of error (8%). With 43 patients, a 95% confidence interval for the 30-day mortality rate would be [0%, 15.6%].

7.2 Performance Goals

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

typically have extensive concomitant injuries that would confound the interpretation of statistical comparisons to alternative treatments.

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 10 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 aortic injuries. It is anticipated that the primary and secondary endpoint measures may be related to covariates that reflect this severity, 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 investigator 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 investigator (or his/her 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 strategy is multiple imputation. This method will be used to predict missing endpoint data. For missing primary endpoint data, the multiple imputation technique will be used to generate random Bernoulli observations with probabilities equivalent to the proportion of (non-missing) "Yes"/ "No" entries. It is anticipated that no covariates will be used for this model. 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[15] will be used, supplemented with notes provided by Schafer.[16] The computations will be performed using PROC MI and PROC MIANALYZE in SAS version 9.1 or later. Unless evidence suggests otherwise, missing at random data will be assumed.

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

7.5 Future Use of Study Data

The data collected in this study may be used to justify additional studies of variations on the Zenith® TX2® Low Profile Endovascular Graft including, but not limited to, design variations. It is anticipated that the safety and effectiveness data obtained may serve as prior information in the analysis of the safety and effectiveness of future variations of the Zenith® TX2® Low Profile Endovascular Graft.

8.0 Risk Analysis and Risk Assessment

Please reference the Clinical Investigator Brochure for a summary of the complete risk analysis.

8.1 Risks and Foreseeable Adverse Device Effects

Risks of adverse events are likely to be similar to those reported in recent studies of other endovascular thoracic aortic grafts. Adverse events associated either with the Zenith® TX2® Low Profile Endovascular Graft or the implantation procedure that may occur and require intervention include, but are not limited to:

- Amputation
- Anesthetic complications and subsequent related problems (e.g., aspiration)
- Aortic damage, including perforation, dissection, bleeding, rupture, and death
- Aortic valve damage
- Aortobronchial fistula
- Aortoesophageal fistula
- Arterial or venous thrombosis and/or pseudoaneurysm
- Arteriovenous fistula
- Bleeding, hematoma, or coagulopathy
- Bowel complications (e.g., ileus, transient ischemia, infarction, necrosis)
- Cardiac complications and subsequent related problems (e.g., arrhythmia, tamponade, myocardial infarction, congestive heart failure, hypotension, hypertension)
- Claudication (e.g., buttock, lower limb)
- Death
- Edema
- Embolization (micro and macro) with transient or permanent ischemia or infarction
- Endoleak
- Endoprosthesis: improper component placement, incomplete component deployment, component migration, suture break, occlusion, infection, stent fracture, graft material wear, dilatation, erosion, puncture, perigraft flow, barb separation, and corrosion
- Femoral neuropathy
- Fever and localized inflammation

- Genitourinary complications and subsequent related problems (e.g., ischemia, erosion, fistula, incontinence, hematuria, infection)
- Hepatic failure
- Impotence
- Infection of device or access site, including abscess formation, transient fever, and pain
- Lymphatic complications and subsequent related problems (e.g., lymph fistula, lymphocele)
- Neurologic local or systemic complications and subsequent related problems (e.g., stroke, transient ischemic attack, paraplegia, paraparesis/spinal cord shock, paralysis)
- Occlusion of coronary arteries
- Pulmonary embolism
- Pulmonary/respiratory complications and subsequent attendant problems (e.g., pneumonia, respiratory failure, prolonged intubation)
- Renal complications and subsequent related problems (e.g., artery occlusion, contrast toxicity, insufficiency, failure)
- Surgical conversion to open repair
- Vascular access site complications, including infection, pain, hematoma, pseudoaneurysm, arteriovenous fistula
- Vascular spasm or vascular trauma (e.g., iliofemoral vessel dissection, bleeding, rupture, death)
- Vessel damage
- Wound complications and subsequent related problems (e.g., dehiscence, infection)

8.2 Methods to Minimize Risks

This device will be used only by trained physicians who are experienced in the study procedure. Patients will be selected according to the inclusion/exclusion criteria outlined in this document.

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 and who do not 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 and who do not 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, or were procedure-related, technique-related, and/or device-related.

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

9.3 Adverse Event Reporting

Adverse events are to be reported to the Data Coordinating Center using the appropriate case report form. In cases of adverse device effects or serious adverse events, completed forms should be submitted to the Data Coordinating Center as soon as possible upon knowledge of the event.

The Data Coordinating Center will review the information submitted for possible reporting to the Sponsor. The Sponsor shall, if required according to applicable regulations, report the event to the appropriate Regulatory Authority. The Principal Investigator or designee will notify his/her Ethics Committee (EC)/Institutional Review Board (IRB) of applicable events according to institutional guidelines. If indicated, all investigators/sites will be notified by the Sponsor.

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. 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.

10.2 Data Management and Quality Assurance

Each principal investigator or appropriately trained designee shall enter clinical data into the electronic data capture system. Investigators will provide all applicable clinical data and documentation to the Sponsor. Patient data and documents pertaining to the investigation will be kept and archived by the Sponsor. Data will be reviewed for missing data, data consistency, and reasonableness of responses. Discrepancies will be resolved through a formal query process involving direct contact with investigators or research coordinators. Standard operating procedures will be followed for database management, data verification, and data archiving and retention.

As needed to assist the Sponsor in its research (e.g., during evaluation of an adverse event), data will be accessible to the Sponsor, the participating investigators, the manufacturer, and companies or individuals the Sponsor authorizes.

Pertinent imaging (pre-procedure, procedural, and follow-up) will be sent to MED Institute, Inc., which will coordinate shipment of imaging for independent analysis by the core laboratory.

10.3 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 regulatory bodies and IRBs/ECs as required by local regulations.

10.4 Emergency Situations and Vulnerable Subjects

Patients will not be treated with the Zenith® TX2® Low Profile Endovascular Graft 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.

10.5 Criteria and Procedures for Withdrawal

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 judgment. The investigator must make a reasonable effort to ascertain and record the reason for withdrawal or discontinuation for each patient while fully respecting the patient'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.

10.6 Deviations from Clinical Investigation Plan

Investigators are not allowed to deviate from this clinical investigation plan (CIP) without prior authorization by the Sponsor except under emergency situations when necessary to preserve the rights, safety, and well-being of human subjects. Deviations and non-compliances will be recorded together with an explanation. Deviations or non-compliances that impact the rights, welfare, or safety of patients shall be reported to the Sponsor, regulatory authorities, and IRB/EC as required.

10.7 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.

10.8 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

10.9 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.

10.10 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 modification will be documented. Approval and agreement will be indicated by signing and dating the signature page provided with this document.

10.11 General Information

10.11.1 Sponsor

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

10.11.2 Manufacturer

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

10.11.3 Data Coordinating Center/Monitor

The Data Coordinating Center for this study is MED Institute, Inc. See Appendix A for contact information.

10.11.4 Investigation Compliance

This investigation shall be performed according to the Declaration of Helsinki and 21 CFR 812.

The investigator is responsible for obtaining approval of this clinical investigation by the relevant EC/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. Additional requirements imposed by an IRB, EC, and/or regulatory authority shall be followed, if appropriate.

10.11.5 Investigators

A complete list of the coordinating clinical investigator, principal clinical investigators, and clinical investigators, along with their contact information, will be updated and maintained by the Data Coordinating Center.

10.11.6 Monitoring Arrangements

The monitor for this investigation is MED Institute, Inc. See Appendix A for contact information. Written procedures for monitoring the investigation are maintained by the monitor and can be found in Appendix B.

10.11.7 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 cases of doubt.

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APPENDIX A
Contact Information

Contact Information

Manufacturer
William Cook Europe, ApS
Sandet 6
DK 4632
Bjaeverskov, Denmark

Contact:
Anna Bjerg Jessen / Director of Quality Assurance and Regulatory Affairs
Telephone: +45 5686 8593
Fax: +45 5686 8568
E-mail: Anna.Jessen@CookMedical.com

Sponsor
Cook Incorporated
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Bloomington, IN 47404
USA

Contact:
Scott Williams / Director of Regulatory Affairs
Telephone: (765) 464-0817, 1117
Fax: (765) 497-0641
E-mail: swilliams@medinst.com

Data Coordinating Center / Monitor
MED Institute, Inc.
1 Geddes Way
West Lafayette, IN 47906

Contact:
Alison Conovaloff / Clinical Project Manager
Telephone: (765) 464-0817, 1190
Fax: (765) 497-0641
E-mail: aconovaloff@medinst.com

APPENDIX B
Written Procedures for Monitoring Investigations

Written Procedures for Monitoring Clinical Investigations

A. Selection of the monitor.

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

B. General duties of the monitor.

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

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

C. Reports by the monitor to the sponsor.

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

D. Initiating the investigation.

Prior to initiating any clinical use of the device, the monitor or sponsor representative 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 the local IRB/EC;

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

F. Records of the monitor.

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

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

APPENDIX C
Definitions

Definitions

Aortic-injury-related Mortality:	Any death determined by the independent clinical events committee to be causally related to the initial implant procedure, secondary intervention, or rupture of the transected aorta.
Barb Separation:	Radiographic evidence of detachment of barbs from the stent strut.
Calcification:	Fixation zone and iliac artery calcification will be graded based upon the following: None: Lack of calcification; Mild: Less than 40% circumferential calcification; Moderate: 40-70% circumferential calcification; Severe: Greater than 70% circumferential calcification; or Prohibitive: Severe and cannot be resolved in the opinion of the investigator.
Clinical Utility Measures:	Number of 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.
Device Infolding:	Infolding upon deployment due to anatomic constraint (i.e., device oversizing).[5]
Device Compression/ Collapse:	Failure of the device to maintain its intended expanded diameter after implantation as a result of the dynamic application of external forces (i.e., blood flow).[5]
Type I Endoleak:	A peri-prosthetic leak occurring at the proximal and/or distal fixation zones.

Type II Endoleak:	A leak caused by retrograde flow from patent vessels. Type IIa includes significant subclavian, celiac, or anomalous vertebral arteries. Type IIb includes bronchial and intercostal artery involvement or minor leaks.
Type III Endoleak:	A leak caused by a defect in the graft fabric, or inadequate seal between modular components.
Type IV Endoleak:	A leak caused by graft fabric porosity, often resulting in a generalized blush of contrast into the injury.
Unknown Endoleak:	Continuing blood flow into the injury with undefined origin.
Injury Severity Score:	The Injury Severity Score (ISS) is an anatomical scoring system that provides an overall score for patients with multiple injuries. Each injury is assigned an Abbreviated Injury Scale (AIS) score and is allocated to one of six body regions (head, face, chest, abdomen, extremities (including pelvis), external). Only the highest AIS score in each body region is used. The 3 most severely injured body regions have their scores squared and added together to produce the ISS score.
Major Adverse Events:	All-cause death; stroke; paraplegia; Q-wave MI; cardiac event involving arrest or resuscitation; renal failure requiring permanent dialysis, hemofiltration, or kidney transplant in a patient with a normal pre-procedure serum creatinine level; conversion to open repair; pulmonary embolism involving hemodynamic instability or surgery; graft infection; or wound complication requiring return to the operating room.

MI (Non-Q-Wave):	Clinical evidence of a myocardial infarction with elevated peak CK values greater than or equal to three times the upper limit of normal with elevated CK-MB (above the institution's upper limit of normal) in the absence of new pathological Q-waves or clinical evidence of a myocardial infarction with troponin greater than three times the upper limit of normal, as determined by the investigator.
MI (Q-Wave):	Requires one of the following criteria: • Post-procedure chest pain or other acute symptoms consistent with myocardial ischemia and the presence of new pathological Q-waves in two or more contiguous ECG leads in the absence of timely cardiac enzyme data. • New, post-procedure pathological Q-waves in two or more contiguous ECG leads and elevation of cardiac enzymes.
Occlusive Disease:	Fixation zone and iliac artery occlusive disease will be graded based upon the following: None: Lack of occlusive disease; Mild: Some disease, focal with less than 30% narrowing; Moderate: 30-50% narrowing not requiring interventional techniques to meet inclusion criteria; Severe: Greater than 50% or any patient requiring angioplasty prior to endograft delivery; or Prohibitive: Severe and cannot be resolved in the opinion of the investigator.
Migration (radiographic):	Core laboratory determination of antegrade or retrograde movement of the proximal component of the endoprosthesis > 10 mm relative to anatomical landmarks identified on the first post-operative CT scan.

Migration (clinical):	Antegrade or retrograde movement of the proximal component of the endoprosthesis resulting in the need for a secondary intervention.
Renal Failure:	Acute or progressive renal insufficiency leading to the need for dialysis or hemofiltration.
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.
Success, Device (30-day):	Technical success, with none of the following at 30 days: • Device collapse; • Type I or type III endoleak requiring reintervention; or • Conversion to open surgical repair.
Success, Technical:	Successful access of the injury site and deployment of the Zenith® TX2® Low Profile Endovascular Graft in the intended location. The endovascular graft must be patent at the time of deployment completion as evidenced by angiographic imaging.

Tortuosity:	Fixation zone and iliac artery tortuosity will be graded based upon the following: None: Lack of tortuosity; Mild: Fairly straight arteries; Moderate: Angulation manageable with stiff wires, < 70 degrees; Severe: Angulation difficult, may require surgical exposure for straightening, not straightened entirely with wires; or Prohibitive: Severe and cannot be resolved in the opinion of the investigator.
Traumatic Aortic Injury:	Injury will be graded based upon the following[8,17]: Grade 1: Intimal tear; Grade 2: Intramural hematoma/large intimal flap (LIF); Grade 3: Pseudoaneurysm; or Grade 4: Rupture.

APPENDIX D
Short-Form and Telephone Consent Templates

Medical Research Study to Evaluate The Zenith® TX2® Low Profile Endovascular Graft for Treatment of Blunt Thoracic Aortic Injury
Written Summary to Accompany Short Form Consent

Title: Research study to evaluate the Zenith® TX2® Low Profile Endovascular Graft for treatment of blunt thoracic aortic injury

Sponsor: Cook Incorporated

Investigator:
Name of Hospital:
Study-Related
Phone Number(s):

- You are asked to be part of this research study because you have been diagnosed with a blunt thoracic aortic injury in your thoracic (chest) aorta, the vessel that supplies blood to most of your body. A blunt thoracic aortic injury is an injury to the thoracic aorta that commonly happens as a result of being in a car accident or a fall from height. These injuries can be treated with medical management, open surgery, or endovascular treatment (inserting a graft, or tube reinforced by flexible metal rings, through arteries in the groin).

- In this study, you will have a procedure called endovascular treatment (inserting a graft through arteries in the groin). The purpose of this study is to evaluate the safety and effectiveness of endovascular treatment using the Zenith® TX2® Low Profile Endovascular Graft. This study has been reviewed by the US Food and Drug Administration (FDA) and by an *<Institutional Review Board (IRB) or Ethics Committee (EC)>*, a group that reviews studies at your hospital or medical center to make sure your rights as a clinical study participant are protected.

- The Zenith® TX2® Low Profile Endovascular Graft is an investigational device, which means it has not been approved by the FDA for treatment of blunt thoracic aortic injury. If you are eligible to be in the study, and depending on the measurements of your aorta, you will receive endovascular treatment.

- Your decision to be in this study is voluntary. You do not have to agree to be part of this study in order to be treated for your medical condition. If you are not part of the study, the Zenith® TX2® Low Profile Endovascular Graft will not be used in your care. Other treatments may also be available that could help you. Your treatment choices may include other endovascular grafts, open surgical treatment, or medical management. Ask your doctor about it.

- Study follow-up visits are scheduled for within 7 days of treatment, at approximately 30 days, 6 months, and 12 months after the endovascular graft has been placed, and yearly thereafter for 5 years. During the follow-up visit within

7 days of treatment, you will have a physical examination including blood work. During the other follow-up visits with your doctor, you will have a CT scan (a special x-ray) of your chest and a physical examination.

- If you decide to be in this study and then later change your mind, you can leave the study at any time by contacting the study doctor <*Add Contact Information*>. If you choose to withdraw from the study, the study product will not be removed from your body unless there are complications (problems). The doctor or the Sponsor can remove you from the study without your approval. Possible reasons could be if participation appears to be medically harmful to you, if it is discovered that you do not meet eligibility requirements, or if the study is cancelled. Should you be removed from the study or if you decide to stop before completing the study, you may be asked (for your own safety) to undergo final study assessments, examinations, and laboratory tests. You will not lose any benefits if you withdraw from the study.

- It is expected that this study will enroll up to 50 participants.

- The common risks of the endovascular procedure include discomfort after the procedure and pain or tenderness from your incisions. You will have to limit your activities for a certain period of time while recovering. Other risks include the following:
  Anesthesia risks – The procedure will be done under anesthesia. Anesthesia complications may include breathing problems, slowed or irregular heartbeat**,** blood pressure problems, and death.
  Aortic injury repair risks – You may experience bleeding, accidental damage to internal organs, blood clots, lodging of blood clots in lungs (pulmonary embolus, which sometimes results in death), aneurysm formation or dissection due to aortic damage, infection or fever, heart problems, kidney problems, bowel problems, lung problems, reactions to the graft (inflammation or allergic reaction), impotence (not able to have an erection), loss of blood flow to the spine (resulting in paralysis), legs, or other organs, amputation of toes or legs due to loss of blood flow to the legs, and stroke.
  Catheterization risks – During the procedure, x-rays will be used to guide the graft to the aorta. For more accuracy, you will receive injections of a fluid (called contrast medium) that allows the doctor to better see your blood vessels. This procedure of placing catheters (long slender tubes) through blood vessels is recognized as safe, but has known risks, including less than a 1 in 1,000 chance of serious complications such as serious allergic reaction, heart attack, stroke, or death. The potential for damage to the kidneys from contrast medium also exists.
  Endovascular treatment risks – You may experience misplacement or shifting in position of the graft, graft wear, folding/collapse of the graft, allergic reaction to graft material that may require surgery to remove the graft, continuing blood flow into the aortic injury that may require repair, dislodgement of existing plaques or clots from your blood vessel, and the need to finish your aortic repair

through open surgery for a number of reasons including bleeding or difficult anatomy.

Anticoagulant (blood thinner) risks – You may be treated with aspirin, heparin (a blood thinner), and other medications as determined by the study doctor. These medications may result in bleeding complications.
Radiation risks – This study involves exposure to radiation from the x-rays used during the procedure and also from follow-up testing. The endovascular procedure involves a radiation dose from the x-rays used to guide and place the graft. Generally, the exposure time is expected to be less than 28 minutes. The follow-up after the endovascular procedure involves a radiation dose due to the CTs scheduled at 30 days, 6 months, 12 months, and yearly for 5 years. If you have complications from the procedure, you may have more than the scheduled x-rays, leading to a higher radiation dose. Contrast medium ("x-ray dye") is often used to increase the quality of CTs. The risks due to exposure to contrast medium include hives or itching, shortness of breath, or seizures, which may be life-threatening. The potential for damage to the kidneys also exists.
Reproductive risks – You should not participate in this study if you are pregnant, breastfeeding, or planning to become pregnant in the next 5 years. If you become or suspect you are pregnant during the study, you must notify the study doctor immediately. A child conceived (created) during the study may develop birth defects. This risk is largely due to the need for x-ray follow-up. Men who undergo endovascular or open surgical repair may experience impotence.

There may be potential risks to you (or an embryo or fetus if you are or should become pregnant) that the investigators are not currently aware of and that they are not able to predict.

- If significant new information becomes available that might affect your willingness to participate in the study, the investigator will discuss this with you. If you decide to continue in the study, you may be asked to sign an updated consent form.

- We cannot promise that you will receive any benefits from this study. Future patients may benefit from the knowledge gained from this study. You will not be paid to be in the study.

- The Sponsor, Cook Incorporated, may be paying the study doctors, hospital, and clinical study staff for their work related to this study.

- There are no additional charges to participate in this study. The charges for services that would be performed even if you were not participating in this study will be billed to you or your insurance provider; these will not be paid by the Sponsor. Any co-payment or deductible required by your insurance provider will be your responsibility.

- All records related to your participation in this clinical study will be kept confidential. If you choose to be in this study, the study investigator(s) will get personal information about your health from talking with you and from looking at your past and current medical records. It will also come from the test results, imaging (CT scans), and examinations that are part of the study. Parts of your medical records and the data collected for the study will be sent to and/or looked at by persons authorized by the Sponsor. They also may be looked at by representatives of domestic and/or global regulatory authorities as well as Ethics Committees or Institutional Review Boards to check that the study is being carried out correctly. Your study information may be used to help obtain market approval for the device. If the study data are published, your identity will remain confidential. You may change your mind about letting us collect your confidential medical information at any time. If so, no new information about you will be collected. Any information already collected may still be used.

- A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

- Your agreement to participate in this study does not waive any of your legal rights.

- If you have questions about any part of this study, contact <*name of contact person*> at <*contact information*>.

- If you have questions about your rights as a participant in this study, contact <*name of contact person*> at <*contact information*>.

- If you believe you have been injured as a result of being in the study, contact <*name of contact person*> at <*contact information*>.

- No commitment is made by <*insert Name of Institution*> to provide free medical care or compensation for participation in this study. Medical services will be offered at the usual charge. If taking part in this research study harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action.

More detailed information about this study will be provided in a separate consent form. You will be asked to read and then sign that consent form after your condition is stabilized if you agree to participate in the research.

SIGNATURE

I have explained to the subject the nature and purpose, the potential benefits, and possible risks associated with participation in this research study. I have answered all questions that have been raised.

Signature of Person Conducting Informed Consent Discussion	Date
Printed Name of Person Conducting Informed Consent Discussion	

IMPARTIAL WITNESS STATEMENT

I confirm that the information in the consent summary was accurately explained to, and apparently understood by, the subject.

Impartial Witness's Signature	Date
Impartial Witness's Printed Name	

Site Number:
Patient Enrollment Number:

SHORT FORM CONSENT

To participate in a medical research study to evaluate the Zenith® TX2® Low Profile Endovascular Graft for Treatment of Blunt Thoracic Aortic Injury

I confirm that the purpose of the research, the study procedures that I can expect, the possible risks and discomforts, the potential benefits that I may have, and alternatives to my participation in the study have been explained to me.

I agree:

- To give my consent to voluntarily participate as a patient in this research study. I understand that I am free to withdraw (drop out) at any time, without giving any reason, and without my medical care or legal rights being affected.
- That personal health information about me may be used for ongoing research purposes as described above and that my medical records may be looked at by persons authorized by the Sponsor, regulatory authorities, and/or IRBs or ECs where it applies to my taking part in research. I give permission for these individuals to have access to my medical records.
- To give my consent to inform my personal doctor about my participation in the study.
- That I have had the opportunity to ask questions and my questions have been answered.

	X	
Patient Name (Printed)	**Patient's Signature or Signature of Legal Representative. If signed by other than the patient, state relationship/authority to sign**	**Date**

I confirm that the information in the consent form was accurately explained to, and apparently understood by, the subject. The subject freely consented to participate in the research study.

	X	
Name of Impartial Witness (Printed)	**Signature of Witness**	**Date**

Site Number:
Patient Enrollment Number:

Medical Research Study to Evaluate The Zenith® TX2® Low Profile Endovascular Graft for Treatment of Blunt Thoracic Aortic Injury
Written Summary for Telephone Consent

Title: Research study to evaluate the Zenith® TX2® Low Profile Endovascular Graft for treatment of blunt thoracic aortic injury

Sponsor: Cook Incorporated

Investigator:
Name of Hospital:
Study-Related
Phone Number(s):

- The patient is asked to be part of this research study because the patient has been diagnosed with a blunt thoracic aortic injury in his/her thoracic (chest) aorta, the vessel that supplies blood to most of the body. A blunt thoracic aortic injury is an injury to the thoracic aorta that commonly happens as a result of being in a car accident or a fall from height. These injuries can be treated with medical management, open surgery, or endovascular treatment (inserting a graft, or tube reinforced by flexible metal rings, through arteries in the groin).

- In this study, the patient will have a procedure called endovascular treatment (inserting a graft through arteries in the groin). The purpose of this study is to evaluate the safety and effectiveness of endovascular treatment using the Zenith® TX2® Low Profile Endovascular Graft. This study has been reviewed by the US Food and Drug Administration (FDA) and by an *<Institutional Review Board (IRB) or Ethics Committee (EC)>*, a group that reviews studies at the patient's hospital or medical center to make sure his/her rights as a clinical study participant are protected.

- The Zenith® TX2® Low Profile Endovascular Graft is an investigational device, which means it has not been approved by the FDA for treatment of blunt thoracic aortic injury. If the patient is eligible to be in the study, and depending on the measurements of his/her aorta, the patient will receive endovascular treatment.

- The decision to be in this study is voluntary. The patient does not have to be part of this study in order to be treated for his/her medical condition. If the patient is not part of the study, the Zenith® TX2® Low Profile Endovascular Graft will not be used in his/her care. Other treatments may also be available that could help the patient. Treatment choices may include other endovascular grafts, open surgical treatment, or medical management. You can ask the patient's doctor about these other treatment options.

- Study follow-up visits are scheduled for within 7 days of treatment, at approximately 30 days, 6 months, and 12 months after the endovascular graft has been placed, and yearly thereafter for 5 years. During the follow-up visit within 7 days of treatment, the patient will have a physical examination including blood work. During the other follow-up visits with his/her doctor, the patient will have a CT scan (a special x-ray) of his/her chest and a physical examination.

- If the patient is in this study and then later changes his/her mind, the patient can leave the study at any time by contacting the study doctor <*Add Contact Information*>. If the patient chooses to withdraw from the study, the study product will not be removed from his/her body unless there are complications (problems). The doctor or the Sponsor can remove the patient from the study without his/her approval. Possible reasons could be if participation appears to be medically harmful to the patient, if it is discovered that the patient does not meet eligibility requirements, or if the study is cancelled. Should the patient be removed from the study or if he/she decides to stop before completing the study, the patient may be asked (for his/her own safety) to undergo final study assessments, examinations, and laboratory tests. The patient will not lose any benefits if he/she withdraws from the study.

- It is expected that this study will enroll up to 50 participants.

- The common risks of the endovascular procedure include discomfort after the procedure and pain or tenderness from the incisions. The patient will have to limit his/her activities for a certain period of time while recovering. Other risks include the following:
  Anesthesia risks – The procedure will be done under anesthesia. Anesthesia complications may include breathing problems, slowed or irregular heartbeat**,** blood pressure problems, and death.
  Aortic injury repair risks – The patient may experience bleeding, accidental damage to internal organs, blood clots, lodging of blood clots in lungs (pulmonary embolus, which sometimes results in death), aneurysm formation or dissection due to aortic damage, infection or fever, heart problems, kidney problems, bowel problems, lung problems, reactions to the graft (inflammation or allergic reaction), impotence (not able to have an erection), loss of blood flow to the spine (resulting in paralysis), legs, or other organs, amputation of toes or legs due to loss of blood flow to the legs, and stroke.
  Catheterization risks – During the procedure, x-rays will be used to guide the graft to the aorta. For more accuracy, the patient will receive injections of a fluid (called contrast medium) that allows the doctor to better see the blood vessels. This procedure of placing catheters (long slender tubes) through blood vessels is recognized as safe, but has known risks, including less than a 1 in 1,000 chance of serious complications such as serious allergic reaction, heart attack, stroke, or death. The potential for damage to the kidneys from contrast medium also exists.
  Endovascular treatment risks – The patient may experience misplacement or shifting in position of the graft, graft wear, folding/collapse of the graft, allergic

reaction to graft material that may require surgery to remove the graft, continuing blood flow into the aortic injury that may require repair, dislodgement of existing plaques or clots from blood vessels, and the need to finish the aortic repair through open surgery for a number of reasons including bleeding or difficult anatomy.

Anticoagulant (blood thinner) risks – The patient may be treated with aspirin, heparin (a blood thinner), and other medications as determined by the study doctor. These medications may result in bleeding complications.

Radiation risks – This study involves exposure to radiation from the x-rays used during the procedure and also from follow-up testing. The endovascular procedure involves a radiation dose from the x-rays used to guide and place the graft. Generally, the exposure time is expected to be less than 28 minutes. The follow-up after the endovascular procedure involves a radiation dose due to the CTs scheduled at 30 days, 6 months, 12 months, and yearly for 5 years. If the patient has complications from the procedure, he/she may have more than the scheduled x-rays, leading to a higher radiation dose. Contrast medium ("x-ray dye") is often used to increase the quality of CTs. The risks due to exposure to contrast medium include hives or itching, shortness of breath, or seizures, which may be life-threatening. The potential for damage to the kidneys also exists.

Reproductive risks – The patient should not participate in this study if pregnant, breastfeeding, or planning to become pregnant in the next 5 years. If the patient becomes or suspects she is pregnant during the study, she must notify the study doctor immediately. A child conceived (created) during the study may develop birth defects. This risk is largely due to the need for x-ray follow-up. Men who undergo endovascular or open surgical repair may experience impotence.

There may be potential risks to the patient (or an embryo or fetus if she is or should become pregnant) that the investigators are not currently aware of and that they are not able to predict.

- If significant new information becomes available that might affect the patient's willingness to participate in the study, the investigator will discuss this with the patient. If the patient decides to continue in the study, he/she may be asked to sign an updated consent form.

- We cannot promise that the patient will receive any benefits from this study. Future patients may benefit from the knowledge gained from this study. The patient will not be paid to be in the study.

- The Sponsor, Cook Incorporated, may be paying the study doctors, hospital, and clinical study staff for their work related to this study.

- There are no additional charges to participate in this study. The charges for services that would be performed even if the patient was not participating in this study will be billed to the patient or the patient's insurance provider; these will

not be paid by the Sponsor. Any co-payment or deductible required by the patient's insurance provider will be the patient's responsibility.

- All records related to the patient's participation in this clinical study will be kept confidential. If the patient chooses to be in this study, the study investigator(s) will get personal information about his/her health from talking with the patient and from looking at his/her past and current medical records. It will also come from the test results, imaging (CT scans), and examinations that are part of the study. Parts of the patient's medical records and the data collected for the study will be sent to and/or looked at by persons authorized by the Sponsor. They also may be looked at by representatives of domestic and/or global regulatory authorities as well as Ethics Committees or Institutional Review Boards to check that the study is being carried out correctly. The patient's study information may be used to help obtain market approval for the device. If the study data are published, the patient's identity will remain confidential. The patient may change his/her mind about letting us collect his/her confidential medical information at any time. If so, no new information about the patient will be collected. Any information already collected may still be used.

- A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify the patient. At most, the Web site will include a summary of the results. You can search this Web site at any time.

- Agreement to participate in this study does not waive any of the patient's legal rights.

- If the patient has questions about any part of this study, contact <*name of contact person*> at <*contact information*>.

- If the patient has questions about his/her rights as a participant in this study, contact <*name of contact person*> at <*contact information*>.

- If the patient believes he/she has been injured as a result of being in the study, contact <*name of contact person*> at <*contact information*>.

- No commitment is made by <*insert Name of Institution*> to provide free medical care or compensation for participation in this study. Medical services will be offered at the usual charge. If taking part in this research study harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action.

This study consent form will be sent to you. You will be asked to sign and return the consent form in order for the patient to participate in the research. More detailed information about this study will be provided in a separate consent form. You or the patient will be asked to read and then sign that consent form after the patient's condition is stabilized if you agree to

allow the patient to participate in the research. <Please provide instructions on how the form must be sent to the institution and also whether any supporting documentation (such as a photo identification) must be sent along with the signature page.>

SIGNATURE

I have explained to the subject the nature and purpose, the potential benefits, and possible risks associated with participation in this research study. I have answered all questions that have been raised.

Signature of Person Conducting Informed Consent Discussion	Date
Printed Name of Person Conducting Informed Consent Discussion	

Site Number:
Patient Enrollment Number:

TELEPHONE CONSENT FORM

I confirm that the purpose of the research, the study procedures that I can expect the patient to have, the possible risks and discomforts, the potential benefits that the patient may have, and alternatives to the patient's participation in the study have been explained to me.

I agree:

- To give my consent to voluntarily allow the patient to participate in this research study. I understand that the patient is free to withdraw (drop out) at any time, without giving any reason, and without his/her medical care or legal rights being affected.
- That personal health information about the patient may be used for ongoing research purposes as described above and that the patient's medical records may be looked at by persons authorized by the Sponsor, regulatory authorities, and/or IRBs or ECs where it applies to the patient taking part in research. I give permission for these individuals to have access to the patient's medical records.
- To give my consent to inform the patient's personal doctor about his/her participation in the study.
- That I have had the opportunity to ask questions and my questions have been answered.

_____
Patient Name (Printed)

_____	X _____	_____
Legal Representative Name (Printed)	**Signature (State relationship/authority to sign)**	**Date**

I have explained to _____
Legal Representative Name
the purpose of the research, the procedures required, and the possible risks and benefits.

_____	X _____	_____
Name of Person who Obtained Consent (Printed)	**Signature of Person who Obtained Consent**	**Date**

Site Number:
Patient Enrollment Number:

APPENDIX E
Mortality Rate Literature Review

Studies of Patients with Blunt Aortic Injury since 2008

Abbreviated citation	Thoracic Endovascular Aortic Repair (TEVAR)	
	Total number patients	Number of patients who died within 30 days
From Xenos (2008):†		
1 Amabile (2004)	9	0
2 Andrassy (2006)	15	2
3 Broux (2006)	13	2
4 Buz (2007)	39	3
5 Chung (2008)	26	2
6 Doss (2003)	4	0
7 Kasirajan (2003)	5	1
8 Kokotsakis (2007)	22	1
9 Kuhne (2005)	5	0
10 Lebl (2006)	7	1
11 McPhee (2007)	8	2
12 Ott (2004)	6	0
13 Pacini (2005)	15	0
14 Riesenman (2007)	14	2
15 Rousseau (2005)	29	0
16 Stampfl (2006)	5	0
From Walsh (2008):		
17 Reed (2006)	13	3
From Takagi (2009):		
18 Demetriades (2008)‡	125	9
19 Moainie (2008)	26	4
20 Mohan (2008)	14	1
From Tang (2008):		
21 Agostinelli (2006)	15	2
22 Bortone (2004)	14	0
23 Daenen (2003)	7	1
24 Dunham (2004)	16	1
25 Fattori (2002)	11	0
26 Fujikawa (2001)	6	1
27 Hoornweg (2006)	28	4
28 Lawlor (2005)	7	0
29 Marcheix (2006)	33	0
30 Marty-Ane (2003)	9	0
31 Melnitchouk (2004)	15	1
32 Orend (2002)	11	1
33 Orford (2003)	9	1
34 Pratesi (2006)	11	1
35 Scheinert (2004)	10	0
36 Steingruber (2007)	22	1
37 Tehrani (2006)	30	2
38 Thompson (2002)	5	0
39 Wellons (2004)	9	1
From Murad (2011):		
40 Alsac (2008)	28	5
41 Arthurs (2009)	95	17
42 Botta (2008)	28	1
43 Brown (2008)	20	1

	Thoracic Endovascular Aortic Repair (TEVAR)	
Abbreviated citation	**Total number patients**	**Number of patients who died within 30 days**
44 Canaud (2008)	27	1
45 Day (2008)	27	2
46 Dessl (2004)	15	1
47 Feezor (2009)	23	1
48 Juszkat (2007)	13	1
49 Karmy-Jones (2003)	11	3
50 Kaya (2009)	42	1
51 Khoynezhad (2008)*	12	1
52 Kurimoto (2009)	13	2
53 Lachat (2002)	12	1
54 Methodius-Ngwodo (2008)	29	1
55 Michelet (2005)	10	0
56 Neuhauser (2004)	13	0
57 Peterson (2005)	11	0
58 Rosenthal (2008)	31	2
59 Scharrer-Pamler (2002)	15	2
60 Yamane (2008)	14	0
From Takagi (2008):		
61 Akowuah (2007)	7	0
62 Midgley (2007)	12	0
From Hoffer (2008):		
63 Attia (2007)§	11	2
64 Bent (2007)	13	0
65 Caronno (2006)	7	0
66 Ferrari (2006)	18	1
67 Go (2007)	10	0
68 Kato (2004)	6	0
69 Kwok (2006)§	8	0
70 Leurs (2004)	50	3
71 Livi (2007)§	13	0
72 Neschis (2007)	20	4
73 Pratesi (2006)	11	1
74 Raupach (2007)	10	1
75 Rodriguez (2007)	11	0
76 Saratzis (2007)	9	0
77 Tespili (2007)§	16	1
78 Thompson (2007)	21	0
79 Veeraswamy (2006)§	7	1
From Dake (2011) ¥		
80. Dake (2011)	60	5

† Several errors appear in the Xenos study table (page 1349) and in other listed sources with patient numbers and publication dates. The correct data are represented in this table, verified by a review of the initial publication abstracts and with comparison to citations in other meta-analyses. In some cases, full-text was also reviewed if discrepancies remained.

‡ This publication was a prospective, nonrandomized, multicenter trial. Unless otherwise noted, other reports listed were nonrandomized, retrospective, cohort studies.

* This publication was a prospective study.

§ Unable to verify mortality data in abstract.

¥ This publication included data from five single-center physician-sponsored IDE clinical trials.

Reports cited:

- Xenos ES, Abedi NN, Davenport DL, Minion DJ, Hamdallah O, Sorial EE, et al. Meta-analysis of endovascular vs open repair for traumatic descending thoracic aortic rupture. J Vasc Surg. 2008;48:1343-51.
- Walsh SR, Tang TY, Sadat U, Naik J, Gaunt ME, Boyle JR, et al. Endovascular stenting versus open surgery for thoracic aortic disease: systematic review and meta-analysis of perioperative results. J Vasc Surg. 2008;47:1094-8.
- Takagi H, Manabe H, Kawai N, Goto SN, Umemoto T. Endovascular versus open repair for blunt thoracic aortic injury. Ann Thorac Surg. 2009;87:349-50.
- Tang GL, Tehrani HY, Usman A, Katariya K, Otero C, Perez E, et al. Reduced mortality, paraplegia, and stroke with stent graft repair of blunt aortic transections: a modern meta-analysis. J Vasc Surg. 2008;47:671-5.
- Murad MH, Rizvi AZ, Malgor R, Carey J, Alkatib AA, Erwin PJ, et al. Comparative effectiveness of the treatments for thoracic aortic transection. J Vasc Surg. 2011;53:193-99.21-21.
- Takagi H, Sawai N, Umemoto T. A meta-analysis of comparative studies of endovascular versus open repair for blunt thoracic aortic injury. J Thorac Cardiovasc Surg. 2008;135:1392-4.
- Hoffer EK, Forauer AR, Silas AM, Gemery JM. Endovacular stent-graft or open surgical repair for blunt thoracic aortic trauma: systematic review. J Vasc Interv Radiol. 2008;19:1153-64.
- Dake MD, White, RA, Diethrich EB, Greenberg RK, Criado FJ, Bavaria JE, et al. Report on endograft management of traumatic thoracic aortic transection at 30 days and 1 year from a multidisciplinary subcommittee of the Society for Vascular Surgery Outcomes Committee. J Vasc Surg. 2011:53:1091-6.