

Branched Thoracic Endovascular Grafts for the Treatment of Thoraco-abdominal Aortic Aneurysms: An Investigator-Initiated Study (short title: B-TEVAR)

July 8, 2016



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**PROTOCOL SUMMARY**

<b>Sponsor</b>	The University of Washington
<b>Protocol Title</b>	Branched Thoracic Endovascular Grafts for the Treatment of Thoraco-abdominal Aortic Aneurysms (B-TEVAR)
<b>Study Description</b>	<p>An investigator-initiated, prospective, consecutively enrolling, non-randomized single institution clinical evaluation of the safety and effectiveness of either: 1) physician modification of a currently FDA- approved off the shelf thoracic aortic stent graft (COOK Zenith<sup>®</sup> TX2<sup>®</sup>); or</p> <p>2) Thoracoabdominal Custom Branch/Fenestrated Endovascular Stent-Graft (Cook Medical); or 3) Cook t-Branch Endovascular Stent Graft or 4) Cook Low Profile (LP) t-Branch or Custom Made Device (CMD) to preserve branch vessels when used in the treatment of patients with thoraco-abdominal aortic aneurysms.</p>
<b>Study Objectives</b>	<p>The primary objectives of this study are to determine whether physician modified branched endovascular grafts are a safe and effective method of treating patients with thoraco-abdominal aortic aneurysms.</p> <p>The safety of physician modified endovascular grafts will be determined by evaluating the proportion of patients that experience a rate of Major Adverse Events.</p> <p>The effectiveness of physician modified endovascular grafts will be determined by evaluating the proportion of patients that achieve Treatment Success at 12 months post-procedure.</p>
<b>Study Primary Endpoints</b>	<p>The primary safety endpoint is defined as the proportion of subjects who experience a Major Adverse Event within 30 days of the B-TEVAR procedure.</p> <p>The primary effectiveness endpoint is the proportion of subjects that achieve Treatment Success. Treatment Success is a composite endpoint assessed at 12 months following implantation of the B-TEVAR device that requires the following criteria to be met:</p> <ul style="list-style-type: none"> <li>• Technical Success, defined as successful delivery and deployment of the physician modified graft with preservation of unimpeded flow to those branch vessels intended to be preserved.</li> <li>• Freedom from Type I &amp; III endoleaks</li> <li>• Freedom from stent graft migration</li> <li>• Freedom from aortic aneurysm enlargement</li> <li>• Freedom from aortic aneurysm rupture</li> <li>• Freedom from conversion to open repair</li> </ul>

<b>Study Secondary Endpoints</b>	<p>The following secondary safety endpoints will be evaluated at 30 days, 12 months and annually to 5 years after implantation of the B-TEVAR device:</p> <ul style="list-style-type: none"> <li>• Mortality rates</li> <li>• Aneurysm related mortality</li> <li>• Major Adverse Events (MAE)</li> <li>• Conversion to open repair</li> <li>• Aneurysm rupture</li> </ul> <p>The following secondary effectiveness endpoints will be evaluated at 30 days, 12 months and annually to 5 years after implantation of the B-TEVAR device:</p> <ul style="list-style-type: none"> <li>• Technical Success</li> <li>• Freedom from Type I &amp; III endoleaks</li> <li>• Freedom from stent graft migration</li> <li>• Freedom from aortic aneurysm enlargement</li> <li>• Freedom from aneurysm rupture</li> </ul>
	<ul style="list-style-type: none"> <li>• Freedom from conversion to open repair</li> <li>• Radiographic evidence of device integrity</li> <li>• Freedom from thromboembolic events</li> <li>• Freedom from re-intervention</li> </ul>
<b>Clinical Utility Measurements</b>	<p>The following Clinical Utility Measurements will be evaluated:</p> <ul style="list-style-type: none"> <li>• Conduit usage</li> <li>• Blood loss</li> <li>• ICU stay</li> <li>• Length of hospital stay</li> <li>• Type of anesthesia</li> <li>• Secondary interventions</li> </ul>
<b>Patient Population</b>	<p>The total Treatment Group includes 60 patients, including those who are planning to undergo single or two-staged approach to repair.</p>
<b>Follow-Up Intervals</b>	<p>Treatment Group follow up intervals will consist of 1, 6, and 12 months following the B-TEVAR implant procedure, then annually through 5 years.</p>

<b>Follow- Up Events</b>	<p>Treatment Group follow up:</p> <ul style="list-style-type: none"> <li>• Physical exam</li> <li>• Contrast Enhanced Spiral Chest/Abdominal/Pelvic CT</li> <li>• Device/aneurysm assessment based on imaging</li> <li>• Laboratory Assessment</li> <li>• Assessment of Adverse Events</li> <li>• Assessment of concomitant medications (only anticoagulants, anti-platelets, antibiotics, statins, Beta blockers and ACE inhibitors/ARB)</li> </ul>
<b>Investigational Sites</b>	<p>The University of Washington (University of Washington Medical Center and Harborview Medical Center) will be the only site involved in this trial.</p>
<b>Anatomic Criteria</b>	<p>Adequate proximal and distal seal and fixation sites:</p> <p>A. Non-aneurysmal proximal aortic seal zone:</p> <ol style="list-style-type: none"> <li>1. with a length of 25 mm of proximal seal in non-aneurysmal aorta, with or without coverage of the left subclavian artery,</li> <li>2. with an outer wall diameter of no less than 15 mm and no greater than 42 mm, and</li> </ol> <p>B. Non-aneurysmal distal aortic or iliac landing zone:</p> <ol style="list-style-type: none"> <li>3. With a length of at least 15 mm,</li> <li>4. Aortic seal zone no less than 15 mm and no greater than 42 mm or</li> <li>5. Iliac seal zone with an outer wall diameter of no less than 8 mm and no greater than 23 mm.</li> </ol> <p>No greater than 5 visceral vessels <math>\geq</math> 4 mm in diameter requiring revascularization</p> <p>Femoral/Iliac arterial access to allow introduction of the device into the aorta with or without the use of a conduit</p> <p>* The Cook t-Branch option has additional anatomic inclusion criteria that are specified below in section 4.0.3</p>
<b>Principal Investigator:</b>	<p>Dr. Matthew P. Sweet  University of Washington Medical Center  Assistant Professor of Vascular Surgery  University of Washington</p>
<b>Sub-investigator:</b>	<p>Dr. Benjamin W. Starnes  Harborview Medical Center  Professor and Chief of Vascular Surgery  University of Washington</p>

<b>Data Safety Monitor(DSM)</b>	Dr. Kei Togashi University of Washington Medical Center Assistant Professor of Anesthesiology and Pain Medicine University of Washington
<b>Monitoring</b>	Institute of Translational Health Services (ITHS)
<b>Electronic Data Capture (Host)</b>	University of Washington 
<b>Core Lab</b>	N/A

A list of all articles referenced in this protocol is contained in **Appendix I: References**.

## 1.0 STUDY GOAL AND OBJECTIVES

The goal of this study is to evaluate the performance of Branched Thoracic Endovascular Aneurysm Repair (B-TEVAR) with visceral vessel (i.e. celiac, superior mesenteric, inferior mesenteric, renal and anterior spinal artery) preservation in subjects with thoraco-abdominal aortic aneurysms. The specific objectives of the study are to:

1. Evaluate the safety of the branched thoracic endovascular grafts at 30 days, 6 and 12 months and annually for 5 years post-implant.
2. Evaluate the ability to deliver physician modified thoracic endovascular grafts within the peri-visceral aorta in order to preserve unimpeded blood flow into vital visceral vessels that arise from an aneurysm.
3. Evaluate the ability of physician modified thoracic endovascular grafts to exclude the thoraco-abdominal aortic aneurysm.

## 2.0 BACKGROUND AND RATIONALE

13,000 Americans die each year from rupture of an aneurysm in the aorta, which is the ninth leading cause of death in men over age 55.<sup>1</sup> Aortic aneurysms are four times more common in men than in women and usually occur in those over age 50. Approximately one percent of men between the ages of 55 and 64 will have a significant aneurysm, and the likelihood increases to about four to six percent of those men over the age of 75.

Aortic aneurysms that involve the arteries to the intestines and kidneys are called thoraco-abdominal aortic aneurysms (TAAA) and are classified according to the Crawford classification system as modified by Safi.<sup>2,3</sup> The risk factors for degenerative TAAA include tobacco use, hypertension, hyperlipidemia, male sex, and family history. Approximately 80% of TAAA are due to aortic atherosclerotic degeneration. An additional 20% develop TAAA as a consequence of aortic dissection with dilation of the false lumen.

Elective treatment of TAAA is done to prevent rupture. Without operation, about 25% of patients not deemed fit for surgery die within 1 year due to rupture.<sup>4</sup> Traditional surgical therapy



involves an extensive incision extending from the chest to the abdomen. Cardiopulmonary bypass is often required. The operation carries significant risk of morbidity and mortality. Large population based studies have found a 20% peri-operative mortality which rises to 30% at 1 year.<sup>5,6</sup>

Endovascular therapy has been developed to treat aneurysms involving the thoracic and abdominal aorta. Endovascular stent grafts have significantly reduced the peri-operative risk of surgery. Given the morbidity associated with open operation for TAAA, there is great optimism that endovascular therapy may significantly reduce the peri-operative risk of TAAA repair as well. Because TAAA involve the vital visceral blood vessels to the intestines and kidneys, an endovascular treatment must preserve flow to these branches while excluding flow from the aneurysm. Currently, there are no commercial endografts available to treat aneurysms involving the peri-visceral aorta.

Physician modification of commercial stent grafts to create a branched endograft has been used to treat aneurysms involving the juxta-renal and peri-visceral aorta in several centers around in the United States. We seek to evaluate the safety and effectiveness of B-TEVAR using a physician modified FDA-approved, off-the-shelf device in order to treat TAAA. It is our hypothesis that such endovascular therapy is effective and has reduced risk of peri-operative complications compared to open surgical repair.

## **2.1 Treatment of Thoraco-abdominal Aortic Aneurysm**

The current (standard) treatments for thoraco-abdominal aortic aneurysms include observation alone ("watchful waiting"), open surgical repair of the aorta using a fabric substitute or "hybrid" visceral debranching with aortic stent graft placement. B-TEVAR is not currently considered conventional treatment in the United States.

### **2.1.1 Observation**

If an aortic aneurysm is small and not causing symptoms, the treating physician may perform an ultrasound, a CT or MRI scan every 6 to 12 months to assess changes in the size or shape of the aneurysm. Along with serial radiographic measurement, optimal medical therapy is instituted. This includes smoking cessation, blood pressure control, and administration of aspirin and a statin (cholesterol lowering medication that may slow the rate of aneurysm growth). Observation is usually used for aneurysms that are smaller than 5-6 cm in diameter, fusiform in shape, and those that are growing slowly,  $\leq 10\%$  per year. If the TAAA is large, irregular in shape, rapidly expanding, or is causing symptoms, it will require prompt treatment to prevent death due to rupture of the aneurysm.

Most patients with TAAA also have advanced medical co-morbid illnesses. In one large study, 40% of patients with TAAA referred to the major aortic center in Scotland were deemed unfit for open repair due to the severity of their medical illnesses.<sup>4</sup> This number is likely an underestimate, as the most medically ill were not referred. Fifty-five percent of untreated patients had died by a median of 12 month follow up, half due to rupture.

### **2.1.2 Open Surgical Repair**

Open surgical repair has long been the standard treatment for *good risk* patients harboring thoraco-abdominal aortic aneurysms. Centers of excellence have reported the best outcomes with an estimated 5-8% peri-operative mortality among such good risk patients.<sup>7-10</sup> One review of outcome data after more than 7,000 open TAAA repairs reported a 10% peri-operative mortality.<sup>11</sup> These results are those achieved by centers of excellence among patients deemed to be satisfactory candidates for major open operation. They exclude the outcomes of those patients whose medical co-morbidities preclude open aortic replacement. In larger, population based datasets, the estimated peri-operative mortality exceeds 20% and rises to 30% at 1 year.<sup>5,6</sup> These data reflect the “real world” experience with open surgery for TAAA, and indicate both a need to better risk stratify patients pre-operatively and to regionalize treatment to specialized centers focused on the care of these patients.

### **2.1.3 Hybrid Repair with Surgical Debranching**

“Hybrid” endovascular repair involves the creation of surgical bypasses from the iliac artery to the visceral arteries along with placement of an aortic stent graft to exclude flow to the aneurysm. This off-label technique was developed to mitigate the major physiologic stress of cardiopulmonary bypass, thoracotomy and proximal aortic cross-clamping that is required for open repair of TAAA. This approach has gained favor with some surgeons as it can readily be performed using commercially available stent grafts. Unfortunately, although aortic cross-clamping is avoided, the operation still confers the substantial risks of a major open vascular operation. The outcomes after hybrid repair vary widely, as some centers have used the technique for good risk patients and case series are enriched by lower extent TAAA (i.e. Crawford extent IV). Among good risk patients, mortality rates as low as 4% have been reported.<sup>12</sup> When applied specifically to patients with TAAA who were not candidates for open repair, the outcomes are worse, with a 22% peri-operative mortality in one large series from a center of excellence.<sup>13</sup> Pooling data from multiple case series, the peri-operative mortality rate is estimated to be around 15%.<sup>14</sup> The hybrid approach is optimal for patients at increased risk from open repair whose anatomy is not amendable to branched endovascular repair, such as patients with aortic dissection involving the visceral vessels.

### **2.1.4 Branched Endovascular Stent Graft Repair**

There are several studies describing endovascular technologies for preserving vital aortic branch vessels during the course of endovascular repair of TAAA. Three treatment options have been reported. The first two utilize commercially manufactured stent grafts by Cook Medical. This includes a custom modified device (CMD) and the t-Branch standardized device. These devices are not FDA approved and are only in use under Physician Sponsored IDE studies in the USA. They are approved for use in Europe and are currently available for use there. The alternative option is physician modification of a commercial endograft to create reinforced fenestrations. This study currently utilizes physician modified endografts, and the purpose of this supplement is to add the commercial manufactured grafts as options for subjects in this study.

The largest in-human experience currently available for endovascular treatment of TAAA comes from two centers in the USA that have used a combination of a CMD and the standardized t-Branch option manufactured by Cook Medical. The CMD devices are customized to the patient's anatomy and require 6-12 weeks for manufacture in Australia prior to implantation. The t-Branch option is a single design that utilizes 4 down-going cuffs to allow for intra-operative flexibility in treating variable branch anatomy. Initial results from these centers have been very encouraging, and important lessons have been learned.

Dr. Timothy Chuter at the University of California San Francisco has reported on his initial 50 patients treated with the Zenith t-Branch device.<sup>15,16</sup> All patients were considered to be at elevated risk for open repair. His group recently published a subsequent report of 81 patients, some of whom were included in the initial reports.<sup>17</sup> In these reports, he has demonstrated excellent effectiveness and safety, with 100% implant success, 4% peri-operative mortality, and 6% overall aneurysm related mortality. Among the first 22 patients, there was a 41% incidence of major morbidity. All patients suffered from “some combination of fever, leukocytosis, anorexia, malaise, thrombocytopenia and coagulopathy.” The most recent series reports a 3.7% incidence of permanent paralysis and a 20% incidence of temporary spinal cord injury, all of which occurred in the peri-operative period. These data demonstrate that the operation can be done safely in very sick patients, but that medical complications are common and are to be expected. In this report, there was a high incidence of re-intervention at 40%. Most of these reinterventions were performed endovascularly or were minor surgical procedures at access site and were well tolerated by the patients. Overall, 90% of the patients were “treated without procedure-related death, dialysis, paralysis, aneurysm rupture, or conversion to open repair.”

Dr. Roy Greenberg has reported on 189 patients undergoing elective repair of TAAA using a variant of the Cook branched device.<sup>7</sup> In this large series, there was 100% implant success and no intra-operative deaths. Post-operative mortality rates were 6.3% and 18.5% at 30 days and 1 year, respectively. Permanent spinal cord injury occurred in 7.1%. These data are remarkably similar to those achieved by Dr. Chuter and his group at the University of California San Francisco. The Cleveland Clinic group is a high volume center of excellence for both open and endovascular TAAA repair. As such, patients had access to highly experience providers for either treatment modality. Among the 428 patients seen with TAAA in this study, 44% were deemed to be best treated with endovascular repair, again reflecting the prevalence of advanced medical co-morbidities in patients with TAAA. In a subsequent report with over 9 years of follow up, they report excellent branch stent performance. Incidence of re-intervention was 4-6% after a mean of 3 years follow up, and only 3 of 650 patients (0.4%) died due to branch stent complications.<sup>18</sup> These data demonstrate that once successfully treated, the device can provide durable effectiveness.

The outcomes reported by two large European centers of excellence are similar to those from UCSF and the Cleveland clinic. Dr. Stephan Haulon in Lille, France, reported the outcomes

of 89 patients treated on an elective basis with the Cook Custom Thoracic Branched Device.<sup>19</sup> Thirty day mortality was 9%, spinal cord injury was seen in 8%, and 1 year survival was 87%. Dr. Timothy Resch in Malmo, Sweden, published the results of 72 patients, including 21 patients treated on an acute/emergent basis.<sup>20</sup> These patients were treated with variants of the Cook Custom Thoracic Branched Device and the t-Branch design. Thirty day mortality was 7%, temporary spinal cord injury was seen in 31%, but this improved in a majority of patients. The most recent group of patients had a 13% incidence of permanent spinal cord injury. Adverse outcomes were highest among the patients treated for rupture, with mortality for elective, symptomatic, and ruptured patients of 4%, 7%, and 29%, respectively. These studies show that the endovascular treatment of TAAA is feasible, although the procedure remains a high risk undertaking.

The Cook CMD and t-Branch devices have performed admirably in patients with TAAA, particularly as these results have been achieved amongst patients deemed to be unfit for or at high risk of open repair. There are, however, some patients who cannot be treated with a custom device. As a custom device takes 6-8 weeks to manufacture, a subset of patients with large or symptomatic aneurysms cannot tolerate that delay and require a more rapidly available option. There are two such options, the Cook t-Branch device, which is a variant of the custom device, and a physician modified device. It is estimated that 10-15% of patients with TAAA will not be eligible for repair using the t-Branch device.<sup>21</sup> This is due to anatomic constraints of the device. The t-Branch device utilized cuffs which are axially oriented. This design requires sufficient working room within the aneurysm sac around the stent graft. In some cases, the ability to use reinforced fenestrations is preferable as there is a high degree of flexibility in fenestration location and they do not require much space within the aneurysm sac. Furthermore, the t-Branch device is designed to treat 4 branches, so patients with more branches are ineligible, as are some patients with a Type 1 TAAA that may not require coverage of the renal vessels.

The addition of the Cook Low Profile devices- t-Branch and Custom Modified (CMD) would provide additional benefits. The Cook Low Profile devices use an 18F delivery sheath. The standard t-Branch device uses a 24F sheath. This size difference is clinically significant, as a significant number of patients, particularly women, have smaller iliac arteries than will accommodate a 24F sheath. Reduction of the sheath diameter is expected to dramatically increase the number of patients eligible for endovascular repair of their aneurysms.<sup>30</sup> The smaller delivery sheath both improves eligibility of patients for the study and reduces the likelihood of access site injury or need for an ilio-femoral surgical conduit operation. This is best demonstrated in the report from the University of California San Francisco comparing the two device constructs used in their IDE study.<sup>31</sup> Within our current IDE study, we have had several screen failures due to small caliber iliac access. This modification falls within the existing IDE study as it adds a newer generation of the commercially manufactured branched and fenestrated-branched endografts that are

currently in use in the study. The device materials are currently used in an FDA approved commercially available thoracic endograft.

Concurrent with the PS-IDE studies assessing the Cook Medical commercial devices, some surgeons have sought to individually modify existing stent grafts to create a customized fenestrated device. The design of the Zenith<sup>®</sup> TX2<sup>®</sup> endovascular graft (Cook: Bloomington, IN) lends itself to device modification. The graft can be unsheathed under sterile conditions on a back table and precise measurements can be used to create an appropriate series of reinforced fenestrations and/or cuffs that correspond to the patient's branch vessel anatomy (Figure 1). Gold or platinum markers are hand sewn into place along with PTFE graft or stent grafts to create reinforced fenestrations or short cuffs for anchoring and sealing covered stents into the branch vessels.

Along with the creation of fenestrations and cuffs, sutures can be used to tailor the graft diameter to the patient's unique anatomy. This modification facilitates precise alignment of the fenestrations in each unique patient's anatomy. (Figure 2) The device is then re-sheathed and implanted into the patient similar to a standard endovascular repair. Subsequently, wires and catheters are used to cross through the fenestrations and cuffs into the target arteries. Over these wires, stent grafts are deployed and sealed into the main modified endograft, creating sealed branches. (Figures 3 and 4)

Several centers have conducted these operations in an effort to fulfill the urgent clinical need for TAAA repair among patients at high risk for open repair. Dr. Mark Fillinger at Dartmouth Hitchcock Medical Center presented his personal experience with 85 physician modified branched endovascular aneurysm repairs among patients deemed to be at high risk of open repair.<sup>22</sup> Sixty-three of these cases were TAAA treated according to the protocol described here as B-TEVAR, using physician modification of the Zenith<sup>®</sup> TX2<sup>®</sup> with reinforced fenestrations/cuffs. The Zenith<sup>®</sup> TX2<sup>®</sup> thoracic device was used in conjunction with the Zenith<sup>®</sup> Flex<sup>®</sup> device as well as with the AFX<sup>™</sup> device for distal seal and fixation. One additional patient was treated using a chimney. Among these 64 patients treated for TAAA, there were 4 peri-operative deaths (6.25%) and 2 patients with permanent spinal cord injury (3%). Of 245 successfully completed branches, there were no occlusions and 3 Type 3 endoleaks requiring percutaneous re-intervention. This study demonstrates an exceptional level of safety and effectiveness among this very high risk patient cohort.

Dr. Sweet studied under Dr. Fillinger and assisted with 15 of the reported B-TEVAR procedures. The technique described here is based on this clinical experience. The component parts described in this IDE application are those utilized in the performance of these repairs. Specifically, proximal aortic stent grafts consisted of the Zenith<sup>®</sup> TX2<sup>®</sup> platform. In cases where the distal aorta was not aneurysmal, the TX2<sup>®</sup> would be used to

seal, even if this required utilization of permanent diameter reducing ties. In cases where there was no suitable infra-renal aorta for seal, then an Endologix AFX™ device or Zenith® Flex® device would be deployed to seal in the common iliac arteries. In patients who had undergone prior endovascular therapy for aortic or visceral artery disease, the same devices would be used and oversized appropriately for the existing aortic stent grafts, even if they were manufactured by a different company. As described above, one of the critical advantages of B-TEVAR over the T-branch design is that it can be highly adaptable to atypical anatomy. Such anatomy is often found in patients with TAAA.

To construct the reinforced fenestrations and branches, the radio-opaque Boston Scientific fibered coil or the tip of a Cope wire was used as a marking metallic ring. A similar procedure has been done using the Amplatz snare, as is done by Dr. Starnes in his PMEG IDE trial. The function of these different options seems equivalent based on clinical experience. Selection of these different devices is a function of radiographic visualization, cost and ease of re-packaging the material. The loop snare has excellent radio-opacity. However, at 0.053 in diameter it is substantially bulkier than the coil or wire tip, which measures 0.018 in. In the case of multiple fenestrations that are at the same cranio-caudal level, for example, the added bulk of the larger snare in conjunction with the PTFE cuffs, may make re-constraining the device more difficult. Conversely, in a large patient where visualization may be more challenging and re-packaging is not anticipated to be difficult, the loop snare would be advantageous to provide improved radio-lucency and visualization. As such, different component parts are needed in different cases, as the physician must assess the competing interests of visualization, ease of repackaging, and cost.

The fenestrations are reinforced with Atrium PTFE which provides bulk to increase the seal zone for the branch as well as strengthens the fenestration. In B-TEVAR, the branch stents must seal into the fenestration, as Type III leaks would perfuse the TAAA. In Dr. Fillinger's experience, this composite device of the Zenith® TX2® with a heat-sealed fenestration, reinforced with a radio-opaque metallic marker (tip of a Cope wire or Boston Scientific coil) and Atrium PTFE has been used for >200 branches without evident material failure. Three type III endoleaks were successfully treated with percutaneous re-intervention as reported by Dr. Fillinger. This technique then utilizes balloon expandable iCast stent grafts that are deployed across these fenestrations and proximally flared by overdilation to increase the contact between the branch stent and the Zenith® TX2® device. Self-expanding stents are used within the balloon expandable stent graft in selected cases to increase outward radial force, smooth the transition from the stiff iCast stent to a tortuous target artery, or correct a target vessel dissection or kink caused by the branch stent.

Thus far, at the University of Washington, 33 patients have been treated using the physician modified TX2 endograft with reinforced fenestrated branches as of the last reporting period. Twenty-eight of these patients have been treated within this IDE study. The complete details of this initial case series were published in the Journal of Vascular Surgery, Vol 62, Issue 5, P1160-1167 and have been further detailed in the Interim Report dated March 31, 2016.

Briefly, of the 33 subjects patients, 28 have achieved treatment success as defined in section 7.1. The 5 subjects who did not achieve technical success were:

- **Subject 001** had unsuccessful cannulation of his renal arteries and underwent bilateral ilio-renal bypass
- **Subject 009** had unsuccessful cannulation of her left renal artery
- **Subject 005** had one embolized stent in the superior gluteal branch of the left hypogastric artery that had no clinical impact on the patient. There is flow around the stent, so it is not blocking flow in the artery. The patient's aneurysm has been successfully excluded with all branches functioning properly
- **Subject 019** had left renal artery branch pull back out of the renal artery due to a very short seal there due to the tortuosity of the renal artery. A revision was attempted to re-stent the branch and extend it further into the renal artery. This was not possible due to the tortuous nature of the artery. Therefore, the branch was occluded to prevent flow into the aneurysm. This resulted in occlusion of the left renal artery and loss of function of the left kidney.
- **Subject 029** had very tortuous anatomy and the endograft was not implanted.

One (3%) subject died within 1 month of surgery. One (3%) subject died 4 months after surgery. One subject died at day 888 due to cancer. One (3%) patient is alive 23 months after successful operation but has permanent paralysis. All 26 other patients have had complete aneurysm exclusion, are living at their pre-operative functional status and are clinically well, including 2 of the 3 patients with failure of renal branch creation.

The physician modified construct has been shown to provide similar safety and overall treatment success as commercially manufactured devices at short term follow up. Longer term follow up is ongoing and will be essential to prove the long term effectiveness.

Furthermore, Dr. Starnes, the sub-investigator, has demonstrated the feasibility, safety and effectiveness of doing physician modification of aortic stent grafts under a physician sponsored IDE here at the University of Washington. He holds an IDE for using physician modified stent grafts (PMEG) for juxta-renal AAA and a paper was accepted at the Western Vascular Society for presentation in for presentation at the September 2015 meeting providing the midterm report of the on-going One hundred twenty-two (122) fenestrations were made for 91 renal arteries and 31 superior mesenteric (SMA) arteries. The mean procedure time was 165.5 minutes (range 91-427) and the mean blood loss was 200 cc (range 20-1000 cc). There were no unanticipated or major adverse device events. A single re-intervention was required for a minor device event. There was one Type I endoleak due to renal stent separation, a Type III endoleak with left renal separation, a Type III endoleak involving bilateral limb separation and finally, a type Ib endoleak at a distal limb. These data have been submitted in the most recent annual report for Dr. Starnes' IDE dated February 2015. These data highlight our institutional track record of success using physician modification techniques for complex endovascular intervention as well as our institutional success administering an IDE.<sup>23</sup>

Thus far, the use of branched thoracic endografts has been limited to patients deemed to be at high risk of open repair. This was necessary as a first step to determine that the technique can safely be performed prior to use in a patient who has an option of open repair. The distinction of who is, and who is not eligible for open repair, remains a subjective one. It is insufficiently discriminatory to divide patients into high or low risk, as a large number of patients with TAAA suffer from major medical comorbidities that put them at moderate risk. The above described studies of branched endovascular TAAA repair report post-operative mortality rates of 6% among over 330 patients who were deemed to be at high risk for open repair. This overall mortality rate is nearly half that of contemporary open case series, those procedures being done in presumably healthier patients. As such, it is our belief that there is genuine equipoise to utilize and study B-TEVAR among patients at both moderate and high risk of open repair. We would suggest that there are insufficient data to treat a low risk patient with a TAAA using B-TEVAR, as the effectiveness and durability of open repair are well established. In the absence of an accurate pre-procedure risk assessment tool, we feel it is appropriate to leave the distinction between low and moderate risk to the discretion of the treating surgeon. The protocol requires that the treating surgeon specify what clinical criteria it is in their judgment that puts the patient at moderate or high risk. These data may, in time, be useful in better developing pre-operative risk stratification for patients with TAAA. Studies such as this one are necessary to improve our understanding in this regard.

Another important area of interest is the treatment of patients who have had prior aortic surgery. As described above, a significant number of patients with TAAA have undergone some form of prior aortic surgery, whether open or endovascular. Re-operative surgery, whether after prior open or endovascular repair, is associated with increased morbidity. As such, it is these patients who may stand to benefit most from B-TEVAR. Each of the above described case series included patients who had prior aortic surgery. Among the 189 patients treated by Dr. Greenberg, 18% had undergone prior thoracic aortic surgery, and 28% had undergone prior infra-renal aortic surgery.<sup>7</sup> Among the 81 patients in Dr. Chuter's series, 47% had undergone prior aortic surgery.<sup>17</sup> One of the significant benefits of B-TEVAR is that it allows for a significant degree of design flexibility and customization. In the longer term, when commercially available "off-the-shelf" stent grafts for TAAA are available to treat most patients, it is likely to be this specific design flexibility that will make B-TEVAR an important tool for the minority of patients with TAAA and unusual or complex anatomy. Furthermore, we anticipate that re-operative surgery is likely to become increasingly common as endovascular technology is used more often and our patients live longer. As such, we feel it is important to include such patients in this study. The interaction between existing endovascular devices or prior open repair and the B-TEVAR construct does add an additional layer of complexity, but, in our opinion, the risk of these interactions can be mitigated with careful case planning and patient selection. The case report forms will track such prior surgery, and this should allow subsequent analysis of the safety and effectiveness in such patients.



Patients who have had prior aortic surgery will consist of two groups, those with a remote history of prior aortic surgery as well as those undergoing a staged approach to long extent TAAA repair (e.g. Crawford extent 1 or 2.). Patients who have had remote prior aortic surgery are described above in the case series reported by Drs. Greenberg and Chuter. These are patients who have experienced a discrete aneurysm above or below a prior repair, and those with degenerative anastomotic pseudoaneurysms (excluding infected pseudoaneurysms) that occur remotely from the index aortic procedure.

The second group consists of patients with long extent TAAA in whom the optimal method of repair remains uncertain. The uncertainty can be due to either: an expectation that the patient may indeed be healthy enough to tolerate an open peri-visceral repair; or due to the concern that the patient is not healthy enough to tolerate long extent of aortic coverage required for B-TEVAR. In other words, a patient's suitability for B-TEVAR may be uncertain due to concern that they are not necessarily "high risk" enough to need B-TEVAR or due to concern that they are too high risk even for B-TEVAR. Patients with TAAA vary significantly in terms of their physiologic and medical condition at presentation. Comprehensive care of these patients requires individualized assessment of their fitness for repair.

Dr. Johnston recently reported on a cohort of 10 Patients with extent 1 or 2 TAAA who underwent a staged hybrid repair. A TEVAR was performed without establishing a definitive distal seal.<sup>24</sup> The patient was allowed to recover. At a mean time interval of 14 weeks, a second operation was performed. The patients were put on femoral-femoral bypass and the peri-visceral aorta was replaced using traditional open techniques, sewing the proximal anastomosis to the TEVAR as an "endovascular elephant trunk" type procedure. This hybrid technique has been devised to reduce the morbidity of open repair of long extent TAAA. Some patients who undergo this first stage TEVAR procedure, however, have a difficult time recovering and are thought to be at high risk of subsequent open peri-visceral repair. Such patients are potentially good candidates for a second stage B-TEVAR procedure.

Another subset of patients with TAAA appear quite frail at initial presentation. Such patients are clearly not candidates for open repair. Based on the data from Scotland reported above, nearly half of patients referred for TAAA are deemed ineligible for open repair.<sup>4</sup> Furthermore, as has been described in prior reports on B-TEVAR and EVAR, the Dacron used in the Cook Zenith stent graft can induce an inflammatory reaction. The severity of this reaction appears to correlate with extent of aortic coverage as well as the size of the excluded aneurysm, as sac thrombosis and platelet activation combine to cause a severe consumptive coagulopathy.<sup>25, 26</sup> Peri-operative deaths have been attributed to this inflammatory reaction and consumptive coagulopathy in prior reports.<sup>17</sup> Furthermore, staging the procedure for long extent of aortic coverage may help reduce the incidence of spinal cord ischemia. A single animal model has shown reduce SCI with a staged

approach,<sup>24,25</sup> and some investigators are currently incorporating this into their practice. Incidence of any spinal cord injury was 13% among patients with Type 2 TAAA undergoing staged aortic coverage and 22% among those undergoing a single stage procedure.<sup>26</sup> Those patients who do not tolerate the TEVAR procedure will undergo no further procedure and will be left incompletely treated. If the patient is not healthy enough to tolerate a TEVAR procedure, they cannot be expected to tolerate additional aortic coverage with B-TEVAR. For those who are able to go on to the second stage, the TEVAR stage may help reduce the morbidity of complete aortic coverage in a single sitting.

Staging the TEVAR to precede the B-TEVAR procedure can be both diagnostic and therapeutic. It serves to help clarify the patient's physiologic reserve to determine what, if any, second stage is optimal for that individual. Furthermore, regardless of whether the second stage is performed with open or endovascular technique, it is expected to result in a lesser physiologic stress than repairing the entire TAAA in a single stage. A staged approach may be the safest way for a frail patient with a long extent TAAA to be treated.

Patients will be enrolled in B-TEVAR study with a plan for 2 different pathways to treatment, either in single sitting or in a staged approach. For those patients in whom a staged approach is planned or considered, consent will be obtained and the patient enrolled prior to undergoing the TEVAR 1<sup>st</sup> stage of the procedure. These patients will be tracked with a separate follow up case report form at 1 and 12 months and annually to 5 years or until they undergo the second stage with a branched device, at which time their outcomes will be followed according to the routine case report forms. Some patients who undergo the 1<sup>st</sup> stage will not go on to have the second stage done with a branched graft. This could be due to the determination that they can indeed tolerate open repair, or due to a complex recovery after the 1<sup>st</sup> stage TEVAR. Such patients will be followed up to 5 years after enrollment. All patients who are enrolled will be followed and reported on. Patients who undergo the first stage, but not the second stage, will be reported as a sub-group of patients in the annual report.

All patients who undergo the first stage TEVAR will be treated with the same TX2 device that is in the B-TEVAR protocol. The specific peri-visceral device used for the second stage could be any one of the 5 device options, CMD, t-Branch, LP CMD or t-Branch or physician modified.

### 3.0 INDICATIONS

Physician modified branched thoracic endovascular grafts (B-TEVAR) are indicated in subjects diagnosed with a thoraco-abdominal aortic aneurysm involving the peri-visceral abdominal aorta having vascular morphology suitable for endovascular repair, including:

- Adequate femoral and/or iliac access compatible with the required delivery system, with or without the use of a surgical conduit
- Between 1 and 5 target visceral arteries that require branch creation (including the celiac, superior mesenteric, inferior mesenteric, renal arteries, and/or a dominant spinal artery)
- All essential branch vessels have seal zones that are  $\geq 4$  mm in diameter
- Proximal and distal aortic +/- iliac seal zones as described below :
  - A. Non-aneurysmal proximal aortic seal zone:
    1. with a length of 25 mm of proximal seal in non-aneurysmal aorta, with or without coverage of the Left subclavian artery, and
    2. with an outer wall diameter of no less than 15 mm and no greater than 42 mm, and
  - B. Non-aneurysmal distal aortic or iliac landing zone:
    3. With a length of at least 15 mm, and
    4. Aortic seal zone outer wall diameter no less than 15 mm and no greater than 42 mm or
    5. Iliac seal zone outer wall diameter no less than 8 mm and no greater than 23 mm.
- No essential spinal artery that cannot be preserved with a branch

The target treatment population are patients with TAAA who are at high risk of morbidity or mortality with open surgical repair as determined at the discretion of the treating surgeon and by having an American Society of Anesthesiologists (ASA) classification of 3 or higher .

#### 4.0 DEVICE DESCRIPTION/ DEVICE MODIFICATION DETAILS

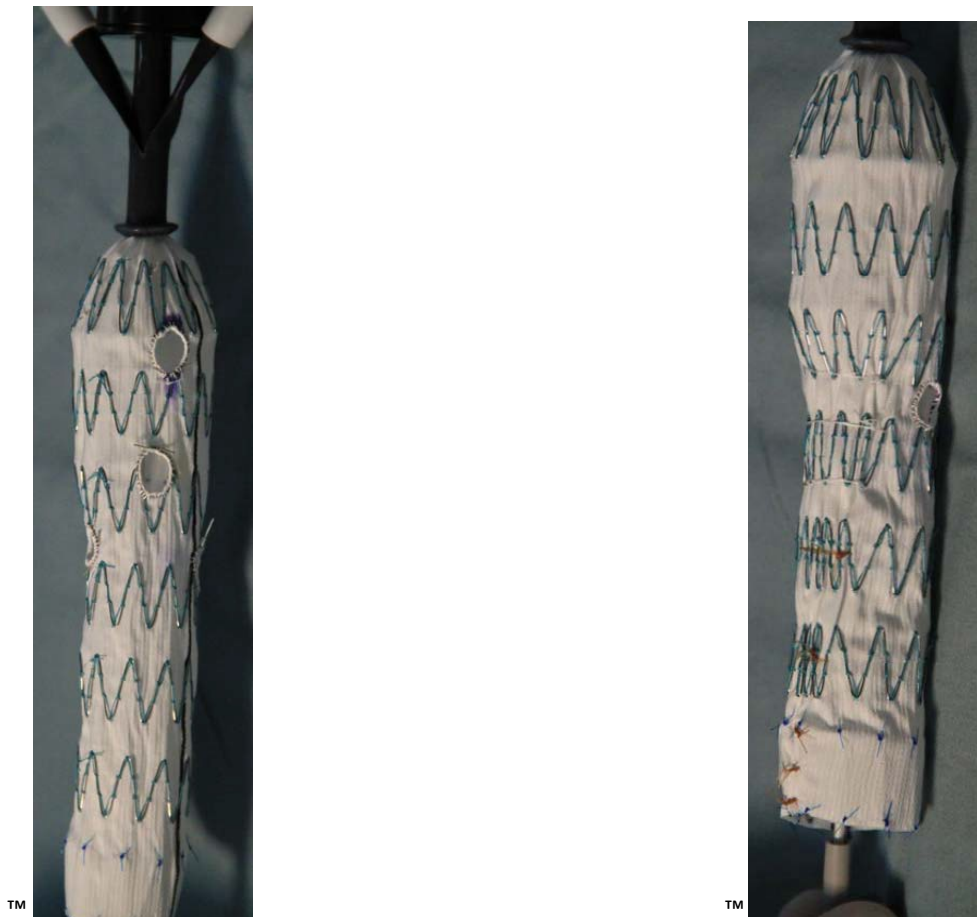
The IDE study will include 3 device options for subjects with TAAA. As described below, subjects will be offered treatment with either a commercially manufactured custom device (CMD), the commercially manufactured standard device (t-Branch) or a physician modified endograft. All 3 devices work on the same principles and utilize similar component parts.

It is expected that most patients will be treated with a CMD device as this offers the optimal advantages of individual customization and commercial manufacturing. CMD will be the preferred device option and is expected to be used in a majority of cases. For some patients, the 6-8 week delay between stages is not feasible, either due to medical urgency (symptomatic aneurysm, large aneurysm size, or concerning aneurysm morphology (i.e. extremely saccular)) or due to logistical difficulty (patient's inability to travel to the University of Washington for repeated visits.) The University of Washington is the only medical center in the 5 state WWAMI region (Washington, Wyoming, Alaska, Montana, and Idaho) that currently offers endovascular treatment of TAAA. Patients have also been referred from Utah, Oregon and California. Some patients have to travel very long distances (at their own expense) and cannot afford to travel for multiple pre-operative visits. In this case, we may elect to use t-Branch or a physician modified device. As described below, the t-Branch device would be used for large and longer extent aneurysms that cannot be delayed for a CMD. Physician modified devices are preferred for aneurysms with a narrow peri-visceral aorta (i.e. dissection, or extent 1/4/5 aneurysms) and for extent 4 aneurysms that can be treated with a shorter length of aortic coverage than a t-Branch would require.

- 4.0.1 Physician modified fenestrated-branched thoracic endovascular grafts are delivered via catheters and sheaths to treat thoracoabdominal aortic aneurysms (TAAA). The technique is based on the Zenith<sup>®</sup> TX2<sup>®</sup> Endovascular Graft which is commercially available in the United States. The stent graft is designed to reline the diseased vasculature, providing an alternate endovascular blood conduit for isolating the aneurysm from the high pressure flow of blood, thereby reducing or eliminating the risk of rupture. The stent graft is a single piece tube graft configuration. The device is intended to be used as a modular device, with proximal seal achieved either by the physician modified Zenith<sup>®</sup> TX2<sup>®</sup> device itself or with one or more proximally deployed un-modified Zenith<sup>®</sup> TX2<sup>®</sup> devices. The distal seal is achieved with either the physician modified TX2<sup>®</sup> device, a more distally deployed un-modified TX2<sup>®</sup> device, or by using commercially available infra-renal aortic stent grafts, including the COOK Zenith<sup>®</sup> Flex<sup>®</sup> and Endologix AFX<sup>™</sup> devices deployed into the iliac arteries.. The customized physician modified fenestrated-branched graft is deployed to reline

the peri-visceral aorta and ensure visceral branch perfusion (i.e. celiac, superior mesenteric, inferior mesenteric, renal and/or dominant spinal arteries) while excluding the thoracoabdominal aneurysm.

The physician modified device offers absolute customization within the anatomic inclusion/exclusion criteria. The device has been successfully narrowed down to 16 mm at the level of 2 renal fenestrations. Fenestration position can be adjusted to within 1mm in arc length. The disadvantage of this construct is that it uses fenestrated-branches, so it requires long branches when the aneurysm is large at the peri-visceral level. Furthermore, as the device is manufactured by the physician, there is not the same standardized manufacturing process used for the commercially manufactured device.



Figures 1

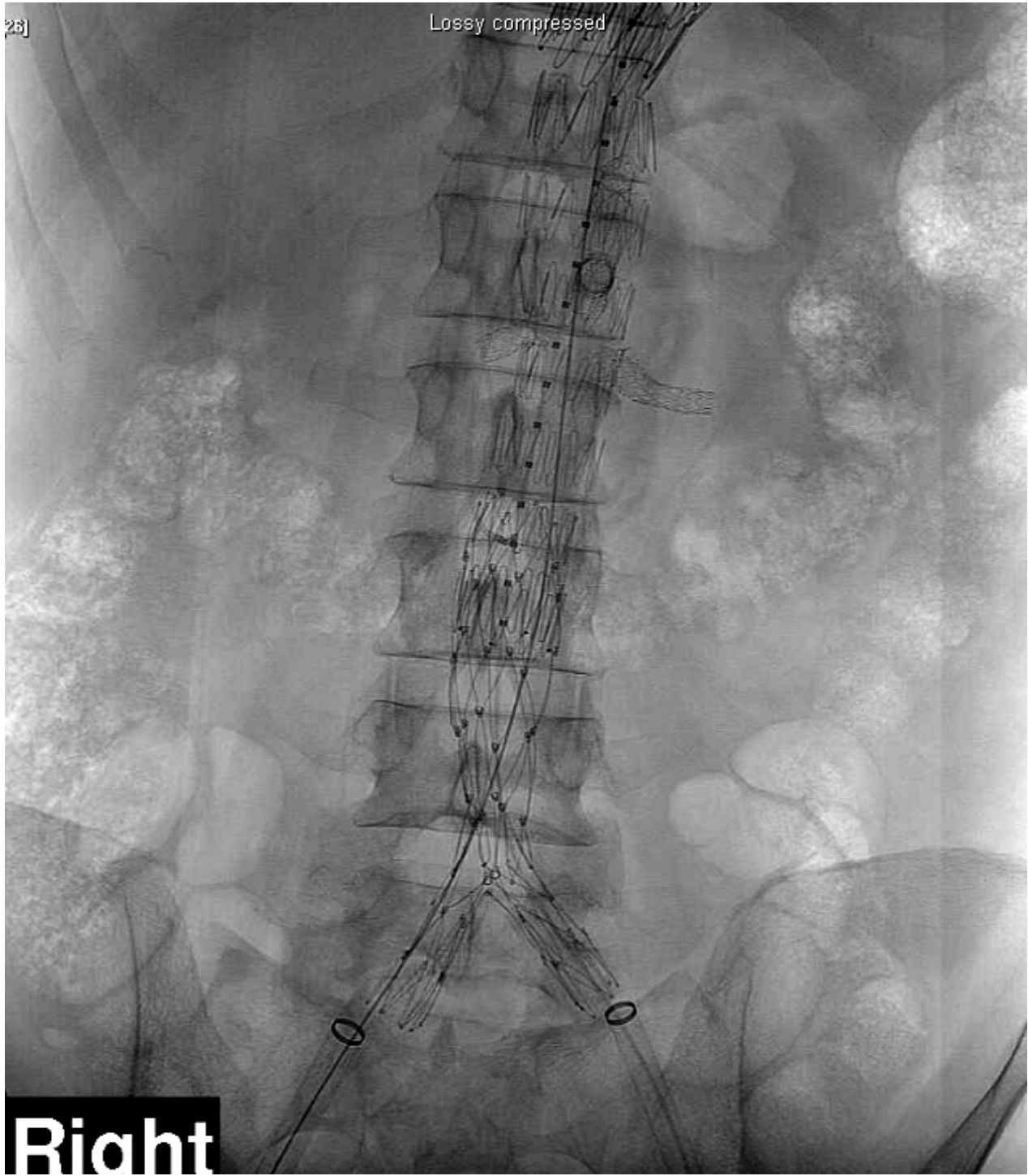


Figure 2



Figure 3



Figure 4

**4.0.2** The Cook CMD branched and/or fenestrated-branched endograft is comprised of similar modular components and works by the same principles as used in the physician modified construct. This system uses a Cook TX2 or Alpha device with cuffs and/or fenestrations that are created according to standardized manufacturing techniques. The cuffs and fenestrations are selected for each subject based on their unique anatomical constraints. The cuffs are discussed below. The fenestrations work in the same



manner as those created in the physician modified construct. As with the physician modified options, the proximal fixation is achieved with unmodified Cook TX2 or Alpha Thoracic endografts or with the branched/fenestrated device itself. The distal seal is achieved either with the distal segment of the branched/fenestrated component, a Cook TX2 or Alpha endograft deployed in the infra-renal aorta, or with the Cook Distal Bifurcated Endovascular Stent Graft (CDBG). The CDBG is a bifurcated stent graft identical to the Cook Zenith Flex graft except that it has no supra-renal fixation. The absence of supra-renal fixation allows the CDBG to be placed within the branched fenestrated graft without interference with the renal branches. The device is bifurcated and designed to be used in a modular device with Cook Spiral Z iliac extension limbs to seal into the iliac arteries. The CMD option includes all the design advantages of the physician modified device, with the additional benefits that down-going cuffs can be used instead of fenestrations in large aneurysm sacs and the reliability of standardized commercial manufacturing. The disadvantage of this option is that it requires 6-8 weeks for graft design, manufacture and importation.

**4.0.3** The Cook t-Branch construct is a specific design of the Cook CMD that is intended to treat a majority of patients with TAAA. It has downgoing cuffs positioned such that most patients with TAAA could be treated with this specific device. Again, proximal and distal fixation is achieved in the same manner as the Cook CMD. As this device can be pre-fabricated and kept available, it can be used for patients with eligible anatomy without having to wait for a CMD device to be manufactured. This device uses 4 downgoing cuffs. Therefore, it requires a minimum of 25 mm of aortic flow channel at the peri-visceral level to have enough working room to selectively catheterize the target vessels. The device length requires that the proximal seal/fixation zone for the device is 24-30 mm as measured 140 mm above the SMA position in a centerline measurement. The minimal length of aortic coverage is therefore at least 14cm above the SMA position and it extends down into both common iliac arteries.

#### **4.0.4** Summary of Advantages of each device option:

##### Advantages of the Cook Custom Modified Device

##### (CMD):

- Downgoing cuffs allow for greater degree of intra-operative adjustability compared to fenestrations and may provide improved stability in very large aortic flow channels by virtue of increased device to device overlap between the aortic and branch stents.
- Downgoing cuffs allow for earlier closure of femoral access to shorten pelvic/leg ischemic time in patients with hostile ilio-femoral access, as branches can be created from arm access after deployment of the aortic devices.
- Downgoing cuffs may facilitate branch stenting of very downgoing branch arteries.
- Downgoing cuffs and fenestrations can be combined to create the optimal device for each specific patient.
- Length of coverage of the aorta can be adjusted based on selection of cuffs or

fenestrations.

- Commercial manufacturing carries assurances of standardized manufacturing protocols, which are not possible in the physician modified option.

Advantages of the Cook t-Branch:

- The t-Branch uses down-going cuffs, so the same advantages apply as described above.
- As the device is pre-manufactured, it is readily available for patients with symptomatic or large aneurysms, or those that cannot delay treatment for 6-8 weeks for a CMD device to be manufactured.

Advantages of the Physician Modified Device:

- Device can be manufactured immediately, so this is preferred for symptomatic patients and those with very large aneurysms at risk of imminent rupture if the patient's anatomy is not amendable to the standardized t-Branch commercial device design.
- Physician modification can allow for very precise fenestration adjustment, including direct permanent diameter reduction of the Z-stents to refine alignment in small aortic flow channels, so it is preferable in some patient anatomies compared to the t-Branch device.
- The physician modified device option can be done with short aortic devices, potentially allowing for treatment with less aortic coverage in selected patient anatomies (e.g. focal peri-visceral pseudoaneurysms). Shorter length of coverage may reduce the risk of spinal cord injury.
- The physician modified device is designed to be implanted from femoral access. The avoidance of brachial access may reduce the risk of periprocedural stroke or neurovascular injury to the arm.

#### **4.0.4 HOW DEVICE SELECTION WILL OCCUR**

Patients enrolled in the B-TEVAR IDE study will meet the same inclusion/exclusion criteria. Once enrolled, patients will be recommended treatment with the CMD option unless one of the following criteria are met:

- 1) they have a symptomatic aneurysm
- 2) they have a very large aneurysm at risk of imminent rupture (fusiform aneurysm >7.5 cm, very irregular saccular aneurysm)
- 3) the patient is unable to afford the required repeated visits for study enrollment and then treatment that would be required by a 6-8 week delay
- 4) the patient prefers to be treated earlier than the 6-8 week delay

For those subjects who meet 1 or more of these 4 criteria, then they will be offered treatment with the t-Branch of physician modified options based on their anatomy. As described above, each option has advantages in different anatomic situations, and this will dictate which device is used. Aneurysms with large peri-visceral component and very

down-going target vessels would be better served with a t-Branch device. Aneurysms with narrow aortic flow channels at the visceral level or those that can be treated with shorter aortic coverage will be better served with a physician modified device. Subjects with small iliac artery access would be better treated with the Zenith cook Low Profile t-Branch or Custom Modified Device.

#### **4.1 IMPLANTS NECESSARY FOR B-TEVAR**

The investigational devices include the physician modified Zenith® TX2® endograft as well as the proximal and distal aortic/iliac grafts, the components used to modify the TX2® device, and the stent grafts used to create the visceral artery branches. The specific anatomy of each patient will determine which devices would be required.

The purpose of this supplement is to specify all of the components that could potentially be implanted during a B-TEVAR procedure. The information on each of the components used in the physician modified subgroup and for all the branches stents is attached to this supplement in the form of the Instructions for Use for each of the devices / materials. The commercial manufactured devices are submitted with reference to the Cook Medical Zenith® Endovascular Graft master file at the FDA.

##### **4.1.1 IMPLANTS NECESSARY FOR PHYSICIAN MODIFIED ENDOGRAFT**

A physician modified branched thoracic endograft is a commercially available, off-the-shelf endograft that has been altered at the time of the procedure by creating reinforced fenestrations in the graft through which covered stent grafts can be deployed to preserve blood flow into vital branch vessels. The graft is deployed on a sterile working table in the operating room. The locations of the fenestrations are marked on the graft according to the pre-procedure measurements. The graft fabric is cut and simultaneously heat sealed using thermal Cautery. These fenestrations/cuffs are marked with medical grade metal markers to facilitate fluoroscopic visualization during the procedure. Furthermore, the fenestrations are reinforced with a short ring of PTFE. This added material is essential as it strengthens the fenestration and creates a ring within which the branch grafts can seal. After the fenestrations have been created, marked, and reinforced, additional metal radio-opaque markers are sewn to the graft to assist in device orientation under fluoroscopy. Additional sutures may be used at that time to constrain the endograft, either in a temporary or permanent fashion to facilitate subsequent deployment. The device is re-constrained and re-sheathed within the original Zenith® TX2® delivery sheath.

The modified stent graft is then deployed to reline the peri-visceral abdominal aorta. Proximal

and distal fixation and seal can be achieved using the modified TX2<sup>®</sup> device, additional unmodified TX2<sup>®</sup> devices and/or the Zenith Alpha<sup>™</sup> Thoracic Endovascular Graft, the Cook Zenith<sup>®</sup> Flex<sup>®</sup> or Endologix AFX<sup>™</sup> devices depending on the aortic anatomy.

Once the aortic stent grafts are deployed, the branches are then created. Wires and catheters are used to cross through the reinforced fenestrations into the target visceral arteries. iCast covered stents are then deployed to extend from the modified aortic graft to the target vessel. The branch stents must create a hemostatic seal with the main endograft as these branches will be constructed within the aneurysm sac. Single or multiple stents may be required for any given branch. In most cases, 1 covered stent graft is sufficient to create a suitable branch. In some cases, a second covered stent graft is required. Self-expanding bare metal stents will be required within the covered stent graft branch in selected cases for several purposes: to add outward radial strength (i.e. in the setting of intrinsic target vessel stenosis); to smooth the transition from the stiff stent graft to a tortuous target visceral artery; or to treat a downstream vessel dissection or intimal irregularity. Therefore, the mean number of stents per branch is 1 with a range of 1-3.

The following devices are considered part of the B-TEVAR physician modified investigational device:

#### Modified Aortic Stent Graft

1. Zenith<sup>®</sup> TX2<sup>®</sup> Endovascular Graft (Cook Medical)

#### Devices used to modify the TX2<sup>®</sup> Graft on the back table

Part to reinforce the fenestration or create cuff:

2. Advanta<sup>™</sup> SST PTFE graft (Atrium Medical)

Parts to create a radiographic marker

3. Amplatz Gooseneck<sup>®</sup> Snare 15mm (ev3 Endovascular, Inc.)
4. Boston Scientific Fibered Platinum Coils (Boston Scientific)

Sutures for graft construction and diameter reduction

5. Gore-Tex<sup>®</sup> CV-6 Suture (W.L. Gore & Associates, Inc)
6. Surgipro<sup>™</sup> Suture (Covidien)
7. Chromic Gut Suture (Covidien)

Devices used to create the branches in the patient

8. iCast<sup>™</sup> stent graft (Atrium Medical)
9. Zilver<sup>®</sup> stent (Cook Medical)

#### Aortic endografts used for proximal and distal extension, seal and fixation

10. Zenith<sup>®</sup> Flex<sup>®</sup> Endovascular Graft (Cook Medical)
11. AFX<sup>™</sup> Endovascular AAA System (Endologix, Inc.)

12. Zenith<sup>®</sup> Fenestrated Distal Bifurcated Body Graft (Cook Medical)
13. Zenith Alpha<sup>™</sup> Thoracic Endovascular Graft

### **1. The Zenith<sup>®</sup> TX2<sup>®</sup> Endovascular Graft (Cook Medical)**

The Zenith<sup>®</sup> TX2<sup>®</sup> Endovascular Graft is a modular system of primary and ancillary components that combine to form multiple endovascular graft configurations. All components in this system use self-expanding Cook-Z<sup>®</sup> stents sewn to traditional, currently marketed Dacron<sup>®</sup> graft material with currently marketed suture material. The TX2<sup>®</sup> TAA Endovascular Graft features a proximal stent ring of the graft containing stainless steel anchoring barbs for additional proximal fixation to resist migration. Each ring within the proximal and distal seal zones contains a self-expanding stent inside the graft material that provides a seal with the aorta to minimize type I or Type III endoleak. Radiopaque markers along the top of the graft promote accurate placement in the intended seal zone. The introduction system has trigger wires for precise, controlled placement of the endograft.

### **2. Advanta<sup>™</sup> SST PTFE graft (Atrium Medical)**

The Avanta<sup>™</sup> SST PTFE is a synthetic graft conduit. It is unique due to its thin wall, impermeability, and its resistance to fracture during balloon dilation. These features make it uniquely suited to B-TEVAR. Short segments of graft (i.e. 2-8 mm) are used to reinforce the fenestrations created in the TX2<sup>®</sup> graft. This material creates added strength to the fenestration, which is critical to allow for subsequent balloon dilation of the stent grafts within the fenestration. This strength is essential to prevent tearing, as the stent grafts must seal within the fenestrations. The graft uses a membrane technology to reduce suture hole bleeding. This reduces the risk of a Type III endoleak at the fenestration. Due to its thin wall, it does not add significant bulk to the graft and facilitates subsequent re-constraining of the device within the delivery sheath.

### **3. The Amplatz GooseNeck<sup>®</sup> Snare Kit (ev3 Endovascular, Inc.)**

The Amplatz GooseNeck<sup>®</sup> Snare Kit contains one Amplatz Goose Neck Snare and one Amplatz Goose Neck Snare Catheter. The Catheter is discarded at the beginning of the procedure and only the gold plated tungsten loop is used to be permanently hand sewn to the edges of the fenestration for visibility. The gold marker is cut to size for the fenestration with a pair of sterile scissors at the time of graft preparation. The snare is constructed of nitinol cable and a gold plated tungsten loop. The snare provides optimal radiographic visualization as the wire is large gauge at 0.053 inches. This is the radio-opaque marker utilized in the PMEG cases performed by Dr. Benjamin Starnes.

#### **4. Boston Scientific Fibered Platinum Coils (Boston Scientific)**

The platinum coils are small caliber wound platinum/tungsten alloy. They are comprised of 92% platinum and 8% tungsten and are highly radio-opaque. These coils are used in the same fashion as the gold loop as a radio-opaque marker around the reinforced fenestration or cuff. These coils are small, measuring 0.018 inch, thereby reducing the bulk of the material to create the fenestration and thereby facilitating subsequent re-sheathing of the endograft in its delivery sheath. The fibers aid in local thrombus formation and may augment sealing at the fenestration. This is the radio-opaque marker utilized in the majority of branches created by Dr. Fillinger in his case series.

#### **5. Gore-Tex<sup>®</sup> CV-6 Suture (W.L. Gore & Associates, Inc)**

GORE-TEX<sup>®</sup> Suture, is a unique, microporous, nonabsorbable monofilament made of expanded polytetrafluoroethylene (ePTFE), the same material used in other GORE Medical Products including the Viabahn stent graft. The material properties of PTFE include: 1:1 needle: suture sizing to reduce needle hole bleeding and better pliability with improved fracture resistance. This suture is used to sew the reinforced fenestrations and cuffs as it has better flexibility than Prolene. This flexibility allows for balloon dilation of the branch stent grafts within the fenestration without causing fracture.

#### **6. Surgipro<sup>™</sup>II~ Surgipro<sup>™</sup> Suture (Covidien)**

SURGIPRO sutures (clear or pigmented) are inert, nonabsorbable, sterile sutures composed of an isotactic, crystalline stereoisomer of polypropylene and contain polyethylene. The suture is pigmented blue to enhance visibility. SURGIPRO polypropylene sutures are indicated for use in general soft tissue approximation and/or ligation, including use in cardiovascular, ophthalmic and neurological surgery. These sutures are used to permanently secure the gold marker(s) around the fenestration(s). This suture is also used to create “restraining ties” along the posterior edge of the graft which facilitate slight rotational movements of the graft prior to full deployment. These sutures remain permanently affixed to the outer aspect of the stent graft. [3]

#### **7. Chromic Gut Suture (Covidien)**

CHROMIC GUT sutures are absorbable sterile surgical sutures composed of purified connective tissue (mostly collagen) derived from the serosal layer of beef (bovine) intestines. They are packaged in a solution of 89% isopropanol, 10% water and 1% triethanolamine. CHROMIC GUT is treated with chromic salt solution. CHROMIC GUT sutures elicit a minimal acute inflammatory reaction in tissues characteristic of foreign body response to a substance. This is followed by gradual loss of tensile strength and suture mass, as the enzymatic process dissolves

the surgical gut until it is completely absorbed. The Chromic sutures are utilized for temporary diameter reduction of the stent graft. They are used to narrow the device during deployment to facilitate rotation of the device while in the patient. Once the device is oriented appropriately, the sutures can be deliberately fractured with a balloon dilatation or by leaving them in place to be re-absorbed. The advantage of these sutures are that they can be used as temporary diameter reducing ties without the need for an additional trigger wire, thereby reducing the difficulty in re-constraining the device within the delivery sheath.

#### **8. iCast™ stent graft (Atrium Medical)**

The iCAST™ Covered Stent is a balloon expandable endoluminal device consisting of a laser cut 316L stainless steel stent with an encapsulated cover made of expanded PTFE. The device is crimped and premounted to a multi-lumen delivery catheter. To facilitate accurate device placement, two radiopaque bands are attached to the catheter shaft marking the ends of the crimped device. This device is provided in various lengths and 5, 6, 7, 8, 9 and 10 mm diameters. The iCast stent graft can be dilated beyond their nominal diameter without fabric tears. The proximal aspect of these stents are typically “flared” with a larger non-compliant balloon at the conclusion of the procedure to maximize seal and prevent endoleak. This is the primary stent used for branch creation. It has the advantages of a small crossing profile, and it can be flared in excess of the nominal size to improve the seal at the fenestration. It has excellent conformability and stiffness. As a balloon expandable stent, it has less continuous outward radial force and is less flexible, so this stent may require re-lining with a self-expanding stent to provide those qualities in specific anatomy. [4]

#### **9. Zilver® stent (Cook Medical)**

The Zilver® Stent is a self-expanding stent made from laser cut nitinol and is electro-polished to prevent corrosion and fracture. The tips are marked with gold markers to improve visibility. It is pre-loaded in a Flexor® sheath which is both highly flexible and kink resistant. It comes in sizes 6-10 mm in diameter and 2 to 8 cm in length. The stent would be used to reline a covered stent used in a visceral branch. This device would add continuous outward radial force in the case of a target vessel occlusive disease or dissection. Furthermore, as these stents have improved flexibility over the covered stent grafts, they can be used to extend beyond the covered stent graft to improve branch stability and reduce downstream vessel kinking.

#### **10. Zenith® Flex® Endovascular Graft (Cook Medical)**

The Zenith® Flex® graft utilizes stainless steel Z stents and Dacron fabric as does the thoracic TX2® device. It is designed to function as a modular component, with a bifurcated main body through which iliac extension limbs are deployed. This device will be used in cases where there is aneurysmal degeneration of the infra-renal aorta and/or iliac arteries such that the endograft must be extended beyond the distal infra-renal aorta. The main body of the device, above in the

iliac flow divider measures between 60 and 127 mm in length, depending on device length, with diameters between 22 and 36 mm. The modified TX2<sup>®</sup> device could be deployed within this device, if there is adequate contact for the Flex device against the infra-renal aorta. Alternatively, this device could be deployed within the modified TX2<sup>®</sup> device if the infra-renal aorta is aneurysmal. In some cases, there may not be enough room for the Flex device to fit within the modified TX2 device without the supra-renal struts covering the renal fenestrations. In order to avoid this, the supra-renal stent ring can be removed from the endograft on the back table. The device can be partially deployed and the sutures constraining the supra-renal struts are cut. This allows the supra-renal stent to be removed. This modification does not alter the fabric or structure of the bifurcated graft itself. The proximal fixation is lost with removal of the supra-renal stents. This same construct is used for the Zenith<sup>®</sup> Fenestrated Distal Bifurcated Body Graft and has shown good durability and seal with a 1:1 sizing and 36-54 mm overlap. The Flex device comes in a full range of diameters. The Zenith<sup>®</sup> Fenestrated Distal Bifurcated Body Graft is available in a 24 mm diameter only. Therefore, the ability to remove the supra-renal stent allows for use of a wide range of sizes.

#### **11. AFX<sup>™</sup> Endovascular AAA System (Endologix, Inc.)**

The AFX Endovascular AAA graft is a bifurcated device comprised of a cobalt chromium metal scaffold surrounded by STRATA ePTFE material. The principle advantage of this device is that it fixates on the aortic bifurcation. Therefore, it provides a solid distal foundation within which the modified TX graft can be deployed when the infra-renal aorta is aneurysmal. The graft material is attached to the outside of the metal scaffold proximally and distally using polypropylene suture. The graft to graft seal between this device and the TX device deployed within it is at the proximal supported ring. The stent grafts however will have metal to metal contact through the length of overlap providing appropriate oversizing. A second advantage of this graft system is that the contra-lateral access requirement is only 9F, so some patients with small iliac access may be eligible for this device. Although the use of this device does entail using different commercial endografts (Endologix AFX<sup>™</sup> with Zenith<sup>®</sup> TX2<sup>®</sup>) within the same patient, this technique has been used with excellent success both in the case series of Dr. Mark Fillinger as well as in one of our cases here at UW. This device is essential as it allows for distal fixation and seal when the Zenith<sup>®</sup> Flex<sup>®</sup> device cannot be used, as in cases with a large aneurysm of the infra-renal aorta or where the supra-renal struts of the Flex<sup>®</sup> device would interfere with the renal fenestrations.

#### **12. Zenith<sup>®</sup> Fenestrated Distal Bifurcated Body Graft (Cook Medical)**

The Distal Bifurcated Body Graft is the same stainless steel Z-stent and Dacron materials used in the TX2 and Flex devices. It is manufactured in a 24mm main body diameter without a supra-renal stent. This device is designed to be used with the ZFEN suite of fenestrated Proximal Body Grafts. The ZFEN Proximal Body Grafts will not be used in the B-TEVAR IDE study as they are designed for treatment of juxta-renal AAA.



### **13. Zenith Alpha Thoracic Endovascular Graft**

The Cook Zenith Alpha Thoracic Graft will be used to establish proximal and distal seal and fixation. It is a cylindrical endovascular graft consisting of proximal and distal components. The proximal component can be either tapered or non-tapered and may be used independently (for ulcers/saccular aneurysms or blunt thoracic aortic injuries) or in combination with a distal component. The stent grafts are constructed of woven polyester fabric sewn to self-expanding nitinol stents with braided polyester and monofilament polypropylene suture. Both components are fully stented to provide stability and the expansile force necessary to open the lumen of the graft during deployment. Additionally, the nitinol stents provide the necessary attachment and seal of the graft to the vessel wall.

To assist with alignment, the proximal component has an uncovered stent. For added fixation and sealing, the proximal component has an internal sealing stent with fixation barbs that protrude through the graft material. In addition, the bare stent at the distal end of the distal component also contains barbs.

On devices with diameters of 40-46 mm, the proximal sealing stent remains constrained to ensure alignment with the inner curvature of the aorta.

To facilitate fluoroscopic visualization of the stent graft, gold radiopaque markers are positioned on each end of the proximal and distal components. Gold markers are placed on stent apices at the proximal and distal aspects of the graft margins, denoting the edge of the graft material, to assist with deployment accuracy.

The device comes in an expanded range of sizes compared to the Cook TX2 graft. The Alpha Thoracic is indicated for use in aortic diameters from 15 to 42 mm. As such, the inclusion criteria of the study have been amended to include aortic diameters where the Alpha Thoracic device can be deployed according to its FDA approved instructions for use.

#### **4.1.2 IMPLANTS NECESSARY FOR THE COOK CUSTOM THORACIC BRANCHED DEVICE**

The commercially manufactured Cook t-Branch and thoracoabdominal custom branch/fenestrated endovascular stent-graft (CMD) utilizes the same principles as the physician modified endograft described above. The suite of Cook devices can be designed to have either reinforced fenestrations or directional short reinforced self-expanding cuffs arising from the main body of the endograft. The custom nature of the device allows for either option to be used for each target vessel. Both cuffs and fenestrations have specific anatomic advantages and disadvantages, and selection of which is used is based on each individual subjects anatomy.

Cuffs are axially oriented reinforced self-expanding extensions from the main body of the device. These cuffs are designed to be deployed above or below the target artery, so that the branch stents have a longer and less angulated course from the main body to the target. As they are longer than a fenestration, the interface between the main body and the branch stent is greater, which may result in fewer stent fractures, component separations or leaks. The distance from the target artery also allows for a greater degree of intra-operative adjustment, so that branches should tolerate minor degrees of mal-alignment without difficulty, and they may be usable even in cases of severe mal-alignment. Cuffs have the disadvantage that they require a greater degree of working room around the main body of the device. They may not be usable in the setting of a narrow aortic flow channel where there is insufficient room to maneuver the branch stent from the cuff to the target vessel. Cuffs that are caudally oriented also require brachial access to place the bridging stents. Such down-going cuffs/branches may provide improved hemodynamics for target vessels that are very down-going, such as the celiac and SMA. Branches also require greater reinforcement as they are longer and subject to greater forces along their length. Due to the increased length and mobility of branches, cuffs use self-expanding stent grafts (Fluency or Viabahn) which are often re-lined with self-expanding stents (Wallstents) to add outward radial force and stability.

The fenestrations used in the Cook Custom Thoracic Branched Device are similar to those used in the Physician Modified device. They are radially oriented and designed to align precisely with the target vessel. Fenestrations have the advantages that they can be aligned within a small aortic flow channel, that they may provide improved hemodynamic flow for target arteries that arise perpendicularly to the axis of the aorta (most renal arteries), and they can be accessed from femoral access. Fenestrations use the iCast balloon expandable stent graft as the bridging branch stent.

The design of each endograft can be individualized to optimize these factors.

**The following devices are potential component parts of the Cook Custom Thoracic Branched graft B-TEVAR investigational device:**

Branched/Fenestrated Stent Graft

1. Thoracoabdominal Custom Branch/Fenestrated Endovascular Stent-Graft

Devices used to create the branches in the patient

2. iCast™ stent graft (Atrium Medical)
3. Zilver® stent (Cook Medical)
4. Fluency® Plus (Bard Peripheral Vascular)
5. Gore® Viabahn® Endoprosthesis (Gore)
6. WallStent™ Endoprosthesis (Boston Scientific)

Aortic endografts for proximal and distal extension, seal and fixation

7. Zenith® Distal Bifurcated Body Endovascular Stent Graft
8. Zenith® TX2® Endovascular Graft (Cook Medical)
9. Zenith Alpha™ Thoracic Endovascular Graft

**1. Thoracoabdominal Custom Branch/Fenestrated Endovascular Stent-Graft (Cook Medical)**

The Thoracoabdominal Custom Branch/Fenestrated Endovascular Stent-Graft is based on the either the TX2 or the low profile Alpha platform. The device can be uniform in diameter or tapered. It can have up to 5 fenestrations or branches. The selection of branch/fenestration type and position is based on each individual patient's anatomic needs. It is designed to work as a modular device. It can establish seal and fixation proximally and distally, or it can be deployed in conjunction with other endovascular stent grafts that establish seal and fixation at proximal or distal locations in the aorta or iliac arteries.

**2. iCast™ stent graft (Atrium Medical)**

As above in section 4.1.1. The Atrium iCast stent graft is used as a branch stent with the Thoracoabdominal Custom Branch/Fenestrated Endovascular Stent-Graft. The iCast is the branching stent used for fenestrations.

**3. Zilver® stent (Cook Medical)**

As above in section 4.1.1. The Cook Zilver stent graft is used as a branch stent with the Thoracoabdominal Custom Branch/Fenestrated Endovascular Stent-Graft.

#### **4. Fluency<sup>®</sup> Plus (Bard Peripheral Vascular)**

The Fluency<sup>®</sup> stent graft is a self-expanding covered stent that has been used as the primary bridging stent for down-going cuffed branches in the existing FDA approved PS-IDE studies in the USA. The device uses a Nitinol skeleton that is wrapped on its inner and outer surfaces with a thin ePTFE coating. The Fluency<sup>®</sup> has a very controlled deployment and has good stiffness to resist bending/kinking. The device is typically lined with a self-expanding stent (Boston Scientific) to improve outward radial force and further reduce kinking/bending of the device. This is the device that has been used most often for branches utilizing downward oriented axial cuffs.

#### **5. Gore<sup>®</sup> Viabahn<sup>®</sup> Endoprosthesis (Gore)**

The Viabahn is a self-expanding stent graft. The external stent is made of Nitinol, and this is lined with a reinforced, heparin bonded ePTFE. This device is highly flexible, the most flexible of the 3 stent graft options used for branch stenting. The device will accommodate significant tortuosity within the aortic flow channel and/or the target artery. The device is less visible under fluoroscopy than is the Fluency; it has less resistance to kinking; and it does not tolerate significant size mismatch between the cuff and the target vessel. Given these issues, it is generally used a secondary option to the Fluency in the existing PS-IDE studies. The flexibility is critical in selected circumstances and as such, this device is an important addition to the overall graft construct.

#### **6. WallStent<sup>™</sup> Endoprosthesis (Boston Scientific)**

The Wallstent is a braided self-expanding stent using an Elgiloy<sup>®</sup> material. The stent is highly flexible, kink resistant, and adapts well to changes in artery diameter and curvature. This stent is used to provide added radial force and kink resistance when deployed inside of a stent-graft, such as the Fluency, iCast, or Viabahn. The stents are longer in length and have better kink resistance, so they would be used for longer and larger branches than the Cook Zilver.

#### **7. Zenith<sup>®</sup> Distal Bifurcated Body Endovascular Stent Graft**

The Zenith Distal Bifurcated Body Endovascular Stent Graft is a bifurcated endograft designed for use as a modular component to treat the infra-renal aorta. The device is designed as a Cook Zenith Flex device however there are no supra-renal struts. This allows the device to be deployed within the branched/fenestrated device without interference with the renal branch stents. This is the same device used in the commercially available ZFEN system that is called the Zenith<sup>®</sup> Fenestrated Distal Bifurcated Body Graft, described above.

## **8. The Zenith® TX2® Endovascular Graft (Cook Medical)**

The Cook Zenith TX2 endograft is used as described above to achieve proximal and/or distal aortic fixation and seal.

## **9. Zenith Alpha™ Thoracic Endovascular Graft**

This device is used as described above to achieve proximal and/or distal aortic fixation and seal.

### **4.1.3 IMPLANTS NECESSARY FOR THE COOK t-Branch DEVICE**

The t-Branch is a standardized design of the CMD device. It uses 4 down-going cuffs. Therefore the component parts are the same as those listed in section 4.1.2 but instead of the CMD itself, the t-Branch device is used. As it uses 4 down-going cuffs, the branching stents would be either the Fluency or Gore Viabahn relined with a Wallstent or a Zilver stent.

#### Branched/Fenestrated Stent Graft

1. t-Branch Endovascular Stent-Graft
2. T-Branch Low Profile Endovascular stent graft

#### Devices used to create the branches in the patient

3. Zilver® stent (Cook Medical)
4. Fluency® Plus (Bard Peripheral Vascular) Gore Viabahn
5. Gore® Viabahn® Endoprosthesis (Gore)
6. WallStent™ Endoprosthesis (Boston Scientific)

Aortic endografts for proximal and distal extension, seal and fixation

7. Zenith® Distal Bifurcated Body Endovascular Stent Graft
8. Zenith® TX2® Endovascular Graft (Cook Medical)
9. Zenith Alpha™ Thoracic Endovascular Graft (Cook Medical)

### **1. t-Branch Endovascular Stent-Graft (Cook Medical)**

1. The t-Branch device is a single pre-fabricated version of the Thoracoabdominal Custom Branch/Fenestrated Endovascular Stent-Graft. It was designed to accommodate the visceral anatomy of a majority of patients with TAAA. It is premanufactured and can be kept available for patients who present with symptomatic TAAA requiring urgent treatment.

#### **2. t-Branch Low Profile Endovascular Stent-Graft (Cook Medical)**

Both the Cook CMD and t-Branch devices can be manufactured using the standard stainless steel Z-stents and standard woven polyester fabric, or they can be manufactured in a low profile (LP) version. The LP version uses the same materials and manufacturing process used for the Cook Alpha thoracic endograft that is currently commercially available. The Z-stents are made of Nitinol

and the fabric is a thin polyester. In either case, the same device design is used. The LP version allows for a significant reduction in delivery sheath size, down to 18F from the current 20-24F. Smaller delivery sheaths will significantly expand the eligibility for patients with TAAA, particularly women. The LP device is more costly to manufacture, and as such will be reserved for patients with small iliac artery access.

3-8: Please see Section 4.1.2 for details.

#### **REFERENCES:**

See Appendix IX for references for each of the above component parts.

The Cook Custom Thoracic Branched Endograft and the Universal Graft reference can be found in the Cook Master File on record with the FDA and are not reproduced here.

## 5.0 STUDY DESIGN

This is a feasibility prospective, consecutive enrolling, non-randomized, single institution clinical evaluation of the safety and effectiveness of physician modified thoracic endovascular grafts when used in the treatment of patients with thoraco-abdominal aortic aneurysms (TAAA).

Sixty (60) study patients will be enrolled at a single center.

### 5.1 Eligibility Criteria

#### 5.1.1 Inclusion Criteria

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

1. Patient is  $\geq 18$  years of age
2. Patients who are male or non-pregnant female (females of child bearing potential must have a negative pregnancy test prior to enrollment into the study)
3. Patient or Legally Authorized Representative has signed an Institutional Review Board (IRB) approved Informed Consent Form
4. Patient is considered by the treating physician and a second attending physician experienced in the care of patients with aneurysmal disease to be at high risk of open surgical repair due to one or more major medical co-morbidities (i.e. CAD, CHF, COPD, CRI, advanced age, generalized deconditioning, or other.) with ASA of 3 or more.
5. The patient has reasonable expectation of surviving the B-TEVAR procedure and has a life expectancy of greater than 1 year as determined by the PI and a second attending physician experienced in the care of patients with aneurysmal disease.
6. The patient has a thoraco-abdominal aortic aneurysm where necessary visceral branch vessels (i.e. the celiac, superior mesenteric, inferior mesenteric, renal and/or dominant spinal arteries) arise from the aneurysm or seal zones necessary for on-label thoracic endovascular repair
7. Patient has a thoraco-abdominal aortic aneurysm that meets **at least** one of the following:
  - aneurysm  $\geq 5.5$  cm in diameter
  - aneurysm has increased in size by 0.5 cm in last 6 months
  - aneurysm is believed to be causing symptoms
8. Patient has sufficient arterial access (femoral and/or iliac) that will allow delivery of the endovascular device with or without the use of a surgical conduit.
9. Patient has suitable proximal (aorta) and distal (aorta or iliac) arteries to allow for adequate fixation and seal:
  - A. Non-aneurysmal proximal aortic seal zone:
    1. with a length of 25 mm of proximal seal in non-aneurysmal aorta, with or without coverage of the left subclavian artery,

2. with an outer wall diameter of no less than 15 mm and no greater than 42 mm, and
- B. Non-aneurysmal distal aortic or iliac landing zone:
  3. With a length of at least 15 mm,
  4. Aortic seal zone no less than 15 mm and no greater than 42 mm or Iliac seal zone with an outer wall diameter of no less than 8 mm and no greater than 23 mm.
10. The patient has no more than 5 necessary visceral arteries that require flow preservation.
11. All target visceral artery seal zones are  $\geq 4$  mm in diameter.
12. Patient must be willing to comply with all required follow-up exams.

### 5.1.2 Exclusion Criteria

Patients that meet ANY of the following are **not** eligible for enrollment into the study:

1. Patient has an active systemic infection
2. Patient has a mycotic aneurysm.
3. Patient has a known hypersensitivity to contrast media that is not amenable to pre-treatment.
4. Patient has an absolute contra-indication to anticoagulation
5. Patient has known sensitivities or allergies to nitinol (nickel, titanium), polyester, polypropylene, gold, stainless steel, or solder (tin, silver)?
6. Patient has a body habitus that would inhibit adequate X-ray visualization of the aorta
7. Patient has a dominant artery to the spinal cord arising from an area of stent graft coverage that is not amenable to preservation using an endovascular branch
8. Patient is currently participating in another investigational device or drug clinical trial
9. Patient has other medical, social or psychological conditions that, in the opinion of the investigator, preclude them from receiving the pre-treatment, required treatment, and post-treatment procedures and evaluations.
10. Patient has a freely ruptured TAAA with hemodynamic instability
11. Patient has unstable angina (defined as angina with a progressive increase in symptoms, new onset at rest or nocturnal angina, or onset of prolonged angina)
12. Patient has had a major surgical or interventional procedure unrelated to the treatment of the aneurysm planned within 30 days of the TAAA repair. Adjunctive procedures for treatment of the TAAA (i.e. carotid-subclavian bypass or iliac conduit) are acceptable.
13. Patient has a history of an aortopathic connective tissue disease (e.g. Marfan or Ehlers Danlos syndromes)

## 5.2 Study Population

### 5.2.1 Treatment Group Patient Selection

Adult male and female patients will be consecutively screened for the study. Eligible patients must meet all of the inclusion criteria and none of the exclusion criteria.



The Treatment Group includes 60 study patients.

### **5.3 Withdrawal and Lost-to-Follow-Up**

Patients may be withdrawn from the study for any of the following reasons:

- Lost-to-follow up despite exhaustive attempts to contact. A minimum of three (3) attempts to contact such patients must be made. One such attempt must include a registered return receipt requested letter. All attempts to contact the patients must be documented.
- Patients may voluntarily decide to withdraw from the study. All reasonable attempts should be made to ascertain the reason for voluntary withdrawal.
- It is in the best interest of the subject to be withdrawn from the study

All patient withdrawals must be documented on the **Study Completion/Exit Case Report Form (CRF)**.

### **5.4 Duration of Study**

Approximately 2-3 patients are seen per month at the University of Washington who may be eligible for B-TEVAR. It is possible that this number will increase in time if the protocol proves safe and effective. It will likely take 18-24 months to recruit 60 patients. Treatment Group patient follow-up visits will occur at 30 days, 6 and 12 months post-implant, and then annually through five years. Subjects who undergo only the TEVAR procedure will be followed at 30 days, 12 months and annually thereafter through 5 years. Therefore, study duration is estimated to run approximately 6-7 years.

## **6.0 STUDY PROCEDURES**

The study will be monitored in accordance with written standard operating procedures consistent with 21CFR812. Treatment of patients enrolled in this study will include tests and procedures listed in **Appendix IV: Schedule of Activities**.

### **6.1 Patient screening**

Prospective candidates are evaluated in a consecutive manner for eligibility for the study at the time they are considered to be candidates for TAAA repair. Initial screening may include diagnostic testing (e.g., imaging, angiogram, laboratory testing, and a physical examination) performed as part of routine medical care.

The following steps outline the process to determine patient eligibility for enrollment. There will be no need for shipment of ANY devices as these devices are currently available off the shelf and are modified according to the procedure described herein for the physician modified graft. The commercially manufactured grafts will be shipped from the Cook center in Australia where they are manufactured

1. Ensure that patient has signed an IRB approved **INFORMED CONSENT FORM**
2. Complete the **INCLUSION/EXCLUSION WORKSHEET**
3. Complete the **DEVICE PLANNING AND SIZING WORKSHEET**

As patients will be enrolled via two pathways, single or two-stage, the following flow diagram will show the breakdown:

#### Step 1: Principle Investigator Evaluation

The PI will perform a history and physical examination and review any pertinent pre-operative studies, including the CT angiogram. Based on this review, the PI will make a determination as to whether or not the patient meets the inclusion/criteria, whether they are “high risk” for open repair, whether the aneurysm anatomy is amenable to repair with B-TEVAR, and whether a single or two-staged procedure is appropriate.

The decision about single vs. staged procedure will be individualized to each subject. The determination will depend on length of aortic coverage, size of the aneurysm, and access anatomy. A single staged procedure is preferable in cases with short aortic coverage (lower risk of spinal cord injury and coagulation abnormalities), large aneurysms (at increased risk of interval rupture), and subjects with difficult access (as re-operation may be complicated by re-operative / difficult access). In each case, the PI will attempt to balance these issues to optimize patient safety and minimize risk. There are insufficient data at this time to prescribe absolute parameters to this decision process, and the decision must be based on best physician judgment.

As discussed in section 4.0.3, device selection will be made based on a balance of the urgency of treatment as well as the specific patient anatomy. For patients requiring urgent treatment, (i.e. those with very large aneurysms or those presenting with symptoms concerning for impending rupture) or patients who must travel long distances and cannot make multiple trips, the physician modified device or the pre-manufactured t-Branch device would be used. The physician modified device is customizable and can be used in small aortic flow channels and can be deployed from femoral access only. The t-Branch device, on the other hand, has downward oriented cuffs which may facilitate implantation in a large aneurysm sac, but it requires brachial artery access. For patients who are deemed to be able to wait the 6-8 weeks for graft manufacture and can make the requisite multiple trips to the University of Washington, they will be treated with the commercially manufactured custom device. It is expected that a majority of subjects will be treated with the commercially manufactured custom device.

#### Step 2: Cardiac Intensivist Evaluation

In order to obtain a second opinion about the safety and effectiveness of the B-TEVAR procedure, all patients who the PI believes would be eligible will be reviewed by a second attending physician experienced in the care of patients with aneurysmal disease. The physicians

who will serve in this role are the attending physicians who staff the cardiothoracic intensive care unit. These physicians are experts in the peri-operative and post-operative care of patients undergoing complex cardio-thoracic and vascular operative procedures. They have extensive experience in the assessment of such patients.

Patients, who the PI believes are appropriate B-TEVAR candidates, will be seen then by the Cardiothoracic Intensive Care Unit (CT ICU) physician. The CT ICU physician will have an opportunity to review the patient's studies, interview and examine the patient. Based on this evaluation, the CT ICU physician will determine 3 things:

- a) Whether or not the patient has a reasonable expectation of surviving the B-TEVAR procedure
- b) Whether or not the patient has a reasonable expectation of survival beyond 1 year with successful repair
- c) Whether or not the patient is high risk for open repair as defined in the Inclusion criteria Section 5.1.1

If the CT ICU physician concurs with the PI that the patient meets all 3 of the above criteria, then the patient will move forward to Step 3.

The CT ICU physician will not determine technical aspects of the B-TEVAR procedure, as they are not experts in the planning or conduct of the procedure itself. Their role is to provide an unbiased, experienced, assessment of the patient's physiologic reserve and life expectancy. As there are no validated tools for estimating patient survival, the study will rely on agreement between two experienced physicians, the PI and the CT ICU physician. These two attending physicians must agree that all 3 of the above criteria have been met by the subject in order to proceed with enrollment. If the PI and CT ICU physician are not in agreement that all 3 criteria are met by the subject, that subject will not be enrolled.

### Step 3: Study Enrollment

Subjects who meet all 3 criteria listed in Step 2, as determined by both the PI and the CT ICU physician, will be provided the opportunity to participate in the study. Signed written consent will be obtained and subject will enroll in the study.

### Step 4: Procedure

The patient will then proceed to have their procedure. The process will differ for single vs. two-staged procedures.

- A) For single staged patients, this first operation will be the B-TEVAR procedure. Their post-operative follow up will follow the protocol as described below, with clinic visits, labs and imaging done at 1, 6, 12 months and annually to 5 years. The B- TEVAR Follow up CRF will be used.

B) For two-staged patients, this first operation will be the TEVAR procedure. Their post-operative follow up will utilize the TEVAR Follow Up CRFs. They will be seen with imaging studies at 1 and 12 months and annually until 5 years or until they proceed with the B-TEVAR second stage. After the patient undergoes the B-TEVAR procedure, they will continue with the routine study follow up at 1, 6, 12 months and annually to 5 years after the B-TEVAR procedure using the B-TEVAR Follow Up CRFs.

The decision to proceed with the second stage will be at the discretion of the PI. That determination will be based on when the patient has returned to their pre-operative level of functional status, their laboratory values have stabilized/recovered, they remain free from major organ system dysfunction as a consequence of the first stage, and the patient agrees to undergo a second operation. If the patient's recovery is complicated by a permanent decline in functional status, or permanent organ system dysfunction (e.g. long term nursing facility residency, permanent spinal cord injury, end-stage renal failure on dialysis), then the PI will determine that the second stage should not proceed. These patients will then continue follow up using the TEVAR CRF until their condition improves and they can undergo the B-TEVAR procedure or they complete 5 years of follow up. As described below in the Risk Analysis, section 10.0, such patients who do not complete the second stage will be left with an incompletely treated aneurysm and will remain at risk of rupture and death. This will be explained in detail to the subjects prior to enrollment.

Step 1

PI Evaluation:

- a) Meet all Inclusion and no Exclusion Criteria
- b) High risk for open repair
- c) Anatomically eligible for B-TEVAR
- d) Single vs. multiple staged repair

Step 2

2<sup>nd</sup> Attending Physician Evaluation:

- a) Patient has a reasonable expectation of survival after operation
- b) Patient has a reasonable expectation of survival to 1 year with successful repair
- c) Patient high risk for open repair

Step 3

Informed Consent Obtained  
Subject Enrolled in B-TEVAR Study

Step 4

Single Stage Repair:

- a) B-TEVAR procedure done
- b) Follow up using B-TEVAR Follow up CRF at 1, 6, 12 months and annually to 5 years

Planned 2-Stage Repair – 1<sup>st</sup> stage:

- a) First stage TEVAR procedure done
- b) Follow up with TEVAR follow-up CRF at 1, 12 months and annually to 5 years or until undergo 2<sup>nd</sup> stage
- c) Determination to proceed to 2<sup>nd</sup> stage per PI based on clinical evaluation as

2-Stage Repair – Complete 2<sup>nd</sup> stage:

- a) B-TEVAR procedure done
- b) Follow up as described for single stage repair in protocol: B-TEVAR Follow up CRF at 1, 6, 12 months and annually to 5 years

2-Stage Repair – Incomplete:

- a) Follow up using TEVAR CRF at 1, 12 months and annually to 5 years

## 6.2 Pre-procedure evaluation

The following assessments will be performed no more than three months prior to the B-TEVAR implant/surgical procedure unless otherwise noted:

- Patient demographics
- Past Medical History/Past Surgical History
- Physical exam
- Concomitant medications (anticoagulants, antiplatelets, antibiotics, statins, Beta blockers and ACE inhibitors only)
- Laboratory testing, which includes renal and coagulation assessments, hematocrit as well as serum pregnancy for female patients of childbearing potential (with the exception of the serum pregnancy test which will be performed within one week of the procedure)
- Contrast enhanced CT scan for aneurysm measurement and device planning. CT scan must be performed within 4 months of the implant date.

If the patient is eligible to be enrolled into the study, the results of these screening assessments are recorded on the **Baseline CRF** and the **Device Sizing and Planning Worksheet**. If a patient does not qualify for enrollment into the study, the baseline screening worksheets will be retained, together with the patient's signed/dated consent(s). The subject will be considered a Screen Failure.

## 6.3 Treatment period (surgical procedure)

The following assessments and data collection will be performed at the time of the implant/surgical procedure:

- Investigational device accountability- documentation of product information (e.g., lot number, serial number)
- Exact measurements of position and configuration of custom made fenestrations
- Type of anesthesia
- Anticoagulation
- Description of delivery system access on both ipsilateral and contralateral sides (e.g. femoral cut down, percutaneous access, closure device)
- Volume of contrast used
- Total fluoroscopy time during procedure
- Estimated blood loss and replacement requirements
- Size of stents in visceral vessels
- Adjunctive procedures (e.g. stent placement)
- Investigator assessment of TAAA device performance as it relates to:
  - Access success/failure, delivery/deployment success, evidence of endoleak, device integrity issues
- Adverse events

The above events will be recorded on the **Procedure – System Evaluation CRF (either TEVAR alone or B TEVAR CRF)**

#### 6.4 Pre-Discharge

The following assessments and testing will be performed post-procedure, prior to discharge:

- Physical exam
- Laboratory testing, which includes renal function and optional complete blood cell counts and coagulation studies
- Length of ICU and hospital stay
- Concomitant medications (anticoagulants, anti-platelets, antibiotics, statins, Beta blockers and ACE inhibitors/ARBs only)
- Adverse events
- Other relevant data as indicated on the CRF, including optional wound assessment.

The above assessments are recorded in the **Hospital Discharge CRF**. In some instances, patients may experience a prolonged hospitalization post procedure. In those cases, the above assessments should be performed no more than two (2) weeks post procedure.

#### 6.5 Post-Treatment follow-up period

The following assessments and tests will be performed at the following intervals:

Time period post-treatment	Acceptable visit timeframe allowance
1 Month (30 days)	± 14 days
6 Months (180 days)	± 30 days*
12 Months (365 days)	± 45 days
Annually from 2 to 5 years	± 60 days

\*This will not be done for those undergoing TEVAR only

- Physical exam
- Laboratory testing to assess renal function and, if needed, to measure CBC
- Contrast Enhanced Spiral CT of the Chest/Abdomen/Pelvis OR for patients unable to receive IV contrast, a non-contrast thin cut CT scan of the Chest/Abdomen/Pelvis will be performed as well as a duplex of the abdominal aorta to assess the branch patency, velocity and to look for the presence of endoleak and aneurysm sac size (\* for subjects undergoing the TEVAR first stage, no aortic duplex will be performed)
- Device/aneurysm assessment based on imaging (endoleak, migration, integrity, patency, TAAA dimensions)
- Concomitant medications - anticoagulants, anti-platelets, antibiotics, statins, Beta-blockers and ACE inhibitors/ARBs
- Adverse events
- Other relevant data as indicated on the CRF including optional wound assessment.

The above assessments are recorded in the appropriate **Follow-up CRF**.

All subjects who have undergone the B-TEVAR device implantation, whether in a single or multiple stage will be followed with the B-TEVAR Follow-up CRF and will be analyzed as a

single group as well as by subgroup of device type. The date of implantation of the modified device will serve as the start time for follow up. Subjects who do not undergo the second stage of a planned staged repair will be analyzed separately and evaluated for survival and cause of death. With the exception of data points specific to the branched graft (i.e. branch complications, migration, etc.) the same clinical data points will be recorded for patients who only undergo the first stage of a staged repair, including medical demographics, aneurysm size and extent, and major adverse events. Additional information for the TEVAR alone will include a rationale as to why the second stage was not completed. For the two staged approach, the time interval between Stage 1 and Stage 2 will be recorded. Complete data will be reported for each group. Outcomes based on subgroup analysis of those who had single repair, staged repair and those who only had the initial stage and did not complete the second stage will also be reported.

#### **6.6 Unscheduled Follow-up visits**

In the event that a patient visit for an issue associated with the device occurs outside the protocol-specified time frames (i.e., pre-discharge, 30 days, 6 and 12 months and annually from 2-5 years), then data will be recorded from that visit. Possible reasons for unscheduled visit related to the B-TEVAR procedure:

- Patient experiences new symptomology and/or an adverse event
- Surveillance of an existing adverse event

The unscheduled visit information would be recorded in the **Follow-up CRF** where the reason for the unscheduled visit will be specified. Only data pertinent to the reason for the unscheduled visit would be recorded.

#### **6.7 Discontinuation from study**

Patients who choose to discontinue participation in the study prior to study completion will be requested to undergo a final assessment by the investigator at the time notification is made of their decision to discontinue. The final assessment will be recorded in the **Follow-up and Study Completion - Exit CRFs**.

### **7.0 STUDY OBJECTIVES**

The purpose of this clinical trial is to evaluate the safety and effectiveness of physician modified endovascular grafts in the treatment of patients with thoraco-abdominal aortic aneurysms (TAAA).

#### **7.1 Primary Objectives**

The primary objective of this study is to determine if branched endovascular grafts are a safe and effective method of treating TAAAs. Treatment success is defined as successful deployment of the modified endograft and its branches with preservation of unimpeded flow to all target vessels that are intended to be preserved. Failure to exclude the aneurysm (i.e. Type 1 or 3 endoleak), conversion to an open operation, aneurysm rupture, thrombo-embolic complication to a target



vessel, kink/stenosis of a branch stent or flow limiting distal branch vessel dissection will be considered treatment failure. Any such branch related events that are identified intra-operatively and successfully treated will not be considered treatment failures.

The safety of the endovascular grafts will be determined by the proportion of patients with major adverse events. The effectiveness of the endovascular grafts will be determined by the proportion of patients that achieve treatment success.

## **8.0 DEFINITIONS**

### **8.1 Endoleak**

Endoleak is defined by the persistence of blood flow outside the lumen of the endovascular graft and within the aneurysm sac and can be classified as:

*Type I* – Ineffective seal at either the proximal or distal sealing zones

*Type II* – Retrograde blood flow from lumbar arteries, the inferior mesenteric artery, or other collateral vessels into the aneurysm sac

*Type III* – A leak caused by fabric tears or disruption, incomplete seal between components, component disconnection, or graft disintegration

*Type IV* – Blood flow through an intact fabric.

### **8.2 Migration**

Aortic stent graft migration is defined as evidence of proximal or distal movement of the stent graft > 10 mm relative to fixed anatomic landmarks. Spiral CT images will be used to determine migration at regularly scheduled follow-up visits. The 1 month image will be used as the baseline for subsequent assessment.

Branch stent graft migration is defined as evidence of movement of the branch stent graft in relation to fixed anatomic landmarks sufficient to induce a Type 1 or 3 endoleak after a branch had been documented to have adequate seal by CT imaging.

### **8.3 Patency/ Branch Vessel Patency**

Patency is defined as the preservation of unimpeded flow to the treated vessel. Thrombo-embolic complication to a target vessel, kink/stenosis of a branch stent or flow limiting distal branch vessel dissection will be considered loss of branch patency. This may be evidenced by: CT, angiography, ultrasound or other imaging modality, or pathological analysis. Flow limiting findings on screening CT scans or by elevated Creatinine will be evaluated with further confirmatory studies, including clinical examination, duplex, and angiography as indicated.

### **8.4 Loss of Stent Graft Integrity**

The integrity of the stent graft will be evaluated by abdominal CT scans at regularly scheduled follow-up visits. Any fractured stents, and any other issues compromising the integrity of the stent graft will be reported.

### 8.5 TAAA Enlargement

Aneurysm enlargement is defined as a greater than 5 mm (diameter) increase in the orthogonal plane of the aneurysm size. Spiral CT images will be used to determine aneurysm enlargement at regularly scheduled follow-up visits. The 1 month image will be used as the baseline for subsequent assessment.

### 8.6 Surgical Conversion

Surgical conversion occurs when a patient implanted with a physician modified endovascular graft undergoes open surgical repair with explantation of the stent graft. The follow-up for patients who are converted to open surgical repair include collection of the following data: Physical Exam and assessment of Adverse Events. The visits are to occur at 1 month post open conversion and 1 year post open conversion.

### 8.7 Imaging

Study Visit	Images Retained by Investigator
Baseline	Contrast Enhanced Spiral CT of the Chest/Abdomen/Pelvis
1 month	Contrast Enhanced Spiral CT of the Chest/Abdomen/Pelvis <u>or</u> Non-contrast fine cut CT of the Chest/Abdomen/Pelvis with visceral artery duplex if the patient cannot receive IV contrast
6 month	Contrast Enhanced Spiral CT of the Chest/Abdomen/Pelvis <u>or</u> Non-contrast fine cut CT of the Chest/Abdomen/Pelvis with visceral artery duplex if the patient cannot receive IV contrast
12 month and annually for 5 years	Contrast Enhanced Spiral CT of the Chest/Abdomen/Pelvis <u>or</u> Non-contrast fine cut CT of the Chest/Abdomen/Pelvis with visceral artery duplex if the patient cannot receive IV contrast

\*Refer to **Appendix VI: CT Scanning Techniques** imaging requirements.

**Patients who have the first stage repair will be imaged with a spiral CT of the Chest/Abdomen/Pelvis with or without contrast at 1 and 12 months and annually to 5 years or until they undergo the second B-TEVAR stage. Following the second stage, they will undergo imaging as described above at 1, 6, 12 months and annually for 5 years from the date of the second stage.**

### 8.8 Explant Evaluation

The investigator is committed to understanding the effects of the human *in vivo* environment on the stent graft over time. To this end, all explanted devices will be evaluated by a Pathologist at the University of Washington. Refer to **Appendix VII: Explant Procedure** for specific instructions for managing the removal and handling of the explanted TAAA device.

### 8.9 Adverse Events

An adverse event is any new, undesirable medical occurrence or change (worsening) of a pre-existing condition that occurs in a patient, whether or not considered to be associated with the

product. Elective hospitalizations for pre-existing conditions are not adverse events. Requirements for reporting AEs are dependent upon the reviewing IRB policy. Adverse events will be reviewed by a Clinical Events Committee (CEC). The CEC will meet periodically, a minimum of annually. Adverse Event information is recorded in the **Adverse Event CRF**.

For purposes of this study, the following events are not considered adverse events, because they are expected to occur in conjunction with the index procedure or are associated with customary, standard care of patients undergoing endovascular TAAA repair procedures:

- Early post-operative pain (within 72 hours of index procedure) at the access site and/or related to position on procedure table (i.e. low back pain, abdominal pain, groin pain)
- Post-anesthesia/conscious sedation emesis, nausea, or headache (within 72 hours of index procedure)
- Electrolyte imbalance without clinical sequelae following index procedure, even if requiring correction
- Low grade temperature increase (< 100.5 °F)
- Blood loss not requiring transfusion
- Minor, localized tenderness, swelling, induration, bruising, erythema, hematoma etc. at vascular access site that does not require surgical intervention, evacuation, transfusion, or antibiotics
- Non-sustained arrhythmia not requiring treatment or intervention
- Prophylactic administration of atropine
- Prophylactic pacing
- Isolated, non-sustained PVCs/PACs
- Asymptomatic hypotension or hypertension
- Use of vaso-active medications for asymptomatic hypotension in the setting of routine spinal cord protection
- Atelectasis not requiring treatment
- Pleural effusion(s) not requiring treatment
- Urinary retention or hematuria not requiring intervention other than urinary drainage
- Thrombocytopenia not requiring transfusion
- Leukocytosis not requiring treatment
- Delirium, confusion or agitation within the first 72 hours postoperative unless such is found to be attributable to a TIA or Stroke or other new medical condition
- Constipation
- Chest pain that is determined to be non-cardiac in origin
- Peripheral edema not requiring treatment other than diuresis
- Shortness of breath not requiring treatment other than diuresis
- Bruising
- Loss of appetite/anorexia requiring medical treatment
- Weakness not due to spinal cord injury (i.e. fatigue and deconditioning)

The Investigator and/or IRB may require that these events are reported as adverse events. In this case, the Investigator will report these observations based on his medical judgment and requirements of the IRB.

### **8.10 Serious Adverse Events (SAE)**

A serious adverse event (SAE) is defined as one that suggests a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the investigation. This includes, but may not be limited to, any event that:

- Is fatal
- Is life-threatening
- Requires or prolongs (>24 hours) inpatient hospitalization
- Is a persistent or significant disability or incapacity
- Is considered an important medical event

Important medical events may be considered serious by the investigator although they may not be immediately life threatening or result in death or prolong hospitalization. Such important medical events are those that may jeopardize the patient, require intervention to prevent one of the outcomes listed above, or result in urgent investigation. Examples include, but are not limited to, allergic bronchospasm, convulsions, and blood dyscrasias.

Serious Adverse Events will be recorded in the **Adverse Event CRF**. The investigator is also required to adhere to the reviewing IRB requirements for reporting of SAEs.

### **8.11 Major Adverse Events (MAE)**

The following specific events will be considered major adverse events (MAE) for the purpose of evaluating the primary (30 day) and secondary (1 year) safety endpoints:

- Death
- Paralysis (excludes paraparesis)
- Myocardial Infarction
- Stroke (excludes TIA)
- Renal Failure (excludes renal insufficiency)
- Respiratory Failure (excludes COPD or pulmonary complications)
- Bowel Ischemia
- Lower Extremity Ischemia
- Procedural Blood Loss ( $\geq 1,000$  cc)

A MAE may or may not be considered related to the device. Mortality will be reported as “all cause” and “TAAA related.” All deaths occurring in the first 30 days post-index procedure are considered “TAAA related.”

The Clinical Events Committee (CEC) shall determine which adverse events in addition to those listed above in Section 8.11 are considered Major Adverse Events for evaluation of the primary (30 days) and secondary (1 year) safety endpoints.

### **8.12 Unanticipated Adverse Device Effect (UADE)**

An unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. UADEs are to be recorded in the **Adverse Event CRF** and the event is to be submitted to the FDA as a supplement and to all reviewing IRBs and investigators within 10 business days after the sponsor first receives notice of the adverse event. The investigator is also required to adhere to the reviewing IRB requirements for reporting of any UADE.

### **8.13 Conversion to Open Surgical repair**

Conversion to open surgical repair may occur either at the initial implant procedure or subsequent to the initial procedure. Information regarding the surgical conversion will be recorded on the **Open Surgical Conversion CRF** and the **Adverse Event CRF**. In the event that a patient requires conversion from endovascular to open surgical repair, the explanted device should be sent to a pathologist for examination. Explant information will be recorded on the **Explant -CRF**. Surgical conversions will be reported in the progress report. The Follow-up visit schedule for surgically converted patients is at one month and one year post open conversion.

### **8.14 Technical Failures**

In the event that a branched stent graft could not be deployed due to a technical failure, device failure information will be captured on the **Device Failure CRF**.

### **8.15 Deaths**

Any deaths that are device related must be reported to the FDA via an IDE supplement within 10 business days of knowledge of the event. Any deaths that are not device related are reported annually. The investigator is also required to adhere to the reviewing IRB requirements for reporting of deaths. In addition, patients with an implanted device who expire before completing the study should have the device explanted for evaluation by a pathologist if possible.

Aneurysm related death is defined as:

- any death occurring within 30 days of the B-TEVAR procedure, regardless of cause,
- death due to aneurysm rupture or
- within 30 days following any secondary procedure intended to treat the aneurysm.

## 8.16 Explants

Specific instructions for managing the removal and handling of the explanted device can be found in **Appendix VII: Explant Procedure** and Manual of Operations. Explant information will be recorded on the **Explant CRF**.

## 9.0 ENDPOINTS AND TECHNIQUES FOR MEASUREMENT

**The same endpoints will be measured for all different graft constructs. They will be reported as both a pooled group as well as separately by aortic endograft construct (physician modified, CMD, and t-Branch.)**

### 9.1 Primary Endpoints

#### 9.1.1 Safety

The primary safety endpoint is the rate of major adverse events (MAE) at 30 days post branched TEVAR repair. The following specific events will be considered major adverse events: MAEs are defined as any one of the following events:

- Death
- Paralysis (excludes paraparesis)
- Myocardial Infarction
- Stroke (excludes TIA)
- Renal Failure (excludes renal insufficiency)
- Respiratory Failure (excludes COPD or pulmonary complications)
- Bowel Ischemia
- Lower Extremity Ischemia
- Procedural Blood Loss ( $\geq 1,000$  cc)

MAEs may or may not be considered related to the device. Mortality will be reported as “all cause” and “TAAA related.” All deaths occurring in the first 30 days post-index procedure are considered “TAAA related.”

#### 9.1.2 Effectiveness

The primary effectiveness endpoint is the proportion of treatment group subjects that achieve treatment success with the B- TEVAR procedure, whether via the staged approach or done as a single procedure . Treatment success is a composite endpoint assessed at 12 months after the B-TEVAR procedure is performed that requires all of the following criteria to be met in order for a patient to be considered a treatment success:

- Technical Success, defined as successful delivery and deployment of the endovascular graft with preservation of unimpeded flow to those branch vessels intended to be preserved.
- Freedom from Type I & III endoleak. Type I and III endoleaks will be assessed by the investigator using Spiral CT images.
- Freedom from stent graft migration. Migration of the aortic stent graft is defined as evidence of proximal or distal movement of the stent graft >10 mm relative to fixed anatomic landmarks. Migration of a branch is defined as movement of the stent in relation to fixed anatomic location that results in a Type I or III endoleak. Spiral CT images will be used by the investigator to determine migration from the one month (baseline) CT image.
- Freedom from TAAA enlargement. Sac enlargement is an increase in aneurysm diameter (>5 mm) from the one month (baseline) post-operative measurement will be considered TAAA enlargement, as determined by the investigator.
- Freedom from TAAA rupture
- Freedom from conversion to open repair

## 9.2 Secondary Endpoints

### 9.2.1 Safety

The following secondary safety endpoints will be evaluated at 30 days, 12 months and annually to 5 years:

- All-cause mortality
- TAAA Related Mortality
- Freedom from permanent spinal cord injury
- Major Adverse Events (MAE)
- TAAA rupture
- Surgical conversion

The CEC will meet annually to review all MAE. All deaths that occur in the study will be adjudicated by the CEC. TAAA related death is any death determined by the CEC to occur as a result of the initial procedure (first 30 days or prior to hospital discharge), TAAA rupture, conversion to open surgical repair, or due to secondary intervention after B-TEVAR.

### 1.2.2 Secondary Effectiveness

The following secondary effectiveness endpoints will be evaluated at 30 days, 12 months and annually to 5 years:

- Need for re-intervention

- Treatment success as defined in section 9.1.2

### **9.3 Clinical Utility Measurements**

The following Clinical Utility measurements associated with both the B-TEVAR and the TEVAR alone will also be assessed:

- Conduit use
- Amount of blood loss
- Days spent in ICU
- Days spent in hospital
- Type of Anesthesia
- Placement of lumbar drain
- Rationale for planned staged approach and for any patient who is unable to undergo a second stage
- Discharge status to home, nursing facility, and assessment of functional status

## **10.0 RISKS AND RISK ANALYSIS**

Treatment of a thoraco-abdominal aneurysm with both endovascular and open surgical repair poses significant inherent risks to the patient. The mortality risk of open surgical repair of a TAAA is greater for those patients with risk factors, such as advanced age and medical comorbidities (i.e. cardiac, renal and pulmonary).<sup>1</sup>

Endovascular treatment of a TAAA has been shown to be an effective, less invasive procedure that may result in reduced early mortality and morbidity, reduced need for blood products, shorter hospital stays and recovery time, as well as improved quality of life in the early postoperative period.<sup>7,17,19</sup>

In order for patients to participate in the Treatment Group of this study, they must agree to adhere to a strict follow-up schedule to continuously monitor their long term safety.

Our understanding of the risks associated with the use of branched and fenestrated-branched aortic endografts are outlined in Section 2.1.4. Although the adverse events associated with the use of endovascular grafts may be less than for standard open surgical repair, inherent risks exist, as with many medical procedures. However, risks that have been associated with repair of TAAAs with this type of device include, but may not be limited to:

- Cardiac events such as congestive heart failure (CHF), volume overload, arrhythmias, myocardial infarction (MI), chest discomfort or angina, elevations in creatinine phosphokinase (CPK), hypotension, hypertension



- Pulmonary events such as pulmonary insufficiency, pneumonia, respiratory depression or failure, pulmonary edema, pulmonary embolism
- Cerebral events such as cerebrovascular accident (hemorrhagic or embolic), reversible ischemic neurologic deficit, transient ischemic attacks (TIA)
- Acute and chronic renal insufficiency or failure, need for dialysis, renal artery stent occlusion or renal embolization, need for re-intervention
- Operative and post-operative bleeding disorders, hemorrhage and coagulopathy
- Insertion and other vascular access site complications such as infection, bleeding, delayed healing, hematoma, dehiscence, seroma, nerve injury/damage, neuropathy, neuralgia, vasovagal response
- Vascular injury including damage to blood vessels and surrounding tissues, vessel dissection, perforation, plaque dissection, collateral vessel occlusion, tissue loss, arterial fistula, limb loss, gangrenous disease, worsened or new onset claudication, edema
- Neurological complications, such as paralysis (temporary or permanent), paraplegia, monoplegia, paresis, spinal cord ischemia, hemiplegia, bowel or bladder incontinence
- Multi-system organ failure
- Embolic and thrombotic events such as deep vein thrombosis, thromboembolism, microembolism, thrombophlebitis, pulmonary embolism, air embolism
- Gastrointestinal events such as paralytic or adynamic ileus, obstruction, fistulas, and Intestinal ischemia due to visceral artery injury, branch failure, or embolization
- Impotence, erectile dysfunction
- Urinary events such as hematuria, urinary retention, and urinary tract infection
- Radiation injury, late malignancy
- Allergic reaction to x-ray dye such as flushing, nausea, vomiting, itching, hives
- Generalized inflammatory response that may be associated with elevated levels of systemic mediators of inflammation, elevated temperature
- General discomfort related to the procedure or tests, sore throat, pain
- Infection— systemic or localized, sepsis, endograft
- Device events such as endograft occlusion, migration, dislodgement, endoleak, failure to align the fenestrations with the visceral arteries and/or stent fracture
- Irreversible (permanent) tissue loss (for example loss of fingers, toes hands and/or feet)
- Potential whole body reaction (SIRS - Systemic Inflammatory Response) to the grafts that are placed causing an acute inflammatory (protective tissue response to injury or destruction of tissues) response that is seen by an increased heart rate, increased breathing rate, a white blood count that is either increased or decreased, increased or decreased body temperature. These conditions may lead to organ failure such as kidney failure potentially requiring the need for dialysis, respiratory failure potentially requiring the need to be on a ventilator (breathing machine), anemia potentially requiring the need for transfusions

- Branch vessel occlusion
- Aneurysm rupture
- Conversion to open surgical repair
- Death

The subset of patients who undergo a planned staged procedure will be at risk of interval rupture and death between the initial TEVAR procedure and the second B-TEVAR procedure. The specific risk is unknown as there are no data to inform this risk estimate.

Patients who do not tolerate the TEVAR procedure and therefore do not go on to the second completion stage will remain at risk of death from aneurysm rupture.

Potential benefits of endovascular grafts compared to open surgical aneurysm repair may include, but are not limited to:

- Freedom from open surgery;
- Reduction of complications;
- Freedom from general anesthesia and/or the ability to use other forms of anesthesia that do not require mechanical ventilation; and
- Reduction in hospitalization and recovery time.

## **11.0 STUDY RESPONSIBILITIES**

### **11.1 Responsibilities of Investigator**

The investigator is responsible for properly conducting the investigation, ensuring that proper monitoring, IRB review and approval are obtained, submitting the IDE application to the FDA and ensuring that reviewing IRBs and the FDA are promptly informed of significant new information about the study.

The FDA retains the right to terminate the study at any time. Specific instances, which may precipitate study termination, are:

- Unsatisfactory patient enrollment with regard to quality and quantity.
- Deviations from protocol, without prior approval from the FDA.
- Inaccurate, incomplete, and/or untimely data recording on a recurrent basis.
- The incidence and/or severity of adverse experiences in this or other studies indicating a potential health hazard caused by the device.

### **11.2 FDA and IRB approval**

The investigator will not begin an investigation until an IRB and the FDA have both approved the IDE.

### **11.3 Data Safety Monitoring Plan**

The investigator will develop and maintain a DSMP to be managed by monitor(s) qualified by training and experience to monitor the study in accordance with applicable FDA regulations.

### **11.4 Accountability and Control of Devices**

The investigator shall maintain adequate records of the disposition of all investigational devices. As this device is currently commercially available and approved by the FDA, device lot numbers will be recorded.

### **11.5 Monitoring Investigations**

Monitoring visits to the principal investigator's site will be made periodically during the study, to ensure that the clinical trial is being conducted in strict accordance with the protocol, in compliance with Good Clinical Practice as defined by the FDA and by Harmonized Tripartite Guidelines, and that the clinical data can be validated against source documentation at the investigative site. Original source documents will be reviewed for verification of data recorded on the CRFs and/or in the electronic database. The investigator guarantees direct access to original source documents by the FDA, their designees, and appropriate regulatory authorities. In the event that the original medical record cannot be obtained for a patient that is seen by a non-study physician at a non-study institution, photocopies or fax documentation of the original source documents must be made available for review.

### **11.6 Source Documentation**

Investigators are responsible for maintaining information in the study patients' medical records and/or paper source documents that are kept in the subject study binder that corroborate data entered into the CRF. The following documents will be maintained and made available as required by the investigators, designated monitors and/or regulatory inspectors:

1. Medical and surgical history/physical condition of the patient prior to participation in the study in order to verify protocol entry criteria.
2. Dated and signed notes in the patients' medical record and/or subject study binder that verify that informed consent was obtained.
3. Dated and signed notes from each patient visit.
4. Description of device implantation procedure (date, time, medications, etc)
5. Dated printouts of diagnostic reports of assessments (CT, etc)
6. Adverse event reporting and follow-up of the AE.
7. Patient's condition upon completion of or withdrawal from the study.

### **11.7 Maintaining Records**

The investigator will maintain hard or electronic copies of correspondence, data, devices, adverse device effects, and other records related to the clinical trial for at least two (2) years after study completion.

It is the responsibility of the investigator and the study staff to maintain a comprehensive and centralized filing system of all relevant study documentation which may include:

- Patient Files - which substantiate the data entered in the electronic and/ or paper Case Report Forms for all required tests and procedures.
- Patient Identification Log - a list correlating all patient names, appropriate identifying information, etc., to the investigator - assigned patient number.
- Screening Log - which should reflect the reason any patient was screened for the study and found to be ineligible.
- Monitoring Visit Log - which lists dates of monitor visits.
- IRB Correspondence - includes approval letter(s), and any adverse event reporting or other correspondence with the IRB.
- Site Correspondence - letters or fax sent to the FDA from the investigator or study coordinator.
- Signed Informed Consent for each patient
- Device log-acknowledging receipt and return, if necessary, of the t-Branched or CMD devices.

In compliance with current regulatory guidelines regarding the monitoring of clinical studies, it is requested that the investigator permit the study monitor to review and duplicate information, in a de-identified format, in the patient's medical record that is directly related to the study. This information may include relevant study documentation, including the patient's medical history, to verify eligibility, laboratory test results to verify transcription accuracy, x-ray reports, admission and discharge summaries for hospital or outpatient admissions occurring while the patient is participating in the study, and autopsy reports for deaths occurring during the study (if available).

As part of the required content of informed consent, the patient must be informed that his/her medical record will be reviewed and, possibly, duplicated by monitor or government regulatory authorities. Should access to the medical record require a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the patient in writing before the patient is entered into the study.

### **11.8 Study Deviations**

A study deviation is defined as an event where the investigator did not conduct the study according to the investigational plan or protocol. The deviation event will be collected on the **Master Deviation Log**. The investigator is responsible for reporting deviations in accordance with the reviewing IRB policies.

FDA regulations require that investigators maintain accurate, complete, and current records, including documents showing the dates of and reasons for each deviation from the protocol. The following information outlines requirements for the reporting of protocol deviations:

Type of Deviation	Investigator to notify:	Reporting timeline
Emergency procedures to protect the life or physical well-being of a patient	Reviewing IRB and FDA	Within 5 business days of event
Changes in or Deviations from the investigational plan	<u>Prior</u> approval from: IRB and FDA	Prior to use
Non-urgent protocol deviation	IRB (if required)	Deviations directly related to the study endpoints will be summarized and submitted in an annual report to the FDA

### 11.9 Termination of Study

The FDA retains the right to terminate the study at any time. Specific instances, which may precipitate study termination, are:

- Unsatisfactory patient enrollment with regard to quality and quantity.
- Deviations from protocol, without prior approval from the FDA.
- Inaccurate, incomplete, and/or untimely data recording on a recurrent basis.
- The incidence and/or severity of adverse experiences in this or other studies indicating a potential health hazard caused by the device.
- Submission of fraudulent data.

## 12.0 STUDY COMMITTEES

### 12.1 Data Safety Monitoring Plan

A Data Safety Monitor (DSM) will review the progress of the clinical study. The monitor will be responsible for reviewing the data associated with the device and the patients. The monitor will provide independent recommendations to the investigator based on his review of the data. The monitor will meet with the Clinical Events Committee annually, at a minimum. Dr. Kei Togashi will serve as the DSM. Dr. Togashi has extensive experience in the clinical care of patients with TAAA both in the operating room and in the intensive care unit.

### 12.2 Clinical Events Committee

The Clinical Events Committee (CEC) will be used to review and adjudicate all device related adverse events and all serious adverse events regardless of the relatedness to the device. The

CEC shall also determine which adverse events (other than those listed in Section 9.1.1) are considered Major Adverse Events for evaluation of the primary and secondary safety endpoints. The committee shall consist of at least three (3) physicians representing multiple specialties familiar with thoraco-abdominal aortic aneurysm repair. The CEC will be comprised of Drs., Joseph Cuschieri, Elizabeth Kaplan, Ronald Pauldean and John Bramhall. Joseph Cuschieri, MD is a Professor of Surgery and Director of Surgical Critical Care at Harborview Medical Center. Elizabeth Kaplan, MD, is an Acting Instructor in the Department of Medicine and a member of the Medicine Consult Service at University of Washington Medical Center and the Seattle Cancer Care Alliance. Ronald Pauldine, MD is a Clinical Professor with the Department of Pain and Anesthesia.. John Bramhall, MD PhD is an Associate Professor of Anesthesiology with expertise in the study of quality and safety. The CEC will provide their review to the DSM and will meet annually at a minimum.

### **13.0 INFORMED CONSENT**

All patients or designated patient representatives must provide written informed consent in order to join the Study Group, in accordance with the reviewing IRB policy and procedures. The process of obtaining informed consent must be documented in the patient's medical record and/or Subject Study Binder. If changes to the investigator's informed consent template are to be made, these changes must be approved by the local IRB. A template for the Informed Consent is provided in **Appendix V: Informed Consent Template**.

## APPENDIX I: REFERENCES RELATED TO BRANCHED REPAIR OF TAAA

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## **APPENDIX II: REFERENCES RELATED TO COMPLICATIONS**

1. Piazza M, Ricotta JJ. Open Surgical Repair of Thoracoabdominal Aortic Aneurysms. *Ann Vasc Surg* 2012 (epub ahead of print)

## **APPENDIX III: ASA CLASSIFICATION SYSTEM**

### **American Society of Anesthesiologists Classification System**

The American Society of Anesthesiologists (ASA) presents a graded scale assessing a patient's risk of undergoing anesthesia. The scale represents the significance of the patient's underlying illnesses prior to anesthesia. The following provides a description of the four grades of the ASA scale:

#### **ASA I**

Healthy individual *without any systemic disease*, undergoing elective surgery. Patient not at extremes of age. (*Note: Age is sometimes ignored as affecting operative risk; however, patients at either extreme of age are thought to represent increased risk.*) Some examples are a fit man with an inguinal hernia, and a fibroid uterus in an otherwise healthy woman.

#### **ASA II**

Individual *with one system, well-controlled disease*. Disease does not affect daily activities. Other anesthetic risk factors, including mild obesity, alcoholism, and smoking can be incorporated here. Examples include non-limiting or only slightly limiting organic heart disease, essential hypertension, anemia, or mild diabetes.

#### **ASA III**

Individual *with multiple system disease or well controlled major system disease*. Disease does limit daily activities. No immediate danger of death from any individual disease. Examples include severe organic heart disease, severe diabetes with vascular complications, moderate to severe degrees of pulmonary insufficiency, angina or healed myocardial infarction.

#### **ASA IV**

Individual in imminent danger of death. Surgery is viewed to be last resort at salvaging life. Individual not expected to live through the next 24 hours. In some cases, the individual may be healthy prior to catastrophic event that led to the current medical condition. Examples include ruptured abdominal aortic aneurysm with profound shock; major cerebral trauma with rapidly increasing intracranial pressure; massive pulmonary embolus.

## APPENDIX IV: SCHEDULE OF ACTIVITIES

Procedure	Baseline	Treatment	Discharge	1 Month Follow-Up	6 Month Follow-Up <sup>7</sup>	12 Month Follow-Up	Annual Follow-Up
Medical/Surgical History	X <sup>2</sup>						
Physical Exam	X <sup>2</sup>		X	X	X	X	X
Spiral Contrast Enhanced CT	X <sup>5</sup>			X <sup>6</sup>	X <sup>6</sup>	X <sup>6</sup>	X <sup>6</sup>
Laboratory Assessment (creatinine, PT, PTT, INR, CBC)	X <sup>3,4</sup>		X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>
Adverse Event Assessment		X	X	X	X	X	X
Concomitant Medication Assessment (anticoagulants, antiplatelets, antibiotics, ACE inhibitors, Beta blockers and statins only)	X		X	X	X	X	X
Device/aneurysm assessment based on imaging (endoleak, migration, integrity, patency)				X	X	X	X

<sup>1</sup> CBC, PT, PTT and INR are optional after Baseline.

<sup>2</sup> Baseline med/surgical history, physician exam performed no more than 3 months prior to the implant/surgical procedure.

<sup>3</sup> Laboratory assessments performed no more than 3 months prior to surgical/implant procedure

<sup>4</sup> Serum pregnancy HCG test for females of childbearing potential performed no more than one week prior to surgical/implant procedure

<sup>5</sup> Baseline contrast enhanced CT must be obtained within 4 months of anticipated treatment date.

<sup>6</sup> If subject not able to tolerate contrast enhanced CT, a non contrast CT and visceral branch duplex ultrasound can be performed

<sup>7</sup> Subjects who undergo TEVAR only will not have the 6 month visit

## **APPENDIX V: Informed Consent Form**

### **UNIVERSITY OF WASHINGTON CONSENT FORM**

#### **Branched Thoracic Endovascular Grafts for the Treatment of Thoraco-abdominal Aortic Aneurysms: An Investigator-Initiated Study**

##### **Researchers:**

Matthew Sweet, M.D.

Division of Vascular Surgery, University of Washington Medical Center  
206-598-1154, 206-797-2487 to have Dr. Sweet paged

Benjamin Starnes, MD

Chief, Division of Vascular Surgery/Harborview Medical Center  
206.744.3033, 206.744.3000 to have Dr. Starnes paged.

##### **Study Coordinator:**

Billi Tatum, R.N., CCRC

Division of Vascular Surgery, Harborview Medical Center  
206-744-3369, 206-540-4229 (pager)

Wendy Hamar, CCRP

Division of Vascular Surgery, Harborview Medical Center  
206-744-8257, 260-314-1581 (pager)

**24-hour emergency telephone number-** *If you need immediate assistance please call the University of Washington Paging Operator at 206-797-2487 any time and ask for the on-call vascular surgeon.*

##### **Researchers' statement**

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether to be in the study or not. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions, you can decide if you want to be in the study or not. This process is called "informed consent." We will give you a copy of this form for your records.

#### **PURPOSE OF THE STUDY**

You are being asked to be a part of this clinical research study designed to determine the safety and effectiveness of Branched Thoracic Endovascular Aneurysm Repair (B-TEVAR). This study

uses five types of stent-grafts to treat thoraco-abdominal aortic aneurysms. The first through four options are stents made by Cook Medical. The third option is a stent that is modified in the operating room by your surgeon at the time of surgery.

You may be selected, based on the physician's assessment of your aneurysm, to have a graft custom-made by Cook Medical. In this case, the physician will take measurements of your aorta and then Cook will manufacture it. This process requires 6-8 weeks to complete.

Two of the Cook devices, the Low Profile t-Branch and Custom Made Device are used specifically for subjects whose arteries in the leg (Iliac arteries) are too small or tortuous (twisty) for the other devices. All the risks for the use of these devices is not as well-known due to lack of published data but is expected to be similar to that listed for the other devices.

If you and the physician feel that the 6-8 week delay is unsafe, then there are two treatment options. Cook Medical manufactures a standard device, called t-Branch. This device is designed to fit most patients. Alternatively, if the anatomy of your aorta does not fit the t-Branch device, then your physician will manufacture a graft for you in the operating room. This is called a physician modified endograft.

The devices manufactured by Cook Medical are investigational and are only available in FDA approved studies. The graft used in a physician modified device is not investigational and is approved by the FDA. The modifications to the graft are investigational and are not FDA approved.

In either case, the graft will include one to five holes (fenestrations or branches) that allows the graft to be located at the visceral arteries (the blood vessels that supply blood flow to your intestines and kidneys) without blocking the blood flow to them. These arteries will also be treated with a stent to direct blood into the intestine and kidneys without letting blood fill the aneurysm.

You may have already had prior aortic repair or you may have part of your aneurysm treated to see how well you will do and then you may come back to have the rest of your aneurysm repaired. This is called a "Staged Approach". If you are not able to have the rest of your aneurysm treated with the Investigational Device, you will continue to be at risk for potential rupture of your aneurysm. It is possible that you could suffer complications of the first stage of the procedure, including all those listed below. Until the second stage repair is completed, there is a risk of death from aneurysm rupture.

This study will be conducted at the University of Washington Medical Center and Harborview Medical Center and will enroll up to 60 patients.

A thoraco-abdominal aortic aneurysm is a bulge in the aorta (the main artery leaving the heart) caused by a weakening in the artery wall. If left untreated, this bulge may continue to grow larger and ultimately rupture (break open), resulting in serious internal bleeding. The information

collected from this study will be used to evaluate (show) how well patients do when treated with the branched graft, both immediately after surgery and over a long period of time. If participate in this study, your medical condition will be carefully monitored.

Treatment of your TAAA (Thoraco-abdominal Aortic Aneurysm) with the physician modified graft or the commercially made graft, involves the placement of specially designed grafts (fabric tubes) in your aorta. The graft is enclosed in a small catheter (a long, flexible tube) that is placed into your aorta through the femoral artery in your groin (top of your leg). The grafts are then placed in the correct position in your aorta by releasing them from the catheters. These grafts are investigational because they have been changed by the research physician to match your anatomy (body make up) while protecting the blood flow to vital vessels. Once the grafts are attached inside your aorta, they will support the area of your aorta that is weakened and bulging from your aneurysm. This procedure is called an endovascular aneurysm repair because the grafts are delivered through your blood vessels.

In standard surgical aneurysm repair, the surgeon makes a large incision (cut) in your chest and abdomen and actually cuts into your aorta and sews a graft in place. There are no endovascular TAAA repair devices that are approved for use by the Food and Drug Administration (FDA) in the United States (U.S.) You also have the choice to have no treatment for your thoraco- abdominal aneurysm.

### **STUDY PROCEDURES**

The following procedures/tests being performed for this study would be done if you were scheduled to undergo standard surgery to repair your aneurysm. You will have the following procedures performed:

- a physical examination by the study doctor,
- an evaluation of your medical history and surgical history as well as a review of your current medications and any risk factors,
- a check of the blood pressures in your arms
- You will also have approximately 2 tablespoons, or 30 milliliters, of blood drawn from a vein using a needle, so that tests of your kidney function, test to determine if you are anemic and a test that will determine your body's blood-clotting abilities can be performed. If you are a female with child bearing potential, you will also have a blood pregnancy test performed to make sure you are not pregnant.

Since your doctor has already diagnosed your aneurysm, you may have already had a special x- ray, called a CT scan. If you have not had a CT scan, if the CT Scan is older than 3 months or if the CT scan information is not detailed enough to let your doctor evaluate your aneurysm, you will be required to have a CT scan.

As the procedure begins, you will receive a drug in your hand or arm to help sedate you, or you might receive general anesthesia depending upon your particular circumstance. Your surgeon will clean your skin and shave hair around the place where the device will be inserted through a catheter (flexible tube) into your body. The study doctor may then make an incision (cut) into the skin in order to get access to the femoral artery in your groin (top of leg) and also in the upper arm. The study doctor

will then thread a very thin wire into your artery to guide it to the aneurysm. Because you have no nerve endings inside your arteries, you will not feel the wires or catheters as they move through your body. You may feel a slight pressure or a sensation of mild tugging during this part of the procedure.

**For the purpose of the study, the following procedures will be performed.** If you are having the physician modified graft, the main catheter containing the first piece of the graft will be changed to create holes (fenestrations) exactly matching your anatomy and based on measurements taken by the investigator from your CT images. The device will then be re-packaged and guided through your femoral artery up to a level in the aorta above the aneurysm, and side to side as to where the vital branches are located. If you are having the commercially made graft, the device will come out of the packaging and be ready to insert into your aorta. The graft will be released from the catheter and the catheter will be pulled away. Then, catheters will be used to place stents into vital arteries feeding the kidneys and bowel. Sometimes, additional stents will be needed in the aorta above and/or below the stent that has been modified. Once all the stents are in place, all the catheters will be removed leaving the graft in place inside your aorta. The incisions in your groin arteries and in your skin will be closed by your doctor.



Photographs of the modified graft device will be taken after the graft has been modified. No information will identify you.

After the procedure has been completed and you have had time to recover from the sedation, you will be kept in the hospital until your doctor allows you to go home. Prior to your discharge from the hospital, you will have the following done:

- a physical examination,
- blood tests that will require approximately 2 tablespoons, or 30 millimeters, of blood to be drawn
- review of your current medications
- review of any Adverse Events

## **FOLLOW-UP EVALUATIONS**

If you decide to participate in this research study, you will be required to return to your doctor for follow-up evaluations at one (1) month, six (6) months, and twelve (12 months) after the procedure, as well as every year thereafter until five (5) years after the procedure.

At each of the follow-up visits, you will have the following performed:

- a physical exam,
- a CT scan. If you are unable to receive contrast, a duplex ultrasound and a non contrast CT scan.
- blood tests that will require approximately 2 tablespoons, or 30 millimeters, of blood to be drawn.
- review of your medications
- Review of any Adverse Events

If you experience any problems with your grafts, your physician may ask to see you more frequently and additional tests may be done.

If you have had the TEVAR procedure only, you will not be required to return for the 6 month visit. All other visits will remain the same

It is very important to complete these follow-up visits even if you are feeling well and not having any symptoms. These visits are important for documenting how well the treatment has worked. It is also very important that you contact your doctor if you have any symptoms that may be related to the treatment that you received so that your condition can be properly checked.

In the event of death, the investigator will request an autopsy. This is so that the cause of your death can be investigated. It will allow the study device to be examined. You can decline an autopsy by indicating “No” on the “Autopsy and Removal of Device at Death” Form which is at the end of this consent form.

## **RISKS, STRESS, OR DISCOMFORT**

Not all risks associated with the use of this study device are currently known. Although the adverse events associated with the use of Branched Thoracic Endovascular Grafts for the Treatment of Thoraco-abdominal Aortic Aneurysms may be the same, less or more than for standard open surgical repair, natural risks exist, as with many medical procedures. However, risks that have been associated with repair of TAAAs with this type of device in clinical trials or that are currently marketed include, but may not be limited to:

- Heart problems like heart attack, heart failure, abnormal heart rhythm, chest pain, low or high blood pressure
- Lung problems such as pneumonia, need for oxygen, need for intubation and assistance from a breathing machine, blood clot to the lungs



- Spinal cord injury with temporary or permanent paralysis (loss of feeling or movement of the legs) and/or incontinence (loss of bowel or bladder control)
- **You may have as much as a 1 in 4 chance of having a spinal cord injury**
- Stroke, permanent brain injury
- Kidney failure, either temporary or permanent, possible need for dialysis
- Bleeding problems that could cause clots or bleeding, possible need for transfusion (need for blood products)
- Complication at the site where the artery is accessed, like bruising, bleeding, injury requiring re-operation, infection, nerve pain (burning/shooting pain), vaso-vagal symptoms (fainting), leakage of lymph fluid
- Worsening of the blood flow to the pelvis or legs that could cause leg pain or intestinal ischemia with need for operation
- Failure of multiple organ systems, including liver, kidneys, lungs and/or heart, requiring prolonged treatment in the intensive care unit
- Abnormal blood clots that could cause leg swelling, leg pain, or move to the lungs and cause breathing problems
- Intestinal problems like slow movement of the intestine and inability to eat, or lack of blood flow to the intestine requiring abdominal operation, possible removal of part of the intestine, possible creation of a stoma( an opening created by the surgeon from the outside of the body to the inside), or bleeding from the intestine
- Impotence or erectile dysfunction (for men- unable to have an erection)
- Urinary problems like blood in the urine, or difficulty urinating requiring a catheter, or urinary tract infection
- Radiation injury causing burns to the skin or risk of developing a cancer in the future
- Allergic reaction to the contrast dye or components of the graft which could cause flushing, nausea, hives, and itching
- Inflammation of the body with fevers, elevation of the white blood cells in the blood and feeling tired and sick
- General discomfort of the procedure, such as back pain, throat pain,
- Infections of the access sites (groins and arm) or of the graft, or of the skin, lungs, bladder or other body part
- Device problems like stent fracture; leak; branch occlusion (blockage) resulting in loss of blood flow to one or more blood vessels to the kidneys or intestines; or migration (movement of the graft away from its original position) of some or all of the device parts. Device problems could also include failure to fix the aneurysm with continued growth of the aneurysm which could require re-operation or possible removal of the graft.
- Inability to open the graft in the right place resulting in the need to stop the procedure and/or convert(change) to open surgical repair
- Coverage of a vital blood vessel to the kidneys or intestine requiring urgent open surgical repair

- Inability to access the selected blood vessels through the fenestrations (special holes created to get to the selected blood vessel(s)) which could lead to the need for another procedure or operation. If the blood vessels are not able to be accessed either through another procedure or surgery, loss of blood flow to one or more blood vessels to the kidneys or intestines may occur
- Aneurysm rupture (breaking open)
- Need to change to an open operation
- Irreversible (permanent) tissue damage (for example, loss of fingers, toes, feet, or hands)
- Potential whole body reaction (SIRS- Systemic Inflammatory Response) to the grafts that are placed causing an acute inflammatory (protective tissue response to injury or destruction of tissues) response that is seen by an increased heart rate, increased breathing rate, a white blood count that is either increased or decreased, increased or decreased body temperature. These conditions may lead to organ failure such as kidney failure potentially requiring the need for dialysis, respiratory failure potentially requiring the need to be on a ventilator (breathing machine), anemia potentially requiring the need for transfusions
- Death

Complications common to all patients undergoing standard surgical aneurysm repair include, but may not be limited to:

- paralysis
- bleeding during the surgery that may require the need for a blood transfusion;
- bleeding after the surgery that may require the need for a blood transfusion;
- hematoma (deep bruise);
- bleeding disorders;
- respiratory failure;
- pneumonia;
- pulmonary embolism (blood clots in the lung);
- myocardial infarction ( Heart Attack);
- congestive heart failure (decreased ability of the heart to pump blood, causing fluid buildup in the body and lungs);
- irregular heart beat requiring treatment;
- kidney failure;
- wound infection;
- bowel complications such as paralysis of the bowel; blockage of the bowel; or decreased blood flow to the bowel tissue;
- mild or severe blockage of blood flow to your legs or arms due to blood clots or damage to the blood vessels;
- amputation;
- stroke;

- impotence ( not able to have an erection);
- blood clots or infection in the graft;
- graft dilatation (stretching);
- development of a hole between the aorta and the intestines or the aorta and the vena cava (major blood vessel carrying blood to the heart);
- separation of the walls of the aorta;
- a false aneurysm(blood leaking from the artery into the tissue surrounding the artery) developing at the point where the graft is secured;
- re-operation (additional surgery);
- need for prolonged hospitalization, or prolonged recovery in a nursing facility;
- High or low blood pressure that may require treatment and
- death.

Your doctor will make every effort to minimize the risks and discomforts of the procedures. Most of the complications and discomforts listed above can be treated with medications or surgery that can be given to you if your doctor feels it is needed. In the event of a serious complication or injury, it may be necessary to surgically remove the study device.

### **Radiation risks**

This study involves exposure to radiation from the x-rays used during the procedure, and also from follow-up testing.

- The follow-up after the endovascular procedure involves a radiation dose due to the CTs scheduled at one month, six months, one, two, three, four and five years. If you have complications from the procedure, you may have more than the scheduled x-rays, leading to a higher radiation dose.
- To increase the quality of these pictures, a drug (“x-ray dye” or contrast media) is often given by injection into a vein prior to the CT scan. Infrequent risks (1 to 10% of people) include hives or itching as a result of the x-ray dye. Rare risks (less than 1%) include severe reactions such as shortness of breath, or seizures, which may be life-threatening. The potential for damage to the kidneys from contrast medium also exists.
- If you have problems with your kidneys, tests may be done that do not use contrast dye. Your kidney functions will be monitored by laboratory tests throughout the study

### **ALTERNATIVES TO TAKING PART IN THIS STUDY**

There are several hospitals in the United States with experience treating complex aortic aneurysms who are performing similar studies. You have the option of being referred to one of those hospitals for treatment if you prefer. You also have the choice to have no treatment for your aneurysm or you may choose to have standard surgical repair. In standard surgical repair, the surgeon makes a large incision (cut) in your chest and abdomen, cuts into your aorta and sews a graft in place. You should discuss with your surgeon about how the potential benefits and risks of each of these options apply to you.

## **BENEFITS OF THE STUDY**

Potential benefits of treatment with any of the three options listed previously compared to open surgical aneurysm repair may include, but are not limited to:

- Not having open surgery;
- Less time under general anesthesia and/or the ability to use other forms of anesthesia that do not require mechanical ventilation;
- Reduction of complications; and
- Reduction in hospitalization and recovery time.

Any potential benefits cannot, however, be guaranteed. There may be no direct benefit to you from your participation in this study, but it is hoped that the information gained from your participation in this study may benefit others with a condition similar to yours.

## **FINANCIAL INTEREST**

Dr. Matthew Sweet, the principle investigator, has no financial relationship with Cook Medical, the company that manufactures the stent graft. Dr. Benjamin Starnes has a financial relationship with Cook Medical. Dr. Starnes is a consultant with intellectual property rights. Dr. Starnes receives compensation for these activities in addition to his salary from the University of Washington. Dr. Starnes also is co-founder of a company called AORTICA which is a company designed to help streamline the planning process for these complex procedures thereby making it easier for more vascular surgeons to learn the technique. This financial interest and the design of the study have been reviewed and approved by the University of Washington. A Management Plan was developed to minimize any possible effect of this financial interest on your safety or welfare. The Plan will also protect the quality and reliability of the research.

## **OTHER INFORMATION**

Any significant new information about this study will be made available to you.

You may refuse to participate and you are free to withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled.

The information obtained about you due to taking part in this study will be kept confidential to the extent allowed by law. However, if we learn that you intend to harm yourself or others, we must report that to the authorities.

Total confidentiality cannot be guaranteed. However, all medical records and research materials that would identify you will be held confidential. Your identity will remain confidential unless the law requires disclosure. By signing this consent form, we are asking for your permission for medical information about you obtained during this study to be made available to authorized representatives of the FDA and other government agencies. We are also asking for permission for this medical information to be made available to the following people:

- The Investigator and study team listed on this form

- The University of Washington Institutional Review Board (IRB)
- Safety Monitors

The results of this research study may be published or used for teaching purposes; however, patients will not be identified by name in those publications or teaching materials. You will be assigned a special study code that will not reveal your name or personal identity.

You will be asked to review and sign a special document, along with this informed consent form, that describes the privacy law, Health Insurance Portability and Accountability Act (HIPAA), so that the researchers can use or disclose your protected health information for research purposes.

Government or university staff sometimes reviews studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

### **COMPENSATION FOR INJURY**

If you think you have an injury or illness related to this study, contact the study staff right away. The study staff will treat you or refer you for treatment.

We will bill you and your insurer for treatment of problems that result from your Thoraco-abdominal Aortic Aneurysm or from standard clinical care.

We will bill you and your insurer for the treatment of any problems related to your TAAA or any problems that occur with care that's provided as part of routine care for this condition to include surgical and post-operative care.

However, if you have a physical injury that happens as a direct result of the modification of the device in this research study, you will receive medical treatment that is needed to assist with your recovery from the injury. The UW will pay up to \$10,000 to reimburse you for the treatment of an injury or illness that is caused by this research study such as graft failure.

During the study, the study doctor may become aware of an illness or condition that you may have that is not related to the study. The study doctor may advise you to seek medical care for any illness unrelated to the purpose of the study. No money has been set aside to pay for things like lost wages, lost time, or pain.

However, you do not waive any rights by signing this consent form.

---

Printed name of study staff obtaining consent

---

Signature of staff obtaining consent

Date

Subject's statement

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, I can ask one of the researchers listed above. If I have questions about my rights as a research subject, I can call the Human Subjects Division at (206) 543-0098. I give permission to the researchers to use my medical records as described in this consent form. I will receive a copy of this consent form.

By initialing this box, I confirm that I have been told if the staged approach is used to treat my aneurysm and I cannot tolerate the second stage of the repair, my aneurysm will remain untreated and I stand a risk of the aneurysm rupturing

---

Printed name of subject

---

Signature of subject

---

Date and Time

**When subject is not able to provide informed consent**

---

Printed name of Legally Authorized Representative

---

Signature of Legally Authorized Representative

---

Date and time

---

Relationship of Legally Authorized Representative to subject

Copies to Researcher; Subject; Subject's Medical Record (If applicable)

**Autopsy and Removal of Device in the event of death**

If you decide not to allow an autopsy, you may still be part of this study. There will be no consequences for this decision.

If you die while you are in the study, you agree to allow an autopsy to be done to look for the cause of death and to examine the study devices. This is important because looking at the study device(s) and the tissue next to the study device(s) may provide helpful information about this procedure and these types of devices.

Your decision about the autopsy may be changed at any time. For your protection we recommend that you put your decision in writing.

*Please **Initial** the Appropriate Line Below Regarding Your Decision, then Sign and Date this Consent form.*

YES \_\_\_\_\_, I agree to allow an autopsy in the event of my death.  
NO \_\_\_\_\_, I do not agree to an autopsy.

---

SIGNATURE OF SUBJECT \_\_\_\_\_ DATE \_\_\_\_\_

**When subject is not able to provide informed consent**

---

Printed name of Legally Authorized Representative \_\_\_\_\_

---

Signature of Legally Authorized Representative \_\_\_\_\_ Date and time \_\_\_\_\_

---

Relationship of Legally Authorized Representative to subject \_\_\_\_\_

## APPENDIX VI: CT SCANNING TECHNIQUES

### Reminders:

- This study requires contrast enhanced Spiral CT data for reconstruction.
  - Data must be uncompressed DICOM
  - Patient motion should be avoided during scan. If possible, avoid scanning non-patient objects in field of view. Do not change patient position, table height, or field of view during scan. If patient moves, repeat the study in its entirety.

	<b>Minimum Protocol (Required)</b>	<b>High Resolution Protocol (Recommended)</b>
<b>Scan Mode</b>	Helical	Helical
<b>Scan Parameters</b>	100-140kVp, Auto mAs <u>or</u> 170-400 mA scan time of 0.5sec	100-140kVp, Auto mAs <u>or</u> 170-400 mA scan time of 0.5sec
<b>Slice Thickness</b>	3mm	0.625 – 2.5mm
<b>Slice Interval</b>	3mm	0.625 – 2.5mm
<b>Pitch</b>	0.984:1	0.984:1
<b>Superior Extent TAAA</b>	Lung apices	Lung apices
<b>Inferior Extent TAAA</b>	<u>Pre-op:</u> Lesser trochanter of femurs to include femoral bifurcations  <u>Post-op:</u> At least 2cm distal to the lowest hypogastric artery origin	<u>Pre-op:</u> Lesser trochanter of femurs to include femoral bifurcations  <u>Post-op:</u> At least 2cm distal to the lowest hypogastric artery origin
<b>Contrast</b>	Standard per Radiology Department	Standard per Radiology Department
<b>Volume</b>	80 – 150 ml contrast with 40ml saline flush or Standard Contrast Volume with Saline Flush per Radiology Department	80 - 150ml contrast with 40ml saline flush or Standard Contrast Volume with Saline Flush per Radiology Department
<b>Rate</b>	4 - 6 ml/sec	4- 6 ml/sec
<b>Scan Delay</b>	ROI – threshold 70-100 HU in aorta	ROI – threshold 70-100 HU in aorta
<b>Field of View</b>	Large Body	Large Body
<b>Reconstruction Algorithm</b>	Standard	Standard



## APPENDIX VII: EXPLANT PROCEDURE

Explant reports will be included in a progress report to the FDA with an Explant CRF.

**Explant During Surgical Conversion:** The objective of device removal is to minimize trauma or damage to the device at the time of surgical excision from the patient, while maintaining the patient's safety. It is also important to minimize surrounding tissue disturbance so that a thorough pathological evaluation can be made.

1. If possible, a swab should be used to obtain material for microbial culture prior to removal of the explant.
2. Attempt to identify all components including their orientation so that they may be maintained in the same relative position as they were *in situ*.
3. Attempt to remove the specimen en bloc from superior to the proximal stent to inferior to the distal stent.
4. The residual blood should be rinsed from the explant surfaces utilizing physiological solutions such as Ringer's lactate or normal saline avoiding disturbance to the inside surface of the explant.
5. All samples should be fixed in 10% neutral buffered formalin.
6. Explant case report forms should be completed at this time
7. An operative report and a separate report from the examining pathologist should be sent to the FDA, if available.

**Explant During Autopsy:** The objective of device removal is to excise en bloc from superior to the proximal stent to inferior to the distal stent. The abdominal aorta and iliacs should not be opened nor should any endovascular device manipulation be done. Photos should be taken, if possible, in anterior-posterior as well as oblique and lateral views. The external characteristics and the relationship to surrounding viscera should be noted based on the guidelines on the case report forms. Adhesions to viscera as well as evidence of fistula formation by erosion of the endograft through the arterial wall should be noted. Any problems or abnormalities of this type should be photographed *in situ*, if possible.

1. If possible, a spiral CT scan with 3-D reconstruction should be obtained of the endograft prior to explantation of the device. Spiral CT should be performed before immersion of the specimen in fixative.
2. Attempt to identify all components including their orientation so that they may be maintained in the same relative position as they were *in situ*.
3. Attempt to remove the specimen en bloc from superior to the proximal stent to inferior to the distal stent.
4. All samples should be fixed in 10% neutral buffered formalin.
5. An autopsy report and a separate report from the examining pathologist should be sent to the FDA, if available.

\*These guidelines have been furnished by the Lifeline Registry of Endovascular Aneurysm Repair.

## APPENDIX VIII: HIPAA AUTHORIZATION



Box 359470  
Seattle, WA 98195-9470  
Phone: 206-543-0098  
Fax: 206-543-9218

## HIPAA Authorization

For the Use of Patient Health Information for Research

Research Title: BRANCHED THORACIC ENDOVASCULAR GRAFTS FOR THE TREATMENT OF THORACO-ABDOMINAL AORTIC ANEURYSM

Lead researcher: Dr. Matthew Sweet

Institution of lead researcher: University of Washington Medical Center and Harborview Medical Center

### A. Purpose of this form

The purpose of this form is to give your permission to the research team to obtain and use your patient health information. Your patient information will be used to do the research named above.

This document is also used for parents to provide permission to obtain the patient information of their minor children, and for legally-authorized representatives of subjects (such as an appropriate family member) to provide permission to obtain patient information of individuals who are not capable themselves of providing permission. In such cases, the terms “you” and “your patient information” refer to the subject rather than the person providing permission.

State and federal privacy laws protect your patient information. These laws say that, in most cases, your health care provider can release your identifiable patient information to the research team only if you give permission by signing this form.

You do not have to sign this permission form. If you do not, you will not be allowed to join the research study. Your decision to not sign this permission will not affect any other treatment, health care, enrollment in health plans or eligibility for benefits.

### B. The patient information that will be obtained and used

“Patient information” means the health information in your medical or other healthcare records. It also includes information in your records that can identify you. For example, it can include your name, address, phone number, birthdate, and medical record number.

#### 1. Location of patient information

By signing this form you are giving permission to the following organization(s) to disclose your patient information for this research.

- UW Medicine (includes University of Washington Medical Center & Clinics; Harborview Medical Center & Clinics; UW Medicine Neighborhood Clinics; University

of Washington Sports Medicine Clinic; UW Medicine Eastside Specialty Center; Hall Health Primary Care Center; University of Washington Physicians)

- Seattle Cancer Care Alliance

Name of health care organization(s) or provider(s):

---

2. Patient information that will be released for research use.

This permission is for the health care provided to you during the following time period:

- From the time you enroll until follow-up is complete.

The specific information that will be released and used for this research is described below:

- All records
- Hospital discharge summary
- Radiology records
- Medical history / treatment
- Consultation
- Radiology films (like CT scans)
- Laboratory / diagnostic tests
- EKG report
- Pathology reports
- Operative report (about an operation)
- Pathology specimen(s) and/or slide(s)
- Diagnostic imaging report
- All inpatient records

**C. How your patient information will be used**

The researcher will use your patient information only in the ways that are described in the research consent form that you sign and as described here.

The research consent form describes who will have access to your information. It also describes how your information will be protected. You can ask questions about what the research team will do with your information and how they will protect it.

The privacy laws do not always require the receiver of your information to keep your information confidential. After your information has been given to others, there is a risk that it could be shared without your permission.

**D. Expiration**

This permission for the researchers to obtain your patient information ends when the research ends and any required monitoring of the study is finished.

**E. Canceling your permission**

You may change your mind at any time. To take back your permission, you must send your **written** request to:

Ms. Billi Tatum, RN, CCRC  
Harborview Medical Center  
325-9<sup>th</sup> Ave, Box 359908  
Seattle, WA 98104

If you take back your permission, the research team may still keep and use any patient information about you that they already have. But they can't obtain more health information about you for this research unless it is required by a federal agency that is monitoring the research.

If you take back your permission, you will need to leave the research study. This means that you would not have any more research treatments or tests. Changing your mind will not affect any other treatment, payment, health care, enrollment in health plans or eligibility for benefits.

**F. Giving permission**

You give your permission to release your information by signing this form.

---

Printed Name of Research Subject Birthdate

---

Signature of Research Subject Date of signature

---

Printed Name of Person Authorized to Give Permission

---

Signature of Person Authorized to Give Permission Date of signature

---

Relationship to Subject and Description of Authority

(Examples: parent of a young child; sister of an individual who is in a coma; researcher who signs for a subject who is unable to physically sign the authorization but was observed by the researcher to read and otherwise agree to the authorization.)

You will receive a copy of this signed form. Please keep it with your personal records.

**APPENDIX IX: DATA SAFETY MONITORING PLAN**

**Branched Thoracic Endovascular Grafts for the Treatment of  
Thoraco-abdominal Aortic Aneurysms:  
An Investigator-Initiated Study  
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## 1.0 TRIAL SAFETY

### 1.1 Potential Risks and Benefits for Participants

#### Potential Risks:

The risks associated with the use of this study device are not currently known. Although the adverse events associated with the use of physician modified endovascular grafts may be less than for standard open surgical repair, inherent risks exist, as with many medical procedures. However, risks that have been associated with repair of TAAAs with this type of device include, but may not be limited to:

- Cardiac events such as congestive heart failure (CHF), volume overload, arrhythmias, myocardial infarction (MI), chest discomfort or angina, elevations in creatinine phosphokinase (CPK), hypotension
- Pulmonary events such as pulmonary insufficiency, pneumonia, respiratory depression or failure, pulmonary edema, pulmonary embolism
- Cerebral events such as cerebrovascular accident (hemorrhagic or embolic), reversible ischemic neurologic deficit, transient ischemic attacks (TIA)
- Acute and chronic renal insufficiency or failure, renal microembolism, dialysis
- Operative and post-operative bleeding disorders, hemorrhage and coagulopathy
- Insertion and other vascular access site complications such as infection, bleeding, delayed healing, hematoma, dehiscence, seroma, nerve injury/damage, neuropathy, neuralgia, vasovagal response
- Vascular injury including damage to blood vessels and surrounding tissues, vessel dissection, perforation, plaque dissection, collateral vessel occlusion, tissue loss, arterial fistula, limb loss, gangrenous disease, worsened or new onset claudication, edema
- Neurological complications, such as paralysis (temporary or permanent), paraplegia, monoplegia, paresis, spinal cord ischemia, hemiplegia, bowel or bladder incontinence
- Multi-system organ failure
- Embolic and thrombotic events such as deep vein thrombosis, thromboembolism, microembolism, thrombophlebitis, phlebothrombosis, pulmonary embolism, air embolism
- Gastrointestinal events such as paralytic or adynamic ileus, obstruction, fistulas, and Intestinal ischemia due to visceral artery injury, branch failure, or embolization
- Impotence, erectile dysfunction
- Urinary events such as hematuria, urinary retention, and urinary tract infection
- Radiation injury, late malignancy
- Allergic reaction to x-ray dye such as flushing, nausea, vomiting, itching, hives
- Generalized inflammatory response that may be associated with elevated levels of systemic mediators of inflammation, elevated temperature
- General discomfort related to the procedure or tests, sore throat, pain

- Infection—urinary tract, systemic or localized, sepsis, endograft
- Device events such as endograft occlusion, migration, dislodgement, endoleak, and/or stent fracture
- Branch vessel occlusion, narrowing or fracture
- Aneurysm rupture
- Conversion to open surgical repair
- Death
- Patients who have the first stage TEVAR repair and do not go on to have the second B-TEVAR stage will remain at risk of aneurysm rupture.

Potential Benefits:

Potential benefits of physician modified endovascular grafts compared to open surgical aneurysm repair may include, but are not limited to:

- Freedom from open surgery;
- Freedom from general anesthesia and/or the ability to use other forms of anesthesia that do not require mechanical ventilation;
- Reduction of complications; and
- Reduction in hospitalization and recovery time.

**1.2 Adverse Event and Serious Adverse Event Collection and Reporting**

An adverse event (AE) is any new, undesirable medical occurrence or change (worsening) of a pre-existing condition that occurs in a patient, whether or not considered to be associated with the product. Elective hospitalizations for pre-existing conditions (e.g., elective cosmetic procedures) are not adverse events. Requirements for reporting AEs are dependent upon the reviewing IRB policy. Adverse events will be reviewed by a Clinical Events Committee (CEC). The CEC will meet periodically, a minimum of annually. Adverse Event information is recorded in the **Adverse Event Case Report Form (CRF)**.

For purposes of this study, the following events are not considered adverse events, because they are expected to occur in conjunction with the index procedure or are associated with customary, standard care of patients undergoing endovascular AAA repair procedures:

- Early post-operative pain (within 72 hours of index procedure) at the access site and/or related to position on procedure table (i.e. low back pain)
- Post-anesthesia/conscious sedation emesis, nausea, or headache (within -72 hours of index procedure)
- Electrolyte imbalance without clinical sequelae following index procedure, even if requiring correction
- Low grade temperature increase (< 100.5 °F)
- Blood loss not requiring transfusion and not resulting in decreased hematocrit.

- Minor, localized tenderness, swelling, induration, bruising, erythema, hematoma etc. at vascular access site that does not require surgical intervention, evacuation, transfusion, or antibiotics
- Non-sustained arrhythmia not requiring treatment or intervention
- Prophylactic administration of atropine
- Prophylactic pacing
- Isolated, non-sustained PVCs/PACs
- Asymptomatic hypotension or hypertension
- Use of pressor medications for asymptomatic hypotension in the setting of routine spinal cord protection
- Atelectasis not requiring treatment
- Urinary retention or hematuria not requiring intervention other than urinary drainage
- Thrombocytopenia not requiring transfusion
- Mild leukocytosis not requiring treatment

The Investigator and/or IRB may require that these events are reported as adverse events. In this case, the Investigator will report these observations based on his medical judgment and requirements of the IRB.

A serious adverse event (SAE) is defined as one that suggests a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the investigation. This includes, but may not be limited to, any event that:

- Is fatal
- Is life-threatening
- Requires or prolongs (>24 hours) inpatient hospitalization
- Is a persistent or significant disability or incapacity
- Is considered an important medical event

Important medical events may be considered serious by the investigator although they may not be immediately life threatening or result in death or prolong hospitalization. Such important medical events are those that may jeopardize the patient, require intervention to prevent one of the outcomes listed above, or result in urgent investigation. Examples include, but are not limited to, allergic bronchospasm, convulsions, and blood dyscrasias. SAEs will be recorded in the **Adverse Event CRF**. The investigator is also required to adhere to the reviewing IRB requirements for reporting of SAEs.

### **1.3 Protection against Study Risks**

**1.0 Informed Consent Process:** The consent process informs a volunteer about the study, indicates the participation is voluntary and he/she has the right to stop at any time. Risks are enumerated in the informed consent form and described orally during the consent process.



**2.0 Protection Against Risks:** Protection against risks includes a wide range of Study Group exclusion criteria, as well as rigorous post-treatment surveillance including follow-up visits at 30 days 6 and 12 months post-treatment, and annually for five years.

## **2.0 INTERIM ANALYSIS**

Interim analysis of the study is planned on an every six (6) month basis with the August Annual Progress Report serving as the starting point.

## **3.0 DATA AND SAFETY MONITORING**

The Principal Investigator (PI) will be responsible for ensuring participants' safety on a daily basis. The DSM will act in an advisory capacity to monitor participant safety, evaluate the progress of the study, and to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses. The PI and DSM will meet at least annually to review safety data.

### **3.1 Frequency of Data and Safety Monitoring**

The DSM will be informed of serious adverse events that are device related and concern patient safety as soon as they occur. The PI will notify the FDA within 10 business days of knowledge of the SAE and the IRB per the reviewing IRB's requirements.

### **3.2 Content of Data and Safety Monitoring Report**

The content of the data and safety monitoring report will adhere strictly to the requirements set forth by the reviewing IRB and the FDA.

### **3.3 Data Safety Monitor**

Kei Togashi, MD of the University of Washington has accepted the position as Data Safety Monitor (DSM). Should there be any questions regarding the independence of the DSM, it will be addressed and corrected if necessary at that time.

### **3.4 Conflict of Interest**

The DSM will sign a Conflict of Interest Statement which includes current affiliations, if any, with pharmaceutical and biotechnology companies (e.g., stockholder, consultant), and any other relationship that could be perceived as a conflict of interest related to the study and/or associated with commercial interests pertinent to study objectives.

### **3.5 Protection of Confidentiality**

Data will be presented in a blinded manner during the meetings of the PI and DSM. At such meetings, data and discussion are confidential.

### **3.6 DSM Responsibilities**

- Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that can affect study outcome;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- Review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;
- Protect the safety of the study participants;
- Prepare a report for submission to the FDA on the safety and progress of the trial;
- Make recommendations to the Principal Investigator, and, if required, to the FDA concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- If appropriate, review interim analyses in accordance with stopping rules, which are clearly defined in advance of data analysis;
- Ensure the confidentiality of the study data and the results of monitoring; and,
- Assist the FDA by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

## **APPENDIX X:**

1. ZENITH<sup>®</sup> TX2<sup>®</sup> ENDOVASCULAR GRAFT ANNUAL CLINICAL UPDATE (2011)
2. ZENITH AAA ANNUAL UPDATE (2012)
3. AFX (ENDOLOGIX) CLINICAL UPDATE (2014)
4. ZENITH FENESTRATED CLINICAL UPDATE
5. ZENITH ALPHA<sup>™</sup> THORACIC ENDOGRAFT Summary of Clinical Data 16 October 2015

### **Previously submitted and not included**

## **APPENDIX XI: INSTRUCTIONS FOR USE/PRESCRIPTIVE INFORMATION**

1. Zenith<sup>®</sup> TX2<sup>®</sup> aortic stent graft (Cook Medical)
2. Advanta<sup>™</sup> SST PTFE graft (Atrium Medical)
3. Amplatzer Gooseneck<sup>®</sup> Snare 15mm (Cook Medical)
4. Boston Scientific Fibred Platinum Coils (Boston Scientific)
5. Gore-Tex<sup>®</sup> CV-6 Suture (W.L. Gore & Associates, Inc)
6. Surgipro<sup>™</sup> Suture 5-0 (Covidien)
7. Chromic Gut Suture 4-0 (Covidien)
8. iCast<sup>™</sup> stent graft (Atrium Medical)
9. Zilver<sup>®</sup> stent (Cook Medical)
10. Zenith<sup>®</sup> Flex<sup>®</sup> Endovascular Graft (Cook Medical)
11. AFX<sup>™</sup> Endovascular AAA System (Endologix, Inc.)
12. Zenith<sup>®</sup> Fenestrated Distal Bifurcated Body Graft (Cook Medical)
13. Fluency<sup>®</sup> Plus (Bard Peripheral Vascular)
14. Gore<sup>®</sup> Viabahn<sup>®</sup> Endoprosthesis (Gore)
15. WallStent<sup>™</sup> Endoprosthesis (Boston Scientific)
16. Zenith Alpha<sup>™</sup> Thoracic Endovascular Graft
17. Zenith<sup>®</sup>-Branch Thoracoabdominal Endovascular Graft

1-16 previously submitted and not included

Appendix XII: Letter from Cook Medical authorizing reference to the Cook Zenith<sup>®</sup> Endovascular Graft master file at the FDA (**D.C. #MAF-1323**)

## **Appendix XIII: Logs**

1. Monitoring Logs
2. Screening Logs
3. Deviation Logs
4. AE Log
5. Delegation of Authority Log
6. Device Log for Cook Medical manufactured devices

### **Previously submitted and not included**