Study Title	A study of the Safety, Efficacy, Longitudinal Costs and Patient Centered Outcomes using a TAAA Debranching Device
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NCT Number	NCT03637374
Document Description	Study Protocol and Statistical Analysis Plan
Document Date	30-Jun-20

JHM IRB - eForm A – Protocol Version 5.0

A study of the Safety, Efficacy, Longitudinal Costs and Patient-Centered Outcomes using a TAAA Debranching Device

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

This study seeks to define longitudinal one year costs of delivery of care for patients who undergo care for complex aortic aneurysm disease. While surgery remains a standard treatment for complex abdominal and thoracoabdominal aneurysms (TAAA), the tolerance of the older patient to recover such extensive and brutally invasive open aortic reconstructions is poor. Endovascular may offer the opportunity to reduce patient risk with less invasive approaches, improve quality of life, and serve to reduce the cost burden to payors which encumbers such difficult surgeries. In this study, we will compare the one year costs of inpatient and outpatient care associated with complex aortic repairs, comparing both the open surgical and endovascular approach with a TAAA debranching technology to solve this difficult clinical scenario, in our hospital wherein we have established expertise in management of patients with aortic diseases and it protean manifestations.

The results of this study will serve to identify safety endpoints of endovascular technology of a TAAA debranching system, provide transparent data concerning both inpatient and outpatient costs of open and endovascular surgery in the older patient group, and patient perceptions about their care and its impact on their quality of life. Commensurate with goals of the Affordable Care Act provisions to examine clinical effectiveness and cost containment, this study may form the basis for refinement of technology used in aortic care which can motivate episode-based payment methods and further develop proper risk adjustment assessments for open and endovascular surgery considerations in the future.

2. Objectives (include all primary and secondary objectives)

Primary

The primary safety endpoint is freedom from major adverse events (MAE) at 30 days or during hospitalization if this exceeds 30 days. Major adverse events include death, bowel ischemia, myocardial infarction, paraplegia, renal failure, respiratory failure, and stroke.

The primary effectiveness endpoint is the proportion of study subjects with treatment success at 1 year. Treatment success is defined as a composite of technical success and freedom from the following:

- Aneurysm enlargement i.e., >5mm as compared to any previous CT measure using orthogonal (i.e, perpendicular to the centerline) measurements
- Aneurysm rupture
- Aneurysm-related mortality
- Conversion to open repair

• Secondary intervention for migration, Type I and III endoleaks, device integrity failure (e.g., fracture), and patency-related events (i.e., device component stenosis or occlusion and embolic events)

The primary non-technical endpoint is improvement in quality-of-life scores (by SF36) and reduced 1 year costs for patients who undergo endovascular repair vs open surgery.**Secondary**

Secondary endpoints include:

- Technical success and the individual components of technical success:
  - Successful delivery
  - Deployment at the intended implantation site
  - Patency of all endovascular graft and stent components
  - Absence of device deformations requiring unplanned placement of an additional device
  - Absence of inadvertent covering of aortic branch vessels
  - Successful withdrawal
- Freedom from the individual components of the primary safety endpoint at 30 days.
  - Death
  - Bowel ischemia
  - Myocardial infarction
  - Paraplegia
  - Renal failure
  - Respiratory failure
  - Stroke
- Freedom from paraparesis at 30 days
- Treatment success and the individual components of treatment success including freedom from the following at each follow-up interval:
  - Aneurysm enlargement
  - Aneurysm-related mortality
  - Aneurysm rupture
  - Conversion to open repair
  - Secondary intervention for:
    - Migration
    - Type I endoleak
    - Type III endoleak
    - Device integrity failure (e.g., fracture)
    - Patency-related events (i.e., device stenosis or occlusion and embolic events)
  - Renal failure
  - All-cause mortality
  - Endoleaks
  - Device integrity failure (e.g., fracture)
  - Patency –related events (i.e., endovascular graft or stent component stenosis or occlusion and embolic events)
  - Other device-related events

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Purpose

The primary objective of the clinical investigation is to assess the use of the Valiant Thoracoabdominal Stent Graft System to repair thoracoabdominal aortic aneurysms in patients having appropriate anatomy, as measured by device safety and preliminary effectiveness, costs of delivery of aortic surgery care, and patient quality of life domains. The study titled: A study of the Safety, Efficacy, Longitudinal Costs and Patient-Centered Outcomes using a TAAA Debranching Device. Within this objective is the primary technical intent of the study is to assess safety acutely (i.e. freedom from major adverse events (MAE) at 30 days) and preliminary effectiveness (i.e., treatment success and technical success) of the device (i.e., the proportion of treatment group subjects that achieve and maintain treatment success at one year). Additionally, the study will assess technical success and treatment success at each follow-up interval.

The primary non-technical endpoint of the study will also measure patient quality of life by validated SF36 surveys at treatment and each follow-up interval and the cost to deliver the care of aortic surgery.

Report of Prior Investigations.

Anatomy

The aorta is the main artery that originates in the left heart chamber, ascends to the arch, and descends through the thoracic cavity and diaphragmatic muscle into the abdomen. The aorta gives a number of side branches throughout its trajectory from the mediastinum to the chest and abdomen. These branches include the coronary arteries, innominate artery, left common carotid artery, left subclavian artery, celiac axis (CA), superior mesenteric artery (SMA), renal arteries and inferior mesenteric artery (IMA) and various lumbar arteries. The aorta terminates at the aortic bifurcation where it divides into the common iliac arteries. Several smaller parietal side branches originate throughout the length of the aorta and include bronchial, intercostal, phrenic and lumbar arteries. A number of anatomical variants and accessory branches have been described. Approximately 15% to 30% of individuals have one or more accessory renal arteries. The hepatic arteries can originate as a separate branch from the aorta, or as replaced branches from the left gastric or SMA in 5% to 15% of individuals[1]. In addition to accessory or replaced anatomy, the diameter, location and angle of the visceral arteries have significant variation, which may have implications with respect to arterial hemodynamics.

Pathophysiology

Aortic aneurysm is a progressive disease characterized by structural deterioration, gradual expansion, and eventual potential for rupture of the aorta if left untreated. The definition of aortic aneurysm is a localized or diffuse dilatation encompassing all three layers of the aorta with diameter >50% larger than the expected normal aortic diameter.

An aneurysm which spans both the thoracic and abdominal cavities defines a thoracoabdominal aortic aneurysm. The expansion rate of thoracoabdominal aneurysms ranges from 2-4mm per year and is not influenced by the size of the aneurysm at the time of diagnosis[2,3]. The expansion rate of thoracoabdominal aneurysms does not appear to increase as individual aneurysms enlarge. The presence of COPD and hypertension are factors associated with an increased rate of enlargement[4,5]. Thoracoabdominal aortic aneurysms become a risk for rupture if they are above 5.5-cm in diameter or if they are less than 5.5-cm in diameter and are growing more rapidly than 0.5-mm in 6 months. The 5-year survival of thoracoabdominal aneurysm patients ranges from 7-20% depending on the percentage of aneurysms secondary to aortic dissection[3,6]. Half of the thoracoabdominal aneurysm deaths are attributed to rupture

and the other half are due to some sort of comorbidity such as myocardial infarction. The overall survival of thoracoabdominal aortic aneurysm patients is often overestimated, because the patients with advanced comorbid medical illness are not included and account for 46-68% of the patients reported in past natural history studies[3,6-9]. Dissecting aneurysms have a higher rate of rupture and have a worse prognosis without intervention.

Most patients with a descending thoracic or thoracoabdominal aneurysm do not have symptoms when first diagnosed[7,10]. They are likely diagnosed with a CT scan for another disease. Some patients have vague chest, back, flank, or abdominal pain. The pain may increase in severity as the aneurysm enlarges, or it may be sudden due to rapid expansion and impending rupture. Symptoms can result from compression of or erosion into adjacent intra-thoracic structures or bony thorax[7,11,12]. Hoarseness from stretching or compression of the left recurrent laryngeal nerve, tracheal deviation, persistent cough, or other respiratory symptoms are sometime seen. Patients with a thoracoabdominal aortic aneurysm may have a palpable pulsatile mass in the upper abdomen.

Emergent/Urgent/Ruptured Aneurysms

A ruptured aneurysm is either an emergent or urgent situation and many times is fatal carrying an overall mortality rate of 90%. Ruptures present in many different ways. One study states that 80% of ruptures present as a retroperitoneal rupture[13]. A retroperitoneal rupture can lead to slow progressive bleeding which forms a large hematoma that is contained by the periaortic tissues. Approximately 4% of ruptured aneurysms are contained ruptures. Surgical treatment is recommended within 24 hours of presentation of a contained rupture. An acute ruptured aneurysm requires immediate intervention and it is said that endovascular techniques may improve the survival for patients with ruptured aneurysms[13].

In a combination of retrospective and prospective IDE data from other sites (G140207), there have been 3/33 subjects treated emergently and 3/33 subjects treated urgently. Of the three treated emergently, there were no intraoperative deaths. All of the emergent subjects had prior open repair that failed and were left with at least one major complication from prior open surgery. One died on day 14, one was discharged and presented with an acute onset of paraplegia and passed away at 30 days, and one survived to 3 months. Recent results have reported the mortality rate of emergent/urgent open repair to be 43% with the average visceral ischemic time of 36 minutes with average blood loss of 2875cc[14]. Another center reported a 36.8% 30-day mortality in patients treated with a hybrid approach[15]. Comparison of this study with prior results of open repair and the fact that there was no ischemic time and an average blood loss of 1250 cc in emergent cases from prospective IDE data, the probable risk of the using the investigational device is no greater than the probable risk of open repair or from the disease.

Three subjects were treated urgently requiring repair within one week of presentation. One subject treated urgently was doing well at his 30 day visit and succumbed to a hemorrhagic stroke at 35 days, one died of leukemia at 14 months, and one is nearing her three year visit and is doing well. Of the subjects treated urgently, none of them died of aneurysm or device related deaths and all but one survived past one year.

Presentation of a subject requiring emergent treatment needs to be treated immediately while urgent treatment needs to be completed within a week of presentation. Due to the many comorbidities of these subjects, an open repair is not recommended for the same reasons as an elective open procedure. Therefore, we feel that treatment with this investigational device is warranted to minimize the risks associated with open repair. This device is an endovascular option that can be used off the shelf and delivered quickly to treat an emergent case while reducing the procedure time and overall blood loss. Due

to the high overall mortality of open repair, the probable risk of the investigational device is no greater than the probable risk from the subject's condition. While these subjects would benefit from the investigational device, these subjects should not be included in the primary study arm as the expanded selection criteria could present confounding results making it challenging to separate the safety and effectiveness of the device from the underlying disease process.

Type B Dissections

A Stanford type B dissection begins distal to the brachiocephalic artery. We plan on treating both type B dissections that are subacute and chronic with aneurysmal changes. Treating dissection subjects involves determining the true and false lumens and which lumen feeds the visceral vessels. The visceral manifold device design does not mimic natural anatomy and has the ability to cross between true and false lumen to treat the dissection, feed the visceral vessels, and accommodate the device even in a small true lumen by utilizing both the true and false lumen as conduits to complete the case. Our device can cross between naturally occurring fenestrations or a laser may be used to create a fenestration between the true and false lumen. The risks of using a laser to create fenestrations include perforating the aorta or branch vessels, extension of the dissection, vascular trauma, embolism, pseudoaneurysm, and bleeding. These risks will be mitigated by utilizing the smallest possible laser and using fluoroscopic guidance to locate and create the area for the fenestration. The risk of potential dissection extension in chronic type B dissections is very low. The risk of potential dissection extension is higher in subacute type B dissections and would be mitigated by controlling blood pressure while deploying, conservative oversizing of the stent graft, and having a cardiothoracic surgeon available if there is a retrograde dissection.

A large number of these patients have been excluded from that study for dissection. 15% (5/33) of subjects were treated electively for TAAA with a dissection (G140207). A laser was used to perforate the aortic wall between the lumens to allow for placement of the graft and limbs when a natural fenestration is not found. All of the procedures were successful and there were no device related events or disease related mortalities. Type II endoleaks were observed in 2 of the 5 subjects, but have not required intervention or lead to aneurysm enlargement. 60% (3/5) of these subjects are doing well at two years post procedure. Of the two that are deceased, one died of a CVA at four months while the other death was self-induced due to alcohol abuse post procedure. Literature cites an in-hospital mortality rate of 29% for open surgical repair of type B dissection. Given the small population treated with the branched endograft to date with no mortalities related to the device or the dissection, we believe the patient population presenting with type B aortic dissection involving the visceral segment could benefit from the use of this device over currently available options. These subjects should be included in the expanded selection arm rather than the primary study arm due to presentation with a concomitant disease process that falls outside the study's intended use.

Aneurysm with Renal Insufficiency

Subjects with known renal insufficiency and renal failure are excluded from the primary study arm due to underlying renal insufficiency that increases their risk of peri-operative renal failure confounding the differences between the efficacy of the device and the underlying disease process. This device would still be beneficial for this subject population because it allows for continued perfusion of the renal arteries and may in some instances treat underlying causes for renal insufficiency.

A 2004 report that evaluated the outcomes of aneurysm repair in patients with established renal failure reported that subjects presenting with chronic renal impairment have a high incidence of concurrent cardiovascular morbidity and are at high risk for aneurysm disease. They also reported that aneurysm subjects with renal dysfunction that were non-operative had a 20% 5-year survival rate, with 39% of subjects dying from rupture of their aneurysm. One study cited a 25% mortality in subjects on

hemodialysis and 67% of subjects with renal insufficiency (creatinine >4 mg/dl) requiring post-operative dialysis[16]. Several precautions are put into place to protect renal function during the procedure including hydration, a minimal volume of nonionic contrast agent, and continual monitoring of post procedure creatinine levels. Subjects undergoing dialysis at the time of procedure will be dialyzed before and after the procedure to protect any remaining renal function. One research study indicates that elevated creatinine levels don't indicate post-op renal failure and that the creatinine level may not be a contraindication for EVAR treatment if proper precautions are used[17].

Aneurysms with Small Branch Vessels <5 mm

Small branch vessels less than 5 mm are excluded from the primary study arm due to an increased risk of increased intimal hyperplasia, branch occlusion, and potential end organ failure. These same principles are true even in open bypass surgery. These subjects would still benefit from the use of this device due to the gradual sweeping endobypasses that deliver more developed flows to reduce the risk of branch vessel occlusion. Additionally, it is extremely rare to see a SMA with a diameter less than 5 mm therefore reducing the risk of fatal branch occlusion. These subjects will still benefit from exclusion of the aneurysm and reduced risk of aortic rupture. Due to the significant mortality associated with rupture or open repair, this patient population is willing to assume a higher risk of renal insufficiency or renal failure.

When treating subjects with impaired renal function, there is an increased probability of subjects having renal arteries < 5 mm or underlying significant stenosis. While this is our current requirement, there have been eight subjects treated with a renal artery less than 5 mm at other sites and one subject with a celiac artery measuring less than 5 mm. These subjects had no adverse events related to the treatment of a smaller vessel. As we open the criteria to increased comorbidities, there will be more subjects presenting will smaller vessels. Current technologies, including T-branch and fenestrated stent grafts, treat vessels with diameters ranging from 4-8 mm.

Aneurysms with Prior Repair

The need for a redo procedures in TAAA repair is common and is primarily due to extension of the aneurysmal disease[18]. Other causes for a late redo procedure include including para-anastomic aneurysms, pseudo-aneurysms, stent graft migration, type I endoleaks, graft infection, or fistulas[19]. Natural history studies and literature reviews cite an incidence rate of 25-60% for patients developing further aneurysmal changes after aortic repair. One center reported the rate of redo operations on TAAA repair to be 14%[18].

Aneurysms with Obstructive Stenting

Patients suffering from thoracic and abdominal aortic aneurysms can benefit from the proven safety and efficacy of open surgical and endovascular stent grafting. However, the repair does not halt disease progression and may lead to future aneurysmal formation in adjacent segments of the aorta. The continued expansion necessitates revision to mitigate the risk of pending rupture. The incidence of revision following aneurysm repair is between 2.4-5.2%[20] in abdominal aortic aneurysms and 14% in thoracoabdominal aortic aneurysms (TAAA)[18].

Treatment Options

Medical Management

Medical management of both fusiform thoracoabdominal aneurysms and type B aortic dissections includes normalizing blood pressure to prevent further dilation or dissection. Close monitoring should be performed. Operation should be limited to patients whose aneurysms are at least 5.5-cm in diameter, whose symptoms persist, whose aneurysms enlarge and are at least 4.5-cm in diameter, or who develop evidence of bleeding. But if any of those conditions are observed (persistent symptoms, aneurysm enlargement, and evidence of bleeding), the patient should be offered repair. For dissections operation is suggested for symptomatic patients and those with complications including malperfusion syndrome or active hemorrhage. For prior repair, if there are persistent endoleaks, loss of seal, or device integrity issues of previously placed graft material repair should be offered.

Open Surgical Repair

Open repair of thoracoabdominal aneurysms, especially in patients with preexisting comorbidities, is fraught with complications. A meta-analysis of 7,833 open repairs of thoracoabdominal aneurysm repairs from 2000 to 2010 found a 30 day mortality rate of 7%, in-hospital mortality of 10%, spinal cord ischemia rates of 7.5%, renal failure rates of 19%, and pulmonary dysfunction rates of 36%[21]. Predictors of adverse events after elective open repair based on pre-existing comorbidities have been established. Advanced age (>70 years)[22-25], respiratory disease[24], renal insufficiency[26], coronary artery disease[22,25], symptomatic aneurysms, extent 1 and 2 aneurysms[27-30], and diabetes[31] are reported to be a predictor of 30-day mortality. Cardiac function[32], extent 1 and 2 aneurysms[28,33-35], symptomatic cases[35], and diabetes[31] are reported to be predictors of paraplegia. The outcomes reported above are in a low- to moderate- risk patient population. It is a logical extension to assume the outcomes in moderate- to high- risk patients would be worse.

Open Surgical Repair of Ruptured, Urgent, and Emergent TAAAs

Open repair of any thoracoabdominal aneurysms, especially in patients with preexisting comorbidities, is fraught with complications. A recent review of emergent patients with a ruptured TAAA looked at the overall mortality of 51 emergently treated patients with TAAA between 1994 and 2014. The study evaluated Crawford Type I, II, III, and IV presenting hemodynamically unstable (94%) and hemodynamically stable (3%). In this study 54.9% (28/51) had true aneurysms and 45% (23/51) had dissecting aneurysms. These were further broken into 94% (48/51) that presented emergently requiring treatment in 2-6 hours and 6% (3/51) that presented urgently and required treatment within 24 hours. The overall mortality in this study was 43% (23/51); 15% (8/51) of these occurring during the procedure and 27% (14/51) occurred post-operatively. Of the 84% (43/51) that survived the initial procedure, 16% (6/42) developed paraplegia/paraparesis, 18.6% (8/43) had acute renal failure, 35% (15/43) had pulmonary insufficiency, and 18.6% (8/43) with post-operative bleeding. The average visceral ischemic time was 36 minutes and the average blood loss was 2875cc[14].

Open Surgical Repair of Chronic Type B Dissections

Open repair of chronic type B dissections is known to have a higher mortality and morbidity rate. A 2014 review of open and endovascular outcomes for patients with chronic type B dissections cited an operative mortality of 6%, stroke rate of 16%, and paraplegia of 9%. The one year major morbidity or mortality in these open repair patients was 25%[36]. Another large study evaluating open repair results in 1542 subjects reported a 30-day mortality of 17.8% [37]. One advantage of open repair compared to endovascular repair of type B dissections is a lower re-intervention rate[36].

Open Surgical Repair of TAAAs with prior repair

Open repair of any thoracoabdominal aneurysm, especially in patients with preexisting repair, is fraught with complications. The outcomes of redo open repair are typically worse compared to the index procedure. If the open repair requires a redo left side thoracotomy this is associated with an increased risk of post-operative respiratory failure, longer operation time, and reduced long-term survival. Additionally, if retroperitoneal redissection is required it increases the risk of major bleeding and damage to abdominal organs. In a literature review of open repair of visceral aortic patch aneurysms with reinclusion technique on the redo open procedure, centers reporting more than one case had a mortality rate ranging from 20-40% and a renal failure rate ranging from 0-50%[19]. Another site evaluating 266 redo open TAAA repair procedures cited a 30-day mortality rate of 23%, post-operative coagulopathy 23%, stroke 6%, respiratory failure 44%, and renal failure 37%. The 5 year mortality was also determined to be 58.1% in redo patients, which is significantly higher than non-redo TAAA patients[18].

Open Surgical Repair of TAAAs with prior repair and obstructive stenting

While revision with open surgical techniques can be an option in certain cases, the outcomes are poor in most patients given the advanced nature of their disease and associated comorbidities. [38,39] Given the extensiveness of these secondary repairs, most patients are either deemed not a surgical candidate or their repair is postponed longer than recommended by the Society of Vascular Surgeons. Others have demonstrated the use of fenestrated and branched stent grafts to revise previous open and endovascular surgery. [40]

Endovascular Repair

Parallel Grafts

Parallel grafts (often referred to as snorkels, chimneys, periscopes, or CHIMPs) are combinations of aortic and branch stent grafts deployed simultaneously. They are typically all straight-tube grafts where the open end is either on the proximal or distal extent (and sometimes both) of the aortic component. The combination of straight tube stent grafts allows for the physician to treat emergent patients beings the assembly does not need to be custom made. There are some criticisms though about the lack of circumferential seal and fixation though with parallel grafts. This lack of circumferential seal and fixation may leave the patient vulnerable to endoleak.

There have been case reports which describe two parallel stent graft techniques used to repair thoracoabdominal aneurysms. The first 'terrace technique' has two chimney stents in contact with a more proximal thoracic graft and two chimney stents in contact with a more distal thoracic graft[41]. The second has two chimney stents going to the celiac and superior mesenteric arteries. Then there are two snorkel stents pulling retrograde flow and going to the renal arteries[42-44].

Snorkel and chimney grafts can be implanted with good technical success rates if care is taken, but long term renal function is in question. Seal and fixation are also in question, so the parallel graft techniques should be avoided in elective settings and reserved for emergent settings[45]. A recent review found that 10.7% of patients in the literature treated for thoracoabdominal aneurysm with parallel grafts experienced type 1 endoleak. The investigator thought the approach would be useful for a recovery maneuver or for emergent cases where fenestrated grafts are not readily available, but long term durability and proximal fixation remain in question[46].

Sandwich Techniques

Two sandwich techniques have been proposed in order to care for patients with an off-the-shelf approach. The first used dual bifurcated infrarenal grafts in the descending thoracic aorta[47]. The second used 3-4 bridging stents sandwiched with a thoracic graft in the descending thoracic aorta[48]. While these sandwich techniques can be used off-the-shelf, they do not provide for circumferential seal and fixation, and long term durability is in question.

Fenestrated Stent Grafts

While combinations of branched and fenestrated endografts can be specified and ordered from manufacturers to be customized for the patient in Europe, there are few studies of purely fenestrated endografts used in the repair of thoracoabdominal aneurysms. A study showed the technique by which endografts can be modified in order to treat urgent cases of thoracoabdominal aneurysms[49]. These authors recently published a case where this technique was used to repair a thoracoabdominal aneurysm in a 74 year old male patient with very asymmetric visceral and renal vessels. The repair was done by sewing Gore Viabahns to the fenestrations as 'mini cuffs' which helped to increase the amount of seal obtained. The patient had been followed for two months[50]. Also a retrospective study in 2011 which reviewed the cases done in Paris, France and Cleveland, Ohio for type 4 thoracoabdominal aneurysms with custom manufactured fenestrated grafts was reported. All patients were considered high risk for open repair. Over a six year period, 231 patients were treated. Thirty day mortality was 2.6% and 2 year survival was 83%. Freedom from secondary intervention was 93% at 30 days and 73% at 2 years[51].

Cook t-Branch Stent Grafts

Branched stent grafts have been used for juxtarenal and pararenal aneurysms. Modified branched stent grafts have only been reported to be used with thoracoabdominal aneurysms to date[50,52]. There are no large scale studies of unibody axially-oriented multi-branched grafts for pararenal aneurysms as they are more frequently used for thoracoabdominal aneurysms.

Branches have been attached to the aortic component to provide for bridging stent overlap, increased overlap encouraged seal and fixation. It also allowed for the use of self-expanding stent grafts which help accommodate tortuosity. Several variations of branch orientation exist including axial, helical, antegrade, and retrograde. Axial branches were deployed proximal to the target vessels. The branches were cannulated from an arm approach, and mating stents were deployed. Bard Fluencies were commonly used and the length of overlap was typically 10-mm. These were sometimes lined with balloon-expandable stents to prevent component separation. Alignment between the axial branch stent and target vessel was noted as a problem if it caused angulation in the bridging stent, potentially leading to bridge stent kink. To increase durability, self-expandable bare metal stents such as Boston Scientific Wallstents were occasionally used. The helical branches exit the aortic component posteriorly and wrap around the main body. The distal end landed 10-mm from the ostium of the target vessel. The longer overlap and gentle sweeping centerline made lining the stents less critical. The branch stent curved to become in-line with the target vessel. The drawback was that the helical stents make for a bulky construct requiring a large diameter delivery system.

Flow Diverting Devices

Flow diverting stents are used in limited applications for repairing thoracoabdominal aortic aneurysms in Europe. They provide for more simplified implant in that the branch vessels do not need to be stented. Instead the three layer micro-woven nitinol mesh significantly slows and alters the flow of blood into the aneurysm sac encouraging thrombus formation. All the while, flow channels are developing to the branch vessels[53-55]. The IFU must be followed very closely so that the stents do not overlap graft cloth, that

20-25% oversizing is followed, and so that larger stents are always deployed within smaller stents. If these instructions are not followed, devastating ruptures may follow[56-58]. Data is limited and largely retrospective in nature[59]. The one registry reported had 380 patients but showed a technical success rate of 0% when the IFU was not adhered to (n=38/38)[60].

Endovascular Repair of Ruptured, Urgent, and Emergent TAAAs

There are no reports we found describing branched grafts being used for TAAA repair in a ruptured or emergent setting. This is likely due to either manufacturer control of the use of the devices or control of the publication of information. However there are several studies of parallel grafts being used in this setting. A meta-analysis published revealed 15 reports of 93 such patients. 24.7% were operated on in an urgent setting, but the results were not compared to results of patients treated in a non-urgent setting. Because of this we cannot draw any conclusions[46]. A further study examined parallel grafts used in ruptured thoracoabadominal aortic aneurysms and pararenal aneurysms used in 9 patients (6 thoracoabadominal aortic aneurysms, 2 pararenal aortic aneurysms, and 1 short neck infrarenal aneurysm). The study mentions stable renal function in all patients and a very low 30-day mortality rate[44]. Yet another study examined 29 patients treated with the parallel graft technique of these14 patients were ruptures and 15 patients were symptomatic. Nine lesions were in the aortic arch, ten were in the descending aorta, and ten were in the branched visceral segment. Twenty two were treated in the first 24 hours and 7 were treated in the first 3 days. Median follow-up was 2 years. There were four 30 day deaths (1 cerebral infarct, 1 visceral ischemia, 1 multiple organ failure, and 1 heart failure). The authors remarked that this technique is promising with low rates of early mortality when considering that the patients were emergent[61]. Three additional cases were reported but the cases focused mainly on technical feasibility and endoleaks, as a means of demonstrating the technique with little focus on the clinical sequelae that may develop during urgent repair of thoracoabadominal aortic aneurysms with endovascular techniques[62-64]. From this limited data set coupled with our current understanding of the outcomes of patients treated with open repair in the urgent setting, it appears that the benefit of endovascular repair may outweigh the risks.

Endovascular Repair of Chronic Type B Dissections

Incidence rates of aortic dissection is estimated to be roughly 3 per 100,000 people per year[65,66]. Until recently acute Stanford type B aortic dissections were managed with blood pressure control[67,68]. If endovascular intervention is offered in acute dissections the goal is typically to cover the proximal entry tear in order to block antegrade flow to the false lumen. This starts the process of aortic remodeling by depressurizing the false lumen[69]. If only the thoracic aorta is to be treated, growth of the true lumen and shrinking of the false lumen are generally not associated with distal reperfusion or endoleak – meaning there is a lower rate of reintervention[70]. As endovascular repair is becoming more prevalent, we are learning that chronic dissections tend to have a thicker fixed septum which leaves the aorta less susceptible to remodeling after repair[71]. Therefore, treating acute Type B dissections with blood pressure management may not be the best approach, because if endovascular repair is needed later the process of remodeling may not happen. If the aneurysm and dissection extend distally beyond the diaphragm, the types of fenestrations that are found in extensive Stanford type B dissections leave the patient prone to distal reperfusion of the false lumen even after cover of the proximal entry tear [72,73]. These patients will require some sort of branched or fenestrated repair. If the patient has an aneurysm complicated by type B dissection where visceral branches arise from both true and false lumen the treatment options are even further limited, and bridging stents will have to cross the septum increasing the technical difficulty of completing the case. Small true lumens and visceral arteries arising from either true- or false- lumen and dissection extending to branches have made endovascular repair sometimes near impossible.

Endovascular Repair of TAAAs with prior aortic repair

The risk of increased mortality and complications in redo open TAAA repair suggest that a less invasive approach such as endovascular repair is warranted. Numerous single site articles have been published regarding branched or fenestrated aneurysm repair following a prior aortic repair. The prior repairs documented include endoluminal abdominal aortic aneurysm repair, aorto-bifemoral bypass, and open repair with a tube prosthesis for post-operative complications including Type I endoleak, suprarenal extension of the aneurysm, and anastamotic aneurysms [20]. The most common risks and complications documented in the endovascular repair of a previous intervention include Type III endoleaks at the modular joint and the increased graft on graft friction making graft maneuverability and repositioning difficult. Despite the risks, it was determined that the option of endovascular repair may be advantageous to this group of patients with a history of multiple abdominal operations or with serious cardiopulmonary risk factors as compared with the more invasive open surgical repair[74].

Endovascular Repair of TAAAs with prior repair and obstructive stenting

While revision with open surgical techniques can be an option in certain cases, the outcomes are poor in most patients given the advanced nature of their disease and associated comorbidities. [38,39] Given the extensiveness of these secondary repairs, most patients are either deemed not a surgical candidate or their repair is postponed longer than recommended by the Society of Vascular Surgeons. Others have demonstrated the use of fenestrated and branched stent grafts to revise previous open and endovascular surgery. [40]

Staged Endovascular Repair

Planned Staged Procedures

Staged procedures have been used in endovascular repair of thoracoabdominal aortic aneurysms in an effort to limit the incident and severity of spinal cord ischemia. The hypothesis behind this is the staging of procedures allows for the development of a collateral network. The collaterals would maintain some perfusion and allow other vessels to compensate reducing the overall impact of spinal cord ischemia. One center studying 87 Type II subjects found that staging reduced the overall SCI rates significantly 57.[75]. The SCI rate in single stage procedures was 37.5% (12/32) and 11% (3/27) in two-stage procedures. The rate was slightly higher in unintentionally staged procedures at 14% (4/28). Unintentional staging was defined as prior aortic repair, 21% (6/28) had prior thoracic repair and the remainder were abdominal aortic repair. In the staged procedures, the two-stage repair SCI events were all temporary and resolved by discharge and the unintentional staging had 10% (3/28) that resulted in permanent SCI. This study had a median time between stages of 5 months (range 1-60 months), but the investigators believe 2-3 weeks to be optimum57.optimum[75]. The investigators also noted that symptomatic patients should be monitored and considered for earlier repair. While there is no specific length of aortic coverage to determine the threshold where one should consider staging, this study cites that aortic coverage of 200 cm or greater may indicate the threshold where subjects would benefit from staging.

There are several techniques used for staging endovascular TAAA repair. Techniques include coverage of the proximal thoracic aorta up to the celiac artery in a staged procedure with visceral stenting performed at the completion procedure. Other techniques reference placing the main aortic stents, but allowing perfusion from an open celiac branch, perfusion branches, or unstented contralateral iliac limb58.limb[76]. The use of perfusion branches may be preferred to allow for better hemodynamics and avoid excessive pressurization of the aneurysm sac.

Bail-out Staged Procedures

There is limited information available on use of staging as a bail-out procedures. Several sites and investigators discuss alternative techniques such as chimney and snorkels as alternative techniques to be used in technically challenging cases complicated by anatomy59anatomy[77], but fail to reference the use of staging and outcomes. Literature also cites several intra-operative techniques for bail-out maneuvers in the operating room60room[78], but currently available TAAA technologies do not allow for staging of the aortic components and limited data is available on the outcomes of these cases.

Summary of Alternative Treatments

A few endovascular options are available for treating thoracoabdominal aneurysms. A limited number of centers have access to commercially available branch-fenestrated devices, but they typically require customization. This customization has an associated lead time of several weeks. The endovascular options present a real problem of patients not being able to either travel to the select sites or being emergent and not having the time to wait for a custom graft. In these instances it may appropriate for the patients to be treated either with off-label devices (sandwich approach) or with physician-modified endografts. Sandwich configurations tend to have excellent patency rates but lack circumferential seal and fixation. Branch-fenestrated grafts have good seal and fixation but tend to have high frequency of reintervention and can be limited by patient anatomy. In all instances careful case planning is in order and all aspects of parallel grafts as well as branch-fenestrated grafts should be carefully considered relative to individual patient anatomy.

Summary of Treatments for Staged Procedure or Staged Bail-out Procedure

Due to the proximal seal zone of this device, several options are available to stage patients with either a planned procedure or as a bail-out procedure. Literature supports the hypothesis that a controlled endoleak or perfusion branch can be protective for SCI events by helping create a protective collateral network. When planned visceral artery bridge endoleak can be provided via a low-risk staged procedure that does not put the patient at significant risk from the intervention. The use and experience with staged procedures as a bail-out method is not widely understood, but still allows the patient to maintain perfusion to the visceral vessels and lower extremities while they recover and prepare for completion of the procedure. The bail-out staging method is only intended to be used in extreme circumstances when patient status declines intraoperatively or unforeseen technical challenges are encountered.

Benefits and Risks of Treatment Options

Open Surgical Repair

Contemporary series have shown that open repair of thoracoabdominal aneurysms, is associated with a significant mortality risk and increase in major complications. One report describes 7,833 open TAAA repairs from 2000 to 2010 found a 30 day mortality rate of 7%, in-hospital mortality of 10%, spinal cord ischemia rates of 7.5%, renal failure rates of 19%, and pulmonary dysfunction rates of 36%[21]. The risks of open repair are significantly higher than any other option for repair. Open repairs are durable but have substantial perioperative mortality and postoperative morbidity. Additionally, due to existing comorbidities and the high risk for complications this is not an option for many patients.

Endovascular Techniques

There is limited availability of data reporting the results of endovascular repair of thoracoabdominal aneurysms. Many of these techniques require off-label use or modification of the grafts, which bring into

question the safety and long-term durability. The literature suggests that snorkel and chimney grafts can be performed with decent technical success rates, but seal and fixation and long term durability are in question and have not been formally evaluated[45]. A recent review found that 10.7% of patients in the literature treated for thoracoabdominal aneurysm with parallel grafts experienced type 1 endoleak.

A 2004 to 2006 study of the novel t-branch device (Cook Medical) was studied in high risk subjects. The study showed a technical success of 93%, thirty-day mortality of 5.5%, major perioperative complications 14% including paraplegia 2.7%, new onset dialysis 1.4%, respiratory failure 6.8%, myocardial infarction 5.5%, and stroke 1.4%. All-cause mortality at twelve months was 6 subjects. There was no evidence of stent migration or aneurysm growth over the twelve month period[75].[79].

In a study of type 4 thoracoabdominal aneurysms with custom manufactured fenestrated grafts over a six year period, 231 patients were treated. Thirty day mortality was 2.6% and 2 year survival was 83%. Freedom from secondary intervention was 93% at 30 days and 73% at 2 years[51].

Experience with the t-branch device evaluating 22 patients between 2010 and 2013 reported a technical success of 100%. The re-intervention rate at 6 months was 90%, branch occlusion was 14%, paraplegia was 5%, and paraparesis in 5%. Again, these lack long-term data to address the durability of the stent grafts. In all endovascular options, close surveillance is mandatory for early identification of visceral or branched vessel stenosis or pre-occlusion.

A retrospective study reported by Sanford Health (IDE Application G140207, Clinical Use Summary) reports the only subjects that would not be ideal candidates include subjects with prior suprarenal fixation stents, dissection, present emergently. The retrospective study examines 12 patients which meet the clinical study criteria that were treated between 2012 and 2014. In this patient population, there was one subject with renal failure and one subject with a respiratory event in the first 30 days. There was one unrelated patient death and one CVA in the first year. Additionally, in this study there was one instance of branch vessel occlusion and secondary intervention.

A large number of subjects may benefit from alternative endovascular treatments that may be performed with less risk of complications and shorter recovery time. For these subjects, endovascular repair with a manifold system that is not based on patient anatomy may be the only treatment option.

Proximal Extension

The overlapping or layering of Valiant stent grafts has been a standard practice in clinical care of subjects with thoracic aortic disease. Data reported by Sanford Health (IDE Application G140207/S034, Clinical Use Summary) include 23 patients treated between 2012 and 2017 using a combination of the Valiant stent graft with the Thoracic Bifurcation no evidence of migration. There were three reinterventions (3/23, 13%) including one for a dissection distal to the thoracic graft and two for endoleaks. There has been a follow-up of over 5 years supporting the safety of this device when layered to extend the proximal landing zone of the thoracic bifurcation. The one year survival of a non-emergent TAA is 82% at one year[76]The one year survival of a non-emergent TAA is 82% at one year[80] and 55.8% at 5 years[77].[81]. This proximal extension is done in two layers to mitigate the risks of material fatigue and wear. Either Valiant Captivia or Valiant Navion may be used as a proximal extension.

Staged Procedures

With the Valiant Thoracoabdominal Stent Graft System, the risks of planned staging via the visceral artery bridge endoleak are comparable to the single stage procedure in the current protocol. We do not believe staging presents any new risks that are not currently covered under the risk profile for the VTAAA system, but these risks may happen at a higher frequency. These risks still present no greater risk than the probable risk from the progression of the patient's condition. The increased risks for a planned stage procedure (visceral artery bridge endoleak or delayed distal seal) are risks from an additional procedure including anesthetic and contrast exposure, compounded physiologic insult from multiples procedures, access site complications, wire injury, device integrity issues from component interaction, paraplegia, spinal cord ischemic event, aneurysm enlargement, aneurysm rupture, and death. Increased risks for a bail-out staged procedure include the above risks and increased procedure time or failure to treat.

Stent graft designs

The manifold system has the advantage of being independent of patient anatomy allowing for use off-the-shelf. It can also adapt to numerous anatomical variations including tortuosity and vessel location. The design allows for continuous flow to the visceral and infrarenal segments throughout the procedure. Additionally, the proximal deployment and delayed distal seal allows for more flexibility in stenting the visceral vessels, multiple bail outs, or staging of the procedure throughout device deployment. The importance of proximal deployment and gradual sweeping branch stents has been reported as a critical element for maintaining vessel patency[82].

Analysis of bridging stent characteristics

It has become evident that the use of the appropriate bridging stent including placement and stent is necessary to minimize risk of target vessel occlusion and kinking[82]. The ideal stent has not been determined or standardized, but currently a balloon expandable stent covered is preferred. The use of a covered stent has the advantages of optimal seal, minimizing risk of endoleak, and improved patency rates[83]. The two most widely used stents are the iCAST covered stent (Atrium Medical) and the JoMed stent (Abbott). The iCAST covered stent has been widely used and reported in the literature, and was the most frequently used stent in the recent GLOBALSTAR registry, with only five of 889 visceral arteries lost during follow up[84]. The JoMed stent has been also widely used and it is the balloon expandable covered stent of choice by the Cleveland Clinic group, with recent report of >95% 5-year visceral artery patency among 632 subjects treated by fenestrated endografts[85]. The long-term risks of stent fracture and dislodgment have not been systematically reported but seem to be exceptionally low with adequate selection of proximal landing zone. The Fluency stent (Bard Peripheral Vascular, Tempe, AZ) has been used by one investigator, with excellent patency rates and low risk of kinking or stent fracture[86].

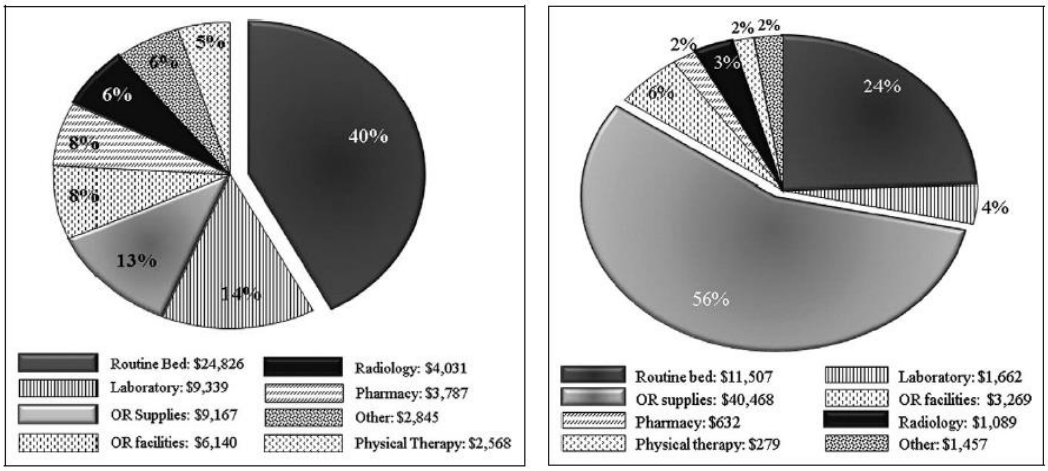
Justification for Specific Patient Selection Criteria Relevant for this Study

Treatment of TAAA aneurysms in all patients that meet entry criteria will be considered for this study. All patients diagnosed with a TAAA repair are considered high risk due to the natural history of a patient with a TAAA. Their options are limited for endovascular repair and due to the comorbidities in this population they are all high risk open repair. Additionally, all patients undergoing open surgical repair of a thoracoabdominal aneurysm are considered to be at high risk for comorbidities and complications. Based on initial clinical experience, we believe that we can treat all patients with outcomes better to those of open surgical repair with less cost over the year. The current approach is an endovascular repair with lower surgical morbidity and mortality rate compared to open repair. Endovascular repair may also decrease the recovery time and length of hospital stay. From the initial clinical evaluation, certain patients may not be a good candidate for this approach have been identified. This patient population includes patients presenting emergently, with compromised renal access, or dissections. The inclusion and exclusion criteria for this study has been refined to present a patient population that we feel may significantly benefit from this

procedure without undue risk. The inclusion criteria listed in section 6 including aneurysm characteristics, access vessel morphology, minimum neck length, diameter of aneurysm, branch vessel size, patency of the four major visceral vessels, and size of distal fixation site are required as inclusion criteria to achieve an adequate seal zone and optimal placement with the stent graft and branches.

The patient population being excluded from this study includes patients with a ruptured aneurysm (or contained rupture), obstructive stenting of the visceral vessels, or a dissection in the treated portion of the aorta. Also patients with thrombus or excessive calcification within the neck of the aneurysm will be excluded as they put the patient at high risk of aneurysmal rupture or embolic event during surgical manipulation. Anatomy that does not allow for primary or assisted patency of the left subclavian artery will be excluded because it is required for access. Additionally, anatomy that would not allow for maintenance of at least one patent hypogastric artery will be excluded in order to prevent organ and/or pelvic ischemia and paraplegia.

In reference to the objective of cost of TAAA delivery, prior studies suggest the one-year costs associated with open TAA repairs are approximately $150,000+/-$10,000. [56]Assuming a power of 80% and alpha=0.05, we would need 20 patients per group to detect a difference of $20,000 between the mean one-year costs of open TAA repair vs TEVAR. Longitudinal costs over a one year period, inclusive of global healthcare costs (readmission, outpatient care, rehabilitation stays) are not available from the literature, but would be analyzed in this study, and thus inform healthcare policy, reimbursement strategies, and hospital administrators.



Cost allocation for Open Thoracic Aortic Surgery (left) versus Thoracic Endovascular Surgery (right). Total cost for open surgery $64,531 vs. 61,909 for endovascular surgery (p=0.4)

There are significant differences in the cost allocations to deliver open surgery versus endovascular TAAA repair, with device charges being central drivers to cost for endovascular TAAA repair and bed charges related to long hospitalization driving cost for open surgery.[57] These costs allocations yield a similar hospitalization cost, yet don't account for substantive differences in post-hospital disposition, wherein further costs may be rapidly accrued by need for subacute or rehabilitation facility more often with open surgery. This study will capture such critical information and inform payor structure.

Rationale for Exposing Target Population to Potential Risks of Staging

The planned staged method via the visceral artery bridge endoleak and delayed distal seal has been used successfully in 6 cases under PS-IDEs G170048 and G170024; 4 patients had their aneurysm successfully excluded (3 via the visceral artery bridge endoleak and 1 via delayed distal seal) in a staged fashion with 2 patients awaiting completion (1 via the visceral artery bridge endoleak and 1 via delayed distal seal). (Dr. Murray Shames, IDE G170024 and Dr. Thomas Maldonado, IDE G170048). There were no intra-operative deaths or SCI events, supporting that the device when used in planned staged procedure can be implanted safely and repeatedly. When compared to literature reported SCI rates for single stage TAAA procedures, this is a viable option for patients at higher risk for SCI events. Given the success we have experienced with patients treated to date and the low risk of the completion procedure, we feel that it is justified to expose the target patient population to the potential risk.

Device Description and Drawings

The Valiant Thoracoabdominal Stent Graft System is made up of two main body components and makes use of several off-the-shelf FDA-approved stent graft components (see Appendix B for system drawing). The two custom main body grafts are the thoracic bifurcation (Figure 1A) and the visceral manifold (Figure 1B). The thoracic bifurcation is deployed in the thoracic aorta and provides the proximal seal for the device. For a Type I or II thoracoabdominal aneurysm the proximal seal is in zone 3, for Type III and V the device seals in zone 4. The two limbs of the thoracic bifurcation allows for continued aortic flow while deploying the visceral segment. The visceral manifold is deployed within the larger 20 mm limb of the thoracic bifurcation to set the stage for the visceral debranching. The branches of the visceral manifold extend to the visceral vessel with the use of covered bridging stents and provide distal seal of the manifold. The smaller 16 mm limb of the thoracic bifurcation extends to the infrarenal segment to either seal in zone 9 for a Type I and V and in zone 10 for Type II and III. All other connections in the device make use of sizes that are modular and independent of patient anatomy.

Figure 1: Valiant Thoracoabdominal Stent Graft System

A

B

Figure 1: Images of the manufactured device A) the thoracic bifurcation main body graft and B) visceral manifold main body graft

Aortic components

The thoracic bifurcation stent graft (Medtronic) seals to the native aorta/healthy tissue/prior surgical graft and bifurcates blood flow in the descending thoracic aorta. The distal end bifurcates into two smaller

legs (20 mm and 16 mm) suitable for modular connection to the visceral manifold stent graft and the visceral bypass stent graft. The thoracic bifurcation is composed of a self-expanding, metallic spring scaffold made from nitinol stents sewn to a polyester fabric graft with nonresorbable sutures and is manufactured in the following sizes:

Proximal Diameter (mm)	Target Vessel Diameter Range (mm)	Visceral Perfusion Manifold Diameter (mm)	Visceral Bypass Diameter (mm)	Overall Length (mm)	Catheter Size (Fr)
32	26-29	20	16	118	22
36	30-32			120	25
40	33-36				
46	37-42			122	

Table 2. Thoracic bifurcation dimensions

The proximal end of the visceral manifold stent graft (Medtronic) deploys into the 20 mm leg of the thoracic bifurcation and quadfurcates to perfuse the celiac, SMA, right, and left renal arteries via bridging stents. The visceral manifold is composed of a self-expanding, metallic spring scaffold made from nitinol stents sewn to a polyester fabric graft with nonresorbable sutures and is manufactured in the following sizes:

	Proximal	Distal				Catheter Size (Fr)
		Leg 1	Leg 2	Leg 3	Leg 4	
Diameter (mm)	24	8	8	8	8	18
Overall Length (mm)	105					

Table 3. Visceral manifold dimensions

Branch components

The limbs of the visceral manifold are extended to the target branch vessel with 9-mm balloon expandable stents (Atrium, iCast). The Atrium iCasts are a stainless steel stent covered with a PTFE film and these are not modified by the physician. The balloon expandable stents are overlapped to reach the target branch vessel and the distal end is appropriately sized to the branch vessel. The interfaces between the branch components are lined with self-expanding bare metal nitinol stents (Medtronic, Complete SE) to improve resistance to kinking and stent graft separation.

Iliac extension components

The visceral bypass (Medtronic) deploys into the 16 mm limb of the thoracic bifurcation to perfuse the iliac segment. The visceral bypass is composed of a self-expanding, metallic spring scaffold made from nitinol stents sewn to a polyester fabric graft with nonresorbable sutures and is manufactured in the following sizes:

Proximal Diameter (mm)	Distal Diameter (mm)	Covered Length (mm)	Catheter Size (Fr)
16	20	199	16

Table 4. Visceral bypass dimensions

The infrarenal bifurcation (Medtronic) deploys into the visceral bypass to bifurcate aortic flow to the iliac segments. The infrarenal bifurcation is composed of a self-expanding, metallic spring scaffold made from nitinol stents sewn to a polyester fabric graft with nonresorbable sutures and is manufactured in the following sizes:

	Proximal (mm)	Ipsilateral Leg (mm)	Contralateral Leg (mm)	Catheter Size (Fr)
Diameter (mm)	24	13	14	18
Overall Length (mm)	120			

Table 5. Infrarenal bifurcation dimensions

The iliac limbs and extenders (Medtronic, Endurant II) will be utilized from a commercially available Endurant II limb or appropriately sized iliac limb extension stent graft. These will be deployed in the infrarenal bifurcation and will provide distal seal of the stent graft system. The iliac limbs will be available in the commercially manufactured sizes and appropriately oversized for implantation in the infrarenal bifurcation.

Principles of Operation

The Valiant Thoracoabdominal Stent Graft System works to bifurcate aortic flow upstream of the target visceral vessels. This bifurcation has a two-fold benefit. First it allows for aortic flow to be compartmentalized into a visceral segment and an infrarenal segment providing for uninterrupted flow to the visceral vessels as well as the infrarenal segment throughout the procedure. If any of the connections cannot be made or the patient status declines during the procedure, then it can be staged and the connections can be made at a later date. Second, the upstream bifurcation encourages more favorable flow conditions in the bridging stents and target vessels which may prevent target vessel occlusion. This is due to the fact that the bifurcations are upstream providing a sweeping transition into the renal arteries that is smooth providing for relatively laminar flow conditions. The design demonstrates that more central aortic flow is obtained with this design increasing flow rates in the visceral vessels to potentially increase target vessel patency (Figure 2).

The device can be used as an off-the-shelf system, negating the need for lead times associated with custom-built devices. The critical sizing that will need to be done is with the proximal end of the thoracic bifurcation, distal landing zone in the aorta or iliac arteries, and the bridging stents. The proximal end of the thoracic bifurcation can be sized by choosing any of the available sizes of the Medtronic TAAA thoracic bifurcation stent grafts, and the sizes of the bridging stents can be manipulated by choosing any of the commercially available sizes of the Atrium iCast. The Atrium iCasts are added to the system in-vivo and connected with passive fixation which negates the need to size the main body components based on the

target vessel sizes. All other connections in the device make use of sizes that are the same, independent of patient anatomy.

The deployment of this device is also independent of device alignment. Angular alignment of the thoracic bifurcation and the visceral manifold has very little impact on the outcome of the case. Longitudinal alignment is more important, but a safety factor has been built-in by calling for the distal ends of the visceral manifold to be deployed above their target vessels by 1-2 cm. The longitudinal landing should be optimized so that the graft is not landed too low so that the connection with the visceral vessels is challenging to make.

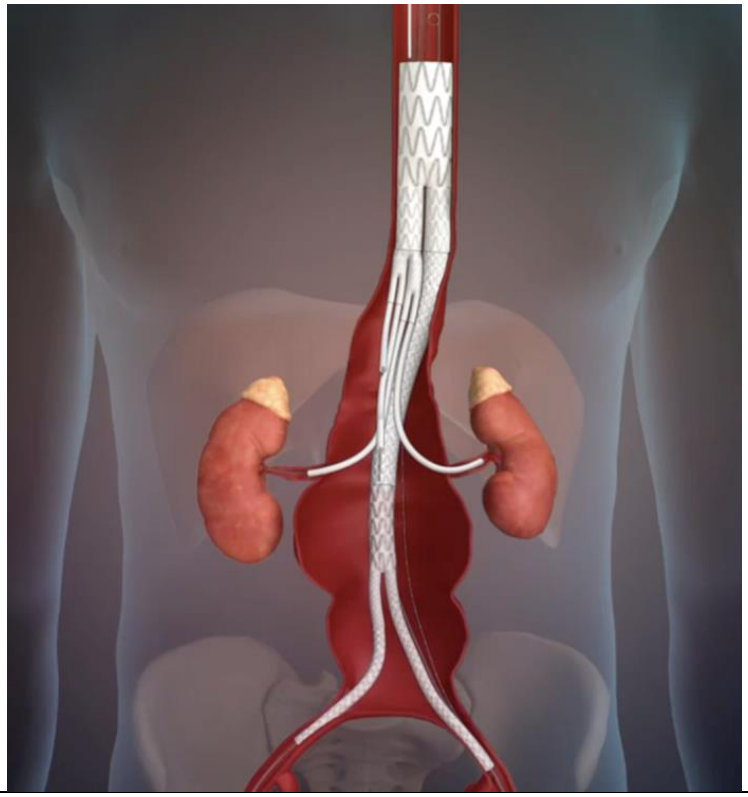


Figure 2: Assembly drawing showing the thoracic bifurcation, the visceral manifold, the branch stents, and the infrarenal grafts, all deployed within an idealized aneurysm sketch.

Intended Use/Indications for Use

The Valiant Thoracoabdominal Stent Graft System is indicated for the endovascular treatment of thoracoabdominal aortic aneurysm (Crawford Type 1, 2, 3 and5) in patients with the following characteristics:

- An aneurysm with a maximum diameter of > 5.5 cm or 2 times the normal diameter just proximal to the aneurysm using orthogonal (i.e., perpendicular to the centerline) measurements
- Aneurysm with a history of growth > 0.5 cm in 6 months
- Saccular aneurysm deemed at significant risk for rupture
- Symptomatic aneurysm greater than or equal to 4.5 cm
- Axillary or brachial and iliac or femoral access vessel morphology that is compatible with vascular access techniques, devices or accessories, with or without use of a surgical conduit
  - Proximal landing zone for the thoracic bifurcation stent graft that has:

  - ≥ 2.5 cm of healthy/nondiseased tissue including both native tissue and previously placed graft, (neck) distal to the left subclavian artery (LSA) with a diameter in the range of 26-42 mm
  - Adequate distance from the celiac artery, in order to accommodate cannulation from the antegrade access point when considering the total deployed length of the thoracic bifurcation and visceral manifold
- Iliac artery or aortic distal fixation site, including both native tissue and previously placed graft, greater than or equal to 15 mm in length and diameter in the range of 8 – 25 mm
- Age: ≥ 18 years old
- Life expectancy: > 1 year

Reference to Regulatory Submissions for Nonclinical Testing Information

This device is currently under clinical investigation in the United States under IDE #G140207. The proposed device is manufactured and tested by Medtronic. Non-clinical data to support the investigational device is listed in the Medtronic Valiant Thoracoabdominal Stent Graft System Master File, MAF-2551.

Summary of Nonclinical Information to Support Study Initiation

All non-clinical testing to support the manufactured device was performed by Medtronic and is reported in the Valiant Thoracoabdominal Stent Graft System Master File, MAF-2551.

Rationale for the Selection of Tests

The rationale for the selection of tests is described in a device evaluation strategy table describing the Valiant Thoracoabdominal Stent Graft System as a whole. This device evaluation strategy table describes the device procedure, performance, and basic safety-related attributes and addresses the potential failure modes and subsequent clinical mitigation strategies for the proposed investigational device. This is attached in Appendices.

Report of Prior Investigations Synopsis

The outcomes from prior clinical evaluation of the study device, including successfully treating 99% (84/85) of the intended target vessels and 96% (27/28) limb patency observed at one year, demonstrate the potential benefits of the device. When contrasted with open repair's significant complication rates and branch fenestrated device's significant anatomic and logistic limitations, the potential risk of the proposed novel graft does not outweigh the potential benefit of widened anatomic availability and improved patency rates. Given the potential benefits, we feel that it is justified to expose the target patient population to the potential risk. The non-clinical testing performed by Medtronic and the clinical results reported by Sanford Health show adequate safety of the device to support a durable comparison of longitudinal cost and patient centered outcomes for patients treated with the Medtronic Valiant Thoracoabdominal Stent Graft System, and provide a valid comparison of open and endovascular surgical outcomes for TAAA patients.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Patient Population
The study will evaluate 16 patients with type I, II, III, and V thoracoabdominal aneurysms meeting protocol inclusion criteria. The patient population includes both male and female patients greater than 18 years old with a life expectancy of at least one year.

Study Type and Duration
This study is a prospective, single-center, non-randomized, multi-arm study to evaluate the therapeutic benefit of the Valiant Thoracoabdominal Stent Graft System. A total of 16 patients (10 in the primary ptudy arm; 6 in the expanded selection criteria arm) will be enrolled in the study for treatment with the Valiant Thoracoabdominal Stent Graft System. The duration of the Investigation is anticipated as follows:

- Time to Complete Enrollment: 24 months
- Subject Follow-up Time: 5 years from last subject enrollment
- Total Duration Time: 7 years

Intended Use
The Valiant Thoracoabdominal Stent Graft System is indicated for the endovascular treatment of thoracoabdominal aortic aneurysm (Crawford Type 1, 2, 3 and 5) in patients with the following characteristics:

- o An aneurysm with a maximum diameter of > 5.5 cm or 2 times the normal diameter just proximal to the aneurysm using orthogonal (i.e., perpendicular to the centerline) measurements
- o Aneurysm with a history of growth > 0.5 cm in 6 months
- o Saccular aneurysm deemed at significant risk for rupture
- o Symptomatic aneurysm greater than or equal to 4.5 cm
- o Axillary or brachial and iliac or femoral access vessel morphology that is compatible with vascular access techniques, devices or accessories, with or without use of a surgical conduit
- o Proximal landing zone for the thoracic bifurcation stent graft that has:
    - ≥ 2.5 cm of healthy/non-diseased tissue including both native tissue and previously placed graft, (neck) distal to the left subclavian artery (LSA) diameter in the range of 26-42 mm
    - Adequate distance from the celiac artery, in order to accommodate cannulation from the antegrade access point when considering the total deployed length of the thoracic bifurcation and visceral manifold
- o o Iliac artery or aortic distal fixation site, including both native tissue and previously placed graft, greater than or equal to 15 mm in length and diameter in the range of 8 – 25 mm
- o Age: ≥ 18 years old
- o Life expectancy: > 1 year

Patient Enrollment and Screening
The investigator will assess potential study subjects with thoracoabdominal aortic aneurysms for their suitability for enrollment into the clinical study. If the patient appears to meet eligibility criteria, either for the primary study arm or the expanded selection arm, then the investigator or clinical study coordinator will discuss the study with the patient and provide patient education materials to adequately inform the patient of potential risks and benefits, required follow-up procedures, and answer any questions. The clinical study coordinator will facilitate the informed

consent process. After the patient has been properly consented, the patient will complete additional screening procedures that need to be completed. If the patient does not sign the informed consent, they will not be enrolled in the study. Information to be collected for screening includes:

- Patient demographics
- Medical history
- Current health status
- Physical examination
- Ankle Brachial Index (ABI)
- Pregnancy test (for female patients of childbearing age)
- CTA or CT with contrast of the chest, abdomen and pelvis if renal function allows. If renal function does not allow CT with contrast, an alternative contrast-enhanced imaging modality or, at a minimum, CT non-contrast in conjunction with Duplex ultrasound will be used at physician discretion to evaluate:
    - Access vessels for compatibility with vascular access techniques
    - Obstructive stenting of the visceral vessels
    - Vessels diameters suitable for use with the Valiant Thoracoabdominal Stent Graft System
    - Aneurysm rupture
    - Dissection
    - Patency of left subclavian artery, hypogastric arteries, lumbar arteries, and all four visceral vessels
    - Thrombus or excessive calcification in the neck of the aneurysm
    - Presence and location of any previously placed graft material
- Complete blood count to evaluate white blood cells, hemoglobin, and platelets
- Basic metabolic panel to evaluate creatinine
- For patients with a history of smoking a pulmonary function test
- Cardiac clearance

Case Planning

From the pre-op CT, the surgeon will make the following measurements to size the endografts.

1. Length of the proximal seal zone, the distance required to land the thoracic bifurcation stent graft, this requires ≥ 2.5 cm section of healthy aorta or previously placed graft material, distal to the left subclavian artery or ≥ 2.5cm of surgical graft.
2. Diameter of the proximal landing zone to define the required diameter of the thoracic bifurcation stent graft. The diameter of the thoracic bifurcation stent graft should be 10-15% larger than the diameter of the aorta to proper oversize the stent graft.
3. Maximum aortic diameter within the treated aorta
4. Distance from the top of the celiac to the top of the most cephalic renal.
5. Distance from the top of the proximal seal zone to the takeoff of the celiac.
6. Distance from the top of the celiac to the SMA.
7. Angulation at the mid-thoracic aorta.
8. Angulation at the diaphragm.
9. Angulation at the renal arteries.
10. Distance from the right renal to the ispilateral internal iliac artery.
11. Distance from lower renals to aortic bifurcation.
12. Diameter of the branch vessels (celiac, SMA, left renal, and right renal) to determine the diameter bridging stents needed and percent patency.
13. Diameter of the right and left common iliac to secure the distal seal of the infrarenal bifurcation.
14. Diameter of the distal aorta to secure the distal seal in aorta

15. Minimum diameter of the access sites (right and left femoral and brachial access site).
16. Length from the access sites to the target treatment zone (right and left femoral and brachial access site).
17. Length between distal edge of LSA and start of aneurysm
18. Length of proximal seal zone
19. Length of aneurysm

Note: If treating a dissection under the expanded selection arm the true and false lumen as well as any naturally occurring fenestrations will be evaluated to determine placement of the device and which lumen feeds the branch vessels.
Note: If treating a patient with previously placed graft material, either proximally or distally, it must be determined if the landing zones will be within the previously placed graft material or if it the landing zones extend beyond the limits of the previously placed graft material.

Pre-operative procedures

The patient will be removed from anti-coagulants prior to surgery. The day of surgery the following labs will be taken:

- Complete blood count to evaluate white blood cells, hemoglobin, and platelets
- Basic metabolic panel to evaluate creatinine
- Prothrombin time (at physician discretion)
- Partial thromboplastin time (at physician discretion)
- Pregnancy test (for female patients of childbearing age)

The patient will be treated with general anesthesia under standard medical practices along with placement of a lumbar drain when possible. The management of anesthesia and the lumbar drain will be performed by the staffed anesthesia team. Standard heparinization practices will be followed and active clotting time will be monitored throughout the procedure. The patient will be prepped in normal sterile fashion from the clavicle to mid-thigh. Additionally contrast will be diluted 50/50 in saline to reduce contrast exposure. Radiation reduction procedures will be followed as allowed.

Thoracic Grafts as a method of staging.

Use of thoracic grafts as a method of staging as a pre-operative adjunct procedure.

a. Thoracic Graft Placement
   i. This refers to implanting stent-grafts into the thoracic aorta prior to enrollment into the IDE clinical study.
   ii. Device Visualization and Preparation

Refer to the Instructions for use provided for the thoracic components to be used.

iii. Device Placement

Ensure that the distal edge of the thoracic graft is 5-7 cm proximal to the celiac artery.

iv. Thoracic Aorta Component Deployment

Follow the study protocol or IFU for deploying the thoracic graft components.

v. Completion

The date of the index procedure will be targeted for within 6 weeks of the thoracic graft placement, but will be based on physician discretion, clinical presentation, and patient compliance.

Implant Procedures

Note: The design of the Valiant Thoracoabdominal Stent Graft System is modular in nature and allows for bailouts and staging of the procedure following the deployment of each device. The procedure can be stopped at the completion of deployment of each component of the system and the patient has the opportunity for alternate endovascular, open repair techniques, or completion of the procedure at a later date if such conditions arise.

A. The implantation of the Valiant Thoracoabdominal Stent Graft System is conducted under fluoroscopic/angiographic guidance. Refer to the Medtronic Valiant Thoracoabdominal Stent Graft System Instructions for Use (IFU) for techniques and methods for device deployment and implantation.
B. The Valiant Thoracoabdominal Stent Graft System may be implanted in a staged procedure per physician discretion (in either a planned or bail-out fashion). The physician may choose to perform the procedure in two or more stages due to the following conditions/scenarios including but not limited to: hypogastric patency, LSA patency, visceral vessel patency, decreased MEP/SEP potentials, at risk dominant segmental arteries, pulmonary status, or any patient whose physiologic limitations places them at risk because of the expected length of surgery. The preferred method for planned staging is to create a controlled endoleak which provides limited and temporary perfusion to the aneurysm sac. These methods include but are not limited to placing a bare metal stent in the celiac artery bridge, placing a bare metal stent in the bridge to an alternate visceral artery (ie:SMA or renal), or not completing distal seal in the aorta or iliac arteries.
    a. Planned Staged Procedure: Visceral artery bridge endoleak
        i. This refers to leaving open a portion of the covered stent bridge between the visceral manifold and target vessel. This is achieved by combining bare metal stents with covered stents to leave ~1-2cm of uncovered conduit along the pathway. This intentional endoleak is resolved in a subsequent intervention where the open portion is covered over by an additional covered stent. It is preferable to achieve this configuration with the bridge to the celiac artery but it can be done in analogous fashion with either the SMA or renal arteries.
        ii. Device Visualization and Preparation
        Refer to the Instructions for use provided for the bare metal stent for visualization and preparation instruction.
        iii. Bridging Stent Deployment
        Follow directions in the IFU when deploying bridging stents. Always deploy a covered stent in the leg of the visceral manifold per the Valiant Thoracoabdominal Stent Graft System IFU (9mm iCast at 8atm inflation pressure). When possible, covered stents should be used in the target vessel. The chain of covered stents should be non-continuous in nature with at least one bare metal balloon expandable stent connecting them. The segment of completely bare stent should be short (~1-2cm) with 2-3cm overlapping with covered stent on either side. Creation of the uncovered segment in as straight a configuration as the anatomy allows will facilitate wire passage during the completion procedure below.
        Note: The controlled endoleak should never be created by leaving a visceral manifold limb unconnected to a visceral vessel or with an uncovered segment >2cm due to the pressurization of the aneurysm sac. If a visceral vessel is occluded, the corresponding visceral manifold limb should be plugged with a vascular plug and an alternative (patent) vessel utilized for the staging procedure. The placement of the non-continuous chain of covered bringing stents and a bare metal stent helps direct flow while creating a controlled endoleak.
        iv. Completion
        Completion of the staged procedure is targeted for 4-6 weeks following the index procedure, but will be based on physician discretion, clinical presentation, and patient compliance.
        Note: The physician may choose to complete the procedure earlier if the patient is symptomatic or has other concerns for aneurysm sac growth or rupture.

Completion procedure may be performed under local or general anesthesia.
Vascular access will be established in the brachial or axillary artery. The staged limb of the visceral manifold will be cannulated and the bare segment will be covered over by at least one iCast.

b. Planned Stage Procedure: Delayed distal seal
    i. This refers to completing the visceral debranching (manifold to target arteries) with covered stents and subsequently leaving out one or more of the distal aortic/iliac components.
    ii. Device Visualization and Preparation
    Refer to the Instructions for use provided for the distal aortic/iliac components to be used.
    iii. Distal Aortic/Iliac Component Deployment
    Follow the study protocol or IFU for deploying the distal aortic/iliac components.
    iv. Completion
    Completion of the staged procedure is targeted for 4-6 weeks following the index procedure, but will be based on physician discretion, clinical presentation, and patient compliance.
    Note: The physician may choose to complete the procedure earlier if the patient is symptomatic or has other concerns for aneurysm sac growth or rupture.
    Completion procedure may be performed under local or general anesthesia.
c. Bail-out Stage Procedure
    i. A bail-out method may be used for staging in the event patient status declines during the case or inability to technically complete the case.
    ii. Device Visualization and Preparation
    Refer to the Instructions for use provided for the components to be used.
    iii. Device Deployment
    Refer to the Valiant Thoracoabdominal Stent Graft System (IFU) for device deployment and implantation of the remaining components.
    iv. Completion due to patient status decline
    Completion of a bail-out staged procedure due to patient status should be completed as soon as clinically feasible following the index procedure, but will be based on physician discretion, clinical presentation, and patient compliance.
    Note: The physician may choose to delay staging if the patient has complications or there are concerns with completing the secondary procedure.
    v. Completion due to inability to technically complete the case
    Completion of a bail-out procedure due to technical challenges have the following options that present no more risk than the alternative of no treatment.
        a. Complete case at another date
        b. Medical management
        c. Convert to open surgical repair
        d. Referral to another facility/investigator that can complete the procedure

Note: If treating a dissected aorta, naturally occurring fenestrations will be utilized first, and if necessary, there may be the additional use of an excimer laser or perforating needle and catheter to perforate the intimal membrane. This perforation will be used to enter either the false or true lumen in order to accommodate placement of the device.

Note: Caution should be taken when relining previously placed graft material to prevent complications from graft on graft friction including decreased graft maneuverability and challenges repositioning.

Note: *For type 1 and 5 aneurysms the distal end of visceral bypass (VB) should be sized to provide the distal seal with the aorta and then proceed to Completion Procedures, listed below. For type 2 and 3, proceed to deployment of the infrarenal bifurcation and Endurant II limb stent graft instructions in the Medtronic Valiant Thoracoabdominal Stent Graft System IFU.*

Note: *For proximal extension of the thoracic bifurcation, two Valiant thoracic grafts, either Valiant Captivia or Valiant Navion, can be used. One to extend the landing zone more proximally and one to layer to prevent wear. Deploy the Valiant Captiva or Navion thoracic grafts according to their respective manufacturer's IFU and continue according to the Medtronic Valiant Thoracoabdominal Stent Graft System IFU.*

Note: *If the VB is too short or too small to provide distal seal, a Valiant Captivia Free-Flo stent graft or Endurant Limb may be used in place or in conjunction with the Visceral Bypass to provide adequate distal seal. For type 2 and 3 proceed to deployment of the infrarenal bifurcation and Endurant II limb stent graft instructions in the Medtronic Valiant Thoracoabdominal Stent Graft System IFU. If a commercially available Endurant limb or Valiant stent graft is used as the Visceral Bypass a commercially available Endurant mainbody stent graft with suprarenal fixation and a Gore cuff is required for adequate fixation. See below for deployment procedures.*

Note: *If treating a subject with an occluded visceral vessel, a vascular plug may be used to occlude the extra limb of the TAAA Visceral Manifold stent graft.*

C. Surgical Decision Pathway and Bailouts

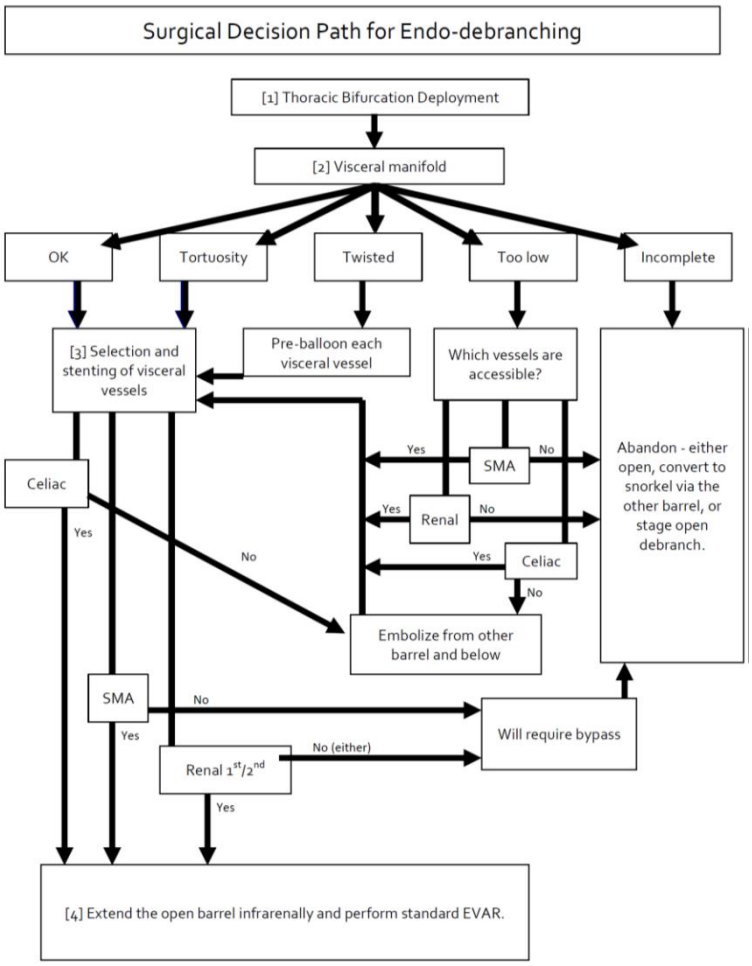


Figure 4: Surgical decision path and possible bailouts

D. Visceral Bypass (VB) Instructions (Endurant Long Limb)

1. Insert a guidewire from the groin through the 16-mm limb of the thoracic bifurcation.
2. Refer to the manufacturer's IFU (Endurant) for visualization and preparation instructions.
3. The proximal radiopaque marker of the VB stent graft should be aligned with the bifurcation of the thoracic bifurcation.
4. Verify there is a 5 cm overlap with the 16 mm leg of the thoracic bifurcation.
5. Deploy the VB according to the manufacturer's IFU (Endurant).
6. Leave the guidewire in place and remove the delivery system according the to manufacturer's IFU (Endurant).

E. Infrarenal Bifurcation (IB) Instructions (Endurant Mainbody)

1. Refer to the manufacturer's IFU (Endurant) for visualization and preparation instructions.
2. Identify the guidewire that passes through the VB stent graft.
3. From the ipsilateral groin access point, insert the delivery system over the guidewire.
4. Slowly advance the bifurcated graft into the VB stent graft.
5. Verify there is a 4-5cm overlap with the VB stent graft.
6. Confirm the distal portion of the contralateral leg is above the aortic bifurcation.
7. Confirm the radiopaque ring marker on the distal end of the contralateral leg is in a position to allow for cannulation from the contralateral iliac artery.
8. Confirm the distal target landing zone relative to anatomical landmarks (i.e. internal iliac artery).
9. Deploy the bifurcated graft according to the manufacturer's IFU (Endurant).
10. Release the tip capture mechanism according to the manufacturer's IFU (Endurant).
11. Remove the delivery system according the to manufacturer's IFU (Endurant).
12. Complete distal seal of the bifurcated graft into the common iliacs according the manufacturer's IFU (Endurant).
13. If the Endurant mainbody with suprarenal fixation is used deploy a Gore Aortic Extender Endoprosthesis according to the manufacturer's IFU (Gore Excluder) over the suprarenal fixation stent of the bifurcated graft (Endurant mainbody) to seal and prevent endoleaks in the event the suprarenal fixation stent were to puncture the graft material.

E. Use of spinal drain.

- The use of a spinal drain is required for all non-staged procedures on subjects being treated for a Crawford Type I, II, III or V thoracoabdominal aneurysm
  - In the case of prior spinal surgery or any reason that would put the patient at higher risk for complications, the use is at the physician's discretion
- The use of a spinal drain on staged procedures is at the physician's discretion

Completion Procedures

1. At the physician's discretion, line the bridging stent grafts with self-expanding bare metal stent(s) to provide additional radial support. Note: In the event a bridging stent or self-expanding stent needs reinforcement a Viabahn stent graft of appropriate sizing may be used.
2. Begin to optimize spinal perfusion.
3. After deployment of all stent grafts, all contact points will be balloon angioplastied.
4. Perform an angiogram to verify stent graft apposition, seals, patency, device defects and any endoleaks. Perform additional procedures, such as ballooning, cuff placement, or use of covered stent grafts as necessary to treat endoleaks or device failures.

5. Remove all sheaths, wires, and remaining accessories and repair of arterial access sites using standard surgical closure techniques.
6. Dopperable signals will be confirmed in bilateral lower extremities and the access upper extremities.
7. Once adequate perfusion is confirmed, heparinization will be reversed.
8. In the event of patient death an autopsy may be performed.

Post-operative Care

Patients may remain intubated and be transferred to the ICU standard post-operative care. Patients with a spinal drain will remain in bed with optimization of spinal perfusion pressure for 48-72 hours whenever possible. Post-operative care will be tailored to the patient taking into account events of surgery as well as pre-operative comorbidities to optimize the patient's recovery. On post-operative day two, attempts will be made to normalize the MAP and clamp the spinal drain if used. Prior to spinal drain removal all coagulopathies and low platelet counts are corrected. The patient's neurological status is closely watched for the next 4-6 hours. If it remains stable, the drain is removed and the patient is monitored for hypoxia, anemia, and hypotension. In the event of patient death an autopsy may be performed. Prior to discharge from the hospital, the following tests will be performed:

- Physical examination
- Complete blood count to evaluate white blood cells, hemoglobin, and platelets
- Basic metabolic panel to evaluate creatinine
- Prothrombin time (at physician's discretion)
- Partial thromboplastin time (at physician's discretion)
- CTA or CT with contrast of the chest, abdomen and pelvis if renal function allows. If renal function does not allow CT with contrast, an alternative contrast-enhanced imaging modality or, at a minimum, CT non-contrast in conjunction with Duplex ultrasound will be used at physician discretion

Follow-up Visits

All patients will undergo follow-up at one month, six months, twelve months and then annually for five years (as depicted below in Table 5: Follow-Up). At each of the follow-up visits the following tests will be performed:

- Physical examination
- SF36 survey testing
- Complete blood count to evaluate white blood cells, hemoglobin, and platelets
- Basic metabolic panel to evaluate creatinine
- CTA or CT with contrast of the chest, abdomen and pelvis if renal function allows. If renal function does not allow CT with contrast, an alternative contrast-enhanced imaging modality or, at a minimum, CT non-contrast in conjunction with Duplex ultrasound will be used at physician discretion
- Pregnancy test (for female patients of child bearing age)
- Device x-ray may be used if potential device integrity issues are identified but unable to be confirmed by CT. This will be done per local standard of care with A/P, Lateral and Bilateral Oblique Images obtained.

b.

Study duration and number of study visits required of research participants.

Patients included in the study will undergo follow-up at one month, six months, twelve months and then annually for five years. In the event of patient death, an autopsy may be performed.

Table 5. Follow-up Table

						Month						
	Pre-op	**Intra-op Index**	**Pre-discharge**	**Intra-op Completion (if staged)**	**Pre-discharge (if staged)**	**1**	**6**	**12**	**24**	**36**	**48**	**60**
CTA/CT with contrast of Chest, Abdomen, and Pelvis	X[2,3]		X[2, 8]		X[2, 8]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Angiography	X[3]	X										
Blood Tests	X[4]	X[5, 6]	X[4, 8]	X[4]	X[4, 8]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
Clinical Exam (including ABI)	X[7]		X[8]		X[8]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]
Branch Patency (duplex ultrasound)						X	X	X	X	X	X	X

1 Device X-ray may be requested to provide more focused imaging if potential device integrity issues are identified, but are unable to be confirmed, using CT.
2 If renal function does not allow for CTA or CT with contrast, an alternative contrast-enhanced imaging modality or, at a minimum, non-contrast CT in conjunction with duplex ultrasound may be used at physicians discretion.
3 Pre-procedure angiography may be requested at discretion of film reviewer.
4 Blood tests include CBC for hemoglobin and BMP for creatinine.
5 Blood test for ACT.
6 Other intra-op labs for anesthesia.
7 Urine pregnancy test (for female patients of childbearing age).
8 CT, Duplex, ABI and labs are optional at the pre-discharge and one month visits between staging procedures.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

N/A

d. Justification of why participants will not receive routine care or will have current therapy stopped.

N/A

e. Justification for inclusion of a placebo or non-treatment group.

N/A

f. Definition of treatment failure or participant removal criteria.

N/A

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

N/A

5.

5. Inclusion/Exclusion Criteria

Modified Inclusion Criteria

A patient may be entered into the study if the patient has at least one of the following:

- An aneurysm with a maximum diameter of ≥ 5.5 cm or 2 times the normal diameter just proximal to the aneurysm using orthogonal (i.e., perpendicular to the centerline) measurements
- Aneurysm with a history of growth ≥ 0.5 cm in 6 months
- Saccular aneurysm deemed at significant risk for rupture
- Symptomatic aneurysm greater than or equal to 4.5 cm
- Axillary or brachial and iliac or femoral access vessel morphology that is compatible with vascular access techniques, devices or accessories, with or without use of a surgical conduit
- Proximal landing zone for the thoracic bifurcation stent graft that has:
    - ≥ 2.5 cm of healthy/nondiseased tissue (including previously placed graft material) (neck) distal to the left subclavian artery (LSA) and a diameter in the range of 26-42 mm
    - Adequate distance from the celiac artery, in order to accommodate cannulation from the antegrade access point when considering the total deployed length of the thoracic bifurcation and visceral manifold
- Minimum branch vessel diameter greater than 5 mm
- Iliac artery distal fixation site, including both native tissue and previously placed graft, greater than or equal to 15 mm in length and diameter in the range of 8 – 25 mm
- Age: ≥ 18 years old
- Life expectancy: > 1 year

Exclusion Criteria

General exclusion

- Patient is a good candidate for and elects open surgical repair
- Can be treated in accordance with the instructions for use with a legally marketed endovascular prosthesis
- Is eligible for enrollment in a manufacturer-sponsored IDE at the investigational site
- Unwilling to comply with the follow-up schedule
- Inability or refusal to give informed consent by patient or legal representative
- Patient is pregnant or breastfeeding
- Patient has a contained rupture
- Patient has a ruptured aneurysm
- Patient has a dissection in the portion of the aorta intended to be treated
- Obstructive stenting of any or all of the visceral vessels
- Poor performance status including two major system failures (including but not limited to cardiovascular, pulmonary, renal, hepatobiliary, and neuromuscular)
- Prior aneurysm repair that would involve relining of the previously placed graft material requiring placement of the investigational system in a landing zone that expands beyond any limits of the previously placed graft material

Medical exclusion criteria

- Known sensitivities or allergies to the materials of construction of the devices, including nitinol (Nickel: Titanium), polyester, platinum-iridium, polytetrafluoroethylene (PTFE), platinum, gold, polyethylene, or stainless steel.
- Known hypersensitivity or contraindication to anticoagulation or contrast media that cannot be adequately medically managed
- Uncorrectable coagulopathy

- Body habitus that would inhibit x-ray visualization of the aorta or exceeds the safe capacity of the equipment
- Patient has had a major surgical or interventional procedure unrelated to the treatment of the aneurysm planned < 30 days of the endovascular repair
- Unstable angina (defined as angina with a progressive increase in symptoms, new onset at rest or nocturnal angina)
- Systemic or local infection that may increase the risk of endovascular graft infection
- Baseline creatinine greater than or equal to 2.0 mg/dL
- History of connective tissue disorders (e.g., Marfan Syndrome, Ehler's Danlos Syndrome)

Anatomical exclusion criteria

- Thrombus or excessive calcification within the neck of the aneurysm
- Anatomy that would not allow maintenance of at least one patent hypogastric artery
- Anatomy that would not allow primary or assisted patency of the left subclavian artery

Expanded Selection criteria

Subjects who fail to meet inclusion criteria for the primary study arm may be enrolled under an expanded selection arm. The study team will report at intervals of every five patients treated under the IDE regardless of study arm. The interim report will be submitted to the FDA within ten days following the 30-day follow-up of the fifth patient enrolled.

Inclusion Criteria

- Patients that meet the criteria for inclusion in the primary study arm but have one or more of the following criteria which would exclude them from the primary study arm:
  - Minimum branch vessel diameter less than 5 mm
  - Urgent or emergent presentation
  - Patient has a contained rupture
  - Patient has a ruptured aneurysm
  - Patient has a type B dissection (subacute or chronic) in the portion of the aorta intended to be treated
  - Poor performance status including two major system failures (cardiovascular, pulmonary, renal, hepatobiliary, and neuromuscular)
  - Baseline creatinine greater than or equal to 2.0 mg/dL
  - Anatomy that would not allow for maintenance of at least one hypogastric artery
  - Anatomy that would not allow for primary or assisted patency of the left subclavian artery
  - Prior aneurysm repair that would involve relining of the previously placed graft material requiring placement of the investigational system in a landing zone that expands beyond any limits of the previously placed graft material
  - Obstructive stenting involving any or all visceral vessels

Or

- Patients that meet the criteria for inclusion in the primary study arm and:
  - Would not be eligible for the primary study arm per a documented reason other than those outlined above, and

- Per the opinion of the Principal Investigator, with concurrence of the IRB, alternative therapies are unsatisfactory and the probable risk of using the investigational device is no greater than the probable risk from the disease or condition.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.
b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.
c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

Potential Study Device Benefits and Risks Based on Leveraged Clinical Information

Patients diagnosed with TAAA have a poor natural history and require surgical intervention to extend life. Several repair techniques have been developed, but each carry risk. As discussed previously, open repairs are durable but have substantial perioperative mortality and postoperative morbidity. Endovascular techniques are plagued by high procedural complexity and poor branch vessel patency, leading to accrual of costs over time. Parallel techniques may have poor seal and may be prone to endoleak. In contrast, the manifold approach has circumferential seal at the proximal end of the system. It has relatively simple case planning and it has virtually no ischemic time. Due to these advantages, we believe the novel proposed technique may overcome some of the current clinical risks with other approaches and may be associated with reduced costs and better quality of life for the recipient.

Patients who participate in this study may benefit from having a less invasive procedure compared to open repair of their thoracoabdominal aortic aneurysm. We expect the amount of discomfort, total blood loss, recovery time, and overall hospital stay to be less than open repair. Many of the patients presenting with a thoracoabdominal aneurysm are not candidates for open repair due to existing comorbidities. With the progressive nature of the disease, these patients have limited options for medical intervention and are willing to assume a higher amount of risk.

Patients who have a planned staged procedure may benefit from reduced SCI events, contrast exposure, fluids, procedure time, and less overall insult to their pulmonary status. We expect the amount of discomfort, total blood loss, recovery time, and overall hospital stay to be similar to an unstaged repair. These subjects would be placed at increased risks related to a second procedure including those identified in the risk analysis. With the progressive nature of the disease, these patients have limited options for medical intervention and may be willing to assume a higher amount of risk.

Patients after treatment with the Valiant Thoracoabdominal Stent Graft System may also have a better quality of life measure on objective QOL instruments. Using the Medical Outcomes Study Short Form 36 Item Survey (SF-36), we will study the physical functioning of the patients, role limitations as a result of physical problems, bodily pain, general health perception, vitality (frequency of feeling full or tired), social functioning, and general mental health. Prior investigations have not been performed to identify these critical patient focused outcomes after endovascular repair of TAAA.

Institution Experience and Infrastructure

Johns Hopkins patients receive the most advanced care and treatment that today's medical research offers through over 350 clinical trials. As part of Johns Hopkins's legacy in clinical research, Johns Hopkins physician scientists lead nationally sponsored cooperative group study programs. Additionally, a growing variety of industry-sponsored and physician-investigator drug and device trials are conducted through the Johns Hopkins Center for Research Excellence in Surgical Trials (CREST). Johns Hopkins Hospital is the primary teaching hospital of Johns Hopkins School of Medicine, University of Baltimore, Maryland.. Johns Hopkins also has an advanced electronic medical record and clinical information system for data management and access. Johns Hopkins Research makes use of an internet-based database platform and clinical research management suite for managing clinical research and specialized medical records. The Vascular Surgery Department at Johns Hopkins has several dedicated resources from CREST. There is a full time sr. clinical research program manager, two full time research coordinators, and a full time sr. research nurse. There is also a biostatistician available and research monitors can be made available on an as-needed basis. Johns Hopkins CREST has performed industry-sponsored IDE trials along with several industry-sponsored post approval studies. Johns Hopkins Hospital is affiliated with six Institutional Review Boards to review human subject protections and has a dedicated conflict of interest committee which reviews and identifies Johns Hopkins Investigator conflicts of interest and develops appropriate conflict of interest management plans.

7. Study Statistics

A. Primary outcome variable.

The primary technical safety endpoint is freedom from major adverse events (MAE) at 30 days or during hospitalization if this exceeds 30 days. Major adverse events include all-cause mortality within 30 days of the procedure, bowel ischemia, myocardial infarction, paraplegia, renal failure, respiratory failure, and stroke.

The primary effectiveness endpoint is the proportion of study subjects with treatment success at 1 year. Treatment success is defined as a composite of technical success and freedom from the following:

- Aneurysm enlargement i.e., $\geq$5mm as compared to any previous CT measure using orthogonal (i.e., perpendicular to the centerline) measurements
- Aneurysm rupture
- Aneurysm-related mortality
- Conversion to open repair
- Secondary intervention for migration, Type I and III endoleaks, device integrity failure (e.g., fracture), and patency-related events (i.e., device component stenosis or occlusion and embolic events)

The primary non-technical endpoint is improvement in quality-of-life scores (by SF36) and reduced 1 year costs for patients who undergo endovascular repair vs open surgery.

B. Secondary outcome variables.

Secondary endpoints include:

- Technical success and the individual components of technical success:

  - Successful delivery
  - Deployment at the intended implantation site
  - Patency of all endovascular graft and stent components
  - Absence of device deformations requiring unplanned placement of an additional device
  - Absence of inadvertent covering of aortic branch vessels
  - Successful withdrawal
- Freedom from the individual components of the primary safety endpoint at 30 days.
  - Death
  - Bowel ischemia
  - Myocardial infarction
  - Paraplegia
  - Renal failure
  - Respiratory failure
  - Stroke
- Freedom from paraparesis at 30 days
- Treatment success and freedom from the following at each follow-up interval:
  - Aneurysm enlargement
  - Aneurysm-related mortality
  - Aneurysm rupture
  - Conversion to open repair
  - Secondary intervention for:
    - Migration
    - Type I endoleak
    - Type III endoleak
    - Device integrity failure (e.g., fracture)
    - Patency-related events (i.e., device stenosis or occlusion and embolic events)
  - Renal failure
  - All-cause mortality
  - Endoleaks
  - Device integrity failure (e.g., fracture)
  - Patency –related events (i.e., endovascular graft or stent component stenosis or occlusion and embolic events)
  - Other device-related events

C. Statistical plan including sample size justification and interim data analysis.

Sample Size Justification

The sample size for the study is limited to 16 patients (10 subjects in the primary study arm and 6 subjects in the expanded selection criteria arm), as this is adequate to provide preliminary clinical safety data and effectiveness of the device and provide the comparator group for open thoracoabdominal surgery patients. The device, while novel, has been evaluated in a clinical setting and has initially demonstrated both safety and effectiveness. The limited sample size allows adequate patient data to be collected under a controlled protocol without exposing a large patient population to the risk associated with a novel device design. The safety and effectiveness data collected in this study will be pooled with other physician sponsored investigational device exemptions (PS-IDEs) evaluating the Visceral Manifold System and should be sufficient to develop an appropriate pivotal study.

In reference to the objective of cost of TAAA delivery, prior studies suggest the one-year costs associated with open TAA repairs are approximately $150,000+/-$10,000. [56]Assuming a power of 80% and alpha=0.05, we would need 20 patients per group to detect a difference of $20,000 between the mean one-year costs of open TAA repair vs TEVAR. Longitudinal costs over a one year period, inclusive of global healthcare costs (readmission, outpatient care, rehabilitation stays) are not available from the literature, but would be analyzed in this study, and thus inform healthcare policy, reimbursement strategies, and hospital administrators.

Data Presentation and Analysis Plan

The primary purpose of this study is to evaluate the safety of this device as there are no or very limited devices and clinical options available for this patient population. The primary safety endpoint of this study is freedom from major adverse events (MAE) at 30 days or during hospitalization if this exceeds 30 days. Major adverse events include death, bowel ischemia, myocardial infarction, paraplegia, renal failure, respiratory failure, and stroke. The primary safety endpoint will be analyzed to determine statistical significance when compared to a target performance goal. A literature review of outcomes of open surgical repair was used to create the performance goal as there is not a comparable endovascular option to use for analysis. The performance goal was selected based on the range of subjects experiencing a major adverse event at 30 days. The range was calculated based on assumptions of the minimum and maximum number of subjects experiencing at least one MAE in the historical open surgical repair group (Table 6). Based on the literature reviewed and the above assumptions the range of subjects experiencing at least one MAE in the open surgical repair group is 30.5% to 77.4%.

The primary effectiveness endpoint is the proportion of the study subjects with treatment success at 1 year. Similarly, the data will be presented as quality outcomes with the number of study subjects with treatment success compared to the overall patient population.

The primary non-technical endpoint is patient quality of life domains at one year by SF36 testing at one year, and other follow-up intervals.

Additionally, data outcomes from this study will be entered into a common vascular database so that data can be pooled with other PS-IDEs. This would provide consistent reporting across the PS-IDEs. Additionally, the PS-IDEs will be evaluating the same device and endpoints to allow for a pool-ability of data across the sites. The data will be separated into two separate study arms: primary study arm and expanded selection arm. The primary cost related outcomes are total, global healthcare costs from time of surgery to one year after treatment with the Valiant Thoracoabdominal Stent Graft System.

Statistical Methods

The primary hypothesis of the Visceral Manifold Study is the number of subjects experiencing a major adverse event through 30 days will be less than a target performance goal (PG) of 50%. The PG was determined by using a conservative target that is approximately the average of the open surgical repair MAE rate calculated above (30.5%-77.4%, Table 6). The anticipated test device 30 day MAE rate was based on the current rate of MAE's (26%, Table 7) observed in 20 subjects meeting inclusion criteria into the primary study as of June 2016.

The sample size for the Visceral Manifold Study was determined using an exact method based on a one-sided 2.5% significance level and an anticipated 26% investigational device 30 day major adverse event rate. Based on these assumptions, a sample size from the pooled PS-IDE data of 46 subjects provides at least 80% power to test the primary hypothesis.

Table 6. Historical Comparison for Primary Safety Endpoint (MAE Rate at 30 days for Open Repair)

Reference	# of Patients	Mortality	Bowel Ischemia	Myocardial Infarction	Paraplegia	Renal Failure	Respiratory Failure	Stroke
Rigberg et al	1010	191 (19%)						
Becquemin et al	1678	90 (5.4%)	51 (3%)	20 (1.2%)	16 (1%)	289 (17.2%)	124 (7.4%)	12 (0.7%)
Murana et al	542	46 (8.5%)			22 (4.2%)			
Ferrer et al	257	16 (6.2%)			53 (20.8%)	31 (12.3%)	31 (12.3%)	
Bensley et al	450	45 (10%)		10 (2.4%)		48 (10.7%)	202 (45.1%)	9 (2.2%)
Nathan et al	83	6 (5.6%)						
Dayama et al	682	68 (10%)		87 (12.9%)		117 (17.2%)	286 (42%)	
Ferrante et al	200	5 (2.5%)		25 (12.8%)		22 (11%)	27 (13.8%)	
Tsilimparis et al	1091	58 (5.4%)		87 (8%)		109 (10%)	229 (21%)	
Piazza et al	7833	1331 (17%)			587 (7.5%)	1488 (19%)	2819 (36%)	
Total	**13826**	**1855/13826**	**51/1678**	**229/4101**	**678/10310**	**2104/12191**	**3718/12191**	**21/2128**
Rate of MAE at 30 Days for Open Surgical Repair		**13.4%**	**3.0%**	**5.6%**	**6.6%**	**17.3%**	**30.5%**	**1.0%**

Table 7. Historical Comparison for Expected Investigational Device 30 Day MAE Rate (Outcomes of subjects treated with the Visceral Manifold System and meeting inclusion into the primary study as of June 2016)

Dataset	Mortality	Bowel Ischemia	Myocardial Infarction	Paraplegia	Renal Failure	Respiratory Failure	Stroke
Subjects meeting VMS PS-IDE I/E criteria	0/20 (0%)	0/20 (0%)	0/20 (0%)	2/20 (9.5%)	1/20 (5%)	3/20 (14%)	0/20 (0%)

Limitations of the Study

Limitations of the study are that it is a single center study with a small patient population.

Risk Analysis

The risk analysis includes a description and analysis of all increased risks to the research subjects and how these risks will be minimized. The risks can be separated into three categories: procedural-related risks, device performance-related risks, and device material-related risks.

D. Early stopping rules.

The Sanford DSMB will be responsible for examining accumulated safety and other relevant data at prespecified points during the course of the study in order to make recommendations concerning continuation, termination, or modification of the study. Based on the results of its deliberations, the DSMB can recommend continuation of the study unchanged, study interruption, study termination, modification of the study, or alteration in the data monitoring plan.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.
b. Steps taken to minimize the risks.
c. Plan for reporting unanticipated problems or study deviations.
d. Legal risks such as the risks that would be associated with breach of confidentiality.
e. Financial risks to the participants.

The risk analysis includes a description and analysis of all increased risks to the research subjects and how these risks will be minimized. The risks can be separated into three categories: procedural-related risks, device performance-related risks, and device material-related risks.

Procedural-related risks

Procedural related risks including general and device specific procedural risks can result in several serious harms to the patient. These risks can be mitigated in a number of ways including strict adherence to the investigational protocol, patient eligibility criteria, procedures performed by trained and qualified physicians, use of standard surgical and endovascular techniques, and regular follow-ups. Although the risk is lowered by following these mitigation strategies the risk cannot be completely eliminated. However, the potential benefit of the Valiant Thoracoabdominal Stent Graft System as compared to other surgical techniques outweighs the potential procedural related risks to the patient.

General procedure related risks:

Contrast toxicity can result in renal insufficiency or renal failure. Increased procedural difficulty may lead to an increase in the volume of contrast required. Adhering to the patient selection criteria should mitigate the risk of contrast induced nephropathy, but it can still occur.

Allergic response to anticoagulation can occur. Patients who undergo the proposed procedure will require anticoagulation. A complete history of the patient before the procedure and adhering to the anticoagulant's product standards will mitigate the risk of hypersensitivity reaction.

Central nervous damage and subsequent paraplegia can occur when a significant amount of the aorta has stent graft coverage and a patient then becomes hemodynamically unstable. Conformance to patient selection criteria and proper spinal cord protection measures will mitigate the risk of spinal cord ischemia and subsequent paraplegia, but they can still occur.

Peripheral nerve damage can occur at the surgical access sites. This procedure has 3 surgical access sites. Utilizing accepted surgical techniques performed by trained physicians will mitigate the risk of peripheral nerve damage, but some nerve damage can still occur.

Paraplegia can occur when a stent graft is deployed in the aorta and blocks the lumbar arteries resulting in spinal cord ischemia. Although the risk can be mitigated by employing proper spinal protection measures (i.e. spinal drain), by screening patients for major lumbars feeding the spinal cord where the graft is intended to go, and for screening patients for occluded internal iliac arteries, paraplegia can still happen.

Injury to access vessel from sheath placement can occur as a result of improper sheath sizing or placement. Adherence to good surgical technique minimizes the risk of damaging sites of sheath placement.

Dissection of a vessel can result from excessive wire manipulations due to an inability to access target vessels. Using proper endovascular technique and coming from a left arm access (provides a more direct path to the aorta) can mitigate this risk, but dissection can still occur.

Embolism due to excessive wire manipulations may result in embolization in the arch or in the descending thoracic aorta resulting in occlusion of a great vessel, visceral branch vessel, or an extremity. Using proper endovascular and surgical techniques as well as accessing through the left arm to provide a straighter path to the aorta lessen the risk, but emboli may still occur.

Branch artery or parenchyma damage of ischemia can occur from blockage or occlusion of a branch vessel. Using fluoroscopic guided placement of devices, careful case planning, careful measuring when modifying devices, verification of alignment when resheathing devices, partial deployment to ensure proper placement, use of appropriate sized branch vessel stents and complaint transition zone between stents and native vessels, and monitoring devices over time will help mitigate this risk, but damage from ischemia can still occur.

Systemic effects including increased risks of morbidity and mortality may be associated with this surgery. Using proper endovascular technique, strict adherence to the investigation protocol, and monitoring of device over time can mitigate this risk, but system effects can still occur.

Local effects at the access site including wound infection, hematomas, and seromas, arterial or venous damage may occur. The risk can be mitigated by using accepted surgical technique by a trained physician, but local effects may still occur.

Device-specific procedure related risks:

Failure to access the aorta can result in vessel damage from wire manipulations and procedural failure. Using proper endovascular technique, coming from a left arm access (provides a more direct path to the aorta), proper patient selection, and careful case planning for sizing can mitigate this risk, but vessel damage and procedural failure may still occur.

Inaccurate deployment of the thoracic bifurcation due to mal-rotation or inaccurate placement may lead to vessel occlusion and end organ or limb ischemia. Although the risk of inaccurate deployment can be mitigated by careful case planning, use of partial deployment and pre-cannulated wires to aid positioning, and use of radiopaque alignment markers, mal-rotation or inaccurate placement may still occur.

Inaccurate deployment of the visceral manifold due to mal-rotation or inaccurate placement may lead to vessel occlusion and end organ or limb ischemia. Although the risk of inaccurate deployment can be mitigated by careful case planning, use of partial deployment and pre-cannulated wires to aid positioning, and use of radiopaque alignment markers, mal-rotation or inaccurate placement may still occur.

Inaccurate deployment of visceral bypass due to mal-rotation or inaccurate placement may lead to vessel occlusion and end organ or limb ischemia. Although the risk of inaccurate deployment can be mitigated by careful case planning, pre-cannulated wires to aid positioning, and use of radiopaque alignment markers, mal-rotation or inaccurate placement may still occur.

Inaccurate deployment of infrarenal bifurcation due to mal-rotation or inaccurate placement may lead to vessel occlusion and end organ or limb ischemia. Although the risk of inaccurate deployment can be mitigated by careful case planning, pre-cannulated wires to aid positioning, and use of radiopaque alignment markers, mal-rotation or inaccurate placement may still occur.

Inaccurate deployment of iliac limbs due to mal-rotation or inaccurate placement may lead to vessel occlusion and end organ or limb ischemia. Although the risk of inaccurate deployment can be mitigated by careful case planning, pre-cannulated wires to aid positioning, and use of radiopaque alignment markers, mal-rotation or inaccurate placement may still occur.

Failure to deploy the thoracic bifurcation may result in increased procedural time, conversion to open, or procedural failure. The risk can be mitigated by having additional components available and having tools prepared to perform open surgical repair if necessary.

Failure to deploy the visceral manifold may result in increased procedural time, conversion to open, or procedural failure. The risk can be mitigated by having components available and having tools prepared to perform open surgical repair if necessary.

Failure to deploy the visceral bypass may result in increased procedural time, conversion to open, or procedural failure. The risk can be mitigated by having additional components available and having tools prepared to perform open surgical repair if necessary.

Failure to deploy the infrarenal bifurcation may result in increased procedural time, conversion to open, or procedural failure. The risk can be mitigated by having additional components available and having tools prepared to perform open surgical repair if necessary.

Failure to deploy the iliac limbs may result in increased procedural time, conversion to open, or procedural failure. The risk can be mitigated by having additional components available and having tools prepared to perform open surgical repair if necessary.

Inaccurate deployment of the iCast covered, balloon expandable branch vessel stent due to mal-rotation or inaccurate placement may lead to vessel occlusion and end organ or limb ischemia. Although the risk of inaccurate deployment can be mitigated by careful case planning, pre-cannulated wires to aid positioning, and use of radiopaque alignment markers, mal-rotation or inaccurate placement may still occur.

Failure to deploy the iCast covered, balloon expandable branch vessel stent may result in increased procedural time, conversion to open, or procedural failure. The risk can be mitigated by having additional components available and having tools prepared to perform open surgical repair if necessary.

Displacement of the thoracic bifurcation due to incomplete apposition of the stent graft, non-compatible or damaged components/accessories, or size mismatch can result in endoleak, aneurysm enlargement, aneurysm rupture, vessel occlusion, end organ or limb ischemia. Although the risk can be mitigated with the use of careful case planning, strict adherence to the investigation procedure, completion angiograms, regular follow-ups, and treatment with cuffs, ballooning, or additional stent grafts, the risk of displacement still exists.

Displacement of the visceral manifold due to incomplete apposition of the stent graft, non-compatible or damaged components/accessories, or size mismatch can result in endoleak, aneurysm enlargement, aneurysm rupture, vessel occlusion, end organ or limb ischemia. Although the risk can be mitigated with the use of careful case planning, strict adherence to the investigation procedure, completion angiograms, regular follow-ups, and treatment with cuffs, ballooning, or additional stent grafts, the risk of displacement still exists.

Displacement of the visceral bypass due to incomplete apposition of the stent graft, non-compatible or damaged components/accessories, or size mismatch can result in endoleak, aneurysm enlargement, aneurysm rupture, vessel occlusion, end organ or limb ischemia. Although the risk can be mitigated with the use of careful case planning, strict adherence to the investigation procedure, completion angiograms, regular follow-ups, and treatment with cuffs, ballooning, or additional stent grafts, the risk of displacement still exists.

Displacement of the infrarenal bifurcation due to incomplete apposition of the stent graft, non-compatible or damaged components/accessories, or size mismatch can result in endoleak, aneurysm enlargement, aneurysm rupture, vessel occlusion, end organ or limb ischemia. Although the risk can be mitigated with the use of careful case planning, strict adherence to the investigation procedure, completion angiograms, regular follow-ups, and treatment with cuffs, ballooning, or additional stent grafts, the risk of displacement still exists.

Displacement of the iliac limbs due to incomplete apposition of the stent graft, non-compatible or damaged components/accessories, or size mismatch can result in endoleak, aneurysm enlargement,

aneurysm rupture, vessel occlusion, end organ or limb ischemia. Although the risk can be mitigated with the use of careful case planning, strict adherence to the investigation procedure, completion angiograms, regular follow-ups, and treatment with cuffs, ballooning, or additional stent grafts, the risk of displacement still exists.

Displacement of the iCast covered, balloon expandable branch vessel stent due to incomplete apposition of the stent graft, non-compatible or damaged components/accessories, or size mismatch can result in endoleak, aneurysm enlargement, aneurysm rupture, vessel occlusion, end organ or limb ischemia. Although the risk can be mitigated with the use of careful case planning, strict adherence to the investigation procedure, use of industry standard seal zone lengths and oversizing, completion angiograms, regular follow-ups, treatment with cuffs, ballooning, or additional stent grafts, the risk of displacement still exists.

Inadvertent internal iliac occlusion and ischemic colitis due to vessel occlusion can occur. The risk can be mitigated with the use of careful case planning, using proper endovascular technique, completion angiograms, and regular follow-ups.

Device-related risks

There are device-related risks of the modular components succumbing to material fatigue resulting in component separation, endoleak, kinking, or migration. These risks can be mitigated several ways including adhering to industry standard seal zone lengths, proper oversizing, lining branch stents with self-expanding stents, regular follow-ups to identify early evidence of migration or separation and allow for appropriate treatment, by the use of completion angiography coupled with cuffs, ballooning, or additional stent grafts if evidence of endoleak.

Migration can occur when a stent graft is deployed with inadequate landing zone, improper oversizing, resulting in vessel occlusion, endoleak, aneurysm enlargement, or aneurysm rupture. Although the risk of migration can be mitigated by using industry accepted overlaps, proper oversizing, accepted suture techniques, and adhering to the follow up schedule, it can still occur.

Component separation can occur when a stent graft is deployed with improper overlap, improper oversizing, or when a suture line fails, resulting in vessel occlusion, endoleak, aneurysm enlargement, or aneurysm rupture. Although the risk of component separation can be mitigated by using industry accepted overlaps, proper oversizing, accepted suture techniques, and adhering to the follow up schedule, it can still occur.

Graft occlusion due to angulation, kink, or mal-alignment modular components can lead to implant thrombosis. Using careful case planning for appropriate sizing, adherence to the investigational protocol, lining with self-expanding stents and regular patient follow-up can mitigate this risk, but graft occlusion can still occur.

Endoleak and endotension due to inadequate seal between graft and components, graft permeability, poor graft seal, improper oversizing, suture line holes, or graft wear can result in aneurysm enlargement, aneurysm rupture, or retrograde flow from branch arteries. Although the risk can be mitigated with completion angiograms, regular follow-ups, and treatment with secondary procedures or devices (cuffs, balloons, and stents), endoleak or endotension can still occur.

Graft infection can result in fever, sepsis, and conversion to open repair. The risk can be mitigated by following the investigational protocol, administering post-operative blood tests to monitor condition, use of antibiotics, and regular follow-up. Even with these mitigation strategies the risk of graft infection still exists.

Branch stent graft kink or crush can result from aneurysm sac remodeling, stent graft migration, or fatigue of implant. Although the risk can be mitigated by lining the bridging stents with self-expanding bare metal stents, kink can still occur. And if it does it may result in vessel occlusion or embolism.

Aortic stent graft kink may result in misalignment of kink of components ultimately resulting in vessel occlusion or embolism. Although the risk can be mitigated by careful case planning, proper subject selection, lining bridging stents with self-expanding stents, adherence to the investigational protocol, and regular subject follow-ups, it can still happen.

Stent breakage due to manufacturer flaw, fatigue, poor placement of stent, or compatibility with other components can result in vessel occlusion, embolism, migration, separation, vascular trauma, and vessel rupture. Although the risks can mitigated with the use of careful case planning for placement and sizing, proper oversizing, use of compatible components, and regular follow-up, stent breakage can still occur.

Branch vessel stent crush due to aneurysm remodel, longitudinal or rotational movement, placement, fixation, or material fatigue and subsequent decreased kink resistance can result in branch vessel occlusion, lumen obstruction, end organ or limb ischemia. These can be mitigated with the use of careful case planning for appropriate sizing, adherence to the investigational protocol, lining bridging stents with self-expanding stents to increase radial resistance, and regular follow-up.

Barb fracture/separation due to placement, fixation, or fatigue can result in migration, separation, vascular trauma, or embolism. This can be mitigated with the use of careful case planning for subject selection and regular follow-up.

Fabric wear due to material fatigue can result in endoleak, component separation, or migration. Using proper placement of devices and regular follow-up, but fabric wear can still occur.

Type III endoleak due to a defect in the graft or inadequate seal between modular graft components can lead to aneurysm enlargement, aneurysm rupture, or retrograde flow from branch arteries. Although the risk can be mitigated with careful construction of the grafts, proper seal between grafts, completion angiograms, regular follow-ups, and treatment with secondary procedures or devices (cuffs, balloons, and stents), endoleaks can still occur.

Biocompatibility risks due to use of materials that are not biocompatible can lead to adverse reactions in subjects. This can be mitigated by only using commercially available materials that have acceptable biocompatibility profiles. Even with these mitigation strategies, adverse reactions can occur.

4.5.2 Mitigation of Risks

Significant care and thought has gone into designing the Valiant Thoracoabdominal Stent Graft System and investigational procedure for proper delivery and deployment of devices to minimize risks to patients to the greatest degree possible. The design of the stent graft is bifurcated to provide flow to uninterrupted blood flow to the visceral and infrarenal segments during the repair process, negating the need for aortic clamping utilized in open repair. Additionally, the design of the stent graft system is modular to allow for bailouts and staging of the procedure throughout device deployment. At any point in the procedure, the patient still has the opportunity for alternative treatments such as open surgical repair or other endovascular techniques.

All efforts will be made to minimize the identified risks including:

- Adherence to eligibility criteria and screening procedures to ensure that appropriate patients are selected and enrolled.

- Adherence to the investigation protocol and clinical methods for case planning, device modification, and implantation will be followed.
- Patients will be carefully monitored throughout the study period.
- The investigator will evaluate the adverse events during the course of the study.

Monitoring Procedures

Study monitoring and auditing will be performed by experienced and appropriately trained personnel appointed by the sponsor/investigator to ensure that the investigation is conducted in accordance with FDA IDE regulations through the Johns Hopkins Office of Human Subjects Research (OHSR). Compliance Monitoring Specialists of the Johns Hopkins OHSR will conduct a monitoring visit for investigators holding an IDE to determine compliance with sponsor requirements in 21 CFR 812 before initiation of research.

On-site monitoring for the study will be conducted and will be a continuous, interactive process to ensure that high-quality data are obtained in compliance with the clinical investigational plan and regulatory requirements. A comprehensive review of case report forms will be performed to check for completeness and accuracy. Accuracy of data reported on CRFs will be verified by comparison to source documents. On-site monitoring will be frequent enough to assure continued acceptability of the data. Monitoring will occur at the following intervals: prior to the start of the clinical trial, at initiation of the study (at first implant and shortly thereafter with more frequent and intensive monitoring at the beginning of the study), at quarterly and/or interim periods and upon completion of the clinical study. The monitor will oversee the progress of the investigation and may be an employee of the sponsor.

Informed Consent

- Review 100% of all informed consents to ensure:
- That the subject signed and dated the informed consent form for him/herself.
- A valid (current IRB-approved version) copy of consent form was used.
- Review documentation of informed consent process.

Protocol

- Confirm that the study staff is conducting the study in compliance with the protocol approved by the IRB.

Source Document Verification

- Review first five subject charts for:
- Trial eligibility. If there are any subjects that did not meet trial eligibility, then five additional charts will be monitored. These additional charts will be chosen randomly.
- Primary and secondary safety and efficacy data- If there are discrepancies/errors discovered with reporting this data, then five additional charts will be monitored. These additional charts will be chosen randomly.
- Any correction made to the source documents is dated, initialed, and explained. The original entry should not be obscured.
- The protocol specific source documents are on file.
- Source documents are completed in ink.

- Note to files are made for missing or incomplete data and to explain any discrepancies or additional comments.

Electronic Case Report Forms and Electronic Data Capture

Ensure the data reported on the eCRF is consistent with the source documents.

- Discrepancies between the source documents and eCRF are explained in a note to file or captured in a comment in the eCRF.
- Study team members will have access to Sanford's electronic data capture system (EDC) and will export de-identified data originating from JHU to this centralized database which is hosted by NAMSA.

  Sanford's central EDC was originally set-up as a data pooling mechanism to fulfil a CMS reimbursement requirement for parallel IDE sites using the same investigational device. Sanford is leading the effort now to aggregate de-identified data from each independent IDE site. Sites can only access their specific data.

  NAMSA: Services provided by NAMSA includes EDC access and data table generation for annual progress reports to the FDA and interim analysis reports for DSMB meetings or any instances where patient safety signals may trigger an interim analysis or pooled data analysis for DSMB review.

  Sanford and Medtronic will have read-only access and will not have the ability to modify/edit eCRFs.

Adverse Events & Serious Adverse Events

- Monitor will review all subject research chart and medical records to ensure the following:
- All AEs and SAEs have been reported including any abnormal physical exam findings determined to be clinically significant.
- They have been reported in a timely manner defined as within ten (10) business days between the time the site staff became aware of the event to the time it has been recorded and entered in eCRF.
- AEs have been reviewed; attribution has been assigned and signed by investigator in a timely manner.
- Ensure any AEs and SAEs have been submitted to the IRB and FDA that meets IRB/FDA reporting criteria.
- All subject deaths have been reported appropriately.

Protocol Deviations

- Ensure all protocol deviations that meet reporting requirements have been reported to the IRB as well as reported in eCRF.

Investigational Product

- Ensure investigational product has been properly handled and stored.

Reporting

All reports to FDA will be identified as SI-IDE Reports:

Deviations from the investigational plan: The sponsor-investigator will notify the reviewing IRB and FDA of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. The notice will be provided as soon as possible but no later than 5 working days after the emergency occurred. If the change or deviation may affect the scientific soundness of the investigational plan or the rights, safety or welfare of the subject, the sponsor will obtain prior IRB approval and also FDA approval for the deviation by submitting an IDE supplement.

Unanticipated adverse device effects: The sponsor-investigator will report the results of an evaluation of an unanticipated adverse device effect to FDA and all reviewing IRBs within 10 working days after the sponsor-investigator first receives notice of the adverse effect.

Withdrawal of IRB approval: The sponsor-investigator will notify FDA of the withdrawal of IRB approval of an investigation (or any part of an investigation) within 5 working days of receipt of the withdrawal of approval.

Progress report or annual reports: The sponsor will provide progress reports to all reviewing IRBs and to the FDA using the suggested format provided at:

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046717.htm#sugforforidefin

To describe the follow-up compliance for the study, the sponsor will include a table in the annual progress report.

Interim Reporting: As requested by the FDA, the sponsor will report at intervals of every five patients treated under the IDE regardless of study arm. The interim report will be submitted within ten days following the 30-day follow-up of the fifth patient enrolled.

Recalls and device dispositions:

The sponsor-investigator will notify FDA and all reviewing IRB's of any request that a sponsor-investigator return, repair, or dispose of any unit of an investigational device. The notice will be made within 30 working days after the request is made and will state why the request was made.

Final report:

The sponsor-investigator will notify FDA and all reviewing IRBs within 30 working days of the completion or termination of the investigation. The sponsor-investigator will also submit a final report to FDA and all reviewing IRBs and participating investigators within 6 months after the completion or termination of the investigation. The suggested format for final IDE reports will be utilized in preparing the final report as described at:

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046717.htm#sugforforidefin

Clinical Trial Database report:
The sponsor-investigator with an applicable study registered with the National Institutes of Health (NIH) National Library of Medicine's (NLM) ClinicalTrials.gov will report results of the study within 12 months of the trial reaching its completion data regardless of outcomes or if the study is terminated early.

Failure to obtain informed consent:
The sponsor-investigator will submit a report of the use of a device without first obtaining informed consent. The report will be made to FDA within 5 working days after receipt of the notice of such use.

Other reports:
The sponsor-investigator will provide accurate, complete, and current information about any aspect of the investigation upon request from the reviewing IRB or FDA.

Data and Safety Monitoring

This study will have oversight by Sanford Data Safety Monitoring Board (DSMB) consisting of independent scientific and bio-statistical expertise, who are not participating as investigators in the study. Sanford is an integrated healthcare system comprised of hospitals, physicians, and other healthcare providers and facilities located in Sioux Falls, SD. The Sanford DSMB will comprise at least 1 physician experienced in treating the study population and an independent biostatistician (including NAMSA statistical support). The Sanford DSMB will work with the PI to monitor and evaluate the safety of subjects and progress of the study. The board will meet after every 5th patient receiving the investigational device and annually during the follow-up period to review subject data. The board will also meet at unscheduled times according to clinical necessity. The data safety reports reviewed at each meeting will contain enrollment data and all documented adverse events experienced by the participants and treatment outcomes. The focus of the analysis is to determine whether enrollment should continue or be closed and whether the trials should continue as originally designed or require modification/amendment.

Definitions

Aortic aneurysm enlargement: ≥5mm as compared to any previous CT measure using orthogonal (i.e., perpendicular to the centerline) measurements

Aortoiliac aneurysm: aneurysm of the abdominal aorta and including one or both of the iliac arteries

Aneurysm-related mortality:

Death occurring within 30 days or during hospitalization following the index procedure, unless there is evidence of accidental or self-inflicted death;

Death occurring within 30 days or during hospitalization following conversion to open repair or a secondary intervention for migration, Type I and III endoleaks, device integrity failure (e.g., fracture), or patency-related events (i.e., device stenosis or occlusion and embolic events), unless there is evidence of accidental or self-inflicted death;

Death occurring within 30 days or during hospitalization for a complication of the aneurysm or a complication associated with the device, such as:

- aortic rupture
- fistula formation (e.g., aorto-enteric)
- embolization
- malperfusion of organ(s) or limb(s)

Arterial fistula formation: formation of an abnormal connection or passageway between an artery and adjacent structures

Conversion to Open, Early: any open repair within 30 days of the index procedure involving the vasculature in the abdomen and/or pelvis.

Conversion to Open, Late: any open surgical repair involving stentgraft removal after 30days post index procedure

Chronic Obstructive Pulmonary Disease (COPD): forced expiratory volume (FEV1) < 1.0 liter or receiving home oxygen

Crawford Type IV TAAA: aneurysmal dilatation originating within 5cm of the celiac artery

Disabling stroke: Modified Rankin Score MRS >2

Distal landing zone: aortic fixation site furthest from the heart

Embolization: dislodging of an upstream particle that travels downstream causing blockage of free flow further downstream. Embolization could result in malperfusion

Embolus: blood clot that forms at one location (presumably from the aneurysmal sac, aortic neck, or adjacent vessels) and is dislodged to another location resulting in ischemic changes

Emergent: an aneurysm requiring immediate treatment

Endoleak:

Type I: leak occurring at the proximal or distal fixation site, including leakage around fenestrations

Type Ia: leak occurring at the proximal fixation zone of the stent-graft

Type Ib: leak occurring at the distal fixation zone of the stent graft

Type Ic: leak occurring at the distal fixation zone of the covered stents in the visceral vessels incorporated by the fenestrations

Type II: leak caused by retrograde flow from patent lumbar or inferior mesenteric arteries

Type IIIa: leak caused by a defect in the graft fabric

Type IIIb: leak caused by inadequate seal between modular graft components

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

Type V: aneurysm enlargement without visualized leak

Endoleak, Early: any endoleak observed within 30 days after device deployment

Endoleak, Late: any endoleak observed later than 30 days after deployment that was not documented during the first 30 days after deployment

Estimated Glomerular Filtration Rate (eGFR): estimated GFR (mL/min/1.73 m2) = 175 x (Serum creatinine)-1.154 x (Age)-0.203x (0.743 if female) x (1.210 if African-American)

Graft Relining: placement of the investigational system that results in landing zones that extend beyond

the limits of the previously placed graft material

Limb occlusion: the presence of thrombus within any graft limb that creates occlusion

Major adverse events: all-cause mortality, bowel ischemia (requiring medical or surgical management), myocardial infarction, paraplegia, renal failure, respiratory failure, and stroke

- **All-Cause Mortality:** any death occurring within the first 30 days post procedure
- **Bowel Ischemia:** Bowel ischemia due to limb or arterial occlusion, graft placement, or embolization.
- **Myocardial infarction**: raised levels of cardiac biomarkers or ECG changes
- **Paraplegia:** spinal cord ischemic event resulting in complete loss of motor function with or without loss of sensation in the lower extremities
- results in a serum creatinine >2.0 mg/dl that does not spontaneously resolve
- **Renal Failure**: acute or progressive renal insufficiency leading to the need for dialysis or hemofiltration
- **Respiratory failure:** ventilator support >24 hours after spinal drain removal and/or reintubation. This definition does not put the patient at any increased risk. The high risk patient population being treated in this study is prone to pre-existing comorbidities, including COPD and decreased respiratory function, and may require extended ventilator support while in the supine position for spinal drainage.
- **Stroke:** neurological deficit that lasts > 24 hours

Malperfusion of organ(s) or limb(s): loss of flow through a particular vascular bed has been partially or completely compromised leaving the said organ or limb ischemic

Migration, clinically significant: antegrade or retrograde migration that requires surgical or endovascular intervention

Paraparesis: spinal cord ischemic event resulting in partial neurologic deficit in the lower extremities

Parietal arteries (branches): inferior phrenic, lumbars and middle sacral arteries

Patency: the state of a vessel that has unimpeded flow into and out of the vessel

Proximal landing zone: the aortic fixation site closest to the heart

Proximal fixation length: the aortic fixation site measured from the proximal edge of the graft to the start of the aneurysm

Renal insufficiency: rise in serum creatinine of more than 50% above pre-procedure level which results in a serum creatinine >2.0 mg/dl that does not spontaneously resolve

Technical success:

- successful delivery (i.e., ability to deliver the implant to the intended implantation site, without the need for unanticipated corrective intervention related to delivery);
- successful and accurate deployment, defined as:
  - deployment of the endovascular stent-graft at the intended implantation site;
  - patency of all endovascular graft and stent components; absence of device deformations (e.g., kinks, stent eversion, mal-deployment, misaligned deployment) requiring unplanned placement of an additional device;
  - absence of inadvertent covering of aortic branch vessels; and
- successful withdrawal (i.e., successful withdrawal of the delivery system, without need for unanticipated corrective intervention related to withdrawal)

Thrombus: a blood clot that forms due to injury of a vessel. If the thrombus becomes dislodged and travels it is referred to as an embolus

Treatment success: a composite of technical success and freedom from the following:

- aneurysm enlargement i.e. >5-mm as compared to any previous CT measuring orthogonal (i.e., perpendicular to centerline) measurements
- aneurysm-related mortality
- aneurysm rupture
- conversion to open repair
- secondary intervention for migration, type I and III endoleaks, device integrity failure (i.e., fracture), and patency-related events (i.e., device stenosis or occlusion and embolic events)
- Renal failure

Type B – Chronic Dissection: a dissection that takes off distal to the left subclavian artery that is greater than 30 days old

Type B – Subacute Dissection: a dissection that takes of distal to the left subclavian artery that is 15-30 days old

Urgent: An aneurysm requiring repair within 1 week
Visceral arteries (branches): celiac, superior mesenteric, inferior mesenteric, renal arteries

9. Benefits

a. Description of the probable benefits for the participant and for society.

To find potential benefits after complex aortic surgery for patient outcomes and health.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants will not receive payment/remuneration.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There is no cost to participate in the study. The procedures are covered under guidelines for Medicare/Medicaid in the standard delivery of care.

Medicare Generalizability

The Valiant Thoracoabdominal Stent Graft System is intended to treat thoracoabdominal aortic aneurysms and the highest incidence of this disease is observed in Medicare eligible patients. A 2013 market survey of inpatient data revealed that 79.8% (1642/2058) of all thoracoabdominal aortic aneurysms occurred in patients over the age of 65. In that same survey, Medicare was the principal payer in 76.3% of those cases and the secondary payer in 82.6% of those cases[58].

Aneurysmal degeneration occurs more commonly in the aging population. Aging may lead to weakening of the aortic wall due to changes in the collagen and elastin. Additionally, comorbidities that may increase the risk for aneurysm formation are smoking, chronic obstructive, pulmonary disease, hypertension, atherosclerosis, male gender, older age, high body mass, genetic disorders, and family history[87].

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