NYU Langone Health

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Clinical Protocol

Visceral Manifold Study for the repair of thoracoabdominal aortic aneurysms

Protocol Number: IP-01-001 Version 8

Device: Valiant™Thoracoabdominal Stent Graft System

IDE Approval Date: March 21, 2017

IDE Number: G170048

Title: Visceral Manifold Study for the repair of thoracoabdominal aortic aneurysms

Protocol Number: IP-01-001 Version 8

I confirm that I have read this protocol. I will comply with the protocol and the principles of Good Clinical Practice (GCP), as described in the United States Code of Federal Regulation (CFR) 21 Parts 11, 50, 54, 56, and 812 and the appropriate International Conference on Harmonisation guidance documents.

Signature

July 29, 2020

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2. Protocol Synopsis

Investigational Plan Synopsis	
Study Title	Visceral Manifold Study for the repair of thoracoabdominal aortic aneurysms.
Investigational Devices	Valiant™ Thoracoabdominal Stent Graft System
Sponsor/Principal Investigator	Dr. Thomas Maldonado, MD
Investigational Sites	New York University Langone Medical Center
Purpose	The primary objective of the clinical investigation is to assess the use of the thoracic bifurcation and the visceral manifold to repair thoracoabdominal aortic aneurysms in patients having appropriate anatomy. The primary intent of the study is to assess safety (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.
Number of Subjects	15 (6 patients to be enrolled in primary arm, 9 to be enrolled in expanded arm)
Study Type and Duration	Prospective, single center, nonrandomized, multi-arm study. 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: • An aneurysm with a maximum diameter of $\geq$ 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: o ≥ 2.5 cm of nonaneurysmal aortic segment including previously placed graft material (neck) distal to the left subclavian artery (LSA) o Diameter in the range of 26-42 mm o 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
Primary Arm 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

	Other inclusion criteria • 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 nonaneurysmal aortic segment including previously placed graft material (neck) distal to the left subclavian artery (LSA) o Diameter in the range of 26-42 mm o 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
Primary Arm Exclusion Criteria	General exclusion • Patient is a good candidate for and elects for 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 • Urgent or emergent presentation • 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 (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 2.0 mg/dL • History of connective tissue disorders (e.g., Marfan Syndrome, Ehler's Danlos Syndrome) Anatomical exclusion criteria • ranch vessel diameter less than 5 mm • 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 Use Arm **Inclusion Criteria**	An expanded use arm of the study will broaden inclusion criteria to include patients with the following : • Branch vessel diameter <5mm • 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 2.0 mg/dL • Anatomy that does not allow maintenance of at least one hypogastric artery • Anatomy that does not allow 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 of any or all of the visceral vessels

	Treatment of the patient population listed above will be considered for this expanded arm of the study if they are not a candidate for open surgical repair, cannot be treated with approved devices, and do not meet inclusion into the primary study arm as per opinion of the Principal Investigator, with the concurrence of the IRB.
Primary Endpoint(s)	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 the 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)
Secondary Endpoints	Secondary endpoints include: • Technical success and the individual components of technical success: o Successful delivery o Deployment at the intended implantation site o Patency of all endovascular graft and stent components o Absence of device deformations requiring unplanned placement of an additional device o Absence of inadvertent covering of aortic branch vessels o Successful withdrawal • Freedom from the individual components of the primary safety endpoint at 30 days: o Death o Bowel ischemia o Myocardial infarction o Paraplegia o Renal failure

	○ Respiratory failure ○ Stroke • Freedom from paraparesis at 30 days • The following at each follow-up interval: ○ Treatment success and the individual components of treatment success including freedom from the following: – Aneurysm enlargement – 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 – All-cause mortality – Endoleaks – Device integrity failure (e.g., fracture) – Patency-related events (i.e., device stenosis or occlusion and embolic events)

	– Other device-related events
Follow-up Schedule	Patients included in the study will undergo follow-up at one month, six months, twelve months and then annually for five years.
Sample Size Justification	The sample size for the feasibility study is limited to 15 patients, as this is adequate to provide preliminary clinical safety data and effectiveness of the device. 6 will be enrolled in the primary arm of the study and an additional 9 will be enrolled in the expanded use arm. The device, while novel, has been evaluated in a clinical setting and has initially demonstrated both safety and effectiveness[1,2] 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 Valiant™ Thoracoabdominal Stent Graft System and should be sufficient to develop an appropriate pivotal study
Limitations to the Study	Limitations of the study are that it is a single center study with a small patient population.
Study Monitor	Clinical Research Monitoring: Biomedical Research Alliance of New York,

	1981 Marcus Avenue, Suite 210, Lake Success, NY 11042
Study Oversight	Data Safety Monitoring Board

3. Report of Prior Investigations (§ 812.27)

3.1 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[3]. 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.

3.2 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[4,5]. 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[6,7]. 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[5,8]. 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[5,8-11]. 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[9,12]. 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[9,13,14]. Hoarseness from stretching or compression of the left recurrent laryngeal nerve, tracheal deviation, persistent cough, or other respiratory symptoms is sometime

seen. Patients with a thoracoabdominal aortic aneurysm may have a palpable pulsatile mass in the upper abdomen.

3.2.1 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[3]. 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[3].

In a combination of retrospective and prospective IDE data from Sanford Health (IDE Application 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[4]. Another center reported a 36.8% 30-day mortality in patients treated with a hybrid approach[5]. When compared with these results and the fact that Sanford Health had no ischemic time and an

average blood loss of 1250 cc in their emergent cases, the probable risk of the using the investigational device is no greater than the probable risk of open repair or from the disease.

Sanford Health has treated three subjects 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 our investigational device is warranted to minimize the risks associated with open repair. Our 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.

3.2.2 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 the study for dissection. Sanford Health has treated 15% (5/33) of subjects electively for TAAA with a dissection. A laser is 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 four months while the other death was self-induced due to alcohol abuse post procedure (Sanford Health (IDE Application G140207). Literature cites an in-hospital mortality

rate of 29% for open surgical repair of type B dissection. Given the small population treated with our 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.

3.2.3 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[6]. 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 do not indicate post-op renal failure and that the creatinine level may not be a contraindication for EVAR treatment if proper precautions are used[7].

3.2.4 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 has been one subject treated with a renal artery less than 5 mm in the Sanford Health experience. This subject has 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.

3.3 Treatment Options

3.3.1 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.

3.3.2 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%[16]. Predictors of adverse events after elective open repair based on pre-existing comorbidities have been established. Advanced age (>70 years)[17-20], respiratory disease[19], renal insufficiency[21], coronary artery disease[17,20], symptomatic aneurysms, extent 1 and 2 aneurysms[22-25], and diabetes[26] are reported to be a predictor of 30-day mortality. Cardiac function[27], extent 1 and 2 aneurysms[23,28-30], symptomatic cases[30], and diabetes[26] 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.

3.3.2.1 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[4].

3.3.2.2 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% [8]. Another large study evaluating open repair results in 1542 subjects reported a 30-day mortality of 17.8% [9].

One advantage of open repair compared to endovascular repair of type B dissections is a lower re-intervention rate[8].

3.3.3 Endovascular Repair

3.3.3.1 TAAA Repair with 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 being as 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[31]. 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[32-34].

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[35]. 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[36].

3.3.3.2 TAAA Repair with 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[37]. The second used 3-4 bridging stents sandwiched with a thoracic graft in the descending thoracic aorta[38]. 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.

3.3.3.3 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[39]. 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[40]. 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[41].

3.3.3.4 TAAA Repair with 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[40,42]. 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.

3.3.3.5 TAAA Repair with 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[43-45]. 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[46-48]. Data is limited and largely retrospective in nature[49]. 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)[50].

3.3.3.6 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. We did however find 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[10]. 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[11]. 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[12]. 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[13-15]. 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.

3.3.3.7 Endovascular Repair of Chronic Type B Dissections

Incidence rates of aortic dissection is estimated to be roughly 3 per 100,000 people per year[16,17]. Until recently acute Stanford type B aortic dissections were managed with blood pressure control[18,19]. 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[20]. 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[21]. 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[22]. 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[23,24]. 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.

3.3.3.8 Staged Endovascular Repair

3.3.3.8.1 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 [51]. 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 optimum[51]. 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 limb[52]. The use of perfusion branches may be preferred to allow for better hemodynamics and avoid excessive pressurization of the aneurysm sac.

3.3.3.8.2 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 anatomy[53], but fail to reference the use of staging and outcomes. Literature also cites several intra-operative techniques for bail-out maneuvers in the operating room[54], 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.

3.3.3.9 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.3.3.3.9.1 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.

3.4 Benefits and Risks of Treatment Options

3.4.1 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 respiratory failure rates of 36%[16]. 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.

3.4.2 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[35]. 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[55].

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[41].

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 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. This patient population is faced with a serious and life threatening disease and have limited clinical options. The subjects are willing to assume a higher degree of risk with an investigational device due to the progressive nature of the disease and the high mortality and morbidity rates when left untreated.

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.

3.4.2.1 Staged Procedures

With the Valiant Thoracoabdominal stent graft system, the risks of planned staging via the visceral artery bridge endoleak during the procedure 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.

3.4.3 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[56].

3.4.4 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[56]. 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[57]. 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[58]. 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[59]. 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[60].

3.5 Justification for Specific Patient Selection Criteria Relevant for this Study

Treatment of TAAA aneurysms in all patients 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. 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 good candidates 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 4.4.2 including aneurysm characteristics, access vessel morphology, minimum neck length, diameter of aneurysm, branch vessel size, 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.

3.5.1 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). 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.

3.6 Device Description and Drawings

The Visceral Manifold 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 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 1. 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 2. 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 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 3. 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 4. 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 TAAA Debranching Stent Graft 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.

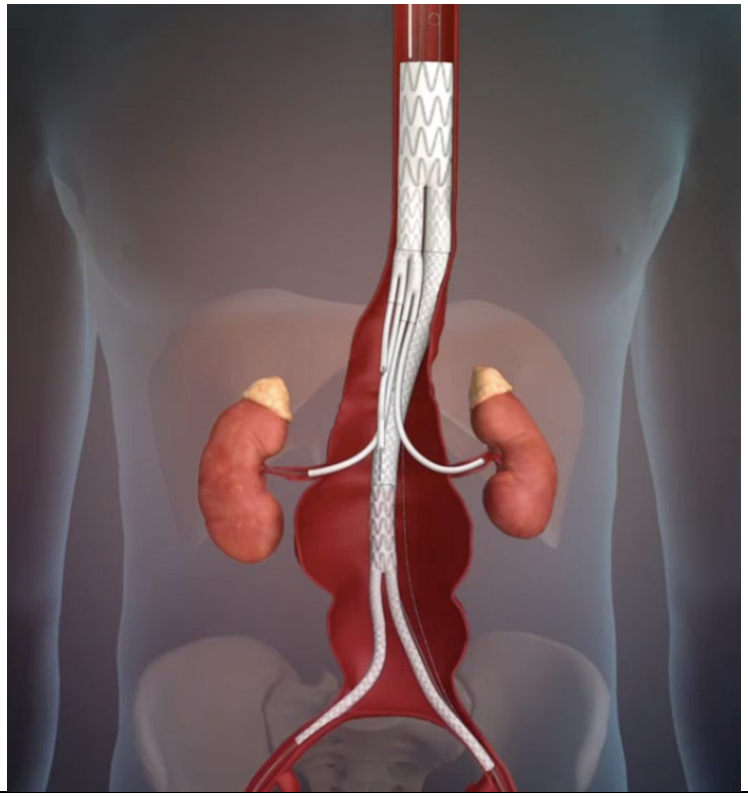

Figure 2: Assembly drawing showing the thoracic bifurcation, the visceral manifold, the branch stents, and the infrarenal grafts, all deployed within an idealized aneurysm sketch.

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, and 5) in patients with the following characteristics:

- An aneurysm with a maximum diameter of $\geq$ 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 $\geq$ 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 nonaneurysmal aortic segment 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
- 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

3.7 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. 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.

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.

3.8 Institution Experience and Infrastructure

The Division of Vascular Surgery at New York University Langone Medical Center is comprised of 11 vascular surgeons and covers three hospitals within the medical center, Tisch Hospital, Bellevue Hospital, and the Manhattan Veterans Administration Hospital. We have a robust experience in endovascular repair of aortic aneurysms and are a regional referral center

for complex aortic pathology including aortic dissection and aneurysmal disease. We have a strong history and collaboration with our cardiothoracic surgery colleagues and function together as part of an Aortic Center with regular multidisciplinary conferences where case management is discussed. NYU Langone Medical Center performs roughly 250 aortic surgeries annually. We have been leaders in the field of endovascular aortic surgery and participated in most industry sponsored clinical trials related to aortic pathology, including the original EVT (ANCURE) trials in the 1990's.

Table of Clinical Trials: Aortic Endovascular Treatment of Aortic pathology

- Phase II: A Clinical Trial of the Endovascular Grafting System as Compared to the Standard Surgical Procedure in the Treatment of Abdominal Aortic Aneurysms (Guidant)
- Enact T Endovascular Aneurysm Clinical Trial-Tube: A Phase III Clinical Study of the Bifurcated Endovascular Grafting System (EGS) Compared to the Standard Surgical Procedure in the Treatment of the Abdominal Aortic Aneurysm (Guidant)
- Enact B Endovascular Aneurysm Clinical Trial - Bifurcated: A phase II Clinical Study of the EGS System as compared to the Standard Surgical Procedure in the Treatment of the Abdominal Aortic Aneurysms (Guidant)
- A Clinical Study Comparing the Use of the Bifurcated Excluder Endoprosthesis to Open Surgical Repair in the Primary Treatment of Infrarenal Abdominal Aortic Aneurysms-Continued Access (Gore)
- Clinical Study of the Ancure tube and Bifurcated systems extended indications evaluation: A Phase III Clinical Study of the ANCURE System as Compared to the Standard Surgical Procedure I the treatment of Abdominal Aortic Aneurysms (Guidant)
- RENU Registry: AAA Ancillary Graft (Cook)
- Medtronic Vascular TALENT Thoracic Endovascular Stent Graft System (Medtronic)
- Valor II: Evaluation of the clinical performance of the Valiant Thoracic Stent Graft System for treatment of Descending Thoracic Aneurysms (Medtronic)Zenith TX2 Thoracic Endovascular Graft Clinical Investigation (Cook)
- Zenith Dissection Clinical Study (Cook)
- STAPLE-2: Pivotal Study of the Aptus Endovascular AAA Repair System (Aptus)
- ANCHOR: Aneurysm Treatment Using the HeliFX™ Aortic Securement System Global Registry-sponsor Aptus Endosystems
- Endurant Stent Graft System US Clinical Study (Medtronic)
- Zenith Fenestrated AAA Endovascular Graft Clinical Study (Cook)
- Zenith Low Profile AAA Clinical Study-Spiral Z (Cook)
- Zenith p_Branch Pivotal Study (Cook)

We currently have four actively enrolling clinical trials and over a dozen investigator driven studies ongoing. We have no competing trials for endovascular treatment of thoracoabdominal aortic pathology. We are academically active. We present our research at our national societal meeting and publish regularly in peer-reviewed journals.

We have been especially active in industry sponsored clinical trials for fenestrated endovascular aortic aneurysm (FEVAR) for treatment of pararenal aortic aneurysms. We were a site for the Cook sponsored FEVAR trial (Zenith Fenestrated AAA Endovascular Graft Clinical Study) and are currently enrolling in the Cook sponsored pivotal-branch trial (Zenith p_Branch Pivotal Study). We have a robust experience in endovascular treatment of thoracoabdominal aortic aneurysms using CHIMPS (CHIminey, Periscope, Snorkel) techniques, having treated over 30 patients in this manner. In addition, we have a significant experience with back table modification of devices. Dr. Maldonado, in particular, has implanted over 40 back-table modified fenestrated and branched devices for thoracoabdominal aneurysms. This experience in particular has provided the greatest education for mastering technique and understanding nuances in endovascular treatment of thoracocabdominal aortic aneurysms (extent III,IV,V).

We have a strong commitment to research and have three research coordinators who assist in patient enrollment for clinical trials, data management, follow-up, facilitating external monitoring and audits, as well as maintaining intramural research databases. Our research coordinators also support our participation in regional/national databases such as the Vascular Quality Initiative (VQI). We work closely with biostatisticians from our Department of Population Health and partner with Biomedical Research Alliance of New York (BRANY)

and/or the NYU School of Medicine Office of Science and Research for research support including assistance with IRB review, contracting and Medicare coverage analysis. For the current proposed PS-IDE we will utilize BRANY as our clinical research monitoring service (BRANY, 1981 Marcus Avenue, Suite 210, Lake Success, NY 11042). Our institutional review board (IRB) meets weekly.

3.9 Report of Prior Investigations Synopsis

The single center experience with the Visceral Manifold Thoracoabdominal Stent Graft System from Sanford Health (Dr. Patrick Kelly; PS-IDE (G140207) were recently reported .[1] . 29 patients were successfully treated between March 2012 and January 2016. Twenty-seven patients were followed up to 1 month, 21 were followed up to 6 months, 16 were followed up to 1 year, and 8 have been followed past 1 year thus far. Using the Crawford classification, there were 8 with a type 1/type 2, 6 type 3, 8 with type 4, and 7 with type 5. 97.3% (108 of 111) of target vessels were successfully stented and 99% (107 of the108) target vessels remained patent throughout follow-up. 15 patients in this experience met inclusion criteria (identical to ours) and were enrolled in the primary arm and 14 did not meet inclusion criteria and were treated as compassionate use. The majority of this latter group would have been considered part of the expanded arm of our protocol. Specifically, 4 were emergency ruptures, 5 were chronic type B dissections, and the remaining 5 had suprarenal fixated stents or an occluded renal (total n=14). In the group meeting IDE inclusion criteria, there was an average length of stay of 7.5 days with no in-hospital or 30-day death, no cases of paraplegia, and one case of renal failure which resolved. There was one death at 11 months from a CVA. In the group not meeting IDE inclusion criteria, there was an average length of stay of 9.5 days, with no in hospital or 30-day death, two cases of paraplegia, and six cases of temporary or permanent renal failure.

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 clinical study.

4. Investigation Plan

4.1 Purpose

The primary objective of the clinical investigation is to assess the use of the thoracic bifurcation and the visceral manifold to repair thoracoabdominal aortic aneurysms in patients having appropriate anatomy. The primary intent of the study is to assess safety (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.

4.2 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:

- An aneurysm with a maximum diameter of $\geq$ 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 $\geq$ 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 nonaneurysmal aortic segment 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
- 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

4.3 Device Description

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. The two custom main body grafts are the thoracic bifurcation (Figure 3A) and the visceral manifold (Figure 3B). 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 and 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.

	
A	B

Figure 3: Images of the manufactured device A) the thoracic bifurcation main body graft and B) visceral manifold main body graft

4.4 Protocol

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 15 patients will be enrolled in this study.

- 6 subjects total will be treated in the primary study arm
- 9 subjects total will be treated in the expanded selection arm

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

4.4.1 Description of the Patient Population

The study will evaluate 15 patients with type 1,2,3 and 5 thoracoabdominal aneurysms meeting protocol inclusion criteria for either the primary study arm or the expanded selection arm. The patient population includes both male and female patients greater than 18 years old with a life expectancy of at least one year.

4.4.2 Eligibility Criteria

Primary Study Arm

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 $\geq$ 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 $\geq$ 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 nonaneurysmal aortic segment 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
- 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

Exclusion Criteria

General exclusion

- Patient is a good candidate for and elects for 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

- Urgent or emergent presentation
- 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 2.0 mg/dL
- History of connective tissue disorders (e.g., Marfan Syndrome, Ehler's Danlos Syndrome)

Anatomical exclusion criteria

- Branch vessel diameter less than 5 mm
- 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 meet inclusion criteria for the primary study arm may be enrolled under an expanded selection arm if they meet the following criteria.

Inclusion Criteria

- Patient that meets the criteria for inclusion in the primary study arm but has 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 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

Or

- Patient that meets 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.

4.4.3 Study Endpoints

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 the 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)

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
- The following at each follow-up interval:
    - Treatment success and the individual components of treatment success including freedom from the following:
        - Aneurysm enlargement
        - 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
- All-cause mortality
- Endoleaks
- Device integrity failure (e.g., fracture)
- Patency-related events (i.e., device stenosis or occlusion and embolic events)
- Other device-related events

4.4.4 Follow-up Schedule

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**	**Pre- discharge**	**1**	**6**	**12**	**24**	**36**	**48**	**60**
CTA/CT Scan with and without	X		X[8]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
X-Ray	X[1]			X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Angiography	X[3]	X								
Blood Tests	X[4]	X[5, 6]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
Clinical Exam (including ABI)	X[7]		X	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]
Branch Patency[2] (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. Per standard of care: A/P, Lateral and Bilateral oblique views.
2 In patients experiencing renal failure during follow-up, duplex ultrasound may be used in conjunction with non-contrast CT.
3 Pre-procedure angiography may be requested at discretion of film reviewer.
4 Blood tests include hemoglobin and creatinine; PTT and prothrombin collected pre-op and pre- discharge only.
5 Blood test for ACT.
6 Other intra-op labs for anesthesia.
7 Urine pregnancy test (for female patients of childbearing age)

8 If deemed necessary by the Principal Investigator

4.4.5 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)

- An X-Ray will be performed per local standard of care. A/P, Lateral and Bilateral Oblique Images will be obtained.
- CTA of the chest, abdomen, and pelvis with 3D reconstruction if renal function allows to evaluate:
    - Access vessels for compatibility with vascular access techniques
    - Obstructive stenting of the visceral vessels
    - Vessel diameters suitable for use with the Valiant™ Thoracoabdominal Stent Graft System
    - Aneurysm rupture
    - Branch stenosis
    - 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
    -
- Complete blood count
- Basic metabolic panel
- For patients with a history of smoking a pulmonary function test
- Cardiac clearance

4.4.5.1 Case Planning

From the pre-op CT, the surgeon will make the following recommended 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, distal to the left subclavian artery.
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. Distance from the top of the celiac to the top of the most cephalic renal.
4. Distance from the top of the proximal seal zone to the takeoff of the celiac.
5. Distance from the top of the celiac to the SMA.
6. Angulation at the mid-thoracic aorta.
7. Angulation at the diaphragm.
8. Angulation at the renal arteries.
9. Distance from the right renal to the ispilateral internal iliac artery.
10. Distance from lower renals to aortic bifurcation.
11. Diameter of the branch vessels (celiac, SMA, left renal, and right renal) to determine the diameter bridging stents needed and percent patency.
12. Diameter of the right and left common iliac to secure the distal seal of the infrarenal bifurcation.
13. Minimum diameter of the access sites (right and left femoral and brachial access site).
14. Length from the access sites to the target treatment zone (right and left femoral and brachial access site).

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.

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4.4.5.2 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
- Basic metabolic panel
- 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.

i. 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

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.

4.4.5.3 Implant Procedures

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

Note II: For subjects with advanced iliac atherosclerosis and calcification, we will selectively perform use of open conduits to deliver devices, rather than percutaneous approach. We will selectively perform on table Dyna CT – angiograms at the completion of the case. This will give us a better 3-Dimensional image of the stent and help determine if there is any degree of compression, which can be treated at that time with further stenting.

A. The 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.

B. The implantation of the Valiant™ Thoracoabdominal Stent Graft System is conducted under fluoroscopic/angiographic guidance. Refer to the Valiant™ Thoracoabdominal Stent Graft System (IFU) for techniques and methods for device deployment and implantation.

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

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 Step 4.4.5.5, Completion Procedures. For type 2 and3 proceed to deployment of the infrarenal bifurcation and Endurant II limb stent graft instructions in the Medtronic TAAA Debranching Stent Graft System IFU.

Note: If the VB is too short or too small to provide distal seal, a Valiant Captivia stent graft or Endurant Limb may be used in place or in conjunction with the Visceral Bypass to provide adequate distal seal. For type 2and 3 proceed to deployment of the infrarenal bifurcation and Endurant II limb stent graft instructions in the Medtronic TAAA Debranching 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 Step 1.4.5.5.3.C and Step 1.4.5.5.4.D. 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.

B. Surgical Decision Pathway and Bailouts

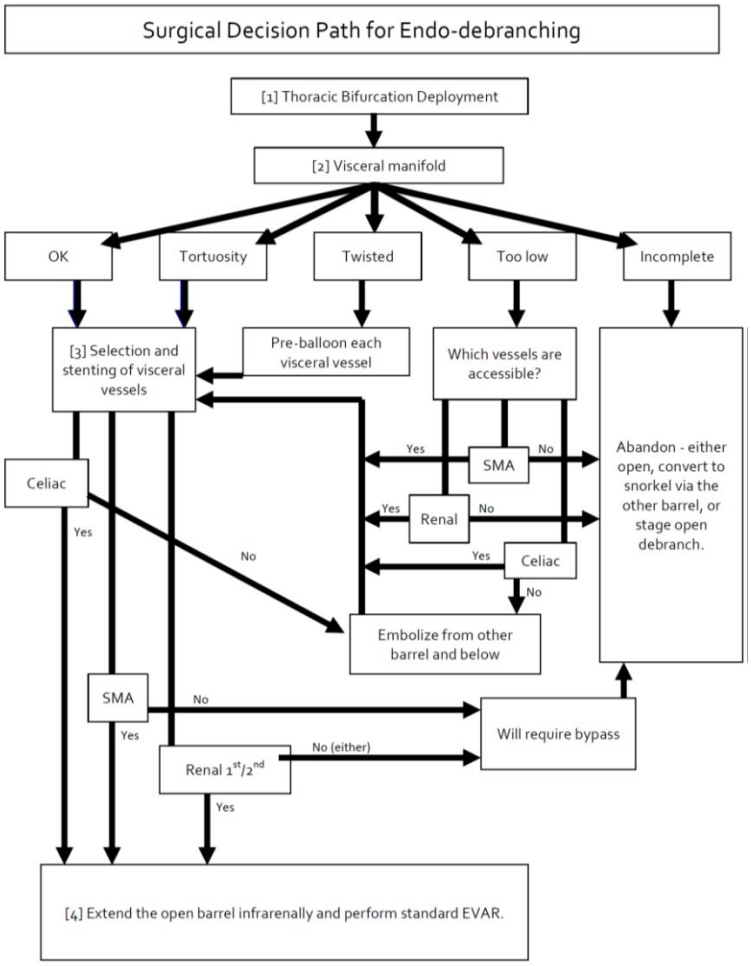

Figure 4: Surgical decision path and possible bailouts

C. 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).

D. 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.

4.4.5.4 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 angioplasties.
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. Perform any adjunct procedures including but not limited to ballooning, atherectomy, or placement of stents to repair or treat any arterial issues or concomitant disease process in the iliac system to maintain flow to the lower extremities or the upper access arm extremity.
5. Remove all sheaths, wires, and remaining accessories and repair of arterial access sites using standard surgical closure techniques.
6. Dopplerable 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.

4.4.5.5 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 of the chest, abdomen, and pelvis if clinically necessary and renal function allows

4.4.5.6 Follow-up Visits

All patients will undergo follow-up at one month, six months, twelve months and then annually for five years (as described in Section 1.4.4). At each of the follow-up visits 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
- Pregnancy test (for female patients of child bearing age)
- CTA of the chest, abdomen, and pelvis if renal function allows
- If deemed necessary by the investigator, an X-Ray may be performed 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.

4.4.6 Sample Size Justification

The sample size for the feasibility study is limited to 15 patients, as this is adequate to provide preliminary clinical safety data and effectiveness of the device We plan for 6 subjects to enroll in the primary arm, and 9 subjects to be enrolled under extended criteria. 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.

4.4.7 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. The data will be presented as quality outcomes, with the number of study subjects who experience treatment success compared to the overall patient population.

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.

4.4.7.1 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%)

4.4.8 Limitations of the Study

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

4.5 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.

4.5.1 Potential Risks

4.5.1.1 Procedural-related risks

Procedural related risks including general and device specific procedural risks can result in several serious harms to the patient including contrast damage, allergic response, paraplegia, peripheral nerve damage, injury to access vessel, dislodging of thrombus, dissection of vessel,

embolism, branch artery or parenchyma damage of ischemia, inadvertent internal iliac occlusion or ischemic colitis, system effects including increased risk of morbidity and mortality, local effects at the access site including wound infection, hematomas, seromas, arterial or venous damage, failure to access the aorta, inaccurate deployment of devices, failure to deploy devices, and displacement of devices. 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 manifold system as compared to other surgical techniques outweighs the potential procedural related risks to the patient.

4.5.1.2 Material-related risks

Material related risks are risks that are associated with physical components of the stent graft including risks related to stent breakage, branch vessel stent crush, barb fracture, fabric wear, biocompatibility, and sterility. Risks of these components include vessel occlusion, embolism, component separation, migration, and infection. These risks can be mitigated several ways including careful case planning for patient selection, device placement, proper sizing, use of compatible components, and regular follow-ups to identify early evidence of migration or separation.

4.5.1.3 Performance related risks

There are performance risks of the modular components succumbing to material fatigue resulting in component separation, endoleak or endotension, graft occlusion, 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.

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.

4.6 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. Monitoring functions will be conducted by dedicated Clinical Research Monitors at Biomedical Research Alliance of New York (BRANY) (1981 Marcus Avenue, Suite 210, Lake Success, NY 11042). Monitoring will be performed according to procedure.

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 in Redcap or equivalent eCRF system

- 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.

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.

Monitoring Intervals:

Monitoring will occur at regular intervals throughout the duration of the trial. Monitoring can be performed on-site or remotely

4.7 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 the reviewing IRB 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:

Table 8. Annual progress report

		# (%)				Adequate imaging to assess the parameter*** # (%)				Events occurring before next interval # (%)			
Visit	Eligible for follow-up*	Subjects with data for that visit	CT	X-ray	Subjects with follow-up pending**	Size Increase	Endoleak	Migration	Fracture	Death	Conversion	LTF	Not due for next visit
Operative				N/A		N/A							
30 day													
6 month													
1 year													
Additional years													

*Eligible for follow-up = previous eligible for follow-up – (previous death + conversion + LTF + not due).
** Subjects still within follow-up window, but data not yet available.
*** Not the number of subjects with these reported events; the number with adequate imaging, such as paired size data to evaluate aneurysm growth.

Additionally, the sponsor will send an Interim Report for every five patients regardless of study arm, and within the report divide those 5 into their respective primary or expanded selection cohorts.

These reports will include basic information on the number of patients enrolled and treated and information on observed adverse events for any subgroups (e.g., device types, extents of disease, lesion types). These interim progress reports are meant to be summaries and not complete progress reports. Details will be captured in any adverse event reports and annual reports to the IDE.

Table 9: Enrollment summary*

	column for each subgroup	Total
Enrolled		
Treated		
Awaiting treatment		
Withdrawn (state reason)		

* A subject is considered enrolled after the device enters the body.

Summary

For each subgroup of patients, a brief narrative description of the procedures completed to date (e.g., how many had devices implanted successfully), any need for additional interventions, and the outcomes of any additional interventions will be provided.

Table 10: Treatment summary

	Number of patients	Procedural success	Perioperative death
One branch			
Two branches			
Three branches			
Four branches			
Total			

Adverse Events

Comments on the most commonly observed challenges or adverse events will be provided.

The following table is an example of how adverse event numbers may be presented for each subgroup. The list will include events observed in the study, not necessarily all that are listed in this example	**1st 5**	**2nd 5**	**Additional groups**	**All**
Aortic dissection				
Branch vessel embolism (renal, celiac, SMA, etc.)				
Branch vessel occlusion (renal, celiac, SMA, etc.)				
Branch vessel dissection (renal, celiac, SMA, etc.)				
External iliac dissection				
Interval iliac occlusion				
Ischemic colitis/Colon necrosis				
Late related death				
Late unrelated death				
Leg ischemia				
Lower extremity embolism				
Lower extremity paralysis				
MI				
Perioperative death				
Renal failure/impairment				
Respiratory failure				
Stroke				
Wound necrosis				

Table 6: Adverse Events

Study subjects who had multiple complications will be designated using symbols (#, *, +) or numbers.

Lessons Learned

The lessons learned from the beginning of the study (e.g., with respect to patient selection, methods to minimize adverse events) will be summarized. Procedures proposed or implemented to mitigate any risks or challenges that were observed during the study will be discussed, as well as any changes in outcomes based on experienced gained during the study.

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.

4.8 Oversight

This study will have oversight by a Data Safety Monitoring Board (DSMB) consisting of independent scientific and bio-statistical expertise, who are not participating as investigators in the study. The DSMB will monitor and evaluate the safety of subjects and progress of the study. The board will meet after every 5th patient enrolled in the primary study arm 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.

4.9 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 .

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)

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

- **Renal Failure**: acute or progressive renal insufficiency leading to the need for dialysis or hemofiltration
- **Respiratory failure:** Prolonged intubation (>48 hours after spinal drain removal or >72 hours total) 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. ≥10-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

5. Manufacturing Information

The Valiant™ Thoracoabdominal Stent Graft System utilizes the Medtronic TAAA Debranching Stent Graft System. Therefore, the manufacturing information for the system is listed in the following Medtronic regulatory submission:

MAF-2551, Medtronic, TAAA Debranching Stent Graft System Master File

6. Investigator Agreement and Certification

The investigator that will be participating in the study includes Dr. Thomas Maldonado. I certify that all participating investigators will sign the investigator agreement and no investigator will be added until the agreement is signed in accordance with 21 CFR 812.29(b)(5).

The names and addresses of investigators will be provided upon request by the FDA and in accordance with 21 CFR 812.150(b) (4).

7. IRB Information

Helen Panageas, CIP
New York University Institutional Review Board
One Park Avenue, 6th Floor
New York, New York 10016

8. Amount to be charged

The amount charged for the devices used in this investigation will be consistent with the amount charged by the manufacturers of the devices to the hospitals.

9. Labeling

The Valiant Thoracoabdominal Stent Graft System utilizes the Medtronic TAAA Debranching Stent Graft System. Therefore, the manufacturing information for the system is listed in the following Medtronic regulatory submission:

MAF-2551, Medtronic, TAAA Debranching Stent Graft System Master File

10. 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[61].

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[62].

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