Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	Valiant EVO US Clinical Trial
Study Product Name	Valiant™ Evo Thoracic Stent Graft System
Sponsor/Local Sponsor	Medtronic Vascular 3576 Unocal Place Santa Rosa, CA 95403 United States
Document Version	1B
Lead Principal Investigator	Ali Azizzadeh, MD Director, Vascular Surgery Cedars-Sinai Medical Center 127 S. San Vicente Blvd Los Angeles, CA 90048

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A SYNOPSIS

Title	Valiant Evo US Clinical Trial
Investigational Device	Valiant™ Evo Thoracic Stent Graft System
Study Design	The Valiant Evo US Clinical Trial is a prospective, multi-center, pre-market, non-randomized, single-arm trial.
Purpose	The purpose of the Valiant Evo US Clinical Trial is to demonstrate the safety and effectiveness of the Valiant Evo Thoracic Stent Graft System in subjects with a descending thoracic aortic aneurysm (DTAA) who are candidates for endovascular repair. The clinical evidence collected as part of this trial will be used in conjunction with data collected during the concurrently enrolling Valiant Evo International Clinical Trial to support PMA-S Approval of the Valiant Evo Thoracic Stent Graft System. The clinical evidence collected as part of this clinical trial may also be used to support obtaining commercial approval in other international geographies.
Primary objective	The primary objective is to demonstrate the safety and effectiveness of the Valiant Evo Thoracic Stent Graft System in subjects with a DTAA who are candidates for endovascular repair.
Secondary objectives	Secondary objectives include descriptive analyses of secondary endpoints as well as acute procedural observations and clinical utility measures.
Primary Endpoints	Composite safety and effectiveness endpoint that is based on the proportion of subjects who experienced: (a) Access and/or deployment failures; and/or (b) Major device effect (MDE) within 30 days post index procedure MDEs include the occurrence of any of the following and are defined in Appendix L.5: • Device-related secondary procedures • Device-related mortality • Conversion to open surgery • Thoracic aortic aneurysm rupture An independent Clinical Events Committee (CEC) will be established and adjudicate MDEs.

Secondary Endpoints	<u>30-day Secondary Endpoints:</u>
	The following secondary endpoints will be evaluated within 30 days post treatment:
	• Peri-operative mortality
	• All adverse events (AE) within 30 days including:
	  • Major Adverse Event(s) (MAE)
	  • Serious Adverse Event(s) (SAE)
	• Secondary procedures
	• Loss of stent graft patency at 30 day visit based on imaging findings
	• Endoleaks at 30 day visit based on imaging findings
	Major adverse events include the occurrence of any of the following:

	• Respiratory complications: atelectasis/pneumonia, pulmonary embolism, pulmonary edema, respiratory failure
	• Renal complications: renal failure, renal insufficiency
	• Cardiac complications: Myocardial infarction (MI), unstable angina, new arrhythmia, exacerbation of congestive heart failure (CHF)
	• Neurological complications: new cerebrovascular accident (CVA)/embolic events, paraplegia, paraparesis
	• Gastrointestinal complications: bowel ischemia
	• Major bleeding complication (procedural or post-procedural), coagulopathy
	• Vascular complications: aortic rupture, aneurysm rupture, hematoma at access site, pseudo or false aneurysm, arteriovenous (AV) fistula, retroperitoneal bleed, limb ischemia, thrombosis
	
	<u>6-month Secondary Endpoints:</u>
	
	The following secondary endpoints will be evaluated:
	• All-cause mortality within 183 days
	• Aneurysm-Related Mortality within 183 days
	• MDEs within 183 days
	• All AEs within 183 days including:
	  • MAEs
	  • SAEs
	• Secondary procedures within 183 days
	• Loss of stent graft patency within 6 months based on imaging findings
	• Endoleaks at 6 months based on imaging findings
	• Stent graft migration at 6 months as compared to 1-month imaging
	• Aneurysm expansion > 5mm at 6 months based on imaging findings relative to the 1-month visit
	
	<u>12-month Secondary Endpoints:</u>
	
	The following secondary endpoints will be evaluated:
	• All-cause mortality within 365 days
	• Aneurysm-Related Mortality within 365 days
	• MDEs within 365 days
	• All AEs within 365 days including:
	  • MAEs
	  • SAEs
	• Secondary procedures within 365 days
	• Loss of stent graft patency within 12 months based on imaging findings
	• Endoleaks at 12 months based on imaging findings
	• Stent graft migration at 12 months as compared to 1-month imaging
	• Aneurysm expansion > 5mm at 12 months based on imaging findings relative to the 1-month visit
	
	For subjects that re-consent to extended study follow up, the above 12-month secondary endpoints will be evaluated at 24, 36, 48, and 60 months.

Additional Observations	The following acute procedural observations and clinical utility measures will be analyzed: • Mean duration (min) of procedure (time between initial skin access to • final skin closure) • Proportion of subjects who underwent general/local/epidural/spinal • anesthesia • Proportion of subjects who underwent percutaneous access • Proportion of subjects requiring blood transfusions, excluding cell saver mean volume (cc) of estimated blood loss

	• Mean duration (min) of radiation exposure • Radiation exposure (mGy) • Mean length of time (hours) in intensive care unit • Mean length of time (days) of hospital stay (from the index procedure to hospital discharge) Health-related quality of life outcomes will be assessed at all scheduled follow-up visits using the EQ-5D questionnaire.
Subject Population	Subject population will include subjects diagnosed with DTAA who are considered candidates for endovascular repair, and who meet the Inclusion/Exclusion Criteria for the Valiant Evo US Clinical Trial.
Number of subjects	Globally, a total of 100 subjects will be concurrently enrolled in the United States and outside the United States to support the primary endpoints. Up to 50% of subject data used to support PMA approval may come from subjects enrolled at sites outside of the US under a separate CE Mark study protocol; called the Valiant Evo International Clinical Trial protocol. The primary endpoint analysis will be completed upon 87 evaluable subjects reaching the 30 day endpoint. The data obtained from these 87 evaluable subjects will be used to support PMA-S Approval of the Valiant Evo Thoracic Stent Graft System. The Valiant Evo US Clinical Trial protocol and Valiant Evo International Clinical Trial protocol will be identical with respect to the inclusion/exclusion criteria.
Number of Sites	The Valiant Evo Global Clinical program will be conducted at up to 37 sites worldwide, with at least 50% of the clinical sites coming from the United States.
Clinical Procedures and Follow Up Schedule	Subjects require follow-up evaluations at the following time points: • 1 month following the index procedure (30 ± 15 days) • 6 months following the index procedure (183 ± 30 days) • 12 months following the index procedure (365 ±60 days) • 24 months following the index procedure (730 ± 60 days) • 36 months following the index procedure (1095 ± 60 days) • 48 months following the index procedure (1460 ± 60 days) • 60 months following the index procedure (1825 ± 60 days) For subjects that re-consent to extended study follow up, the assessments as performed during the 12-month visit are to be repeated at 24, 36, 48 and 60 month visits.
Principal Investigator	Dr. Ali Azizzadeh Director, Vascular Surgery Cedars-Sinai Medical Center 127 S. San Vicente Blvd Los Angeles, CA 90048
Indications for Use	The Valiant Evo Thoracic Stent Graft System is indicated for the endovascular repair of fusiform aneurysms and saccular aneurysms/penetrating ulcers of the descending thoracic aorta (DTA) in patients having the appropriate anatomy including the following: • Iliac or femoral artery access vessel morphology that is compatible with vascular access techniques, devices, or accessories • Nonaneurysmal aortic diameter from 16 mm to 42 mm • Nonaneurysmal aortic proximal neck length ≥20 mm (for FreeFlo configuration) and ≥25 mm (for Closed Web configuration)

	• Distal neck length ≥20 mm
Inclusion Criteria	Candidates for the Valiant Evo US Clinical trial must be appropriate subjects for endovascular repair of aneurysms of the descending thoracic aorta (evidenced by screening contrast-enhanced CT or MRA) and have to fulfill all of the following inclusion criteria to be eligible for recruitment in the study: 1. Subject is ≥18 years old. 2. Subject understands and voluntarily has signed and dated the Informed Consent Form approved by the Sponsor and by the Ethics Committee for this study. 3. Subject presents a DTAA which is localized below the ostium of left subclavian artery (LSA) and above the ostium of celiac trunk 4. Subject has a DTAA that is one of the following: a. A fusiform aneurysm with a maximum diameter that: • is ≥ 50 mm and/or: • is ≥2 times the diameter of the non-aneurysmal thoracic aorta and/or: • is < 50 mm and has grown ≥ 5 mm within previous 12 months b. A saccular aneurysm or a penetrating atherosclerotic ulcer 5. Subject's anatomy must meet all of the following anatomical criteria as demonstrated on contrast-enhanced computerized tomography (CT) and/or on contrast-enhanced Magnetic Resonance Angiogram (MRA) obtained within four (4) months prior to implant procedure: a. Proximal and distal non-aneurysmal aortic neck diameter measurements must be ≥ 16 mm and ≤ 42 mm; b. Proximal non-aneurysmal aortic neck length must be ≥ 20 mm (for FreeFlo configuration) and ≥ 25 mm (for Closed Web configuration) distal to the left common carotid artery (LCCA). Note: Proximal aortic neck length may include covering the LSA (with or without discretionary revascularization) when necessary to optimize device fixation and maximize aortic neck length. If occlusion of the LSA ostium is required to obtain adequate neck length for fixation and sealing, transposition or bypass to the LSA may be warranted. c. Distal non-aneurysmal aortic neck length must be ≥ 20 mm 6. Subject has adequate arterial access site or can tolerate a conduit that allows endovascular access to the aneurysmal site with the delivery system of the appropriate sized device chosen for the treatment.
Exclusion Criteria	Candidates who meet any of the following exclusion criteria will not be eligible for recruitment in the study: 1. Subject has a life expectancy of less than 1 year. 2. Subject is participating in another investigational drug or device study which would interfere with the endpoints and follow-ups of this study. 3. Subject is pregnant. 4. Subject requires planned placement of the covered proximal end of the stent graft to occur in zones 0 or 1. 5. Subject has a thoracic aneurysm with a contained rupture or localized at the anastomosis of a previous graft (pseudo-/false aneurysm). 6. Subject has a mycotic aneurysm.

	7. Subject has a dissection (type A or B) or an intramural hematoma or an aortic rupture in addition to the thoracic aneurysm. 8. Subject requires emergent aneurysm treatment, e.g., trauma or rupture. 9. Subject has received a previous stent or stent graft or previous surgical repair in the ascending and/or descending thoracic aorta, and/or in the aortic arch. 10. Subject requires surgical or endovascular treatment of an infra-renal aneurysm at the time of implant. 11. Subject has had previous surgical or endovascular treatment of an infra-renal aortic aneurysm. 12. Treatment with the Valiant Evo Thoracic Stent Graft would require intentional revascularization of the brachio-cephalic artery, the left common carotid artery or the celiac trunk. 13. Subject has had or plans to have a major surgical or interventional procedure within 30 days before or 30 days after the planned implantation of the Valiant Evo Thoracic Stent Graft. This does not include planned procedures that are needed for the safe and effective placement of the stent graft (i.e., carotid/subclavian transposition, carotid/subclavian bypass procedure). 14. Subject has a significant and/or circumferential aortic mural thrombus at either the proximal or distal attachment sites that could compromise fixation and seal of the implanted stent graft. 15. Subject has a connective tissue disease (e.g., Marfan's syndrome, aortic medial degeneration). 16. Subject has a bleeding diathesis or coagulopathy, or refuses blood transfusion. 17. Subject has had a MI within 3 months of the procedure. 18. Subject has had a CVA within 3 months of the procedure. 19. Subject has a known allergy or intolerance to the device materials 20. Subject has a known allergy to anesthetic drugs 21. Subject has a known hypersensitivity or contraindication to anticoagulants, or contrast media, which is not amenable to pretreatment. 22. Subject has active or systemic infection at the time of the index procedure.
Study Success Criteria	A 30-day premarket safety and effectiveness endpoint (a minimum of 87 evaluable subjects for hypothesis test). The primary endpoint will be tested against a performance goal of 16% MDE rate at 30 days.
Analysis Sets	The primary analysis set will consist of all subjects who were enrolled. The subject will be considered to be enrolled after arterial access is established and the Valiant Evo Thoracic Stent Graft System is introduced. A secondary analysis set will be the Per-Protocol population. This analysis set is comprised of all enrolled subjects who met inclusion and exclusion criteria, received the test device and completed 30-day follow-up (including death but excluding withdrawal or lost to follow-up subjects within the 30-day follow-up period).
Data Oversight	A Data Monitoring Committee, Clinical Events Committee, and imaging core lab will be established to independently evaluate subject health status, device performance, and identify any safety concerns regarding subjects' well-being. Contact details of the committees and the core lab will be available in the investigational site file.

Safety Monitoring	Medtronic Clinical Operations 710 Medtronic Parkway NE Minneapolis, MN 55432
Monitoring	Medtronic Clinical Operations 710 Medtronic Parkway NE Minneapolis, MN 55432

B GENERAL INFORMATION

B.1 Introduction

Background:

An aortic aneurysm is defined as a dilatation of the aortic vessel greater than 50% of its normal diameter for a given segment of the adhering normal vessel.[1] An aneurysm of the Descending Thoracic Aorta (DTA) is defined as involving any portion of the thoracic aorta distal to the LSA and extending to above the diaphragm.[2] In adults, the diameter of the aorta is about 30 mm at the aortic root and about 25 mm at the level of the diaphragm. Age is the major influential factor in the aneurysm diameter size increase and all diameters increase with age.[3] It has been reported that aortic diameters increase about 1 mm per decade during adulthood.[4] Generally, a diameter in the thoracic aorta > 4.5 cm is considered aneurysmal. [1, 2,3,4,5]

A thoracic aortic aneurysm (TAA) is a life-threatening condition. Annually, the incidence of TAA in a population-based study is 10.4 per 100,000 person-years, and the DTA is involved in about 40% of those cases.[6] The number of people diagnosed with an aneurysm of the DTA is thought to be increasing. Factors that contribute to this rise include increased longevity of the population and improved diagnostic capability.[6,7,8]

The natural history of TAAs, including aneurysms of the DTA, is one of progressive enlargement and rupture, and rupture is almost invariably fatal. An early study on the natural history reported that over 90% of patients sustained aneurysm growth during the period of observation.[9] Risk of rupture has been found to be correlated to aneurysm size and growth rate.[5] An average growth rate of 0.19 cm per year has been observed in aneurysms of the DTA in the past.[10] An aneurysm diameter of 6-cm has been generally considered the urgent point of the risk for rupture.

Degenerative change of the aortic wall is the cause of most aneurysms of the DTA. Medial degenerative disease is responsible for most fusiform aneurysms of the DTA. The smooth muscle cells and elastic laminae in the media are replaced by cystic spaces filled with mucoid material, which produces progressive weakening and dilatation of the aortic wall, with eventual aneurysm formation and subsequent complications such as rupture.[11] Arteriosclerosis is a process that primarily involves the aortic intima, which accounts for 80% of the aneurysms found in the thoracic aorta. [12] The intima degenerative change is characterized by raised atheromatous intimal plaques consisting of a lipid core and fibrous cap, which eventually compromises blood flow and weaken the vessel wall. TAAs that are caused by atherosclerosis are frequently saccular, and could result from penetrating atherosclerotic ulcers.[11,12] Current available treatment includes medical treatment, open surgical repair and endovascular stent-graft repair.

Standard surgical treatment involves a thoracotomy, aortic clamping to re-section the aneurysmal segment and replacement using a Dacron graft. Endovascular stent graft repair consists of transfemoral or iliac introduction of the device. When the stent graft device is deployed and expanded within the aneurysmal blood vessel, it creates a new aortic lumen for the blood flow, excluding the aneurysm sac from blood flow while maintaining perfusion to the lower body. Studies comparing open surgical repair versus endovascular repair concluded that the latter offers a less invasive, less expensive alternative, a decrease in mortality and morbidity in high-risk patients, associated with shorter hospital stay and quicker return to normal activities after surgery.[13,14]

However, despite the wide spread adoption of thoracic endovascular aneurysm repair (TEVAR) in modern treatment of TAAs, not all patients are candidates for TEVAR due to anatomical limitations. Since TEVAR devices often require a large-profile delivery system (often outer diameter of 22 Fr to 27 Fr), the presence of large, femoral-iliac arteries is necessary. This represents a significant contributor to the risks of access-vessel injury, which continues to be a significant cause of serious morbidity and even mortality related to thoracic endovascular procedures. Furthermore, female patients make up >30% of TEVAR subjects and tend to have small arteries, which compounds the vessel-access problems described. Other anatomical characteristics such as limited proximal and distal aortic neck lengths and angulated aortic arches

have been identified as risks factors that can limit TEVAR too. Complications associated with challenging proximal neck anatomy include type I endoleak and stent graft migration while limited distal fixation may lead to inadequate distal seal that affects long-term treatment success. In addition, patients that have challenging angulated aortic arches have the potential for significant problems during TEVAR due to non-conformability of stent grafts, especially along the lesser curve. Landing or fixating in the area of the distal arch that transitions into the descending aorta can lead to potentially fatal complications.[18]

Today's commercially available stent graft systems have markedly improved upon first-and second-generation systems dating back from the early 1990s and tend to resolve these issues by addressing such limitations. Manufacturers have designed stent grafts to be more flexible and conformable in addition to enhancing delivery systems with respect to tip design, flexibility, sheaths and other features to improve deployment controllability and accuracy. Delivery system profiles have been reduced with the intent to minimize endothelial trauma that lead to access vessel complications and improve accessibility in patients with smaller access vessels. Despite these enhancements, challenges remain in terms of TEVAR applicability. Next-generation systems are faced with the challenge of minimizing complications and secondary-procedure rates while safely treating increasingly complex and challenging anatomies.

Medtronic has a long history with the design and commercialization of thoracic aortic stent grafts, most recently with the Valiant Captivia Stent Graft System.

The Valiant stent graft on the Xcelerant Delivery System was CE marked in March, 2005 followed by CE marking of the Valiant Captivia stent graft System in September, 2009. Valiant Captivia was commercially released in the European Union in October, 2009. The same stent graft system received FDA commercial approval in April 2011 leveraging data from the VALOR II Clinical Study, the Talent Thoracic stent graft with Captivia Delivery System Clinical Study, and the Valiant Captivia Post-Market Registry. To date, over 75,000 patients (ca. 92,500 units used) have been implanted worldwide with this commercially available device since its launch in October 2009. Medtronic's next generation thoracic aortic stent graft is the Valiant Evo Thoracic Stent Graft.

The Valiant Evo Thoracic Stent Graft System incorporates design changes from the Valiant Captivia Stent Graft System that are targeted to broaden patient applicability, enhance ease of use, and improve vascular access by way of a reduced profile of the delivery system. This device will address an important TEVAR need: a significant reduction of the delivery system profile (profile of 18Fr for stent graft diameters ≤25 mm, profile of 20Fr for stent graft diameters ≤37 mm and profile of 22Fr for stent graft diameters ≥ 40 mm). A lower profile will better facilitate the endovascular treatment of patients with smaller vessel diameters as well as narrow, tortuous and/or calcified iliac arteries. Lower profile will potentially enable a percutaneous approach which could reduce complications related to cut down, shorten procedure time, blood loss, improve patient comfort and reduce the time to ambulation.

The Valiant Evo Thoracic Stent Graft System has incorporated other design changes from the Valiant Captivia Stent Graft System with the following of notable importance:

- Introduction of the Closed Web configuration with the tip capture mechanism as the proximal or distal device
- Reduced length of tapered tip of the delivery system
- Stent graft configurations with longer length (up to 225 mm) and increased taper (5 – 6 mm)
- An optimized size matrix, including 60 mm extensions for use as cuffs in the descending aorta.

These enhancements were incorporated in the Valiant Evo Thoracic Stent Graft System design with an expressed focus on maintaining the high durability and high performance standards established with previous Valiant Captivia Stent Graft System. When designing the features of the Valiant Evo device, it was critical that the durability, clinical safety and performance standards

established with Valiant were maintained. All design changes and device attributes incorporated within the Valiant Evo design will be evaluated via the full suite of planned design verification and validation testing, which includes bench and in vivo testing, to ensure the device with the design modifications meets the pre-established design and performance specifications and to ensure that product performance will be clinically acceptable.

B.2 Device information

The study device being evaluated in this clinical study is the Valiant Evo Thoracic Stent Graft System which is an investigational device manufactured by Medtronic.

B.2.1 Device Description

The Valiant Evo Thoracic Stent Graft System is designed for the endovascular repair of lesions in the DTA. When placed within the target lesion, the stent graft provides an alternative conduit for blood flow within the subject's vasculature by excluding the lesion from blood flow and pressure.

The Valiant Evo Thoracic Stent Graft System is composed of two main components: the implantable Valiant Evo Thoracic Stent Graft and the disposable delivery system. The Valiant Evo Thoracic Stent Graft is preloaded into the delivery system, which is inserted endoluminally via the femoral or iliac artery and tracked through the subject's vasculature to deliver the stent graft to the target site.

B.2.1.1 Valiant Evo Thoracic Stent Graft

A single, primary stent graft may be used by itself if its size is sufficient to provide the desired coverage. Alternatively, it may be used in combination with additional stent graft sections that increases the graft length distally or proximally to the primary section.

All Valiant Evo Thoracic Stent Graft components are composed of a self-expanding, spring scaffold made from nitinol wire sewn to a polyester fabric graft with non-resorbable sutures (see **Figure B-1** and **Figure B-2** below). The metal scaffolding is composed of a series of serpentine stents stacked in a tubular configuration. Platinum-Iridium radiopaque (RO) markers are sewn to the fabric for radiographic visualization of the edge of the graft material and the minimum overlap required when multiple stent grafts are used. The three proximal markers, and the two distal markers, indicate the extremities of the covered stent graft. The single "mid-marker" indicates the minimum amount of overlap required for multiple components. The materials used in the Valiant Evo Thoracic Stent Graft are listed in **Table B-1**.

Table B-1: Valiant Evo Thoracic Stent Graft Materials

Component	Material
Springs	Nitinol wire (55% Nickel, 45% Titanium with trace elements)
Graft Fabric	High-density woven multifilament polyester
Sutures	Ultra-high-molecular-weight polyethylene (UHMWPE) and polyester
RO Markers	Platinum-Iridium

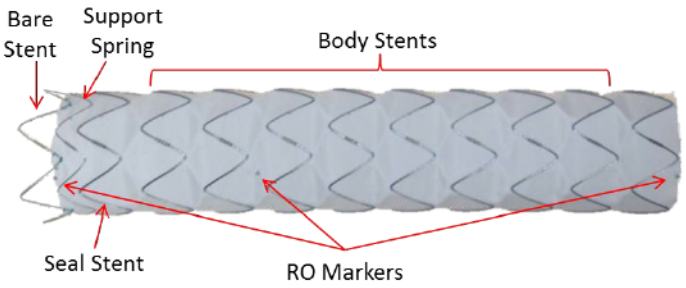


Figure B-1: Valiant Evo FreeFlo Configuration

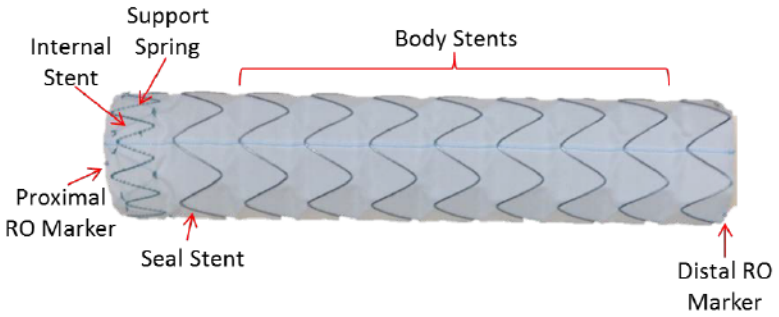
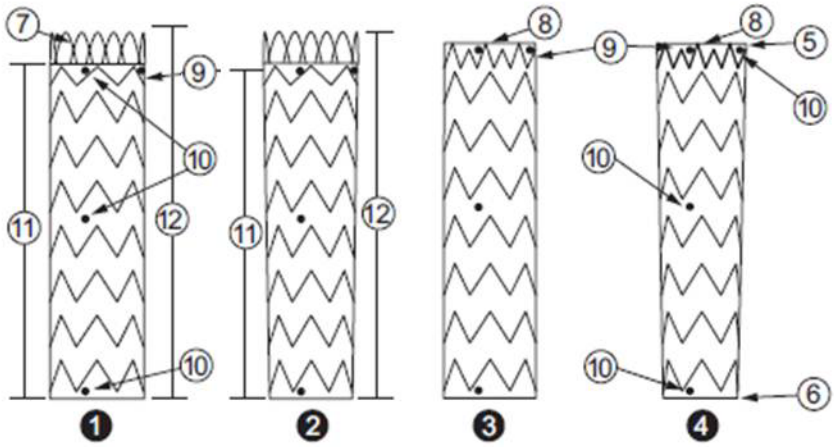


Figure B-2: Valiant Evo Closed Web Configuration

During manufacturing, the Valiant Evo Thoracic Stent Graft will be pre-loaded into the Valiant Evo Delivery System. The nitinol stents are also visible under fluoroscopy.

The Valiant Evo Thoracic Stent Graft System is available in four different configurations (see Figure B-3): FreeFlo Straight, FreeFlo Tapered, Closed Web Straight, and Closed Web Tapered. All configurations can be used either as a proximal or distal component when multiple stent grafts are implanted. Each stent graft consists of a fabric tube on which a series of 6-peak (18 Fr or 20 Fr) or 7-peak (22 Fr) stents and a support spring are sewn. The support spring contributes to diameter recovery of the stent graft following deployment and prevents the stent graft from infolding during and after deployment. Stent graft diameters range from 20 – 46 mm with covered length from 60 – 225 mm (refer to Section B.2.1.3 for full size matrix).



1. FreeFlo Straight
2. FreeFlo Tapered
3. Closed Web Straight
4. Closed Web Tapered
5. Proximal End
6. Distal End
7. FreeFlo
8. Closed Web
9. Support Spring
10. RO marker
11. Covered Length
12. Total Length

Figure B-3: Stent Graft Configuration Components

FreeFlo Straight Configuration
This configuration includes a FreeFlo proximal end and a Closed Web distal end. At the proximal end, a 6-peak (18 Fr or 20 Fr) or 7-peak (22 Fr) bare stent extends past the covered stent graft to provide additional fixation while maintaining transvessel flow. The proximal-end and distal-end diameters of the FreeFlo Straight configuration are constant throughout the covered length of the device. A FreeFlo end should not be placed inside the fabric-covered section of another stent graft.

FreeFlo Tapered Configuration
This configuration includes a FreeFlo proximal end and a Closed Web distal end. At the proximal end, a 6-peak (18 Fr or 20 Fr) or 7-peak (22 Fr) bare stent extends past the covered stent graft to provide additional fixation while maintaining transvessel flow. The proximal end of the FreeFlo Tapered configuration is larger in diameter than its distal end. A FreeFlo end should not be placed inside the fabric-covered section of another stent graft.

Closed Web Straight Configuration
This configuration includes Closed Web proximal and distal ends. The proximal and distal end diameters of the Closed Web Straight configuration are constant throughout the covered length of the device.

Closed Web Tapered Configuration
This configuration includes Closed Web proximal and distal ends. The proximal end of the Closed Web Tapered configuration is larger in diameter than its distal end.

B.2.1.2 Valiant Evo Delivery System

The Valiant Evo delivery system consists of a single-use, disposable catheter with an integrated handle to provide controlled deployment. It is available in an outer diameter of 18, 20, or 22 Fr and a working length of 93 cm. The catheter assembly is flexible and exclusively compatible with a 0.035-in (0.89-mm) guidewire.

The Valiant Evo Delivery System features a tip capture mechanism in which the stent graft is deployed in two stages – (1) retraction of the graft cover, gradually exposing the stent graft while

allowing re-positioning of the implant prior to full deployment (2) release of the first (captured) stent which allows the graft to fully open into position.

The Valiant Evo Delivery System is a multi-lumen device, with each lumen serving a different function:

- The PEEK guidewire tube (inner member) provides a lumen to allow the system to track over a Ø0.035" guide wire.
- The capture tube provides a lumen to actuate the tip capture release mechanism.
- The middle member with flexible stent stop and stent transition tube helps the device track through tortuous anatomy, maintains stent graft position during deployment, and improves kink resistance of the catheter.
- The graft cover (with stainless steel braid) provides a lumen that constrains the stent graft and flexible stent stop during tracking and final positioning of the system. The stent graft is released from the graft cover tube during deployment.

1. Luer Connector
2. Screw Gear
3. Retractor Handle
4. Trigger
5. Front Grip
6. Graft Cover/Introducer Sheath
7. Stent Stop
8. Tip Capture Mechanism
9. RO Marker Band
10. Tapered Tip
11. Back End Lock
12. Tip Capture Release Handle
13. Screw Gear Retainer
14. Flush Port

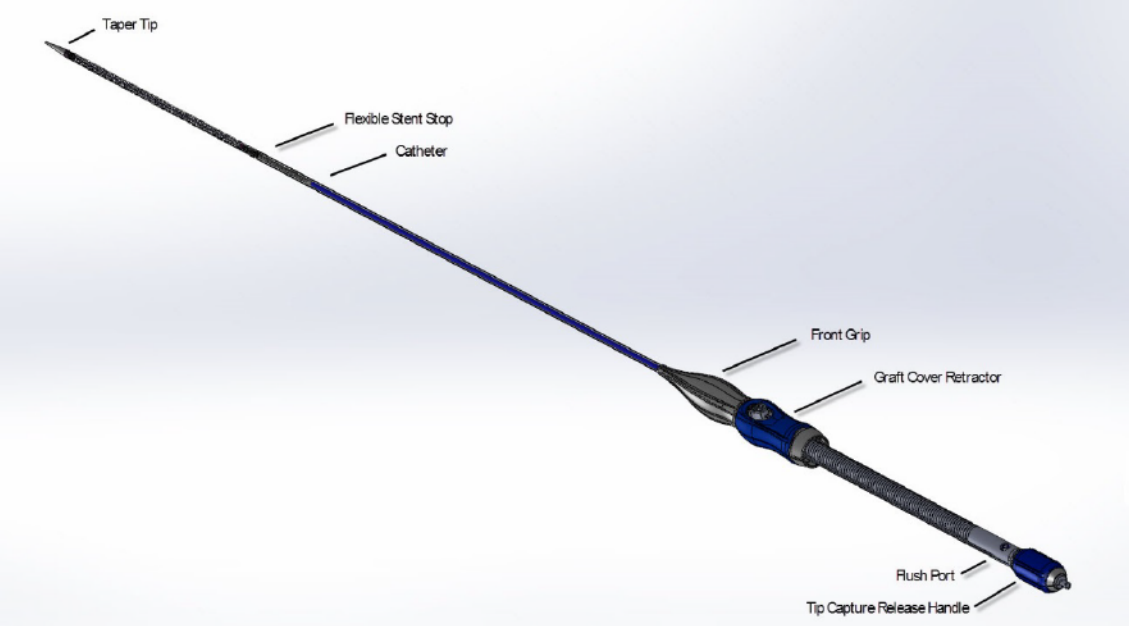


Figure B-4: Valiant Evo Stent Graft Delivery System

The Valiant Evo Thoracic Stent Graft System is an investigational class III device in all geographies and is labeled with all the required statements per geography:

- United States: "CAUTION: Investigational Device. Limited by Federal Law (USA) to Investigational Use"

The use of the Valiant Evo Thoracic Stent Graft System is limited to this clinical investigation and has to be done according to the clinical investigational plan and the Instructions for Use (IFU). Required Investigator training for the use of the Valiant Evo Thoracic Stent Graft System is described in Section E. 4.

B.2.1.3 Device sizes and configurations

Table B-2 presents the proposed sizes and configurations of the Valiant Evo Thoracic Stent Graft System, and the sizing guidelines provided in **Table B-3**.

Detailed information on device sizes and configurations will be included in the IFU. The IFU will be provided with each investigational device.

Table B-2: Valiant Evo Thoracic Stent Graft System Size Matrix

FreeFlo and Closed Web Straight configurations

OD (Fr)	Diameter (mm)	Covered Length (mm)
18	20	100
	22	100, 175
	25	
20	28	
	31	100, 175, 225
	34	60, 100, 175, 225
	37	
22	40	
	43	
	46	

FreeFlo Tapered configurations

OD (Fr)	Proximal × Distal Diameter (mm)	Covered Length (mm)
18	25x20	175
20	28×22	
	31×25	
	34×28	
	37×31	
22	40×34	
	43×37	
	46×40	

Closed Web Tapered configurations

OD (Fr)	Proximal × Distal Diameter (mm)	Covered Length (mm)
18	25×20	175
20	28×22	200
	31×25	
	34×28	
	37×31	
22	40×34	
	43×37	
	46×40	

Table B-3: Sizing guidelines for the treatment of aneurysms

Graft Diameter (mm)	Vessel Diameter Indication (mm)
20	16–17
22	18–19
25	20–22
28	23–25
31	26–28
34	28–31
37	30–33
40	33–36
43	36–39
46	39–42

B.2.2 Indications for Use

The Valiant Evo Thoracic Stent Graft System is indicated for the endovascular repair of fusiform aneurysms and saccular aneurysms/penetrating ulcers of the descending thoracic aorta (DTA) in patients having the appropriate anatomy including the following:

- Iliac or femoral artery access vessel morphology that is compatible with vascular access techniques, devices, or accessories
- Nonaneurysmal aortic diameter from 16 mm to 42 mm
- Nonaneurysmal aortic proximal neck length ≥20 mm (for FreeFlo configuration) and ≥25 mm (for Closed Web configuration)
- Distal neck length ≥20 mm

Detailed information on intended use of the device, indications and contraindications, as well as a complete list of warnings, precautions and potential adverse events, will be included in the IFU. The IFU will be provided with each investigational device.

C STUDY PLAN

C.1 Study objectives

The purpose of the Valiant Evo US Clinical Trial is to demonstrate the safety and effectiveness of the Valiant Evo Thoracic Stent Graft System in subjects with a descending thoracic aortic aneurysm (DTAA) who are candidates for endovascular repair.

The clinical evidence collected as part of this trial will be used in conjunction with data collected during the concurrently enrolling Valiant Evo International Clinical Trial to support PMA Approval of the Valiant Evo Thoracic Stent Graft System.

Clinical follow up requirements will continue to 60 months to provide longer-term evidence on the device's performance, permitting accumulation of additional device use experience and clinical outcomes to support post-marketing surveillance.

The clinical evidence collected through 60 months may be used in conjunction with the data collected from the concurrently enrolling Valiant Evo International Clinical Trial to support commercial approvals in geographies worldwide.

C.1.1 Primary objectives

The primary objective is to demonstrate the safety and effectiveness of the Valiant Evo Thoracic Stent Graft System in subjects with a DTAA who are candidates for endovascular repair.

C.1.2 Secondary objectives

Secondary objectives include descriptive analyses of secondary endpoints as well as acute procedural observations and clinical utility measures. A hypothesis driven endpoint is planned for 12 months as described in Appendix L6.

C.2 Clinical endpoints

C.2.1 Primary endpoints

The primary objective will be assessed by the composite safety and effectiveness endpoint that is based on the proportion of subjects who experienced:

(a) Access and/or deployment failures; and/or

(b) MDE within 30 days post index procedure

MDEs include the occurrence of any of the following:

- Device-related secondary procedures
- Device-related mortality
- Conversion to open surgery
- Thoracic aortic aneurysm rupture

Detailed definitions of MDEs are defined in Appendix L.5.

An independent CEC will be established and adjudicate MDEs.

C.2.2 Secondary endpoints

C.2.2.1 30-day Secondary Endpoint

The following secondary endpoints will be evaluated within 30 days post treatment:

- Peri-operative mortality
- All adverse events (AE) within 30 days including:
    - Major Adverse Event(s) (MAE)
    - Serious Adverse Event(s) (SAE)
- Secondary procedures
- Loss of stent graft patency at 30 day visit based on imaging findings
- Endoleaks at 30 day visit based on imaging findings

Major adverse events include the occurrence of any of the following:

- Respiratory complications: atelectasis/pneumonia, pulmonary embolism, pulmonary edema, respiratory failure
- Renal complications: renal failure, renal insufficiency
- Cardiac complications: MI, unstable angina, new arrhythmia, exacerbation of CHF.
- Neurological complications: new CVA, embolic events, paraplegia, paraparesis.
- Gastrointestinal complications: bowel ischemia
- Major bleeding complication (procedural or post-procedural), coagulopathy.
- Vascular complications: aortic rupture, aneurysm rupture, hematoma at access site, pseudo or false aneurysm, arteriovenous (AV) fistula, retroperitoneal bleed, limb ischemia, thrombosis

Detailed definitions of MAEs are defined in Appendix L.2.2

C.2.2.2 6-month Secondary Endpoints:

The following secondary endpoints will be evaluated:

- All-cause mortality within 183 days
- Aneurysm-Related Mortality within 183 days
- MDEs within 183 days
- All AEs within 183 days including:
    - MAEs
    - SAEs
- Secondary procedures within 183 days
- Loss of stent graft patency within 6 months based on imaging findings
- Endoleaks at 6 months based on imaging findings
- Stent graft migration at 6 months as compared to 1-month imaging
- Aneurysm expansion > 5mm at 6 months based on imaging findings relative to the 1-month visit

C.2.2.3 12-month Secondary Endpoints

The following secondary endpoints will be evaluated:

- All-cause mortality within 365 days
- Aneurysm-Related Mortality within 365 days
- MDEs within 365 days
- All AEs within 365 days including:

- MAEs
- SAEs

- Secondary procedures within 365 days
- Loss of stent graft patency within 12 months based on imaging findings
- Endoleaks at 12 months based on imaging findings
- Stent graft migration at 12 months as compared to 1-month imaging
- Aneurysm expansion > 5mm at 12 months based on imaging findings relative to the 1-month visit

C.2.2.4 24, 36, 48 and 60-month Secondary Endpoints

The following secondary endpoints will be evaluated:

- All-cause mortality up to each timepoint
- Aneurysm-Related Mortality up to each timepoint
- MDEs up to each timepoint
- All AEs up to each timepoint:
  - MAEs
  - SAEs
- Secondary procedures up to each timepoint
- Loss of stent graft patency (site-reported) up to each timepoint based on imaging findings
- Endoleaks (site-reported) at each timepoint based on imaging findings
- Stent graft migration (site-reported) at each timepoint as compared to 1-month imaging
- Aneurysm expansion > 5mm (site-reported) at each timepoint based on imaging findings relative to the 1-month visit

C.2.3 Additional observations

The following acute procedural observations and clinical utility measures will be analyzed:

- Mean duration (min) of procedure
- Proportion of subjects who underwent general anesthesia
- Proportion of subjects who underwent percutaneous access
- Proportion of subjects requiring blood transfusions
- Mean number of units of blood transfused, if required
- Mean volume (cc) of estimated blood loss
- Mean length of time (hours) in intensive care unit
- Mean length of time (days) of hospital stay (from the index procedure to hospital discharge)

Health-related quality of life outcomes will be assessed at all scheduled follow-up visits using the EQ-5D questionnaire.

C.3 Study Hypothesis

The Valiant Evo US Clinical Trial will focus on balancing pre- and post-market clinical data to establish safety and effectiveness.

The primary study endpoint will be tested against a performance goal of 16% at 30 days:

H_0: $p \geq 16\%$ vs. H_a: $p < 16\%$,

where p denotes the true event rate of primary study endpoint in the target population.

If the null hypothesis (H_0) is rejected at the one-sided 0.025 statistical significance level, it is considered that the performance goal for the primary endpoint has been reached.

IDE cohort will be followed up to 1-year and the primary endpoint will be tested against a 20% performance goal at 1 year for the post-approval analysis. Refer to Appendix L-6- PMA-S Post Approval analysis.

C.4 Study population

The study population will include those subjects who are appropriate candidates for endovascular repair of DTAA, and who meet the Inclusion/Exclusion criteria (defined in Section D).

C.5 Study design

The Valiant Evo US Clinical Trial is a prospective, multi-center, pre-market, non-randomized, single-arm trial. The trial is designed to assess the safety and effectiveness of the Valiant Evo Thoracic Stent Graft System in subjects with a descending thoracic aortic aneurysm (DTAA) who are candidates for endovascular repair.

The clinical performance of the Valiant Evo Thoracic Stent Graft will be evaluated in a total of 100 subjects with a hypothesis-based 30-day premarket composite safety and effectiveness endpoint.

The proposed primary composite safety and effectiveness endpoint is based on the proportion of subjects who experienced:

(a) Access and/or deployment failures; and/or

(b) Major Device Effect (MDE) within 30 days post index procedure

MDEs include the occurrence of any of the following:

- Device-related secondary procedures
- Device-related mortality
- Conversion to open surgery
- Thoracic aortic aneurysm rupture

This primary composite endpoint will be compared to a PG of 16% MDE rate at 30 days.

All subjects included will continue to be followed under this investigational protocol beyond the 30-day primary endpoint out to 60 months post-implantation. Subjects will have required follow-up evaluations at the following time points:

- 1-month following the index procedure
- 6-months following the index procedure
- 12, 24, 36, 48 and 60-months following the index procedure

All subjects were consented for up to 2 years of follow-up. This was to accommodate any global clinical investigational requirements, if required. Subjects already enrolled and willing to extend

their follow-up from 12 to 60 months are to be re-consented. Enrolled subjects who decline to continue to participate in follow-up beyond 12-months shall exit the study upon the completion of their 12-month visit.

A Data Monitoring Committee, Clinical Events Committee, and imaging core lab will be established to independently evaluate subject health status, device performance, and identify any safety concerns regarding subjects' well-being. An imaging core lab will not be used to perform independent imaging assessments regarding device performance beyond 12 months of follow-up.

C.6 Randomization and blinding

The study is a single arm study, therefore neither randomization nor blinding are applicable to this clinical trial.

C.7 Sample size

Globally, a total of 100 subjects will be concurrently enrolled in the United States and outside the United States to support the primary endpoints. Up to 50% of subject data used to support PMA approval may come from subjects enrolled at sites outside of the US under a separate CE Mark study protocol; called the Valiant Evo International Clinical Trial protocol.

The Valiant Evo International Clinical Trial protocol and Valiant Evo US Clinical Trial protocol will be identical with respect to the inclusion/exclusion criteria.

One hundred (100) enrolled subjects will ensure 87 evaluable subjects at 30 days. The primary endpoint analysis will be completed upon 87 evaluable subjects reaching the 30 day endpoint. The data from these 87 evaluable subjects at 30-days will be used to file the PMA submission. Based on Valor II study results, Valiant Evo is expected to perform similarly and have 6% of MDEs combined with access and/or deployment failures at 30 days. The sample size of 87 evaluable subjects will provide 85% statistical power for the study hypothesis. The type I error is controlled at the one-sided 0.025 level.

Table C-1: Power Analysis

True rate of MDEs combined with access and/or deployment failures at 30 day with Valiant Evo	6%
Performance Goal	16%
Significance level	0.025
Statistical test	One-sided binomial test
Evaluable sample size	n=87
Enrollment	Minimum of 100 subjects enrolled to ensure 87 evaluable subjects
Statistical power from the 87 evaluable subjects	85%

C.8 Number of Investigational sites and study duration

The Valiant Evo Global Clinical program will be conducted at up to 37 sites worldwide, with at least 50% of the clinical sites coming from the United States. Inclusion will be halted at sites

that reach the 20% inclusion cap. There will be no minimum number of subjects for a single investigational site.

The total enrollment period is expected to be approximately 12 months. Enrolled subjects will be followed up at 1, 6 and 12 months and annually to 5 years post-implantation.

A list of names and addresses of the investigational sites and principal investigators in which the clinical study will be conducted will be kept separate from the clinical investigation plan and provided to the investigators. The sponsor will maintain an updated list.

D SUBJECT SELECTION

D.1 Inclusion criteria

Candidates for the Valiant Evo US Clinical trial must be appropriate subjects for endovascular repair of aneurysms of the descending thoracic aorta (evidenced by screening contrast-enhanced CT or MRA) and have to fulfill all of the following inclusion criteria to be eligible for recruitment in the study:

1. Subject is ≥18 years old.
2. Subject understands and voluntarily has signed and dated the Informed Consent Form approved by the Sponsor and by the Ethics Committee for this study.
3. Subject presents a DTAA which is localized below the ostium of LSA and above the ostium of celiac trunk
4. Subject has a DTAA that is one of the following:
    a. A fusiform aneurysm with a maximum diameter that:
        - is ≥ 50 mm and/or:
        - is > 2 times the diameter of the non-aneurysmal thoracic aorta and/or:
        - is < 50 mm and has grown ≥ 5 mm within previous 12 months
    b. A saccular aneurysm or a penetrating atherosclerotic ulcer
5. Subject's anatomy must meet all of the following anatomical criteria as demonstrated on contrast-enhanced CT and/or on contrast-enhanced MRA obtained within four (4) months prior to implant procedure:
    a. Proximal and distal non-aneurysmal aortic neck diameter measurements must be ≥ 16 mm and ≤ 42 mm;
    b. Proximal non-aneurysmal aortic neck length must be ≥ 20 mm *(for FreeFlo configuration)* and ≥ 25 mm *(for Closed Web configuration)* distal to the left common carotid artery (LCCA). Note: Proximal aortic neck length may include covering the LSA (with or without discretionary revascularization) when necessary to optimize device fixation and maximize aortic neck length. If occlusion of the LSA ostium is required to obtain adequate neck length for fixation and sealing, transposition or bypass to the LSA may be warranted.
    c. Distal non-aneurysmal aortic neck length must be ≥ 20 mm
6. Subject has adequate arterial access site or can tolerate a conduit that allows endovascular access to the aneurysmal site with the delivery system of the appropriate sized device chosen for the treatment.

D.2 Exclusion criteria

Candidates who meet any of the following exclusion criteria will not be eligible for recruitment in the study:

1. Subject has a life expectancy of less than 1 year
2. Subject is participating in another investigational drug or device study which would interfere with the endpoints and follow-ups of this study.
3. Subject is pregnant.
4. Subject requires planned placement of the covered proximal end of the stent graft to occur in zones 0 or 1.

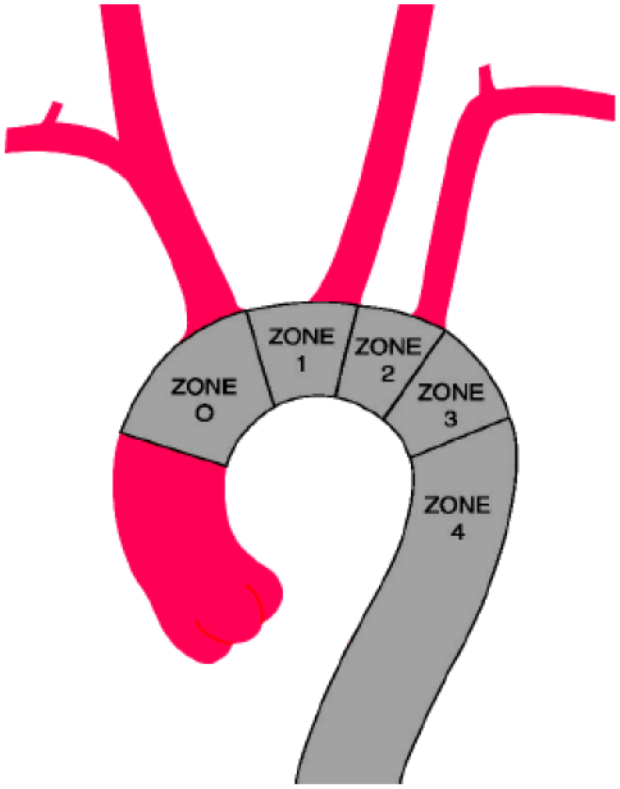


Figure D-1: Landing zones of the thoracic aorta

(See appendix L.2.4 for definitions of zones)

5. Subject has a thoracic aneurysm with a contained rupture or localized at the anastomosis of a previous graft (pseudo-/false aneurysm).
6. Subject has a mycotic aneurysm.
7. Subject has a dissection (type A or B) or an intramural hematoma or an aortic rupture in addition to the thoracic aneurysm.
8. Subject requires emergent aneurysm treatment, e.g., trauma or rupture.
9. Subject has received a previous stent or stent graft or previous surgical repair in the ascending and/or descending thoracic aorta, and/or in the aortic arch.
10. Subject requires surgical or endovascular treatment of an infra-renal aneurysm at the time of implant
11. Subject has had previous surgical or endovascular treatment of an infra-renal aortic aneurysm.
12. Treatment with the Valiant Evo Thoracic Stent Graft would require intentional revascularization of the brachio-cephalic artery or the left common carotid artery or the celiac trunk.

13. Subject has had or plans to have a major surgical or interventional procedure within 30 days before or 30 days after the planned implantation of the Valiant Evo Thoracic Stent Graft. This does not include planned procedures that are needed for the safe and effective placement of the stent graft (i.e., carotid/subclavian transposition, carotid/subclavian bypass procedure).
14. Subject has a significant and/or circumferential aortic mural thrombus at either the proximal or distal attachment sites that could compromise fixation and seal of the implanted stent graft.
15. Subject has a connective tissue disease (e.g., Marfan's syndrome, aortic medial degeneration).
16. Subject has a bleeding diathesis or coagulopathy, or refuses blood transfusion.
17. Subject has had a MI within 3 months of the procedure.
18. Subject has had a CVA within 3 months of the procedure.
19. Subject has a known allergy or intolerance to the device materials
20. Subject has a known allergy to anesthetic drugs
21. Subject has a known hypersensitivity or contraindication to anticoagulants, or contrast media, which is not amenable to pretreatment.
22. Subject has active or systemic infection at the time of the index procedure.

E STUDY PREPARATION PROCEDURES

E.1 Investigator/Investigation site selection

E.1.1 Investigator selection criteria

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical study as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical study.

An investigator may be included in the clinical study if compliant with the following requirements:

- Investigators are appropriately qualified practitioners and experienced in the diagnosis and treatment of subjects requiring an endovascular procedure with a thoracic stent graft
- Investigators have adequate time to follow up on the clinical study
- Investigators are willing to comply with the clinical investigation plan
- Investigators are willing to sign the appropriate clinical trial agreement
- Investigators have past experience with conducting clinical studies or appropriate training
- Investigators are familiar with FDA/ICH-GCP requirements
- Investigators are willing to undergo auditing by sponsor or regulatory bodies
- Investigators are willing to undergo study specific training

E.1.2 Investigation site selection criteria

An investigation site may be selected for participation in the clinical study if compliant with the following requirements:

- Adequate staff (sub-investigator and/or research coordinator) that is accessible and has time to manage the trial and data reporting requirements
- Site personnel has demonstrated experience with conducting clinical (specifically device) trials that comply with applicable regulatory standards

- Site has sufficient annual case volume of DTAA stent graft procedures
- Ability to securely store devices according to the Instructions for Use
- Ability to perform required imaging assessments at site

E.1.3 Clinical Trial Agreement

A clinical trial agreement shall be in place, signed by the participating investigational site and/or principal investigator of each investigational site, as per the local legal requirements, and returned to Medtronic prior to the commencement of any clinical study activities. The investigator is indicating approval of the clinical investigation plan and subsequent amendments, with a fully executed agreement.

E.2 Ethics

E.2.1 EC/IRB approval

Prior to enrolling subjects in this clinical study, each investigational site's EC/IRB will be required to approve the current Clinical Investigation Plan, the Informed Consent Form, including any other written information to be provided to the subjects and, if applicable, materials used to recruit subjects. EC/IRB approval of the clinical study must be received in the form of a letter and a copy provided to Medtronic before commencement of the clinical study at an investigational site. The approval letter must contain enough information to identify the version or date of the documents approved. If this information is not contained in the approval letter, it must be retrievable from the corresponding submission letter. In addition the approval letter needs to be accompanied by an EC/IRB roster or letter of compliance, to allow verification that the investigator, other investigation site personnel, and/or Medtronic personnel are not members of the EC/IRB. If they are members of the EC/IRB, written documentation is required stating that he/she did not participate in the approval process. If the EC/IRB imposes any additional requirements (e.g. safety reports, progress reports), the site must request these additional requirements in writing, and then Medtronic will prepare the required documents and send them to the investigator for reporting to the EC/IRB. Investigators must inform Medtronic of any change in status of EC/IRB approval once the investigational site has started enrollment. If any action is taken by an EC/IRB with respect to the investigation, that information will be forwarded to Medtronic by the respective investigator.

E.2.2 Informed consent process

The investigator or authorized designee must obtain written informed consent before any clinical study related activity takes place.

Well in advance of the consent discussion, the subject should receive the EC/IRB approved Patient Information and Informed Consent Form. During the consent discussion the investigator or his/her authorized designee must fully inform the subject of all aspects of the clinical study that are relevant to the subject's decision to participate in the clinical study.

If a subject is unable to read and/ or write, an impartial witness must be present during the entire informed consent discussion. All items addressed in the Informed Consent Form must be explained. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the Informed Consent Form, to inquire about details of the clinical study, and to decide whether or not to participate in the clinical study. All questions about the clinical study should be answered to the satisfaction of the subject.

Neither the investigator, nor the investigation site staff shall coerce or unduly influence a subject to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the subject's rights.

When the subject decides to participate in the clinical study, the Informed Consent Form must be signed and personally dated by the subject and the investigator or authorized designee. If applicable, the witness shall also sign and personally date the consent form to attest that the information in the Informed Consent Form was accurately explained and clearly understood by the subject, and that informed consent was freely given.

After all persons have signed and dated the Informed Consent Form the investigator must provide the subject with a copy of the signed and dated Informed Consent Form.

E.2.3 Revisions in Informed Consent Form

Medtronic revised the written informed consent template to include the extension of follow-up through 5 years post implant procedure. Subjects who are currently participating in the clinical study shall be asked to sign the updated informed consent to confirm their continuing informed consent in writing for up to 5 years of follow-up. The revised informed consent documents will be provided to the investigational sites for approval by the local EC/IRB.

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The investigator or his/her authorized designee should inform the subject in a timely manner.

If new information becomes available that can significantly affect the subject's future health and medical care, Medtronic will revise the written Informed Consent Form. The revised information will be sent to the investigator for approval by the EC/IRB. After approval by the EC/IRB, if relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

E.2.4 Regulatory submission

In countries where submission to the Regulatory Authority is required per local law, no subjects will be enrolled in the clinical study until the particular Regulatory Authority has approved the current Clinical Investigation Plan of the clinical study and other documents as required according to the local requirements.

If the Regulatory Authority imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the respective authority.

Other documents that are referred to in this Clinical Investigation Plan are listed below and will be made available upon request:

- Monitoring Plan
- Data Management Plan
- Informed Consent Form
- Case Report Forms

E.3 Regulatory compliance

The Valiant Evo US Clinical Trial will be conducted under an FDA Investigational Device Exemption (IDE) in compliance with ICH-GCP, ISO 14155:2011 3.1, 3.15, 3.2, 3.36, 3.37, 3.42 and 21 CFR Parts 11, 50, 54, 56 and 812. 21CFR 803 Medical Device Reporting, 21CFR 814 Premarket Approval of Medical Devices

This study will be publicly registered before recruitment of the first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki (October 2013) on www.clinicaltrials.gov (PL 110-85, Section 810(a)).

In case of conflicting requirements, the regulation affording the greatest protection to the subject will be followed.

E.4 Training requirements

Prior to investigation site activation or subsequent involvement in clinical study activities, the sponsor will provide clinical study training relevant and pertinent to the involvement of personnel conducting clinical study activities. At a minimum, investigator responsibilities, Title 21 CFR, the clinical investigation plan, Informed Consent Form, use of data collection tool, as well as applicable local regulations are required. Furthermore investigators that will perform the index procedure and implantation of the device will be trained on the Valiant Evo Thoracic Stent Graft System. Study-specific training will be documented prior to investigational site activation.

Medtronic and/or its designees are responsible for the training of appropriate clinical site personnel, including the investigator, co-investigator(s), study coordinator(s), and as necessary other site personnel. Initial training will be conducted by Medtronic or its designees at a site initiation visit and/or Investigator meeting to ensure proper reporting of adverse events, uniform data collection and compliance with the protocol, consent processes and applicable regulations.

Also after initial training, Medtronic will provide training to other clinical site study team members. All study specific training must be documented on a formal training record that will be provided by Medtronic.

E.5 Clinical study materials

Medtronic will provide study materials to the site after approval of the site for participation. Before a study site can enroll a subject or have access to the electronic data capture (EDC) system, the investigator must be in receipt of a "Go letter" (this may be an email, fax or other written communication means) from Medtronic.

E.6 Study device/product traceability

E.6.1 Supply of investigational devices/products

Once the site has been activated and an eligible subject has been identified and consented through the protocol required screening process investigational devices/products will be ordered and shipped to the site.

E.6.2 Storage and handling of investigational devices/products

Investigational devices/products must be stored in a secured area. The method of storage shall prevent the use of investigational devices/products for other applications than mentioned in this clinical investigation plan. In addition, all information for the use, storage, and handling of the investigational device/product as indicated in the Instructions for Use must be taken into account.

E.6.3 Device explant and return procedures/products

All non-functioning or explanted investigational devices/products should be returned to Medtronic for analysis. Information pertaining to the explant procedure should be recorded. If a product is explanted and not returned to Medtronic, an explanation should be provided. The final disposition of the device must be recorded on the device disposition log. Relevant information should also be recorded on associated case report forms, e.g., Adverse Event and Study Exit Form. Detailed instructions for the return of non-functioning devices and explant of the device will be provided in the investigational site file and in appendix L.4.

F STUDY METHODS

F.1 Point of Enrollment

Pre Screening:

Investigators will assess potential subjects with a DTAA that are candidates for endovascular repair for their suitability for recruitment in the trial. Initial subject eligibility will be determined by the investigator based upon review of their medical history, disease process and anatomic suitability for inclusion in the trial as evidenced on screening contrast-enhanced CT/MRA. If the subject appears to meet the eligibility criteria, then the investigator will discuss the study with the subject and provide information relating to the potential risks and benefits, and required follow-up procedures per the informed consent process.

Test results that are within the timeframes specified below may be used even though the actual test was done prior to a subject's informed consent. This may be done only for standard of care tests with the intent to minimize stress and discomfort to the subject and reduce costs.

Required screening evaluations include the following.

- Pregnancy test (for female subjects of childbearing potential). Test must be completed per institutional standard of care at the time of screening (prior to) the index procedure. Results must be negative.
- Screening CT or MRA with contrast of the chest, abdomen and pelvis completed within four months prior to the index procedure. This will be used to visualize and assess the characteristics, length, and diameters of the DTAA and the surrounding anatomy.

Screening/ Baseline Assessments:

After the subject has voluntarily signed and dated the Informed Consent Form, the subject will be considered a study candidate. If a subject does not sign the Informed Consent Form, then no further study specific screening procedures can occur.

Collection of screening and baseline information will take place only after the subject has given voluntary, documented informed consent and will include the following:

- Subject demographics
- Medical history
- Current health status
- Risk factors
- ASA Physical Status Classification
- EQ-5D Questionnaire

Screening CT/MRA images will be reviewed by the investigator to confirm eligibility. The imaging will also be sent to a core lab to assess the anatomical inclusion/exclusion requirements. An Independent Physician Reviewer (IPR) will review screening CT/MRA images to confirm eligibility. Approval by the IPR must be obtained prior to a subject's actual inclusion in the study. The decision of the IPR will be communicated to the investigational site by the Sponsor. Those subjects who sign and date the Informed Consent, meet all study eligibility criteria, and are approved by the IPR will be eligible for inclusion in the study. Subjects that are not approved by the IPR are considered screen failures and will not be followed per study protocol.

Subjects who do not qualify for enrollment will be documented as ineligible on the Screening and Enrollment log.

Enrollment:

Those subjects who sign and date the informed consent document, meet all of the study eligibility criteria, and are approved by the IPR will be eligible for inclusion into the Valiant Evo US Clinical Trial. The subject will only be considered enrolled when arterial access is established and an attempt to introduce the Valiant Evo Thoracic Stent Graft is made.

Enrolled subjects will be documented on the electronic Screening and Enrollment Log. Subjects who are enrolled, but not implanted with the device, will be followed through the 1 month follow-up only.

The investigator will maintain a log of all subjects screened and enrolled in the clinical study, assigning an identification code linked to their names, alternative subject identification or contact information.

F.2 Implant or procedure aspects

F.2.1 Index Procedure

All investigators will read, understand and be trained to the Valiant Evo Thoracic Stent Graft System IFU prior to initiation of the procedure. The IFU is packaged with the device and must be followed for implantation of the stent graft system. The index procedure will include the following:

- Arterial access and implantation of the Valiant Evo Thoracic Stent Graft(s) per the IFU.
- Fluoroscopic guidance will be used for placement of the stent graft throughout the procedure.
- Additional procedures performed during the treatment will be documented on the appropriate eCRFs.
- Upon completion of the index procedure, a final run-off angiography should be performed to document the status of the Valiant Evo device(s), the aneurysmal sac, and the surrounding vasculature.

Identification and/or serial numbers for all investigational components of the Valiant Evo Thoracic Stent Graft System used or opened during the index procedure will be recorded.

Adverse event assessment should be done for all subjects as of the moment the subject is considered to be enrolled in the study.

F.2.2 Treatment failure

Inability to implant the Valiant Evo Thoracic Stent Graft System following arterial access due to deployment issues or entrapment of the delivery system will be considered a treatment failure. These subjects will be followed for 1-month and thereafter per institutional standard of care. Serious adverse events will be recorded in the eCRF through the total duration of the trial.

If a primary conversion to open repair is required during the index procedure, then the subject will be followed for 1 month and thereafter per institutional standard of care.

F.2.3 Hospital Discharge

The following assessments will be performed at hospital discharge and respective data will be collected on eCRFs:

- Adverse event assessment
- Duration of intensive care unit stay after index procedure (in hours)

F.2.4 Follow-Up Visits and Procedures

Each subject will have required post-implantation follow-up visits at 30-days, 6, 12, 24, 36, 48 and 60 months. Follow-up visits and associated timeframe windows are summarized in Table F-1.

Table F-1: Post-Implantation Follow-Up Visit Schedule and Windows

Follow-Up Visit	Window Start Day	Target Day	Window Close Day
1 Month (± 15 days)	15	30	45
6 Month (183 ±30 days)	153	183	213
12 Months (365 ±60 days)	305	365	425
24 Months (730 ±60 days)	670	730	790
36 Months (1095 ±60 days)	1035	1095	1155
48 Months (1460 ±60 days)	1400	1460	1520
60 Months (1825 ±60 days)	1765	1825	1885

At all required follow-up visits subjects will undergo the following assessments and procedures:

- Physical Examination
- Chest CT/MRI with contrast
- EQ-5D questionnaire
- Adverse event assessment

A CT/MRI with contrast acquired at discharge (or before day 15) due to medical necessity may be used to meet the 1-month follow-up visit CT/MRI requirement if a CT/MRI with contrast cannot be obtained within the 1-month follow-up window due to the subject's health status based upon physician discretion.

If conversion to open repair is required during the follow-up period, then the subject will be followed for 30 days after the conversion, at which time the subject will be exited from the study.

F.3 Data collection requirements

Clinical data will be collected preoperatively to establish eligibility, at baseline, during the index procedure, throughout the hospital stay, and postoperatively at the required (and any interim imaging) follow-up visits described in Section F.2. The data collection schedule is summarized in Table F-2. Imaging source data will be sent to a Core Lab for analysis up to the 12-month follow-up visit. Any interim imaging of the stent graft region but not linked to a study visit should be recorded on the Interim Image eCRF (e.g. imaging performed as standard of care beyond the protocol required time points and/or when performed further to any issue observed at previous imaging Follow-up).

Imaging source data beyond 12-months post-index procedure will not be sent to the Core Lab for analysis. Instead, study sites are to report the results of the imaging performed as standard of care and in line with local and site requirements directly on the e-CRF. Routinely acquired images may be required for adjudication purposes in case of CEC adjudication or any other safety event.

Study data will be collected using electronic case report forms (eCRFs) as described in Section G.1. Clinical investigators must electronically review and approve all eCRFs. Medtronic monitors will perform source document verification of the eCRFs. The monitoring strategy will be defined in the monitoring plan.

Table F-2: Data Collection Schedule

DATA	Screening / Baseline	Index Procedure	Hospital Discharge	1-Mo. F/U (±15 days)	6-Mo. F/U[d] (±30 days)	12-Mo. F/U (±60 days)	24, 36, 48 & 60-Mo. F/U (±60 days)
GENERAL							
Informed Consent	✓						
Inclusion Criteria/ Exclusion Criteria	✓						
Physical Examination	✓			✓	✓	✓	✓
Medical History	✓						
Current Health Status and Risk Factors	✓						
Device and Procedure Information		✓					
Pre-implant Adjunctive Procedures		✓					
Hospital Discharge Information			✓				
Adverse event assessment	✓[a]	✓	✓	✓	✓	✓	✓
EQ-5D questionnaire	✓			✓	✓	✓	✓
IMAGING							
CT/MRI with contrast [b]	✓[g]			✓[c,e,g]	✓[e,g]	✓[e,g]	✓[e,h]
Angiography		✓[f]					

[a] In case of screen failures, investigators will be requested to enter safety information in the eCRF from time point of enrollment until time point of screen failure
[b] CT evaluation may include "3-phase technique", volume studies, 3-D reconstruction, or computer-aided measurements
[c] A CT/MRI with contrast acquired at discharge (or before Day 15) due to medical necessity may be used to meet the 1-month follow-up visit CT/MRI requirement if a CT/MRI with contrast cannot be obtained within the 1-month follow-up window due to the subject's health status based upon physician discretion.
[d] For subjects enrolled in the Valiant Evo International Clinical Trial in European countries, a six month follow up visit is not required per protocol.
[e] MRI with contrast may be used for those patients experiencing renal failure or who are otherwise unable to undergo contrast-enhanced CT scan, with Transesophageal echocardiography (TEE) being an additional option in the event of suboptimal MR imaging.
[f] Required to complete Procedure eCRF but not expected to be submitted to Medtronic or Core Lab unless further analysis is needed.
[g] Imaging assessed by core lab.
[h] Upon sponsor request, core lab analysis of imaging may be required.

F.4 Role of the sponsor's representatives

Sponsor's representatives may provide support as required for the clinical study, including technical support during implant. The sponsor representative is an experienced expert of device sizing, placement and the technical features of the device and will advise the implanting physician during the implant procedure if needed. The sponsor representative will not be involved actively during the placement and deployment of the Valiant Evo Thoracic Stent Graft System.

F.5 Source documents

Investigators are required to maintain source data of each subject's case history, exposure to the device and clinical follow-ups. Source data is all information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation.

Examples of these original documents and data records include, but are not limited to:

- hospital record (paper and electronic, as applicable),
- subject's screening documentation,
- recording media such as CD, DVD, CT or other imaging reports,
- laboratory reports,
- device accountability records,
- worksheets and subject files at other departments.

Where paper notes and worksheets are retained, these shall be signed and dated by the member of the investigational site team. Where copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by a member of the investigational site team with a statement that it is a true reproduction of the original source document.

Source documents will be used for verification of the data documented in subject's eCRF during monitoring visits, audits and inspections, and for the adjudication of AEs and must be accessible to the Medtronic field clinical support and the clinical study team

The investigator will allow inspections of the study site and documentation by Clinical Research and audit personnel from Medtronic or designee, EC/IRB, external auditors, or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the eCRFs. In order to do this, direct access to medical or clinical records is necessary.

F.6 Adverse events

F.6.1 Definition/classification

For the purpose of this clinical investigation Medtronic will define and classify the following events per ISO14155:2011 and Title 21 CFR part 812.3

All adverse events that meet the study definitions will be reported to the sponsor and documented on the Adverse Event eCRF and in the subject's medical records.

Clinical events that are inherent to a surgical procedure and expected to occur in the majority of subjects for a projected duration may be considered unavoidable. Such events include, but are not limited to, those listed in Table F-3. These events should not be to be reported as adverse events during this study.

Table F-3: Expected and unavoidable adverse events related to the surgical procedure.

Description of the Event	Time Frame from the Index Procedure
Endoleaks observed and resolved during the index procedure	Resolved by the time the subject leaves the OR
Anesthesia-related nausea and/or vomiting	Within 24 hours
Low-grade fever (< 100° F or < 37.8° C)	Within 48 hours
Back pain related to laying on OR table	Within 72 hours
Incisional pain (pain at access site)	Within 72 hours
Sleep problems or insomnia	Within 72 hours
Mild to moderate bruising or ecchymosis	Within 168 hours

Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system.

Adverse Event (AE): *(ISO14155:2011 3.2)*

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device

NOTE 1: This definition includes events related to the investigational medical device or the comparator.
NOTE 2: This definition includes events related to the procedures involved.
NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect (ADE): *(ISO14155:2011 3.1)*

Adverse event related to the use of an investigational medical device

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device

Serious Adverse Event (SAE): *(ISO 14155:2011 3.37)*

Adverse event that
a) led to death,
b) led to serious deterioration in the health of the subject, that either resulted in
   1) a life-threatening illness or injury, or
   2) a permanent impairment of a body structure or a body function, or
   3) in-patient or prolonged hospitalization, or
   4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE): *(ISO 14155:2011 3.36)*

Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event

Unanticipated Serious Adverse Device Effect (USADE): *(ISO 14155:2011 3.42)*
Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Unanticipated Adverse Device Effect (UADE): *(21 CFR 812.3)*
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Device deficiency: *(ISO 14155:2011 3.15)*
Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance

NOTE: Device deficiencies include malfunctions, use errors, and inadequate labelling.

For the Valiant Evo US Clinical Trial Medtronic has defined Major Device Effects (MDEs) which will be used to assess the primary endpoint.

MDEs include the occurrence of any of the following and are defined in Appendix L.2.1:

- Device-related secondary procedures
- Device-related mortality
- Conversion to open surgery
- Thoracic aortic aneurysm rupture

For the Valiant Evo US Clinical trial Medtronic has defined Major Adverse Events which will be used to assess the secondary endpoints.

MAEs include the occurrence of any of the following and are defined in Appendix L.2.2:

- Respiratory complications: atelectasis, pneumonia, pulmonary embolism, pulmonary edema, respiratory failure
- Renal complications: renal failure, renal insufficiency
- Cardiac complications: MI, unstable angina, new arrhythmia, exacerbation of CHF.
- Neurological complications: new cerebrovascular accident (CVA), cerebrovascular embolic events, paraplegia, paraparesis
- Gastrointestinal complications: bowel ischemia
- Major bleeding complication (procedural or post-procedural), coagulopathy.
- Vascular complications: aortic rupture, aneurysm rupture, hematoma at access site, pseudo or false aneurysm, arteriovenous (AV) fistula, retroperitoneal bleed, limb ischemia, thrombosis

F.6.2 Recording and reporting of Adverse Events

Adverse Event (AE) information will be collected throughout the study and reported to Medtronic on the Adverse Event eCRF. All Adverse Events (except the ones listed in table F-3), regardless of relatedness or outcome, must be reported. The investigator is responsible for reporting all AE to Medtronic. See the Adverse Event eCRF for the information to be reported for each Adverse Event.

For Adverse Events that require immediate reporting (see Table F-4), initial reporting may be done by phone, e-mail (contact details will be provided in the investigational site file), or on the eCRF with as much information as is available. In case the investigator requires information from the Sponsor in an emergency situation, the contact details for emergency situations are given in the investigational site file.

F.6.3 Recording and reporting of Device Deficiencies

Device Deficiency information will be collected throughout the study and reported to Medtronic. Device Deficiencies should be reported on a Device Deficiency Form in the eCRF. In case the eCRF is not available the Device Deficiency form needs to be completed manually and must be sent to Medtronic. Contact details are given in the investigational site file. The investigator is responsible for reporting all Device Deficiencies to Medtronic.
See the Device Deficiency eCRF for the information to be reported for each Device Deficiency.
Device deficiencies that did not lead to an Adverse Event but could have led to an SAE

a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate,

require immediate reporting (see Table F-4). Initial reporting may be done by eCRF, phone, e-mail, with as much information as available.

F.6.4 Adverse Event and Device Deficiency review process

All Adverse Events and Device Deficiencies will be reviewed by Medtronic Study Management and/ or designee. This review will include the determination whether the Adverse Event/Device Deficiency meets regulatory reporting requirements (see table F-4). The sponsor will ensure timely Adverse Event/Device Deficiency reporting to meet global and country specific regulatory requirements.

A list of anticipated adverse events that are expected in nature is included in section J.2.

In case the Adverse Event/Device Deficiency is related to a Medtronic market released device used during the study, Medtronic Study Management and/ or designee will immediately report this device related Adverse Event/Device Deficiency to the Product Experience Management (PXM) group. The PXM group will ensure prompt review, and appropriate reporting.

Table F-4: Adverse Event Reporting Requirements

Serious Adverse Device Effects (SADE), including Unanticipated Serious Adverse Device Effect (USADE):	
Investigator submit to:	
Medtronic	As soon as possible, but in no case later than 3 calendar days after the clinical site study team first learns of the event or of new information in relation with an already reported event.
Regulatory Authority	As per local reporting requirement
EC/IRB	Reporting timeframe as per local EC/IRB requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Serious Adverse Events (SAE) and Unanticipated Adverse Device Effects (UADE)	
Investigator submit to:	

Medtronic	As soon as possible, but in no case later than 3 calendar days after the clinical site study team first learns of the event or of new information in relation with an already reported event.
Regulatory Authority	As per local reporting requirement
EC/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Adverse Device Effects (ADE)	
Investigator submit to:	
Medtronic	As soon as possible, but in no case later than 3 calendar days after the clinical site study team first learns of the event.
Regulatory Authority	As per local reporting requirement
EC/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement
EC/IRB	Submit to EC/IRB per local reporting requirement.

All other AEs	
Investigator submit to:	
Medtronic	Submit in a timely manner after the clinical site study team first learns of the event.
Regulatory Authority	As per local reporting requirement
EC/IRB	Submit to EC/IRB per local reporting requirement.
Device Deficiency with SADE potential	
Investigator submit to:	
Medtronic	As soon as possible, but in no case later than 3 calendar days after the clinical site study team first learns of the deficiency or of new information in relation with an already reported deficiency.
Regulatory Authority	As per local reporting requirement
EC/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement
EC/IRB	Submit to EC/IRB per local reporting requirement.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	Submit in a timely manner after the clinical site study team first learns of the deficiency.
Regulatory Authority	As per local reporting requirement

EC/IRB	Submit to EC/IRB per local reporting requirement.

In addition, Investigators are obligated to report adverse events in accordance with the requirements of their IRB/EC and local regulations. The Sponsor is obligated to report adverse events and device deficiencies that occur during this trial to the Regulatory Authorities and IRB/EC as per local requirements. The applicable timeframes are described in the Valiant Evo Clinical Trial safety plan.

F.6.5 Clinical Event Committee

A clinical event committee (CEC) will be established. The CEC is an independent committee made up of clinicians (interventional) with pertinent expertise who are not participants in the study and who do not have any other real or potential conflicts of interest. The CEC will meet periodically to review and adjudicate all MDEs, UADEs, deaths and all DTAA ruptures that occur throughout the conduct of the clinical trial. A charter will be developed that will detail the criteria for selected complications and clinical events that need to be adjudicated as well as the CEC composition, duties, procedures and adjudication rules and meeting frequency.

F.6.6 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established. The DMC is composed of several members with pertinent expertise who are not participants or directly involved in the conduct of the trial.
The responsibility of the DMC is to evaluate safety data during the course of the trial and to advise Medtronic about the continuing safety of the trial, to ensure the wellbeing of the current participants and those yet to be enrolled as well as the continuing validity and scientific merit of the trial.
Medtronic will provide listings of all Adverse Events and Device Deficiencies to the Independent Medical Monitor to evaluate safety of the study device. All events, including any device related events will be reviewed on a case by case base by the Independent Medical Monitor. In case of a safety concern the Independent Medical Monitor can trigger a DMC meeting.
Trial data will be reviewed on a periodic basis as defined in the DMC Charter.

Based on the safety data, the DMC may recommend that Medtronic modify or stop the trial.
DMC composition, duties, procedures, deliberation rules are detailed and documented in the DMC Charter.

F.6.7 Emergency contact details in case of serious AEs

In case of an immediately reportable Adverse Event the investigators can contact the Medtronic Study Manager. Contact details of Medtronic Study Management are given in the Investigational Site File.

In case the investigator requires information in a medical emergency situation the investigator can contact the Medical Expert. Contact details of Medical Expert are given in the Investigational Site File.

F.7 Subject accountability

Every subject should be encouraged to remain in the study until they have completed the required follow up per the study protocol.

If a subject is withdrawn from the clinical study, the reason for withdrawal shall be recorded on the appropriate eCRF and in the subject's hospital record. If discontinuation is because of safety or lack of effectiveness, the subject shall be asked to be followed for collecting safety data outside the clinical study. Subjects will not be replaced in case of premature study discontinuation.

F.7.1 Criteria and procedures for exit from study

The Study Exit Form should be completed at the time a subject is exited from the study. A subject will be considered to have exited from the study for any of the following reasons:

- Subject completes follow-ups required by the investigational plan.
- Subject dies.
- Subject requests to be withdrawn.
- Investigator requests that subject be withdrawn to protect the welfare of the subject.
- Subject is lost to follow-up.
- Other (specify).

F.7.2 Study Withdrawal

Subjects may withdraw from the study at any time and for any reason. If a subject decides to withdraw from the study, the investigator will document the reason for withdrawal and indicate any relationship of the withdrawal to the study or products being investigated in the subject's hospital record in the subject's file. If discontinuation is because of safety or lack of effectiveness, the subject shall be asked to be followed for collecting safety data outside the clinical study as further described in section F.7.6. In addition, subject withdrawal will be documented on Study Exit eCRF.

If the subject is unable to be followed, the investigator has to notify the sponsor in a timely manner.

F.7.3 Missed follow-up

A missed follow-up visit should be documented by the investigator and reported in the eCRF, including the reason. If the date the subject is last known to be alive is obtained, this should be recorded on the Follow-up visit eCRF and the method of obtaining this date should be documented in the medical record.

F.7.4 Lost-to-follow-up

A subject may be considered lost to follow-up once the investigator and/or research staff has made three documented attempts to contact the subject. The third attempt should be made by certified mail to the subject.

F.7.5 Medical care after study exit

After study exit the subjects will be followed as per routine standard of care by the investigational site or a treating physician.

F.8 Study deviations and CIP changes

A protocol deviation is defined as an event where the clinical investigator or site personnel did not conduct the study according to the clinical investigational plan, applicable laws or regulations, or the Investigator Agreement. Every attempt must be made to avoid deviations. All deviations are recorded on a Protocol Deviation Case Report Form. United States regulations (21 CFR 812.140) require that investigators maintain accurate, complete, and current records relating to the clinical study. This includes documents showing the dates and reasons for each deviation from the clinical investigational plan. Depending on the nature of the protocol deviation, expedited reporting and prior approval from Medtronic may be required. All protocol deviations must be reported to the Institutional Review Board (IRB) in accordance with IRB policies and/or local laws. All deviations will be summarized and reported in regular progress reports to the FDA.

Medtronic will assess the significance of all deviations and evaluate the need to amend the clinical investigation plan or to early terminate the investigation, in accordance with Medtronic SOPs.

F.8.1 Request for approval of study deviations

The investigator shall obtain documented approval from Medtronic, before implementation, for any change in- or deviation from the Clinical Investigation Plan. In case of study deviations that can affect the subject's rights, safety and well-being or the scientific integrity of the clinical study, approval from the EC/IRB and Regulatory Authority must also be obtained before implementation. The investigator shall timely contact the Clinical Study Manager for review of the proposed change/deviation.

Prior approval is not always realistic in situations where unforeseen circumstances are beyond the investigator's control. However, also in these cases, the event is considered a deviation, and shall be reported.

In any emergency situation the investigator shall exercise his/her judgment to safeguard the subject's interest. Such deviations from the Clinical Investigation Plan do not require the prior approval of Medtronic. The investigator shall report the deviation as soon as possible to Medtronic and the reviewing EC/IRB, if applicable. Medtronic will inform the Regulatory Authorities, if required.

F.8.2 Reporting requirements for study deviations

The investigator shall adhere to EC/IRB requirements and procedures for reporting study deviations.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, additional training, terminate the study, etc.). Repetitive or serious investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases freeze enrolment or ultimately terminate the investigator's participation in the clinical study:

- Non-compliance to obtain subject's informed consent
- Non-compliance to the inclusion/exclusion criteria
- Failure to follow subjects per scheduled follow-ups
- Failure to submit data in a timely manner
- Failure to follow-up with findings on monitoring reports
- EC approval expiration
- EC suspension of the center

If a center is terminated or suspended, no additional enrollments will be allowed at the center. Unused investigational product allocated to the center will be returned to Medtronic.

Medtronic will provide investigation site-specific reports to the investigators on a periodic basis summarizing information on deviations that occurred at the investigation site.

F.8.3 Amendments to the Clinical Investigation Plan

The investigator will propose any appropriate modification(s) of the Clinical Investigation Plan or investigational device/product or investigational device/product use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic will submit any significant amendment to the Clinical Investigation Plan, including a justification for this amendment, to the appropriate Regulatory Authorities and to the investigators to obtain approval from their EC/IRB. The investigator will only implement the amendment after approval of the EC/IRB, Regulatory Authority and sponsor. Administrative amendments to the Clinical Investigation Plan will be submitted to the EC/IRB and Regulatory Authority (if required) for notification. Furthermore investigators shall sign any approved amendment for agreement.

G QUALITY CONTROL PROCEDURES

G.1 Procedures for database management

G.1.1 Data collection

The investigator must ensure accuracy, completeness and timeliness of the data reported in the CRFs and in all other required reports. Data reported on the CRFs which are derived from source documents must be consistent with the source documents, and discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator, and filed in the subject's medical file.

Only authorized persons can complete CRFs. CRFs shall be signed by investigators (physicians only) as specified on the Delegated Tasks List included in the Investigator Site File.

The Electronic Data Capture (EDC) system maintains an audit trail on entries, changes or corrections in CRFs. If a person is only authorized to complete CRFs or to make changes to an already signed CRF, the investigator shall re-sign this CRF.

Any source documentation, as well as any imaging (e.g., procedure reports, imaging material, lab reports, death certificates, autopsy reports) that is sent to the sponsor, should have all subject identifiers removed and replaced with the subject's study ID.

A paper copy of the eCRFs, as well as access to the EDC system, will be provided to the investigation site prior to subject enrollment.

G.1.2 Source data to be directly recorded on the Case Report Forms

All data reported on the eCRFs shall be derived from source documents and be consistent with these source; any discrepancies shall be explained in writing. There are no data that will be recorded directly on the eCRF without corroborating source documentation.

G.1.3 Time windows for completion and submission of Case Report Forms

All data entry should be completed as soon as possible after the visit takes place. Adverse event and device deficiencies should be reported as described in the section F.6.

G.1.4 Data review and processing

Data management will be done according to Medtronic SOPs and the Data Management Plan for this clinical study. These documents will be made available upon request.

All collected data will be reviewed for completeness, correctness and consistency. In case of issues, queries will be sent to the investigator to complete, correct or comment the data.

G.2 Monitoring procedures

A site qualification visit may be conducted by Medtronic personnel (or designees) to review the clinical investigational plan and, regulatory and study requirements with the investigator and study personnel. A site initiation visit will be performed after it has been verified that the site is prepared for the study and that the site requirements for study participation are met.

Monitoring visits will be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan. Frequency and timing of monitoring visits shall be determined by the Sponsor for each site based on enrollment rate and volume, study compliance and findings from previous visits.

It will be verified whether signed and dated Informed Consent Forms have been obtained from each subject before any clinical study related procedures are undertaken. Medtronic or designee

will conduct site monitoring visits to monitor compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study.

G.2.1 Accessibility of investigation site staff and study materials

The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic field personnel and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the Case Report Form (CRF). Direct access to subject medical files for source data verification will need to be granted and prepared prior to any monitoring visits. If direct access cannot be provided per local laws and regulations, certified copies need to be made available or monitor needs to obtain access by reviewing alongside with study staff.

G.2.2 Audits and investigation site inspections

In addition to regular monitoring visits, Medtronic may conduct audits at participating investigation sites. The purpose of an audit is to verify the adequate performance of the clinical study related activities. Independent of the employees involved in the clinical study. Regulatory bodies may also perform inspections at participating investigation sites. Any Regulatory Authority inspection announcements shall be forwarded immediately to the Clinical Study Manager.

The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform clinical study-related monitoring, audits, EC/IRB review, and regulatory inspections.

G.3 Study suspension or early termination

G.3.1 Early study suspension or termination

Medtronic or Regulatory Authority may decide to suspend or prematurely terminate the clinical study (e.g. if information becomes available that the risk to study subject is higher than initially indicated, if interim analysis indicates that the results significantly differ from the clinical study objectives or statistical endpoints). If the clinical study is terminated prematurely or suspended, Medtronic shall promptly inform the investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC/IRB and the study subjects.

G.3.2 Early investigation site suspension or termination

Medtronic, EC/IRB or Regulatory Authority may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing EC/IRB, non-compliance to the Clinical Investigation Plan or lack of enrollment). If an investigation site is suspended or prematurely terminated, Medtronic shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC/IRB and the study subjects or their legal representative.

If an investigation site is suspended or prematurely terminated:

- Medtronic shall promptly inform the clinical investigator(s) of the termination or suspension and the reason(s) for this
- The investigator shall then promptly inform the reviewing EC/IRB
- The investigator shall then promptly inform study subjects
- The investigator agreement will be terminated
- The investigator will inform the institution (where required by applicable regulatory requirements)

- Medtronic will inform the Regulatory Authority(ies) (where required by applicable regulatory requirements)

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify or immediately stop the clinical study in the respective investigation site and immediately inform the sponsor and EC/IRB, if applicable.

G.3.3 Subject follow-up in case of termination

If the study is terminated early, subjects will be followed as per routine standard of care by the investigational site or a treating physician.

G.4 Study close out

Prior to completion of study close out, all data must be entered and monitored in the EDC system.

Medtronic and/or its designees will notify the site of the intention to close the study. Study close out visits may be performed. During these visits, the monitors will ensure that the investigator's regulatory files are up to date and complete and that any outstanding issues from previous visits have been resolved. Medtronic will notify and inform the site(s) that all requirements have been met with a study closure letter.

If required, EC/IRB and/or Regulatory Authority will be informed by Medtronic about the study close out.

H DATA ANALYSIS AND REPORTING

Any deviations from this section and/or the Statistical Analysis Plan will be described and justified in the Final Clinical Study Report, as appropriate.

H.1 Analysis of clinical data

All endpoints will be analyzed descriptively. In general, qualitative parameters will be described by their distribution frequencies; quantitative parameters will be described by their mean, standard deviation, minimum, maximum, median, and number of subjects with assessable data.

The survival from all-cause mortality over one year time or longer will be described by the Kaplan-Meier survival curve and the associated Kaplan-Meier estimate will be calculated along with its standard error using the Greenwood method.

The primary study endpoint is a dichotomous study outcome; hence, an exact method based on the binomial distribution will be used for the hypothesis testing.

For events such as AEs, deaths and secondary procedures, that can occur or are observed at any time during the study, no time window will be applied. For such events, an event that occurs "within 1 month or 30 days" is an event that takes place between Days 0 to 30, inclusive. Similarly, an event that occurs "within 12 months or 365 days" is an event occurring between Day 0 to Day 365, inclusive. Date of event onset will be used to determine when the event occurred. Day 0 is referring to the day of index procedure.

For image-based assessments, such as stent-graft endoleak, patency, and other observations, the following time windows will be applied for by-visit data summaries:

Table H-1: Time Windows for Statistical Analyses

Study Visit	Target Day	Time Window
Implant	Day 0	Day 0

Study Visit	Target Day	Time Window
1 Month	Day 30	1 – 90 days
6 Months	Day 183	91 – 304 days
12 Months	Day 365	305 – 548 days
24 Months	Day 730	549 – 913 days
36 Months	Day 1095	914 – 1278 days
48 Months	Day 1460	1279 –1643 days
60 Months	Day 1825	1644 – 2009 days

If there are two or more assessments in the same time window, unless otherwise specified, the assessment closest to the target day will be used in the analysis of event rate at a given time point.

In addition to endpoints, summaries of subject disposition, demographics, baseline characteristics, and subject accountability will be provided.

During statistical analysis, imputation of missing data will not be performed except for data related to the onset date of an adverse event or a death. In cases where the onset date of an event or a death is incomplete and unresolvable via data query, the 15th day of the known month or July 1st of the known year will be used.

Sensitivity analysis using tipping point method may be performed, as needed, to assess the impact of missing data for the primary endpoint.

Statistical analyses for this study will be performed using the Statistical Analysis System (SAS) for Windows (Version 9.1 or higher) or other widely-accepted statistical or graphical software.

Subset analyses by-sex, by-race (based on subjects enrolled in the US only, since collection of race and ethnicity data may not be allowed outside the US as per local law and regulation), FreeFlo versus Closed Web configuration as proximal component, percutaneous access versus non-percutaneous, and by-region/study site will be performed on the primary study endpoint using descriptive statistics and reviewed for clinical significant difference.

No inferential statistical analysis is planned for secondary or additional study endpoints. Descriptive statistics will be provided for all endpoints as well as baseline variables.

Analysis Sets:

The primary analysis set will consist of all subjects who were enrolled. Subjects will be considered as enrolled in the study as described in section F.1.

Poolability of the data

The poolability of subjects enrolled in the Valiant Evo US Clinical trial and subjects enrolled in the Valiant Evo International Clinical Trial is assumed given that both study protocols will be similar with respect to, inclusion/exclusion criteria, clinical treatment, definitions of clinical events, one data monitoring plan, Data Monitoring Committee (DMC), Clinical Event Committee (CEC), Independent Physician Reviewer (IPR) and core imaging laboratory.

At the data analysis stage, the data poolability will be reviewed for the primary endpoint. Results from Valiant Evo US Clinical Trial and Valiant Evo International Clinical Trial subjects will be presented separately for clinical review as well as tested using a Chi-square test.

A poolability analysis among geographies/investigational sites will be assessed descriptively for the primary endpoints by geographic regions. Small investigational sites (less than 5 subjects) will be grouped with other nearby sites for the by-region analysis.

H.2 Publication Policy

Publications and presentations referring to this clinical study will be coordinated by Medtronic to allow the use of all available data. The following publication policy will have to be adhered to by all participating investigation sites:

Medtronic may use the study data for Regulatory Authority submission results, may publish the results in peer reviewed scientific journal(s) and present the data at major congresses.

Authorship on any publication(s) resulting from this clinical study will be assigned according to substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published. This is in accordance with the Vancouver principles (The Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, ICMJE, October 2008), as agreed upon by the editors of all major medical journals.

The number of authors will be dependent on the regulations of the concerning journal with a maximum of 10 authors. Names of all participating investigators will appear in the Acknowledgment of the paper.

Based on the principle that Medtronic owns the data of this clinical study, a single investigation site may access and use the data provided by itself for scientific publications following prior approval by Medtronic.

Pooling data from several investigation sites for publication purposes, national projects and international projects all require prior approval from Medtronic.

Medtronic as the owner of the data can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research and development of devices or educational use.

The study sponsor will collect data in such way that no subject can be identified, and monitor study records.

Participating subjects will not be identified by name in any published reports about the clinical study.

I STUDY MANAGEMENT

I.1 Study staff

The study is sponsored by Medtronic Vascular. Study staff contact details will be provided in the investigational site file.

I.2 Advisory committees

I.2.1 I.2.1 Clinical Event Committee (CEC)

A clinical event committee (CEC) will be established. The CEC is an independent committee made up of clinicians (interventional) with pertinent expertise who are not participants in the study and who do not have any other real or potential conflicts of interest. Please refer to section F.6.5 for further details regarding the CEC.

I.2.2 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established. The DMC is composed of several members with pertinent expertise who are not participants or directly involved in the conduct of the study. Please refer to section F.6.6 for further details regarding the DMC.

I.2.3 Publication Committee

A publication committee will not be established for the Valiant Evo US and International Clinical trials. The publication policy for this trial is described in section H.2.

I.2.4 Imaging Core Lab

An imaging core lab will be established to independently analyze images based on the imaging protocol/core lab guidelines. Imaging guidelines will be provided in the investigational site file.

I.3 Records and reports

I.3.1 Investigator records

At a minimum, the following records must be kept by the investigator:

- Clinical Investigation Plan and, if applicable, any amendments
- Instructions for Use
- Medtronic and EC/IRB approved Informed Consent form
- Regulatory Authority approval or notification
- Fully signed Clinical Investigation Agreement and confidentiality agreement (if not included in the Clinical Investigation Agreement)
- Financial disclosures
- Completed Delegation of Authority Form and Curriculum Vitae of all investigation site personnel
- Training documentation of all investigation site personnel
- Relevant communications
- Subject screening log and/or subject identification log
- Signed, dated and fully executed Informed Consent forms
- Fully executed CRFs and corrections
- Reports of Adverse Events and Device Deficiencies
- Device accountability records
- IRB/EC correspondence

I.3.2 Investigator reporting responsibilities

Report	Submitted to	Description
Adverse Events	Sponsor, EC/IRB, and local Regulatory Authority, where applicable	Refer to section F.6 for reporting requirements.

Report	Submitted to	Description
Withdrawal of EC/IRB approval	Sponsor	An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation. (21 CFR 812.150(a)(2)).
Final investigator report	Sponsor, IRB s and Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. (21 CFR 812.150(a)(6)).
Study deviations	Sponsor and IRB	Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. (21 CFR 812.150(a)(4)).
Failure to obtain IC prior to investigational device use	Sponsor and IRBs	If an investigator uses a device without obtaining informed consent, the investigator shall report such use within 5 working days after device use. (21 CFR 812.150(a)(5)).
Other	IRB and FDA	An investigator shall, upon request by a reviewing IRB, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. (21 CFR 12.150(a)(7)).

I.3.3 Sponsor records

At a minimum, the sponsor will keep the following records:

- All essential study documents and correspondence that pertains to the clinical study
- CIP and, if applicable, any amendments
- Instructions for Use
- Sample of labeling attached to the investigational device
- Curriculum Vitae of investigators and investigation site personnel
- Delegation of Authority Form and training records of investigators and investigation site personnel
- EC/IRB approvals/notifications and regulatory approvals/notifications
- Signed Clinical Investigation Agreements and signed agreements with third parties
- Shipping records for investigational devices and clinical-investigation related documents and materials
- Medtronic and EC/IRB approved Informed Consent Forms
- Site selection reports, site initiation reports and monitoring visit reports
- Adverse event and Device Deficiency reports
- Financial disclosure information
- Fully executed CRFs and corrections

I.3.4 Sponsor reporting responsibilities

Report	Submit to	Description
Adverse Events	EC/IRB, Investigators, FDA and relevant authorities, where applicable	Medtronic will report adverse events as required and in compliance with local regulatory requirements, as applicable and described in the Valiant Evo Safety Plan.
Unanticipated Adverse Device Effect	Investigators, IRB, FDA, and relevant authorities	Notification within ten working days after the sponsor first receives notice of the effect. *(21 CFR 812.150(b)(1)).*
Withdrawal of EC/IRB approval	Investigators, IRB, FDA, and relevant authorities	Notification within five working days after receipt of the withdrawal of approval. *(21 CFR 812.150(b)(2)).*
Withdrawal of FDA approval	Investigators, EC/IRB, and relevant authorities	Notification within five working days after receipt of notice of the withdrawal of approval. *(21 CFR 812.150(b)(3)).*
Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. *(21 CFR 812.150(b)(4)).*
Progress Reports	EC/IRB and FDA	Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(4)(5), 812.36(f)*
Recall and device disposition	Investigators, EC/IRB, relevant authorities, and FDA	Notification within 30 working days after the request is made and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6)).*
Failure to obtain Informed Consent	FDA	Investigator's report will be submitted to FDA within five working days of notification. *(21 CFR 812.150(b)(8)).*
Premature termination or suspension of study	Investigators, IRB, and Relevant authorities	Provide prompt notification of termination or suspension and reason(s). *(*ISO 14155:2011*), (MHLW Ordinance 36, Article 32).*
Final Report	Investigators, IRB, and regulatory authorities, where applicable and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and IRBs within six months after completion or termination of this study. (21 CFR 812.150(b)(7)).
Study Deviations	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation.

I.3.5 Record retention

The investigator must retain the Investigator Site File, subject medical files and CRFs in accordance with local law and regulations for a minimum period of 2 year (or longer if local laws require) after market-release in his/her region. The investigator should take measures to prevent accidental or early destruction of the clinical study related materials.

I.4 Miscellaneous

I.4.1 Insurance

Medtronic Vascular is a wholly owned subsidiary of Medtronic Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the EC/IRB.

I.4.2 Subject compensation and indemnification

Subjects will not receive any compensation for their participation in this study (including follow up); however, Medtronic may, at its option, provide reimbursement for participants who will incur extraordinary travel costs related to their participation in the study, including airfare, mileage or hotel expenses. Participating Institution will make such request(s) in writing to Medtronic (de-identified of participant information), detailing the unusual circumstances and the excessive costs that the participant will incur. Medtronic will evaluate requests on a case-by-case basis, and will notify the Participating Institution of its decision in writing.

I.4.3 Subject confidentiality

Subject confidentiality will be maintained throughout the clinical study to the extent permitted by law. That is, every attempt will be made to remove subject identifiers from clinical study documents. For this purpose, a unique subject identification code (site number and subject number) will be assigned and used to allow identification of all data reported for each subject. This will also ensure that the information can be tracked back to the source data.

Study data may be made available to third parties, e.g., in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event that study data are published.

J RISKS AND BENEFITS

J.1 Anticipated Clinical Benefits

The potential benefits of the Valiant Evo Thoracic Stent Graft System have not been documented; nevertheless, they are expected to be similar to those associated with endovascular stent graft systems currently in clinical trials or commercially available.

The minimally invasive endoluminal intervention offers an alternative method of treatment that is potentially less invasive, less expensive, and less risky than standard operative repair [22]. Thoracic aortic endoluminal procedures are likely to have an even greater impact than those of the abdominal aorta, where conventional open surgery offers a low mortality rate for many patients. This minimally invasive endovascular intervention offers an innovative treatment strategy for a significant number of patients with serious thoracic aortic lesions, such as aneurysms, dissections, traumatic disruptions, and penetrating ulcers.

The potential benefits of using stent graft repair in the treatment of DTAA are based on comparing the results of endovascular repair against surgical repair.

The most superior potential benefit is that stent graft repair provides a treatment modality for many patients who otherwise would not be candidates for surgical repair because of their co-morbidities [17, 23, 24].

Other potential benefits include a reduction in short-term and mid-term mortality and morbidity; a reduction of risk of cardiovascular, pulmonary, neurologic and renal complications as a consequence of shorter exposure to general anesthesia, a less invasive procedure, a preservation of the distal aortic pressure due to maintenance of aortic blood flow; reduced estimated blood loss; lower post-operation complications such as paraplegia; decreased length of Intensive Care Unit and hospital stay, shorter recovery time and better quality of life [17,23,24,25,26].

J.2 Risks

Following is a list of potential (expected) risks that may be associated with use of the Valiant Evo Thoracic Stent Graft System. The occurrence of the listed complications may lead to a repeat endovascular intervention and/or open surgical repair. Since the Valiant Evo Thoracic Stent Graft System is an investigational device, all risks may not be known. However, they are believed to be similar to those associated with the existing endovascular devices in clinical use or commercially available, as well as the risks associated with standard open surgical repair of DTAAs.

Table J-1: Potential Adverse Events/Complications associated with the use of the Valiant Evo Thoracic Stent Graft System

- Access failure - Access site complications (e.g., spasm, trauma, bleeding, rupture, dissection) - Adynamic Ileus - Allergic reaction (to contrast, antiplatelet therapy, stent graft material) - Amputation - Anaphylaxis - Anesthetic complications - Aneurysm expansion - Aneurysm rupture - Angina - Aortic valve damage - Aortic vessel rupture - Arrhythmia - Arterial stenosis - Atelectasis - Blindness - Bowel ischemia - Bowel necrosis - Bowel obstruction - Branch vessel occlusion - Breakage of the metal portion of the device - Buttock claudication - Cardiac tamponade - Catheter breakage - Cerebrovascular accident (CVA)/Stroke - Change in mental status - Coagulopathy - Congestive heart failure - Contrast toxicity - Conversion to surgical repair - Death - Deployment difficulties/failures	- Dissection, perforation, or rupture of the aortic vessel & surrounding vasculature - Embolism - Endoleaks - Excessive or inappropriate radiation exposure - Extrusion/erosion - Failure to deliver the stent graft - Femoral neuropathy - Fistula (including aortoenteric, arteriovenous, and lymph) - Gastrointestinal bleeding/complications - Genitourinary complications - Hematoma - Hemorrhage/bleeding - Hypotension/hypertension - Infection or fever - Insertion or removal difficulty - Intercostal pain - Intramural hematoma - Leg edema/foot edema - Lymphocele - Myocardial infarction - Neuropathy - Occlusion - Venous or Arterial - Pain/reaction at catheter insertion site - Paralysis - Paraparesis - Paraplegia - Paresthesia - Peripheral ischemia - Peripheral nerve injury - Pneumonia - Postimplant syndrome	- Post-procedural bleeding - Procedural bleeding - Prosthesis dilatation - Prosthesis infection - Prosthesis rupture - Prosthesis thrombosis - Pseudoaneurysm - Pulmonary edema - Pulmonary embolism - Reaction to anaesthesia - Renal failure - Renal insufficiency - Reoperation - Respiratory depression or failure - Retrograde type A dissection - Sepsis - Seroma - Shock - Spinal neurological deficit - Stent graft migration - Stent graft misplacement - Stent graft occlusion - Stent graft twisting or kinking - Transient ischemic attack (TIA) - Thrombosis - Tissue necrosis - Vascular ischemia - Vascular trauma - Wound dehiscence - Wound healing complications - Wound infection

All efforts will be made to minimize these risks by selecting investigators who are experienced and skilled in using endoluminal aortic devices and who have been adequately trained. Also, risk minimization activities were performed during development and design verification tests of the device. Activities intended to minimize risks include the following.

- Investigator and study personnel training will be conducted to share information regarding the design of the Valiant Evo Thoracic Stent Graft System, its application and pre-clinical results.
- Adherence to eligibility criteria and screening procedures will ensure that appropriate subjects are enrolled.
- Adherence to the Valiant Evo Thoracic Stent Graft System Instructions for Use packaged with the device will ensure the use of validated procedural steps.
- The subjects will be carefully monitored throughout the study period.
- The investigator will evaluate the subject adverse events during the course of the study.
- Data submitted from the investigative centers will be monitored during the course of the study.
- Monitoring visits will be conducted to evaluate protocol compliance and data quality.
- Safety and effectiveness data obtained during the course of the study will be shared with investigators in periodic reports to increase understanding of the device and potential adverse events.
- A data monitoring committee, clinical events committee, and core lab will independently evaluate subject health status, device performance, and identify any safety concerns regarding subjects' well-being.

If a woman is pregnant or becomes pregnant, implantation of the trial device may involve risks to the embryo or fetus that are unknown at this time. Therefore, pregnant women will be excluded from the study. If a female subject becomes pregnant during the conduct of this clinical research study they need to inform the investigational site immediately. The risks will be continuously monitored, assessed and documented by the investigator. Any unanticipated or unforeseen complications will be reported by the investigator (or authorized designee) to the IRB/ EC and to Medtronic. Medtronic will in turn report any necessary findings to the appropriate regulatory agencies in each of the respective geographies.

J.3 Risk-to-benefit rationale

The benefits and risks associated with Medtronic's thoracic stent grafts are well-characterized through robust history of testing and successful clinical results. The Valiant Evo Thoracic Stent Graft System is Medtronic's third generation thoracic stent graft which is not only designed using established design characteristics and long term experience from previous generation Medtronic stent grafts but also uses the same principles of operation and technological characteristics. Furthermore, it has been demonstrated that implantation of thoracic endovascular stent grafts can be performed safely, and that these devices provide benefits over surgical repair.

Any potential risks with this study are minimized by selecting qualified investigators, careful assessment of each subject prior to, during and after implantation. Medtronic has further minimized the possibility of risks by completing product testing prior to the use of the device in this clinical study, implementing quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling.

Although there are risks associated with this trial, they are not anticipated to be worse than the risks normally associated with the use of the predicate device or other commercially available devices.

Risk management for the Valiant Evo Thoracic Stent Graft System is performed in accordance with EN 14971:2012 and the results are detailed in the Report of Prior Investigations.

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L APPENDICES

L.1 Abbreviations

ADE	Adverse Device Effect
AE	Adverse event
ASA	American Society of Anesthesiologists
ASADE	Anticipated serious adverse device effect
AV	Arteriovenous
CEC	Clinical Event Committee
CIP	Clinical Investigation Plan
CRF	Case Report Form
CT	Computed Tomography
CVA	Cerebral Vascular Incident
CRO	Clinical Research Organization
DD	Device Deficiency
DMC	Data Monitoring Committee
DTA	Descending Thoracic Aorta
DTAA	Descending Thoracic Aortic Aneurysm

EC	Ethical Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
IB	Investigator Brochure
ICU	Intensive Care Unit
ICH-GCP	International Conference on Harmonization – Good Clinical Practice
IDE	Investigational Device Exemption
IFU	Instructions for Use
INR	International Normalized Ratio
IPR	Independent physician reviewer
IRB	Institutional Review Board
ISO	International Organization for Standardization
MAE	Major Adverse Event
MDE	Major Device Effect
MI	Myocardial Infarction
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
PET	Polyethylene terephthalate
PMA	Premarket Approval
RA	Regulatory Affairs
RAE	Regulatory Affairs Europe
ROPI	Report of Prior Investigations
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard operating procedure
TAA	Thoracic Aortic Aneurysm
TEE	Transesophageal echocardiography
TEVAR	Thoracic Endovascular Aortic Repair
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

L.2 Definitions

L.2.1 Primary and Secondary Endpoints

Term	Definition
Access failure	Inability to insert device due to mechanical failure or anatomic exclusions of the femoral or iliac arteries
Deployment Failure	Deployment failure due to subject anatomy or mechanical failure. This specifically refers to deployment of the stent graft from the delivery system.
Adverse Event (AE)	See section F.6.1
Serious Adverse Event (SAE)	See section F.6.1
Major Adverse Events (MAEs)	Major Adverse events include the occurrence of any of the following : • Respiratory complications: atelectasis/pneumonia, pulmonary embolism, pulmonary edema, respiratory failure. • Renal complications: renal failure, renal insufficiency. • Cardiac complications: myocardial infarction (MI), unstable angina, new arrhythmia, exacerbation of congestive heart failure (CHF). • Neurological complications: new cerebrovascular accident (CVA), cerebrovascular embolic events, paraplegia, paraparesis. • Gastrointestinal complications: bowel ischemia. • Major bleeding complication (procedural or post-procedural), coagulopathy. • Vascular Complications: aortic rupture, aneurysm rupture, hematoma at access site, pseudo or false aneurysm, arteriovenous (AV) fistula, retroperitoneal bleed, limb ischemia, thrombosis. *See definition of terms in section L.2.2*
Major Device Effects (MDEs)	Major Device Effects include the occurrence of any of the following: • Device-related secondary procedures • Device-related mortality • Conversion to open surgery • Thoracic Aortic Aneurysm rupture
Device-related mortality	Any death related directly to the implantation, the presence, or operation of the investigational device in the medical opinion of the Clinical Events Committee (CEC).

Term	Definition
	Deaths following complications that are associated with the device design as it relates to placement, efficacy or durability (these may involve the implanted device or the delivery system), with endoleak, device migration, and failure to cover the aortic injury are included in this definition.
Peri-operative mortality	All deaths occurring intra-operatively and within 30 days from the primary procedure
All-cause mortality	Death from any cause
Aneurysm-related mortality (ARM)	Any death occurring within 30 days from either the initial procedure or any secondary procedure intended to treat the aneurysm will be considered ARM unless there is evidence to the contrary. Additionally, deaths occurring as a consequence of any procedure intended to treat the targeted aneurysm, aneurysm rupture, or a conversion to open repair will also be considered as ARM. *Ultimate adjudication of relatedness of death will be made by the Clinical Events Committee (CEC). Excluded are aneurysms in anatomic areas other than the targeted segment treated by the Valiant Evo Thoracic Stent Graft System.*
Device-related secondary procedure	Any secondary procedure that is determined by the investigator to be clearly related to any of the implanted stent graft components. *Ultimate adjudication of relatedness of secondary procedure will be made by the Clinical Events Committee (CEC).*
Secondary procedure	Any endovascular or surgical procedure performed following the completion of the operative initial implantation procedure (thus on subsequent occasion after final closure of the last artery access site) which involves the targeted vascular segment treated by the Valiant Evo Thoracic Stent Graft System in which there is either manipulation of the existing Valiant Evo Thoracic Stent Graft, implantation of any additional stent graft devices or manipulation of covered branch(es) by implanted stent grafts.
Conversion to open surgery	Primary Conversion: Conversion from endovascular to open repair required at the time of the original procedure, to treat the lesion intended to be treated with the Valiant Evo Thoracic Stent Graft System. Secondary Conversion: Conversion from endovascular to open repair required at a time beyond the initial endovascular procedure, to treat the lesion originally treated with the Valiant Evo Thoracic Stent Graft System.
Thoracic Aortic Aneurysm rupture	Rupture or perforation of the targeted thoracic aneurysmal sac as detected by angiography, CT scan, or direct observation at surgery or autopsy.

Term	Definition
	Aneurysm rupture should be reported as either procedure-related aneurysm rupture (i.e., perforation of the aneurysm during the course of the implantation procedure) or as a late aneurysm rupture that follows device deployment. *Excluded are aneurysms in anatomic areas other than the targeted segment treated by the Valiant Evo Thoracic Stent Graft System.*
Aneurysm expansion	Aneurysm maximum diameter increase > 5 mm as compared to the 1- month contrast enhanced imaging measurements
Stent graft migration	Evidence of proximal or distal movement of the stent graft (>10 mm) relative to fixed anatomic landmarks (e.g. supra aortic trunks, coeliac trunk), which is not due to remodeling of the subject's vasculature. The 1-month imaging will be used as the baseline for this determination.
Loss of stent graft patency	Defined as a 100% complete blockage (occlusion) of the lumen diameter of any implanted stent graft component(s) as evidenced by CT, angiography, ultrasound, or other appropriate imaging modality, and/or operative pathological analysis.
Endoleak	Defined by the presence of contrast-enhanced blood outside the lumen of the endoluminal graft but within the aneurysm sac. Endoleaks are classified as follows: **Type I a** – Leak at the proximal graft attachment site **Type I b -** Leak at the distal graft attachment site. **Type I c -** Leak around a fenestration, branch end point, or branch occluding plug (e.g., plug occluding a subclavian artery or iliac artery to prevent flow into an aneurysm sac). **Type II** – Retrograde flow from branch arteries arising from the excluded segment. **Type III a** – Endoleak between the segments of the modular graft (junctional endoleak). **Type III b** – Endoleak in the mid-graft region due to the defect of fabric. **Type IV** – Transgraft leak due to fabric porosity. **Type V** – Aneurysm enlargement in the absence of any demonstrable perfusion of the aneurysmal sac **Type undetermined -** Endoleak of undefined origin

L.2.2 Major Adverse Events (MAEs)

Respiratory complications	
Atelectasis	Collapse of part or (much less commonly) all of a lung caused by a blockage of the air passages (bronchus or bronchioles) or by pressure on the outside of the lung. Clinical evidence of atelectasis is determined by physical, radiographic, and laboratory findings requiring treatment with antibiotics, inhalation therapy, intubation, or suctioning.
Pneumonia	Inflammation of the lung, usually caused by an infection. Clinical evidence of pneumonia is determined by physical, radiographic, and laboratory findings requiring treatment with antibiotics, inhalation therapy, intubation, or suctioning.
Pulmonary embolism	Sudden onset of pleuritic chest pain, cough, hemoptysis, hypoxia, tachycardia and a positive ventilation/perfusion (V/Q) scan.
Pulmonary edema	Abnormal accumulation of fluid in the lungs.
Respiratory failure	The need for ventilatory support for >72 hours associated with an inability to wean from the respirator for any reason.
Renal complications	
Renal failure	Sudden reversible failure of renal function caused by shock, interruption of blood flow to the kidneys, direct damage to the kidney's and/or sudden obstruction of urine flow.
Renal insufficiency	Slowly progressive failure of renal function resulting from some disease (e.g., diabetes, cancer, hypertension, glomerulonephritis) that causes gradual destruction of the kidneys or if creatinine levels are available, an increase of >25% above the pre-procedure creatinine level.
Cardiac complications	
Myocardial Infarction (MI)	• Non-Q-wave MI is defined as elevated CK > 2X the upper lab normal with the presence of elevated CK-MB (any amount above the institutions upper limit of normal) in the absence of new pathological Q waves. • Q wave myocardial infarction is defined as development of new, pathological Q waves in 2 or more contiguous leads (as assessed by the ECG core laboratory) with post-procedure CK elevation >2x ULN and CKMB levels elevated above normal.
Unstable angina	Chest pain unrelieved by anti-anginal medications in a subject with known coronary artery disease without significant elevations in cardiac enzymes.

New arrhythmia	The development of new atrial arrhythmia, new ventricular arrhythmia, exacerbation of a prior arrhythmia, a significant increase in severity of a current arrhythmia or any episode of cardiac arrest.
Congestive Heart Failure (CHF)	Failure of the heart to pump blood with normal efficiency. Development of an acute episode of or exacerbation of existing low cardiac output or fluid overload accompanied by peripheral and/or pulmonary edema.
Central and peripheral neurological complications	
Cerebrovascular accident (CVA) / Stroke	Defined as sudden onset of vertigo, numbness, aphasia, or dysarthria due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persisted >24 hours.
Cerebrovascular Embolic event	The obstruction of a blood vessel from the brain by a blood clot or foreign substance (e.g. air, fat, bacteria).
Paraplegia	Complete loss of motor function in the lower extremities and lower portions of the trunk. A thoracic or lumbar injury can affect leg, bowel and bladder control and sexual function.
Paraparesis	Mild loss of bilateral lower extremity motor function; bilateral lower extremity weakness.
Gastrointestinal complications	
Bowel ischemia	A decrease in blood supply to either the large or small intestine that is associated with pain, bleeding, abdominal distension, diarrhea or x-ray or angiographic evidence of reduced organ flow.
Major Bleeding complications	
Bleeding, procedural	A blood loss greater than 750 cc occurring before the subject leaves the OR.
Bleeding, post-procedural	Post-procedural bleeding greater than 750cc occurring after the subject leaves the OR.
Coagulopathy	The development of an abnormal bleeding disorder (e.g., Disseminated Intravascular Coagulopathy or Thrombocytopenia with platelet counts of < 80,000) documented by appropriate laboratory studies requiring therapy with medication or transfusion.
Vascular complications	
Aortic rupture	The tearing apart of the aortic tissue. Signs of aortic rupture include hemothorax, unrelenting chest or back pain, or hypotension refractory to medical management for a period exceeding two (2) days.
Aneurysm rupture	See definition of Thoracic Aortic Aneurysm rupture in section L.2.1.

Hematoma at access site	An abnormal localized collection of blood (clotted or partially clotted) and situated at level of access site(s) used for endovascular procedure.
Pseudo or false aneurysm	Enlargements of the aorta, iliac or femoral arteries, which contain some or all of the medial layer, the adventitia, and periaortic tissue; most commonly associated with previous aortic operative procedures, trauma, and/or infection. Pseudo-aneurysms typically present as a well-defined collection of blood outside the vessel wall from contained rupture.
Arteriovenous (AV) fistula	Formation of an abnormal connection between the lumens of an artery and a vein as documented by CT, ultrasound, angiography or direct observation.
Retroperitoneal bleed	Bleeding into the retroperitoneal space due to trauma, surgery or percutaneous puncture of an artery or vein.
Limb ischemia	A decrease in blood supply to either the inferior or superior limb(s).
Thrombosis	Clotting within a blood vessel which may cause infraction of tissues supplied by the vessel; it may be occlusive or attached to the vessel or heart wall without obstructing the lumen.

L.2.3 Device Deficiencies

As defined in section F.6.1, every Device Deficiency will be reported by the Investigator on a Device Deficiency Form regardless it resulted in an Adverse Event.

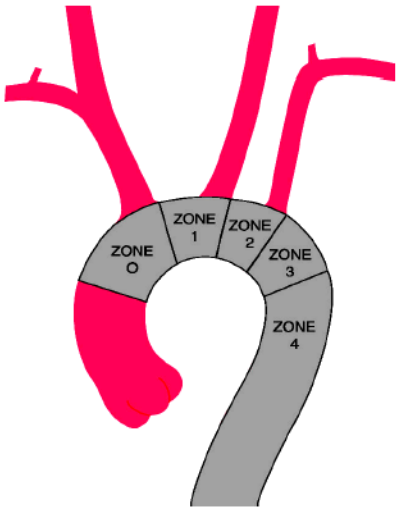
Listing of Device Deficiencies (DD) available in CRF drop down list

Implant procedure-specific DD	Inadequate labeling
	Inadequate packaging
	Use Error (specify : Not following IFU deployment steps, Not following IFU bailout technique instructions, Use of a device with an identified malfunction)
	Access Failure
	Insertion Failure
	Delivery Difficulty
	Delivery Failure
	Deployment Difficulty
	Deployment Failure
	Difficulty to release tip capture
	Failure to release tip capture
	Difficulty to remove delivery system
	Failure to remove delivery system
	Delivery system component breakage (e.g., handle, sheath, tip, etc.)

	Stent graft Incomplete Deployment (device does not fully deploy in target area)
	Misaligned Deployment
	Stent graft Infolding
	Incomplete apposition/mal-apposition of proximal stent with aortic wall (bird beak)
	Stent graft Improper placement (Misplacement) related to marker interpretation, improper manufacturing, physician error
	Any other failure/malfunction of Delivery System during procedure, specify:_____
Other DD:	Use Error – Inappropriate device over sizing
	Use Error – Inappropriate device overlap
	Use Error – Other, specify: _____
	Incomplete sealing, not due to anatomy or disease progression
	Stent graft Fabric porosity, not due to subject's heparinization or other anticoagulant medication
	Stent graft Fabric defect (specify: stent graft rupture, stent graft extrusion/ erosion)
	Stent graft Fracture (Specify: proximal bare stent, wireform)
	Stent graft Kinking*
	Stent graft Twisting*
	Stent graft Dilatation
	Stent graft Migration
	Stent graft Component Separation
	Stent graft Wire Detachment from Fabric (specify location)
	Any other failure/malfunction of Stent graft, specify: _____

* Not intentional and not due to anatomy or disease progression

L.2.4 Additional Definitions

Term	Definition
Landing zones of the thoracic aorta	 The landing zones in the aorta for endovascular stenting are defined as follows: Zone 0 – the proximal edge of the covered endograft lies proximal to the distal end of the innominate artery Zone 1 – from distal end of the innominate artery to the distal end of the left common carotid artery Zone 2 – from the distal end of the left common carotid artery to the distal end of the left subclavian artery Zone 3 – from the distal end of the left subclavian artery to the end of the aortic arch curvature (≤2 cm of the left subclavian artery without covering it) Zone 4 – proximal extent of the endograft is >2 cm distal to the left subclavian artery and ends within the proximal half of the descending thoracic aorta (T6 approximating the midpoint of the descending thoracic aorta)

L.3 Imaging Matrix

Anatomy/Stent Graft Issue Detected	CT with contrast	CT without contrast	MRI with contrast	MRI without contrast	Angiogram/, Aortogram, and Arteriogram
Diameter and Length	1	2	1	2	3
Stent graft migration	1	2	1	2	2-3
Stent graft fracture	2	3	2	3	2-3
Stent graft kinking	2	3	2	3	2-3
Collapse of stent graft	2	3	2	3	2-3
Stent graft twisting	2	3	2	3	2-3
Stent graft patency	1	4	1	4	2-3
Endoleaks	1	4	1	4	2-3
False lumen perfusion	1	4	1	4	2-3
Occlusion	1	4	1	4	2-3
Stenosis	1	4	1	4	2-3
Stent Graft Fabric Defect	1	4	1	4	2-3
1= Highly visible	2 = visible	3 = Not very visible (potential artifacts)			4 = Invisible

L.4 Device Explant and Returned Product Instructions

EXPLANT AND AUTOPSY PROCEDURE FOR ENDOVASCULAR PATIENTS

SURGEON AND SITE RESPONSIBILITY

***NOTE**: Priority should be given to patient health and safety at all times during the explant procedure.*

A. If the explant is part of a late conversion to an open-surgical procedure, consideration of the patient is foremost. The surgeon should remove ONLY the endovascular prosthesis, damaging or altering the device as little as possible yet providing optimal surgical care to the patient.

B. If the explant is performed on a cadaver, the surgeon should carefully view the adjacent body organs and excise the intact aorta containing the endovascular prosthesis, including 1cm of tissue adjacent to the proximal and distal fixation sites to facilitate histological assessment.

C. It is important that care be given during the collection, handling and examination of the implant to ensure that it is not damaged or altered.

- Particular care should be taken to avoid applying force, traction, or torsion to the stent graft during the explant.

- Care should be exercised to avoid excessive manipulation with metallic instruments at the proximal and distal fixation sites whenever possible.
- Stent graft or post mortem specimen should be placed in formalin as is. Do not attempt to clean or remove organic debris.

D. Using the Explant Procedure Observation Form (UC200103088EN), the physician should accurately and fully document the explant procedure and the stent graft ex situ. Any possible trauma applied to the device, e.g., clamping, twisting, torsion, or traction should also be documented.

- Physician operation notes may also be used to document the procedure and the characteristics of the stent graft prior to and after explant from the body.
- Mark components that separate during explant. Attach suture or hemoclip to anterior side and on the proximal end for proximal cuffs and distally for distal components.

E. Follow procedures from Explant Return Instructions (UC200103091) included in the explant kit for packaging and return of device to Medtronic.

EXPLANT RETURN INSTRUCTIONS

1.0 Complete the following forms:

Explant Procedure Observation Form (UC200103088EN) This form is to be completed at the time of the explant procedure.

Explant Identification Peel-off Labels (UC200103089EN) Using permanent ink, complete the two labels provided in the kit. Place one completed label on the inner plastic container, place the second completed label on the outer metal container.

Air bill (pre-printed) Fill in shipper information.

2.0 Secure the explant in the explant kit for shipping. ***Note: Medtronic Monitors/Field Representatives are not authorized to handle formalin/formaldehyde***.

- Place the explanted device and any associated organic tissue into the labeled inner plastic container in a 10% neutral buffered formalin (3.7-4% Formaldehyde) solution to maintain tissue integrity. **(To be completed by hospital staff only)**
  Note: Any specimen too large for the provided inner container may be sent in any securely closed container and placed with provided packing in the metal container and box.
- Seal the plastic container with red tape (provided in kit). The tape should be stretched clockwise around the cap and the container. Place plastic container into the absorbent bag.
- Place the absorbent bag (with plastic container) inside the labeled metal container. Fold the top flaps of the absorbent lining over the top of the plastic container and secure the bag with a twist tie or cable tie (provided in kit). Place lid on metal can and seal with the locking ring provided. Place the can into the inner partition of the cardboard box, and push in the corner tabs on the top of the partition to retain the can.
- Place the completed **Explant Procedure Observation Form**, implant and explant operative reports, and any radiology follow-up reports (if available), inside the moisture-resistant plastic bag provided, and place into the box.
  Note: A Record of Disclosure of Health Information for Public Purposes is included for your convenience and can be placed in the patients file.
  Securely seal the box with clear tape (provided in kit). Affix the shipping airbill to the outside of the box.
- Arrange for pickup from Shipping Company.

If you have questions about shipping the device, need additional information, or desire additional Explant Kits, please contact the Explant Department, at **(707) 591-7672 or 1-800-465-5533, Option 3.**

Thank you for completing the Explant Forms and returning the device. Medtronic uses this information to meet FDA requirements and track product performance.

EXPLANT PROCEDURE OBSERVATION FORM

PATIENT INFORMATION

Patient IDE/ Study ID_____
Name:_____
DOB **(Month/Day/Year)**: _____/_____/_____

IMPLANT INFORMATION

Date of Implant: _____/_____/_____
Implanting Physician: _____
Implanting Hospital Name: _____
City and State:_____
Country: _____

EXPLANT INFORMATION

Date of Explant/Autopsy: _____/_____/_____
Explanting Physician: _____
Name of Hospital: _____
Address: _____
City and State: _____
Country: _____
Telephone: (____)_____

REASON FOR EXPLANT

_____

_____

_____

☐ Planned Surgical Conversion
☐ Emergent Conversion
☐ Autopsy Date of Death: ____/____/____

Remarks about procedure: _____

_____

_____

_____

_____

Evidence of inflammation ☐ Yes ☐ No
Comments:_____
Thrombosis present in the sealzones ☐ Yes ☐ No
Comments:_____
Calcification present in the sealzones ☐ Yes ☐ No
Comments:_____

How well was the device attached to the patient's tissue?
Proximally: ☐ Comes out easily from aortic vessel
☐ Appears firmly attached to aortic vessel
Mid body: ☐ Comes out easily from aneurysm contents
☐ Appears firmly attached to aneurysm contents
Distally (L): ☐ Comes out easily from iliac/aortic vessel
☐ Appears firmly attached to iliac/aortic vessel
Distally (R): ☐ Comes out easily from iliac/aortic vessel
☐ Appears firmly attached to iliac/aortic vessel

Comments _____

_____

Successful Surgical Conversion: ☐ Yes ☐ No

Patient Outcome: ☐ Alive ☐ Expired

EXPLANTED DEVICE INFORMATION

DEVICE	CATALOG NUMBER	LOT NUMBER
Bifurcated Body □ Distal Left □ Distal Right		
Contralateral Limb		
Iliac Extension □ Left □ Right		
Iliac Extension □ Left □ Right		
Iliac Extension □ Left □ Right		
Aortic Cuff		
AUI □ Distal Left □ Distal Right		
Thoracic, Proximal Main		
Thoracic, Distal Main		
Thoracic, Distal Main		
Thoracic, Proximal Extension		
Thoracic, Distal Extension		
Other (Specify)		

Additional Comments

Form completed by: _____

Title: _____

Date: _____

L.5 Informed Consent Template

L.6 Post PMA-S approval Analysis

Following PMA-S approval, the postmarket evaluation will be conducted and results provided to the FDA once the last subject in the study completes the 12-month follow-up visit.

A synopsis of this post-approval proposal along with statistical assumptions is presented in Table L-1 below. Medtronic has used its experience with Valiant Captivia in patients with DTAA to establish the assumptions used in the statistical design of this study. The VALOR II study with the Valiant stent graft system enrolled 160 patients with DTAA and was assessed through 12 months for purposes of PMA (P100040) approval. Through 1-year post-treatment, the rate of MDEs combined with access and/or deployment failures was 7.1% (11/153) (Medtronic internal data using the Valiant Evo proposed definition). Therefore, for the purpose of post approval analysis, the rate of MDEs combined with access and deployment failures at 1-year with Valiant Evo is estimated to be 7.1% (refer to Table L-1 below for power analysis assumptions).

Table L-1: Power Analysis Assumptions for Evaluation of Valiant Evo in Patients with DTAA at 1-year

Estimated rate of MDEs combined with access and/or deployment failures at 1 year with Valiant Evo	7.1%
Performance Goal (PG) at 1-year	20%
Significance level	0.05
Statistical test	One-sided binomial test
Evaluable sample size	N = 63 at 1 year
Enrollment	IDE cohort will enroll a minimum of 100 subjects and is expected to have a minimum of 63 evaluable subjects at 1-year follow up.
Statistical power from 63 or more evaluable subjects	92% (overall study power for passing both hypotheses is 81%)

L.7 CMS Study Criteria

Medicare beneficiaries may be affected by the device because in 2013 more than 63% of TEVAR cases were performed in Medicare beneficiaries, and 59% of claims with principal TAA diagnoses involve patients age 65 or older. Study results are expected to be generalizable within the Medicare beneficiary population based on the prevalence of TAA in patients age 65 and older.

All IRBs should comply with 45 CFR part 46.

M VERSION HISTORY

Version	Summary of Changes	Author(s)/Title
1A	• Not Applicable, New Document	[redacted]
1B	• Synopsis update with schedule of events for extended follow-up • Extended the follow of subjects from 12 months to 60 months • Administrative changes like correction of typo's, font types and alignments, integration of updated corporate template	[redacted]