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A SYNOPSIS

Title	Valiant Evo International Clinical Trial
Investigational Device	Valiant™ Evo Thoracic Stent Graft System
Study Design	The Valiant Evo International Clinical Trial is a prospective, multi-center, pre-market, non-randomized, single-arm trial.
Purpose	The purpose of the Valiant Evo International 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 Valiant Evo International Clinical Trial is a first-in human experience with the objective to provide clinical data for supporting CE marking via case series and descriptive statistics. Data collected during this trial may also be used in conjunction with data collected during a concurrently enrolling IDE trial to support commercial approval of the Valiant Evo Thoracic Stent Graft System in the United States.
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 objective	Secondary objectives include descriptive analyses of secondary endpoints as well as acute procedural observations and clinical utility measures. Safety and effectiveness data will be collected over a one year period following endograft implantation.
Primary Endpoint	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.2.1: • Device-related secondary procedures • Device-related mortality • Conversion to open surgery • Thoracic aortic aneurysm rupture An independent Clinical Events Committee (CEC) will be established to 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), 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
	
	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
	
	Note: Medtronic will classify each Adverse Event according to ISO 14155:2011.
	
	For subjects that re-consented to extended study follow up, the above 12-month secondary endpoints are to be evaluated at 24, 36, 48, and 60 months
	
	Supplementary data analysis will be performed on acute procedural observations and clinical utility measures such as the amount of blood loss, blood products transfused, duration of implant procedure, time in Intensive Care Unit, and overall hospital stay.

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 International Clinical Trial.
Number of subjects	47 subjects will be included and assessed per the study's primary endpoint to support regulatory approval.
Number of Sites	Subjects will be recruited from up to 17 medical centers. Target geographies include, but are not limited to, the Netherlands, Italy, Denmark, France, the United Kingdom and Canada.
Clinical Procedures and Follow Up Schedule	Inclusion: Those subjects who sign and date the informed consent document, meet all of the study eligibility criteria, and are approved by the Independent Reviewer, will be eligible for inclusion into the Valiant Evo International Clinical Trial. A subject will only be considered included when arterial access is established and an attempt to introduce the Valiant Evo Thoracic Stent Graft is made. At all required follow-up visits subjects will undergo the following assessments and procedures:

	<table><tr><th>Procedures</th><th>Screening / Baseline</th><th>Index Procedure</th><th>Hospital Discharge</th><th>1-Mo. F/U (±15 days)</th><th>12-Mo. F/U (±60 days)</th></tr><tr><td>CLINICAL</td><td colspan="5"></td></tr><tr><td>Physical examination</td><td>✓</td><td></td><td></td><td>✓</td><td>✓</td></tr><tr><td>Adverse event assessment</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr><tr><td>EQ-5D questionnaire</td><td>✓</td><td></td><td></td><td>✓</td><td>✓</td></tr><tr><td>IMAGING</td><td colspan="5"></td></tr><tr><td>CT/MRI with contrast</td><td>✓</td><td></td><td></td><td>✓</td><td>✓</td></tr></table> Health-related quality of life outcomes will be assessed at all scheduled follow-up visits using the EQ-5D questionnaire. Any interim imaging of the stent graft region done within one year of implantation should be recorded on the interim image eCRF (e.g. 6-month imaging follow-up when performed as standard of care and/or when performed further to any issue observed at previous imaging follow-up. All subjects will be consented for up to 2 years of follow-up. This is to accommodate any global clinical investigational requirements, if required. For subjects that re-consented to extended study follow up, the assessments as performed during the 12 month visit is to be repeated at 24, 36, 48 and 60 month visits.
Principal Investigator	Prof. Fabio Verzini S.C. Chirurgia Vascolare – VI piano Ospedale S. Maria della Misericordia Piazzale Menghini, 1 06129 Perugia Italy
Inclusion Criteria	Candidates for the Valiant Evo International Clinical trial must be appropriate subjects for endovascular repair of aneurysms of the descending thoracic aorta (evidenced by screening contrast-enhanced computerized tomography (CT) or contrast-enhanced Magnetic Resonance Imaging (MRI)) 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 Patient Informed Consent approved by the Sponsor and by the Ethics Committee for this study. *Note: Patients that belong to vulnerable population groups and are at risk of being influenced to participate in the trial without making a well-informed and voluntary decision will not be considered for participation.* 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[27]: 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 MRI 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)*** 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 *a. Note: A positive pregnancy test may be required by local regulations* 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
Data Oversight	An Independent Medical Monitor, Data Monitoring Committee, Clinical Events Committee, and imaging core lab with and Independent Physician Reviewer will be established to independently evaluate subject anatomical eligibility, 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.

B GENERAL INFORMATION

B.1 Introduction

This clinical investigational plan describes study requirements for the Valiant Evo Thoracic stent graft system International Clinical Trial (hereafter referred to as the Valiant Evo International Clinical Trial).

For further literature review, pre-clinical testing and previous clinical experience refer to the Investigator's Brochure. The purpose of this study is to investigate the safety and effectiveness of the Valiant Evo Thoracic Stent Graft System in subjects with a DTAA who are candidates for endovascular repair. The Valiant Evo International Clinical Trial is a first-in human experience with the objective to provide clinical data for supporting CE marking via case series and descriptive statistics. Additionally, data collected during the international trial described herein may be used in conjunction with data collected during a concurrently enrolling US IDE trial to support the US PMA-S of the Valiant Evo Thoracic Stent Graft System.

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 treatments include 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 trans femoral 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]

In Europe, where thoracic aortic endovascular devices have been commercially available for more than two decades, endovascular stent graft treatment is becoming the standard of care in the management of the whole spectrum of thoracic aortic diseases. Mid-term experiences in using thoracic stent grafts in the management of aneurysm of the DTA have been published reporting satisfactory outcomes.[14, 15, 16] Rapid advances in technology and procedural breakthroughs have contributed to the achievement of a near-complete transformation of the whole field of thoracic aortic surgery less than 15 years after the first report by Dake et al[17] on stent graft repair of thoracic aortic aneurysms.

However, despite the wide spread adoption of TEVAR in modern treatment of TAAs, not all patients are candidates for thoracic endovascular aneurysm repair (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. Anatomical limitations represent 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 arch 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 which 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.

Valiant Evo Thoracic Stent Graft System is designed to allow treatment of patients without the need for alternative access methods, expand overall patient applicability, and improve procedural ease of use of the system. This device will address an important TEVAR need: a significant reduction of the delivery system profile (profile of 18Fr for diameters ≤25 mm, profile of 20Fr for diameters ≤37 mm and profile of 22Fr for 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 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 the 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. This ensures that the modified device meets the pre-established design and performance specifications and to ensure that product performance will not be negatively affected. Residual risks associated with the overall performance of the Valiant Evo Thoracic Stent Graft System will be confirmed in a clinical investigation designed to evaluate system performance.

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 patient'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 patient's vasculature to deliver the stent graft to the target site. Upon deployment, the stent graft self-expands to conform to the shape and size of the seal zones above and below the lesion.

The Valiant Evo Thoracic Stent Graft System does not contain natural rubber latex; however, during the manufacturing process, it may have had incidental contact with latex-containing products.

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 increase the graft length distally or proximally to the primary section.

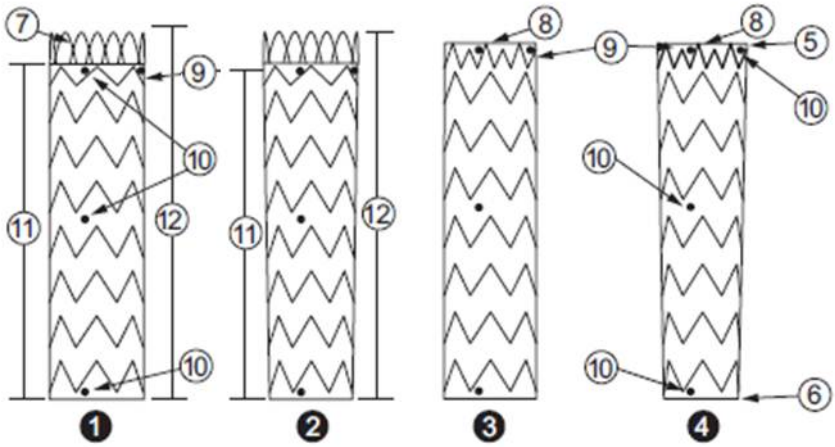
All stent graft components are composed of a self-expanding spring scaffold made from nitinol wire sewn to a polyester fabric graft with non-resorbable sutures. The metal scaffolding is composed of a series of serpentine stents stacked in a tubular configuration. Radiopaque (RO) markers are sewn onto each component of the stent graft to aid in visualization and to facilitate accurate placement. The nitinol stents are also visible under fluoroscopy. 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 (nickel-titanium) alloy
RO markers	Platinum-iridium alloy
Graft fabric	Polyester (PET)
Suture	Polyester (PET) and Ultra-high-molecular-weight polyethylene (UHMWPE)

The Valiant Evo Thoracic Stent Graft System is available in four different configurations (see Figure B-2): FreeFlo Straight, FreeFlo Tapered, Closed Web Straight, and Closed Web Tapered.

Each stent graft configuration can be used either as a proximal or distal component.



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-2: Stent Graft Configuration Components

Note: Figure B-2 and all other product graphics appearing in this document are not drawn to scale. They are for graphical representation only, and the stent graft and delivery system components may appear differently under fluoroscopy.

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 diameters of the proximal end and distal end of the FreeFlo Straight configuration are constant throughout the covered length of the device. A proximal end of a FreeFlo stent graft 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 diameter of the proximal end of the FreeFlo Tapered configuration is larger than the diameter of the distal end. A proximal end of a FreeFlo stent graft 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 diameters of the proximal end and distal end 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 diameter of the proximal end of the Closed Web Tapered configuration is larger than the diameter of the 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.

A flexible tapered tip is attached to the end of the inner member and provides a smooth transition from the guidewire to the outer graft cover. The external surfaces of the tapered tip and graft cover are coated with a lubricious hydrophilic coating. Once activated with a sterile gauze saturated in saline, this coating will facilitate vessel access and tracking through the anatomy. A distal RO marker indicates the graft cover edge under fluoroscopy. A hemostasis valve at the proximal end of the delivery system minimizes blood loss and leakage during the procedure. The stent graft is deployed by rotating or retracting the integrated slider handle. The tip capture release handle at the rear of the delivery system is unlocked and retracted to release the proximal end of the stent graft. The flush port provides access to the graft cover lumen and is used for flushing the system prior to use. The flush port includes a one-way valve that prevents back-flow of flush fluid or blood during the procedure.

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-3: Valiant Evo Thoracic Stent Graft delivery system

For detailed description of the Valiant Evo Thoracic Stent Graft System components, materials, and sizing configurations please see the Instructions for Use (IFU) and the Investigator's Brochure (IB). The IFU will be provided with each investigational device.

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.

Table B-2: Valiant Evo Thoracic Stent Graft System size matrix

Model Numbers/ Customer Facing Numbers (CFNs)	**Catheter Crossing Profile** (Fr)	**Stent Graft Description** (Diameter*length)	**Stent Graft Type**
VEEF3434C60CE	20	34x60mm	FreeFlo Straight Extension
VEEF3737C60CE	20	37x60mm	FreeFlo Straight Extension
VEEF4040C60CE	22	40x60mm	FreeFlo Straight Extension
VEEF4343C60CE	22	43x60mm	FreeFlo Straight Extension
VEEF4646C60CE	22	46x60mm	FreeFlo Straight Extension
VEMF2020C100CE	18	20x100mm	FreeFlo Straight
VEMF2222C100CE	18	22x100mm	FreeFlo Straight
VEMF2525C100CE	18	25x100mm	FreeFlo Straight
VEMF2828C100CE	20	28x100mm	FreeFlo Straight
VEMF3131C100CE	20	31x100mm	FreeFlo Straight
VEMF3434C100CE	20	34x100mm	FreeFlo Straight
VEMF3737C100CE	20	37x100mm	FreeFlo Straight
VEMF4040C100CE	22	40x100mm	FreeFlo Straight
VEMF4343C100CE	22	43x100mm	FreeFlo Straight
VEMF4646C100CE	22	46x100mm	FreeFlo Straight
VEMF2222C175CE	18	22x175mm	FreeFlo Straight
VEMF2525C175CE	18	25x175mm	FreeFlo Straight
VEMF2828C175CE	20	28x175mm	FreeFlo Straight
VEMF3131C175CE	20	31x175mm	FreeFlo Straight
VEMF3434C175CE	20	34x175mm	FreeFlo Straight

Model Numbers/ Customer Facing Numbers (CFNs)	Catheter Crossing Profile (Fr)	Stent Graft Description (Diameter*length)	Stent Graft Type
VEMF3737C175CE	20	37x175mm	FreeFlo Straight
VEMF4040C175CE	22	40x175mm	FreeFlo Straight
VEMF4343C175CE	22	43x175mm	FreeFlo Straight
VEMF4646C175CE	22	46x175mm	FreeFlo Straight
VEMF3131C225CE	20	31x225mm	FreeFlo Straight
VEMF3434C225CE	20	34x225mm	FreeFlo Straight
VEMF3737C225CE	20	37x225mm	FreeFlo Straight
VEMF4040C225CE	22	40x225mm	FreeFlo Straight
VEMF4343C225CE	22	43x225mm	FreeFlo Straight
VEMF4646C225CE	22	46x225mm	FreeFlo Straight
VEEC3434C60CE	20	34x60mm	Closed Web Extension
VEEC3737C60CE	20	37x60mm	Closed Web Extension
VEEC4040C60CE	22	40x60mm	Closed Web Extension
VEEC4343C60CE	22	43x60mm	Closed Web Extension
VEEC4646C60CE	22	46x60mm	Closed Web Extension
VEMC2020C100CE	18	20x100mm	Closed Web Straight
VEMC2222C100CE	18	22x100mm	Closed Web Straight
VEMC2525C100CE	18	25x100mm	Closed Web Straight
VEMC2828C100CE	20	28x100mm	Closed Web Straight
VEMC3131C100CE	20	31x100mm	Closed Web Straight
VEMC3434C100CE	20	34x100mm	Closed Web Straight
VEMC3737C100CE	20	37x100mm	Closed Web Straight
VEMC4040C100CE	22	40x100mm	Closed Web Straight
VEMC4343C100CE	22	43x100mm	Closed Web Straight
VEMC4646C100CE	22	46x100mm	Closed Web Straight
VEMC2222C175CE	18	22x175mm	Closed Web Straight
VEMC2525C175CE	18	25x175mm	Closed Web Straight
VEMC2828C175CE	20	28x175mm	Closed Web Straight
VEMC3131C175CE	20	31x175mm	Closed Web Straight
VEMC3434C175CE	20	34x175mm	Closed Web Straight
VEMC3737C175CE	20	37x175mm	Closed Web Straight
VEMC4040C175CE	22	40x175mm	Closed Web Straight
VEMC4343C175CE	22	43x175mm	Closed Web Straight

Model Numbers/ Customer Facing Numbers (CFNs)	Catheter Crossing Profile (Fr)	Stent Graft Description (Diameter*length)	Stent Graft Type
VEMC4646C175CE	22	46x175mm	Closed Web Straight
VEMC3131C225CE	20	31x225mm	Closed Web Straight
VEMC3434C225CE	20	34x225mm	Closed Web Straight
VEMC3737C225CE	20	37x225mm	Closed Web Straight
VEMC4040C225CE	22	40x225mm	Closed Web Straight
VEMC4343C225CE	22	43x225mm	Closed Web Straight
VEMC4646C225CE	22	46x225mm	Closed Web Straight
VEMF2520C175CE	18	25x20x175mm	FreeFlo Tapered
VEMF2822C175CE	20	28x22x175mm	FreeFlo Tapered
VEMF3125C175CE	20	31x25x175mm	FreeFlo Tapered
VEMF3428C175CE	20	34x28x175mm	FreeFlo Tapered
VEMF3731C175CE	20	37x31x175mm	FreeFlo Tapered
VEMF4034C175CE	22	40x34x175mm	FreeFlo Tapered
VEMF4337C175CE	22	43x37x175mm	FreeFlo Tapered
VEMF4640C175CE	22	46x40x175mm	FreeFlo Tapered
VEMC2520C175CE	18	25x20x175mm	Closed Web Tapered
VEMC2822C200CE	20	28x22x200mm	Closed Web Tapered
VEMC3125C200CE	20	31x25x200mm	Closed Web Tapered
VEMC3428C200CE	20	34x28x200mm	Closed Web Tapered
VEMC3731C200CE	20	37x31x200mm	Closed Web Tapered
VEMC4034C200CE	22	40x34x200mm	Closed Web Tapered
VEMC4337C200CE	22	43x37x200mm	Closed Web Tapered
VEMC4640C200CE	22	46x40x200mm	Closed Web Tapered

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 DTA in patients having the appropriate anatomy, including the following:

- Iliac or femoral access vessel morphology that is compatible with vascular access techniques, devices, or accessories
- Non-aneurysmal aortic diameter from 16 to 42 mm
- Non-aneurysmal aortic proximal neck length ≥ 20mm (for FreeFlo configuration) and ≥ 25mm (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 and the IB. The IFU will be provided with each investigational device.

B.2.3 Device Approval Status

The Valiant Evo Thoracic Stent Graft System is an investigational Class III device in all geographies except for Canada where it is an investigational Class IV device. The Valiant Evo Thoracic Stent Graft System has not received any regulatory approval yet. For the purpose of this study each investigational device will be labelled with "*Exclusively for clinical investigations"* or similar wording in corresponding local language. In Canada, the labelling will be as follows: "Investigational Device: To be used by qualified investigators only / Instrument de recherche: Réservé uniquement à l'usage de chercheurs compétents". '

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.3 Comparator information

No comparator will be used for this clinical trial. All analysis will be descriptive in nature and no statistical comparisons are planned.

C STUDY PLAN

C.1 Study objectives

The purpose of the Valiant Evo International Clinical Trial 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.

The Valiant Evo International Clinical Trial is a first-in human experience with the objective to provide clinical data for supporting CE marking via case series and descriptive statistics. Data collected during this trial may also be used in conjunction with data collected during a concurrently enrolling IDE trial to support commercial approval of the Valiant Evo Thoracic Stent Graft System in the United States.

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.

The Valiant Evo Thoracic Stent Graft System is Medtronic's next generation thoracic stent graft system and this study is designed to assess the design changes from the commercially available Valiant Captivia stent graft system that have been incorporated into the design of the Valiant Evo Thoracic Stent Graft System, as the safety and effectiveness of the Valiant Captivia stent graft system has been established through its clinical trials.

(See section *C.2 Clinical Endpoints* for a detailed description of the evaluation criteria used to assess Primary Objectives.)

C.1.2 Secondary objectives

Secondary objectives include descriptive analyses of secondary endpoints as well as acute procedural observations and clinical utility measures.

Safety and effectiveness data will be collected over a one year period following endograft implantation.

(See section *C.2 Clinical Endpoints* for a detailed description of the evaluation criteria used to assess Secondary Objectives.)

C.2 Clinical endpoints

C.2.1 Primary endpoint

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. 2.1.

An independent CEC will be established to 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 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

Detailed definition of MAEs is defined in Appendix L.2.2.

C.2.2.2 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.2.3 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 International Clinical Trial is not hypothesis driven; all endpoints will be analyzed descriptively. There is no intention to make any clinical claim based on a statistical hypothesis. The limitation of the descriptive design is that there is no statistical comparison or hypothesis to test and thus no pass/fail criteria.

Given the established safety and performance profile of the commercially available Valiant Captivia stent graft system, and the relatively low risk associated with the new features incorporated in the Valiant Evo device design, the goal of this trial is to provide clinical data via descriptive statics demonstrating that the Valiant Evo system performs as expected clinically.

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 International Clinical Trial is a non-randomized, multicenter, open-label, prospective, single-arm trial. The trial is designed to assess the clinical safety and effectiveness of the Valiant Evo Thoracic Stent Graft System. A sample of 47 subjects will be included and evaluated for the 30-day primary endpoint. Data from these 47 subjects will be analyzed and used to support CE Mark approval. All subjects included will continue to be followed under this investigational protocol beyond the 30-day primary endpoint out to 12 months post-implantation. Subjects will have required follow-up evaluations at the following time points:

- 1-month following the index procedure
- 12-months following the index procedure

All subjects will be consented for up to 2 years of follow-up. This is to accommodate any global clinical investigational requirements, if required.

Number of devices being used within this trial:

For subjects that are treated with the 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 in order to cover the complete target lesion length.

C.6 Randomization and blinding

Randomization and blinding will not be utilized as the proposed trial is descriptive in nature, with a single-arm, open-label design, without a control.

C.7 Sample size

A sample of 47 subjects will be included and analyzed to support CE marking. The sample size of 47 subjects is considered adequate to assess the primary endpoint, which is defined as the proportion of subjects who experienced access/deployment failure or MDE within 30-days post index procedure.

Based upon the reported events from the VALOR II study[19] on the Valiant Xcelerant stent graft system, the primary endpoint defined by this protocol would have a failure rate of 5.6% (9/160) within 30 days post index procedure. Considering the failure rate of Valor II, it is expected that Valiant Evo would perform similarly, meaning that 3 out of 47 subjects (6.4%) would likely fail within 30 days of implantation. The precision of this assumed 6.4% point estimate can be assessed by calculating the distance from the calculated 1-sided 95% upper confidence limit. This distance, or margin of error, is calculated to be <10% for this trial; therefore, considered adequate[20, 21] to assess the primary endpoint.

Due to sampling variation, different number of MDEs, anywhere from 0 to 47, might be observed, which would result in different confidence intervals depending on the outcomes as shown in Table C-1.

Table C-1: Sampling Variation and Its Impact to Study Results

Observed number of events (k)	Observed event rate	Probability to observe k events	Probability to observe k or less events	One-sided 95% Upper Confidence Limit	Two-sided 95% Confidence Interval
0	0%	0.0666	0.0666	6.2%	[0%, 7.5%]
1	2.1%	0.1858	0.2524	9.7%	[0.1%, 11.3%]
2	4.3%	0.2535	0.5059	12.8%	[0.5%, 14.5%]
3	**6.4%**	**0.2256**	**0.7314**	15.7%	**[1.3%, 17.5%]**
4	8.5%	0.1472	0.8786	18.4%	[2.4%, 20.4%]
5	10.6%	0.0751	0.9537	21.1%	[3.5%, 23.1%]
6	12.8%	0.0312	0.9849	23.6%	[4.8%, 25.7%]
7	14.9%	0.0108	0.9957	26.2%	[6.2%, 28.3%]

8	17.0%	0.0032	0.9989	28.6%	[7.6%, 30.8%]
9	19.1%	0.0008	0.9998	31.0%	[9.1%, 33.3%]
10	21.3%	0.0002	1.0000	33.4%	[10.7%, 35.7%]

Note: Only 0 to 10 events are tabulated as probability of observing larger number of events is decreasing quickly. Probabilities were calculated based on the 5.6% MDE rate in the target population. An exact method (Clopper-Pearson) was used in calculating confidence interval, the same method to be used for data analysis.

Table C-1 also shows that the probability of observing 3 or less events in a 47-subject sample is 0.7314. The probability of observing 6 or more events is 0.0463 (=1 – probability of 5 or less). Based on this, the expectation is to see less than 6 events in this trial provided that the Valiant Evo performs similarly to its predicate.

Given the sample size of 47 subjects, the confidence interval estimate provides limited but desired precision of a statistical estimation or control of sampling variation (C.I. width) as shown.

C.8 Number of investigation sites and study duration

Forty-seven (47) subjects will be included in approximately 17 investigation sites. Target countries include, but are not limited to the Netherlands, France, Italy, Denmark, Canada and the United Kingdom. No more than 20% of the total study population (i.e. 9 subjects of a total of 47 subjects) will be included from a single investigational site. 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 inclusion period is not expected to exceed 12 months. All included subjects will be followed up at 1 and 12 months post-implantation.

All subjects will be consented for up to 2 years of follow-up. This is to accommodate any global clinical investigational requirements, if required.

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 is stored in the Trial Master File. This list is provided to the investigators. The sponsor will maintain an updated list.

D SUBJECT SELECTION

D.1 Inclusion criteria

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

1. Subject is ≥18 years old

   Subject understands and voluntarily has signed and dated the Patient Informed Consent approved by the Sponsor and by the Ethics Committee for this study.

   Note: Patients that belong to vulnerable population groups and are at risk of being influenced to participate in the trial without making a well-informed and voluntary decision will not be considered for participation

2. Subject presents a DTAA which is localized below the ostium of LSA and above the ostium of celiac trunk
3. Subject has a DTAA that is one of the following[27]:
   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

4. Subject's anatomy must meet all of the following anatomical criteria as demonstrated on contrast-enhanced CT and/or on contrast-enhanced MRI 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)***
   c. Distal non-aneurysmal aortic neck length must be ≥ 20 mm
5. 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

Subject is pregnant

Note: A positive pregnancy test may be required by local regulations

3. Subject requires planned placement of the **covered** proximal end of the stent graft to occur in zones 0 or 1

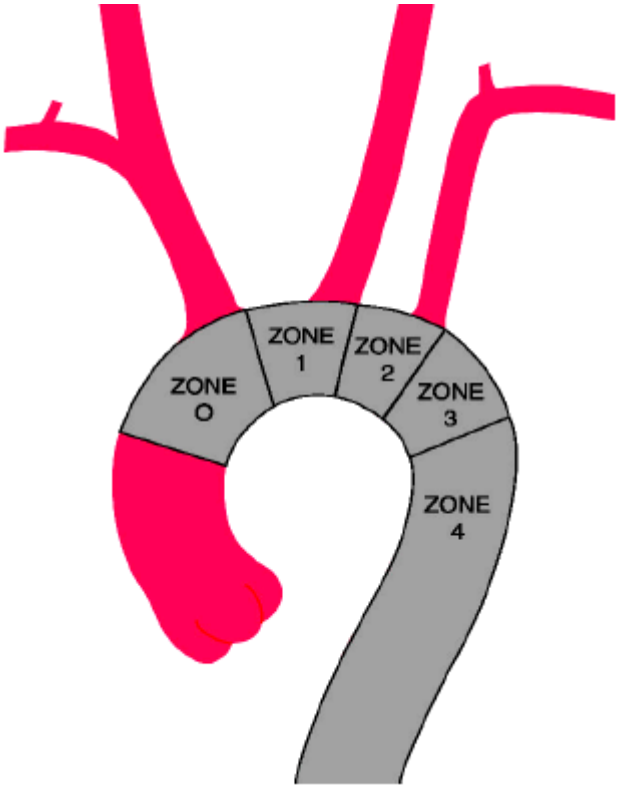


Figure D-1: Landing zones of the thoracic aorta

(See appendix L.2.4 for definitions of zones)

4. Subject has a thoracic aneurysm with a contained rupture or localized at the anastomosis of a previous graft (pseudo-/false aneurysm)
5. Subject has a mycotic aneurysm
6. Subject has a dissection (type A or B) or an intramural hematoma or an aortic rupture in addition to the thoracic aneurysm
7. Subject requires emergent aneurysm treatment, e.g., trauma or rupture
8. 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
9. Subject requires surgical or endovascular treatment of an infra-renal aneurysm at the time of implant
10. Subject has had previous surgical or endovascular treatment of an infra-renal aortic aneurysm
11. 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
12. 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)
13. 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

14. Subject has a connective tissue disease (e.g., Marfan's syndrome, aortic medial degeneration)
15. Subject has a bleeding diathesis or coagulopathy, or refuses blood transfusion
16. Subject has had a MI within 3 months of the procedure
17. Subject has had a CVA within 3 months of the procedure
18. Subject has a known allergy or intolerance to the device materials
19. Subject has a known allergy to anesthetic drugs
20. Subject has a known hypersensitivity or contraindication to anticoagulants, or contrast media, which is not amenable to pretreatment
21. 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 ISO 14155:2011 requirements. If not, Investigators are willing to undergo an ISO 14155:2011 training
- 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. If not, site personnel is willing to undergo an ISO 14155:2011 training
- Site has sufficient annual case volume of TAA 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 Investigation Agreement

A Clinical Investigation Agreement shall be in place, signed by the participating investigation site and/or principal investigator of each investigation 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, by a fully executed agreement. Amendments to this Clinical Investigation Plan shall be agreed upon between Medtronic and investigator(s) and be recorded with a justification for the amendments.

E.1.4 Curriculum Vitae

An up to date signed and dated Curriculum Vitae from all key members of the investigation site team participating in this clinical study as listed on the Delegated task List shall be obtained, evidencing the required qualifications, including the year and where obtained, and including their current position at the investigation site. The signature on the CV must be dated within 3 years prior to the date of activation of the investigation site.

E.2 Ethics

E.2.1 EC approval

Prior to enrolling subjects in this clinical study, each investigation site's EC will be required to approve the current Clinical Investigation Plan, the Patient Information and Informed Consent form, including any other written information to be provided to the subjects and, if applicable, the Investigator's Brochure and materials used to recruit subjects. EC approval of the clinical study must be received in the form of a letter and provided to Medtronic before commencement of the clinical study at an investigation 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 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. If they are members of the EC, written documentation is required stating that he/she did not participate in the approval process. If the EC imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the investigator for reporting to the EC. Investigators must inform Medtronic of any change in status of EC approval once the investigation site has started enrolment. If any action is taken by an EC 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 approved Patient Information and Informed Consent Form. The informed consent template is kept separate from the clinical investigation plan and is stored in the Trial Master File. 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 or write, an impartial witness must be present during the entire informed consent discussion. All items addressed in the Patient Information and 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. Subjects who are unable to make a decision to participate in a clinical investigation and who would need a legal authorized representative will not be enrolled in the study.

The subject must have ample time and opportunity to read and understand the Patient Information and 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 investigator or authorized designee. If applicable, the witness shall also sign and personally date the consent form to attest that the information in the Patient Information and Informed Consent Form was accurately explained and clearly understood by the subject, and that informed consent was freely given. The informed consent process must be documented in the medical records of each consented subject.

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

An implant card will be provided to the sites and can be distributed to all included subjects based on routine practice. This card will be distributed by the investigational team after the implant procedure.

E.2.3 Revisions in Patient Information and Informed Consent Form

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.

Medtronic will revise the written Patient Information and Informed Consent Form whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The revised information will be sent to the investigator for approval by the EC and sent to the Competent Authority (CA)/ Regulatory Agencies (RA) if required by local law and regulations. After approval by the EC and CA/RA as applicable, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

E.2.4 Regulatory submission

No subjects will be enrolled in the clinical study until all applicable Regulatory Authorities have approved the current Clinical Investigation Plan and other documents as required according to local requirements.

If a 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
- Patient Information and Informed Consent Form
- Case Report Forms

E.3 Regulatory compliance

This clinical study will be conducted in compliance with the latest version of the Declaration of Helsinki (October 2013), the international standard ISO 14155:2011 ('Clinical Investigation of medical devices for human subjects'), Medical Device Directive 93/42/EEC, for Canada, SOR/98-282, Sections 79-88, and Canadian Regulatory Guidelines for Mandatory Problem Reporting for Medical Devices, 2011 (H164-145/2011E) and all laws.

In addition, the study will be conducted in compliance with 21 CFR Part 11 and 54 in all participating geographies.

All principles of the Declaration of Helsinki have been implemented in this clinical study by means of the informed consent process, EC approval, study training, clinical trial registration, preclinical testing, risk benefit assessment, publication policy, etc.

The sponsor will avoid improper influence on, or inducement of the subject, monitor, and investigator(s) or other parties participating in, or contributing to, the clinical study by implementing the informed consent process, Clinical Investigation Agreements, EC approval.

This study will be publicly registered in accordance with the Declaration of Helsinki on www.clinicaltrials.gov.
In case of conflicting requirements, the regulation affording the greatest protection to the subject will be followed.

E.4 Training requirements

Prior to investigational site activation or subsequent involvement in clinical study activities, Medtronic will provide clinical study training relevant and pertinent to the involvement of personnel conducting clinical study activities. At a minimum, investigator responsibilities, ISO 14155:2011, the CIP, PIC, use of data collection tools, applicable local regulations, as well as device/product training are required. Study-specific training and any training required by local regulations, when applicable, will be documented prior to investigation site activation.

Performed training will be documented prior to investigation 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. Once the primary endpoint has been reached for all subjects, qualified investigators may also 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 and clinical study-specific equipment

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 an “Activation 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

Medtronic will only allow shipment of investigational devices/products to the investigation site or investigator, after the Clinical Study Manager has declared the investigation site ready to start the clinical study.

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 Investigator’s Brochure and Instructions for use must be taken into account.

E.6.3 Device explant and return procedures/products

Non-functioning or explanted investigational devices/products must be returned to Medtronic as soon as possible for investigation. 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.

E.6.4 Medtronic device/product disposition requirements

Investigational devices/products will be traced during the clinical study by assigning specific unique identifiers to each device/product. The investigator is responsible for maintenance of a Device Accountability Log in the Investigator Site File. On this log, the receipt, use, return and disposal of the investigational devices/products shall be documented. At the end of the clinical study the principal investigator must sign and date the final Device Accountability Log.

F STUDY METHODS

F.1 Point of enrollment and Point of Inclusion

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/MRI. 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 patient'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 evaluations include the following.

- CT or MRI 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 document, the subject will be considered enrolled in the trial. If a subject does not sign the informed consent document, then no further screening procedures for the Valiant Evo International Clinical Trial will 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

Baseline CT/MRI images will be reviewed by the investigator to confirm eligibility. The imaging will also be sent to a core lab for analysis. An Independent Physician Reviewer (IPR) will review the screening CT/MRI images to assess the anatomical inclusion/exclusion requirements and confirm subject 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. However, investigators will be requested to enter safety information in the eCRF **from date of point of enrolment until date of screen failure.** Full IPR review process will be documented in a separate document.
Screen failures will be documented on the Screening, Enrollment and Inclusion log and the reason for screen failure will be documented on the screening eCRF.

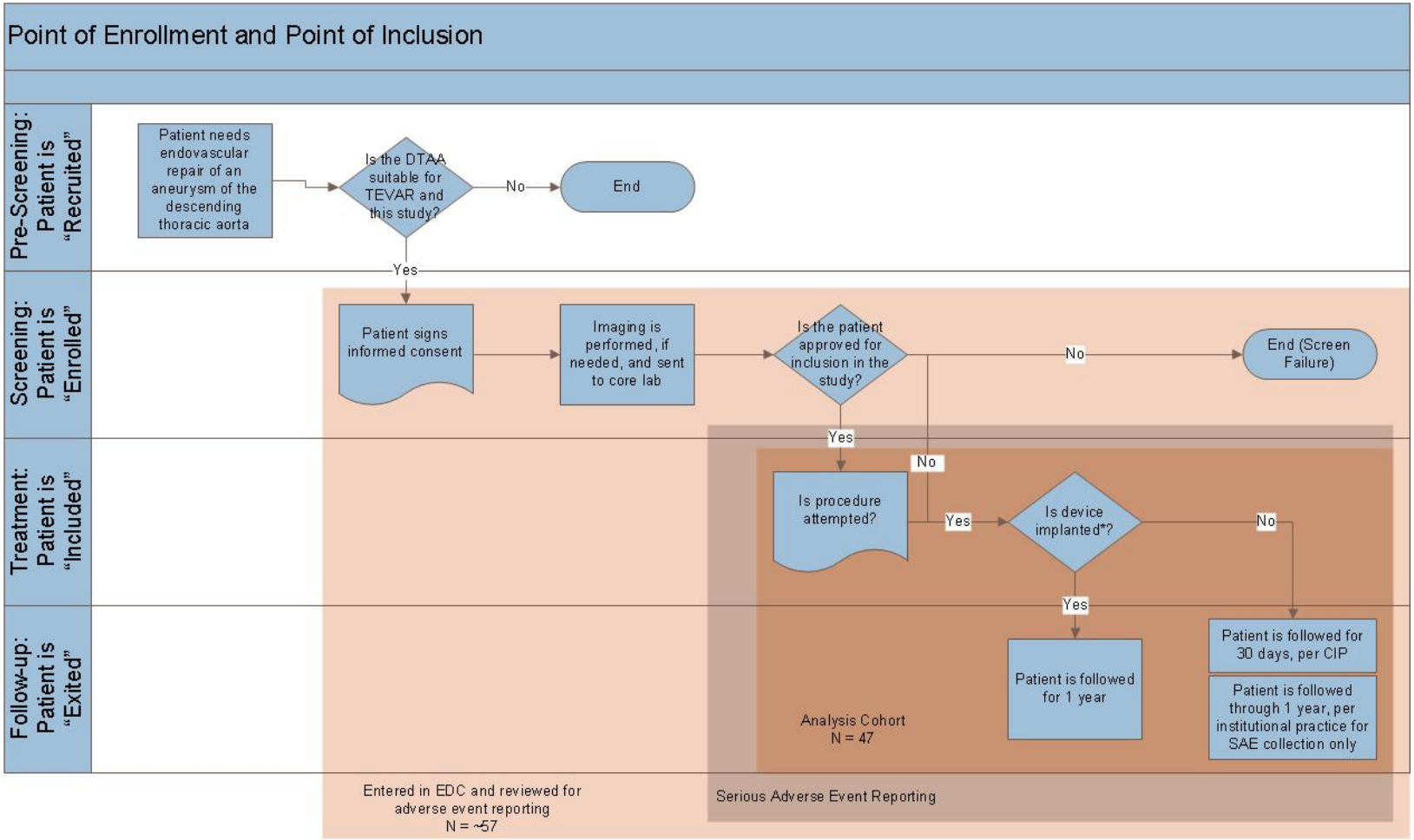
Inclusion:

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

Included subjects will be documented on the Screening, Enrollment and Inclusion log and will be followed per the study protocol. Subjects who are enrolled and attempted to be implanted with the device but the Valiant Evo Thoracic Stent Graft could not be implanted during the procedure (treatment failure) will be followed through the 1 month follow-up per the study protocol and thereafter as per hospital standard of care. Serious Adverse Events will be collected for these subjects over the whole duration of the study. The reason for not including the subjects into the trial will be documented on the Screening, Enrollment and Inclusion log and will be documented on the screening eCRF.

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

As the point of enrollment is considered the point in time the subject signs and dates the Informed Consent Form, which is different from the point that the subject is actually included in the trial, more subjects will be enrolled in the trial than included. A 10 to 20% screen failure rate is expected. Therefore, approximately 57 subjects are expected to be enrolled in order to include 47 subjects.



* The subject will only be considered included when arterial access has been established with an attempt to introduce the Valiant Evo thoracic stent graft.
Note: A patient withdrawing informed consent stops the process on the date of withdrawal.

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. For subjects enrolled in the trial but not included in the trial, adverse event assessments will be done until the point of screen failure and the reason for not including will be documented on the Screening, Enrollment and Inclusion log and on the screening eCRF.

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 30 days and thereafter per institutional standard of care. Serious adverse events will be recorded in the eCRF until the total duration of the trial. At the end of the study the exit form should be completed.

If a primary conversion to open repair is required during the index procedure, then the subject will be followed for 30 days and thereafter per institutional standard of care. Serious adverse events will be recorded in the eCRF until the total duration of the trial. At the end of the study the exit form should be completed.

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 and 12 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
12 Months (365 ±60 days)	305	365	425

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 return for the 30-day follow-up visit, if applicable. Thereafter the subject will be followed per institutional standard of care and. serious adverse events will be recorded in the eCRF until the total duration of the trial. At the end of the study the exit form should be completed.

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 follow-up visits described in Section F.2. The data collection schedule is summarized in Table F-2. Imaging for baseline and follow-up assessments, as specified in Table F.2, will be sent to a Core Lab for analysis. In addition, any interim imaging of the stent graft region done within one year of implantation should be recorded on the interim image eCRF (e.g. 6-month imaging follow-up when performed as standard of care and/or when performed further to any issue observed at previous imaging follow-up). In case further analysis is needed, procedural and interim imaging exams are to be submitted to Core Lab.

Study data will be collected using electronic case report forms (eCRFs) as will be described in Section G.1. eCRFs should be electronically reviewed and approved by the clinical investigators. Medtronic monitors will perform source document verification of the eCRFs. The monitoring strategy will be defined in the monitoring plan.

For test equipment critical for assessing endpoints (e.g., CT scan, MRI, Transesophageal echography (TEE)) maintenance and calibrations will be monitored periodically.

It is expected that the Investigator enrolling the subject at the participating site where the implantation occurred will follow the subject during the course of the study. It is the responsibility of the Investigator to make sure that the subject is followed and that integrity and accuracy of the data is maintained.

Table F-2: Data Collection Schedule

DATA	Screening / Baseline	Index Procedure	Hospital Discharge	1-Mo. F/U (±15 days)	12-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		✓			

DATA	Screening / Baseline	Index Procedure	Hospital Discharge	1-Mo. F/U (±15 days)	12-Mo. F/U (±60 days)
Procedures					
Hospital Discharge Information			✓		
Adverse event assessment	✓[a]	✓	✓	✓	✓
EQ-5D questionnaire	✓			✓	✓
IMAGING					
CT/MRI with contrast [b]	✓			✓[c, d]	✓[d]
Angiography		✓[e]			

[a] In case of screen failures, investigators will be requested to enter safety information in the eCRF from time point of enrolment 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] MRI with contrast may be used for those patients experiencing renal failure or who are otherwise unable to undergo contrast-enhanced CT scan, with TEE being an additional option in the event of suboptimal MR imaging.
[e] Required to complete Procedure eCRF but not expected to be submitted to Medtronic or Core Lab unless further analysis is needed.

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's 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's 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 records of each subject's case history, exposure to the device and clinical follow-ups. Source documents include subject's hospital files (electronic or paper), images, programmer printouts, and device labels. For data that is not recorded as standard in the subject file, separate worksheets that will be marked as source data can be used. The investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical investigation. Note: there may be some country-specific requirements in this regard.

Investigators should maintain source documents to support the data recorded on the study case report forms. Complete medical (clinical and hospital) records include, but are not limited to, the following documentation:

- Medical history/physical condition of the subject before involvement in the study sufficient to verify clinical protocol entry criteria
- Description of device implantation procedure (material used, drugs administered during the procedure, device identification information and disposition, date, time, angiographic and clinical findings, etc.)

- Signed notes in the subject's medical record on the enrollment day that identify and include: the subject's date of enrollment/procedure date, the study sponsor, clinical site name, the subject number, and documentation and confirmation that the appropriate informed consent was obtained
- Dated and signed notes for each subject's study visit
- Lab results
- All CT/MRI reports, etc.
- Dated printouts or reports of special assessments (ECG report, imaging report, etc.)
- Adverse event reporting and follow-up of the adverse events. Information in the medical chart should include at a minimum the following: event description, severity, seriousness, onset date, date site became aware of event, duration, relation to study device, treatment, and outcome of the adverse event
- Study subject's condition upon completion of or withdrawal from the study

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 investigation site team with a statement that it is a true reproduction of the original source document. In case subject contact has been performed by phone, the investigator needs to record as a minimum the date of contact in the subject's hospital file. Furthermore, the reason for withdrawal and actions to trace lost to follow-up subjects should be documented in the medical records of the subjects.

The investigator(s) and study personnel must be accessible to the Medtronic field clinical support and the clinical study team. This accessibility is of particular importance for the completion and clarification of the data on the case report forms and regulatory responsibilities. Access to the subject records and other source data must be provided to study monitors, auditors and/or inspectors.

F.6 Adverse events

F.6.1 Definition/classification

For the purposes of the clinical report, Medtronic will classify each Adverse Event according to ISO 14155:2011.* In case country specific definitions and safety reporting regulations are stricter than mandated per ISO 14155:2011, reporting will be done in compliance with the country specific safety regulations.

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 are listed in Table F-3. These events should not be to be reported as adverse events during this study.

*: For example, the definition of Serious Adverse Event (SAE) in Germany per the MPSV, § 2 nr 5 is the following:
Serious adverse event is any adverse event, which occurs in an approved clinical investigation or performance evaluation and which has led, might have led or could lead directly or indirectly to the death or any serious deterioration in the state of health condition of a subject, a user or any other person without considering if the event has been caused by the medical device.

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	Resolved by the time the subject leaves

the index procedure	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 or post procedural delirium	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): *(ISO 14155:2011 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): *(ISO 14155:2011 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 1: 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): *(21CFR812.3)*

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.

NOTE: Although the collection of UADEs is a US 21CRF812.3 requirement, any event from the Valiant Evo International Clinical Trial that meets the UADE criteria will be reported as such and will be adjudicated by the Clinical Event Committee (CEC) in order to be pooled with data collected during the concurrently enrolling IDE trial.

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 International 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 International 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 section F.6.7.

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.

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	Reporting timeframe as per local EC requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.
EC	Submit to EC per local reporting requirement.
Serious Adverse Events (SAE)	
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	Submit to EC per local reporting requirement.
Sponsor submit to:	

Regulatory Authorities	Reporting timeframe as per local requirement.
EC	Submit to EC 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	Submit to EC per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement
EC	Submit to EC 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	Submit to EC 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	Submit to EC per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement
EC	Submit to EC 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	Submit to EC per local reporting requirement.

In addition, Investigators are obligated to report adverse events in accordance with the requirements of their 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 EC as per local requirements.

F.6.5 Potential Complaint Reporting

Potential complaints sourced from the study are reported to the Global Complaint Handling Unit (GCH)

Potential complaints may be found throughout clinical study data as reported on CRFs and reviewed, or potential complaints may be learned about in alternative fashions within source documents or in discussions with investigational site staff. Potential complaints are considered for the following:

- All adverse events collected deemed related to the procedure/product/therapy
- All product deficiencies or technical observations, if applicable
- All deaths deemed related to the procedure/product/therapy

Relationship is to be determined by the investigator and the sponsor. The CEC will assess relationship for adjudicable events only.

F.6.6 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, 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.6.7 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.

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

In addition to DMC members an Independent Medical Monitor will be appointed. Medtronic will provide listings of all Adverse Events and Device Deficiencies to this Independent Medical Monitor on a monthly basis 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.

F.6.8 Emergency contact details in case of serious AEs

In case of an immediately reportable Adverse Event the investigators can contact Medtronic. 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 subjects 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. 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 there are 3 documented attempts by the investigator and/or research staff to contact the subject. The third attempt should be made by mail to the subject and phone call or mail to the subject's emergency contact.

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 which might be in line with the guidelines described in the ESC (European Society of Cardiology) Guidelines on the diagnosis and treatment of aortic diseases[27].
Relevant medical records may be made available by the investigational sites for the treating physician per local laws and regulations if needed for further subject treatment. As per local law and regulation the trial investigator may be contacted by the treating physician in case of questions related to the study device and treatment.

F.8 Study deviations and CIP changes

A study deviation is an event where the investigator or investigation site personnel did not conduct the clinical study according to the Clinical Investigation Plan or Clinical Investigation Agreement. The investigator is not allowed to deviate from the above mentioned documents except with prior approval and under emergency circumstances. All deviations shall be documented and explained, regardless the reason for the deviation.

Deviations will be recorded at the site and reported to Medtronic on the Study Deviation eCRF.

Medtronic shall review reports of deviations upon receipt and determine appropriate action, including any associated Ethics Committee (EC), and/or regulatory reporting requirements. The clinical study team shall follow up with the center on the implementation and closure of any preventive or corrective actions. Deviations will be entered into a database to allow a comprehensive review on a quarterly basis for identifying trends that warrant additional preventive or corrective actions to mitigate further occurrence. This review shall be conducted by clinical study management.

Specific examples of deviations include but are not limited to:

- Failure to obtain informed consent prior to participation
- Incorrect version of the informed consent form used
- No EC approval before the start of the study
- Enrolled subject did not meet inclusion/exclusion criteria
- CIP required testing and/or measurements not done or incorrectly done
- Subject did not attend follow up visit or follow up visit outside window
- Unauthorized use of investigational devices
- Adverse event not reported by investigators in the required time frame as specified in the CIP
- Control of study devices not maintained
- Source data lost or unavailable
- Enrollment of subjects during elapse of EC approval
- Exceeding inclusion limits specified by Medtronic
- Subject not implanted according to the Instructions for Use.

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.

In case a deviation may occur multiple times over the course of the clinical study in the same subject because of a permanent change (e.g. CT scan/MRI with contrast not performed at Follow Up visits due to renal insufficiency developed post-operatively) deviation should be reported only once per subject at the time of first occurrence.

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 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, if applicable. Medtronic will inform the Regulatory Authorities, if required.

F.8.2 Reporting requirements for study deviations

The investigator shall adhere to EC 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 patient 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 may 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 and Regulatory Authorities, if required. The investigator will only implement the amendment after approval of the EC, Regulatory Authority (if required) and sponsor. Administrative amendments to the Clinical Investigation Plan will be submitted to the EC 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 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, and 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 on 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 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 and the study subjects. Medtronic will inform the Regulatory Authority(ies) where required by applicable regulatory requirements.

G.3.2 Early investigation site suspension or termination

Medtronic, EC or Regulatory Authority may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing EC, 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 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
- 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, 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 which might be in line with the guidelines described in the ESC (European Society of Cardiology) Guidelines on the diagnosis and treatment of aortic diseases.[27]

After study termination relevant medical records may be made available by the investigational sites for the treating physician per local laws and regulations if needed for further subject treatment. As per local law and regulation the trial investigator may be contacted by the treating physician in case of questions related to the study device and treatment.

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 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

The Valiant Evo International Trial is not hypothesis driven. All endpoints will be analyzed descriptively. The limitation of the design for this study is that there are no pass/fail criteria from a statistical hypothesis testing.

All endpoints will be analyzed descriptively. Event rates corresponding to the primary endpoint of the study will be analyzed by calculating the distribution frequencies and the associated 1-sided 95% confidence limits using an exact method.

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.

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 30 days” is an event that takes place between Days 0 to 30, inclusive. Similarly, an event that occurs “within 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 device deficiencies, 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	0 days	Day 0
1 Month	30 days	1 – 90 days
12 Months	365	305 – 548 Days

If there are two or more assessments in the same time window, then 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.

Subset analysis will be performed by-sex separately for the primary endpoint descriptively and reviewed for clinical significant difference.

All analysis will be performed on the modified intent-to-treat analysis set, which includes all included subjects. Subjects will be considered as included in the study as described in section F.1.

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.

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.

Analysis for the Regulatory Submission:

For the primary endpoint, which is defined as the proportion of subjects experiencing an MDE within 30 days post-implantation, a 1-sided 95% confidence interval using the exact method (Clopper-Pearson) will be constructed in addition to event count frequency.

Additionally, a two-sided 95% confidence interval will also be provided. The SAS procedure PROC FREQ will be used for calculation of the confidence interval.

The analysis for the regulatory submission will take place when the first 47 subjects have been implanted with the study device for at least 30 days except that a subject expires early. Endpoints will be analyzed for these 47 included subjects as defined in Section C.2.

Interim Analysis:

No interim analysis is planned prior to the CE Mark Submission.

Annual Report:

An annual report will be provided for all enrolled subjects at the time of reporting according to requirements from notified bodies in the European Union and regulatory agencies in various countries.

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 the Medtronic Bakken Research Center B.V. based in the Netherlands. Study staff contact details will be provided in the investigational site file.

I.2 Advisory committees

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 is not expected to be established for the Valiant Evo International Clinical trial. 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
- Investigator's Brochure and/or Instructions for Use
- Medtronic and EC approved Patient 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
- Insurance certificates
- Completed Delegated Task List 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 Patient Informed Consent forms
- Fully executed CRFs and corrections
- Reports of Adverse Events and Device Deficiencies
- Device accountability records
- EC approval(s) or notification(s) and correspondence

- Monitoring follow-up letter
- Monitor contact list
- Source documents

I.3.2 Investigator reporting responsibilities

Report	Submitted to	Description
Adverse Events	Sponsor, EC, and local Regulatory Authority, where applicable	Refer to section F.6 for reporting requirements.
Progress Report	Sponsor and EC	Provide if required by local law or EC. (ISO 14155:2011)
Withdrawal of EC approval	Sponsor	Investigator will inform Medtronic in case EC approval is withdrawn.
Final Clinical Study Report	EC	A copy of the Final Clinical Study Report will be provided to the EC.
Deviations from Investigational Plan		
Emergency Use	Sponsor, EC, Regulatory Authority	Investigator will report deviation as soon as possible to the sponsor and EC.
Planned deviation	Sponsor, EC, Regulatory Authority	Prior approval from Medtronic must always be obtained from Medtronic. If the deviation affects scientific soundness of the clinical study or the rights, safety, or welfare of the subject and is not an emergency, prior approval must be obtained from the EC and Regulatory Authority.
Other Deviations	Sponsor	Deviations that are beyond the control of the investigator (such as subject who fails to return to follow-up visit) or deviations that do not affect the scientific soundness of the clinical study or the rights, safety, or welfare of the subject and are not an emergency, should be submitted as they are identified by the investigation site or Medtronic staff.

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
- Investigator Brochure and/or Instructions for Use
- Sample of labeling attached to the investigational device
- Curriculum Vitae of investigators and investigation site personnel
- Delegated Task Lists and training records of investigators and investigation site personnel
- EC approvals/notifications and regulatory approvals/notifications
- Signed Clinical Investigation Agreements and signed agreements with third parties
- Insurance certificates,

- Shipping records for investigational devices and clinical-investigation related documents and materials
- Medtronic and EC/IRC approved Patient Informed Consents
- 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, Investigators, and Regulatory Authorities, where applicable	Medtronic will report adverse events as required and in compliance with local regulatory requirements, as applicable.
Withdrawal of EC approval	EC, Investigators, and Regulatory Authorities, where applicable	In case of withdrawal of EC approval Medtronic will suspend the clinical study as described below.
Premature termination or suspension of study	EC, Investigators, and Regulatory Authorities, where applicable	Medtronic will provide prompt notification of termination or suspension and reason(s) to investigator and where required to EC and Regulatory Authorities.
Progress Reports	EC, Regulatory Authority (upon request)	Progress reports will be submitted to the EC and/or Regulatory Authority only if required.
Final Report	Investigators, and Regulatory Authorities, where applicable	Medtronic will provide all investigators with a copy of the Final Clinical Study Report of the clinical study. ECs and Regulatory Authorities will be informed when required.
Study deviation	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.
Emergency Deviations from Investigational Plan	Regulatory Authorities, where applicable	If required, Medtronic will inform Regulatory Authorities as soon as possible about any emergency deviations that affect scientific soundness of the clinical study or the rights, safety, or welfare of the subject.
Significant new information	EC and Regulatory Authority	Ensure that the EC and Regulatory Authorities are informed of significant new information about the clinical investigation (ISO 14155:2011).

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

The Medtronic Bakken Research Center B.V 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 and the Regulatory Authorities.

I.4.2 Subject compensation and indemnification

Medtronic shall reimburse the institution/hospital in which the subjects are treated for reasonable and necessary travel expenses incurred by the subjects enrolled and/or included in the study including, but not limited to travel to/from the hospital, provided that such expenses are properly documented in the subject files and that the study evaluation is not performed under a regularly scheduled follow-up. These expenses will be payable to the institution/hospital upon receipt by Medtronic of a detailed invoice, which, however, shall not contain any identifying characteristics concerning the subjects. Finally the site in which the subject is treated shall be solely responsible for the reimbursement of expenses directly to the subject.

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 or 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 anesthesia - 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 EC and to Medtronic. Medtronic will in turn report any necessary findings to the appropriate regulatory agencies in each of the respective geographies.

Summary of the risk analysis, including identification of residual risks, result of the risk assessment and anticipated risks, contra-indications, warnings, etc. for the investigational device will be described in the Investigator's Brochure.

J.3 Risk-to-benefit rationale

The results of risk analysis, balancing benefits against risks associated with both the device system itself and procedures involved in its use, is included in the Investigator's Brochure.

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 ISO 14971:2012 and the results are detailed in the Investigator Brochure.

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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
CA	Competent Authority
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
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
DTAA	Descending Thoracic Aortic Aneurysm
DTA	Descending Thoracic Aorta
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
ISO	International Organization for Standardization
LSA	Left Subclavian Artery
MAE	Major Adverse Event
MDE	Major Device Effect
MI	Myocardial Infarction
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
PET	Polyethylene terephthalate
PIC	Patient Informed Consent
PMA-S	Premarket Approval Supplement
OD	Outer Diameter
RA	Regulatory Affairs

RAE	Regulatory Affairs Europe
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard operating procedure
TAA	Thoracic Aortic Aneurysm
TEE	Transesophageal Echography
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). Deaths following complications that are associated with the

Term	Definition
	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. *Aneurysm rupture should be reported as either procedure-*

Term	Definition
	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.

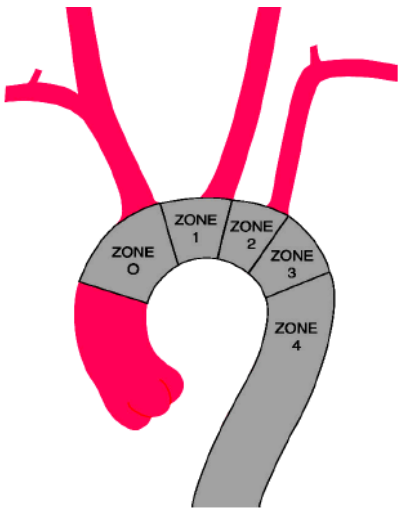
Listing of Device Deficiencies (DD) available in CRF drop down list

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, support spring, body stents, 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. Investigational Plan Extension of Follow-Up Requirements

L.3.1 Background

The purpose of this appendix is to describe the update to the Valiant Evo International Clinical Trial requirements increasing subject follow-up requirements to 60 months (5 years).

L.3.2 Rationale

The reason for the proposed change is to better understand the long-term safety and effectiveness of the Valiant Evo Thoracic Stent Graft System in subjects with a DTAA. The extension of clinical follow up requirements provides longer-term evidence on the device's performance beyond the original 12-month term planned in the study, permitting accumulation of additional device use experience and clinical outcomes to support the marketing application and post-marketing surveillance.

The clinical evidence collected as part of this expanded follow-up period will be used in conjunction with the data collected from the concurrently enrolling Valiant Evo US Clinical Trial to support commercial approvals in geographies worldwide.

L.3.3 Study Plan

L.3.3.1 Secondary Endpoints at 24, 36, 48 and 60 months

Secondary endpoints are to be assessed beyond 12 months. The following secondary endpoints are to be evaluated at 24, 36, 48, and 60 months:

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

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

L.3.3.2 Subject accountability

Subjects already enrolled and willing to extend their follow-up from 12 to 60 months are to be re-consented. Re-consenting is to occur at or prior to the 12-month follow-up visit. 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.

L.3.3.3 Study duration

Subjects are followed under this investigational plan up to 60-months post-implantation. Subjects have additional follow-up evaluations at the following time points:

- 24-months following the index procedure
- 36-months following the index procedure
- 48-months following the index procedure
- 60-months following the index procedure

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

L.3.3.4 Number of investigational sites and study duration

The total enrolment for this study will not exceed 47 patients in up to 17 sites, as originally mentioned in section C.7

The total enrollment period is expected to be approximately 30 months. Enrolled subjects are followed up at 1, 12, 24, 36, 48 and 60-months post-implantation.

L.3.4 Study preparation procedures

L.3.4.1 Revisions in Informed Consent form

Medtronic revised the written informed consent template based on the changes contained within this appendix. Subjects who are currently participating in the 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. Those subjects who have exited the study, or are lost for follow-up, are not contacted for study reasons again and are not re-consented to participate in follow-up beyond 12 months.

The revised informed consent documents are provided to the investigational sites for approval by the EC/IRB and or CA, as applicable by local regulations.

L.3.5 Study Methods

L.3.5.1 Follow-Up Visits and Procedures

Subjects require post-implantation follow-up visits at 30-days, 12, 24, 36, 48 and 60 months. Follow-up visits and associated timeframe windows are summarized in Table L-1:

Table L-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
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

L.3.5.2 Data collection requirements

The data collection schedule is summarized in Table L-2. Imaging source data is to be sent to a core lab for analysis up to the 12-month follow-up visit. Imaging source data beyond 12-months post-index procedure is not to 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.

Table L-2: Data Collection Schedule

DATA	Screening / Baseline	Index Procedure	Hospital Discharge	1-Mo. F/U (±15 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]	✓[f]			✓[c,d,f]	✓[d,f]	✓[d,g]
Angiography		✓[e]				

[a] In case of screen failures, investigators are requested to enter safety information in the eCRF from time point of enrolment 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] MRI with contrast may be used for those patients experiencing renal failure or who are otherwise unable to undergo contrast-enhanced CT scan, with TEE being an additional option in the event of suboptimal MR imaging.

[e] Required to complete Procedure eCRF but not expected to be submitted to Medtronic or core lab unless further analysis is needed.

[f] Imaging assessed by core lab

[g] Upon sponsor request, core lab analysis of imaging may be required

M VERSION HISTORY

Version	Summary of Changes	Author(s)/Title
1	• Not Applicable, New Document	[redacted]

2	• Minor typo changes
	• Changes made in
	  ○ Geographies
	  ○ Principal Investigator
	• Exclusion of vulnerable populations
	• Protocol made compliant to ISO14155
	• Updated to clarify imaging requirements
	• Correction of the process of source data collection
	• Insertion of missing safety and compliance definitions and/or references to study plans
		[redacted]

3	• Added Appendix L to reflect Protocol amendment to extend the follow of subjects from 12 months to 60 months. • Administrative changes like correction of typo's, font types and alignments, integration of new template, • Synopsis update with schedule of events and secondary endpoints for extended follow-up	[redacted]