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# Endurant Evo US Clinical Trial

## Clinical Investigation Plan

## Version 1E, 26 APR 2019

**10173341DOC**

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| Version 1.0 | 5 January 2015 |
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**Sponsor**

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# A SYNOPSIS

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| **Protocol Number** | 10173341DOC |
| **Title** | Endurant Evo US Clinical Trial |
| **Investigational Device** | Endurant™ Evo AAA Stent Graft System |
| **Study Design** | The Endurant Evo US Clinical Trial is a prospective, multi-center, pre-market, non-randomized, single-arm trial. |
| **Purpose** | The purpose of the Endurant Evo US Clinical Trial is to demonstrate that the Endurant Evo AAA Stent graft system is safe and effective for endovascular treatment of infrarenal abdominal aortic or aortoiliac aneurysms. The clinical evidence collected as part of this trial will be used in conjunction with data collected during the concurrently enrolling Endurant Evo International Clinical Trial to support PMA Approval of the Endurant Evo AAA Stent graft system. |
| **Primary Objective** | The primary safety objective is to demonstrate the safety of the Endurant Evo AAA stent graft system for the endovascular treatment of infrarenal abdominal aortic or aortoiliac aneurysms. Safety will be assessed through the proportion of subjects who have a Major Adverse Events (MAE) reported within 30-days post-implantation.<br><br>The primary effectiveness objective is to demonstrate successful delivery and deployment of the Endurant Evo AAA stent graft system with successful removal of the delivery system during the index procedure as well as the treatment success at 12 months. |
| **Secondary Objective** | Secondary objectives include descriptive analyses of secondary endpoints as well as acute procedural and clinical utility measures. |
| **Primary Endpoints** | **Primary safety endpoint:**<br>The primary safety endpoint is defined as the proportion of subjects experiencing a MAE within 30 days post-implantation. MAEs include the occurrence of any of the following events:<br>• All-cause mortality<br>• Bowel ischemia<br>• Myocardial infarction<br>• Paraplegia<br>• Procedural blood loss ≥1000 cc<br>• Renal failure<br>• Respiratory failure<br>• Stroke<br><br>**Primary effectiveness endpoint:**<br>The primary effectiveness endpoint is defined as the proportion of subjects with both technical success at the time of index procedure and treatment success at 12-months post-implantation. Successful aneurysm treatment is achieved based on the following criteria:<br>• *Technical success at the index procedure (as assessed intra-operatively) is defined as successful delivery and deployment of the Endurant Evo AAA stent graft system in the planned location and with no unintentional coverage of both internal iliac arteries or any visceral aortic branches and with successful removal of the delivery system*<br>*AND*<br>• *Treatment success consisting of freedom from:*<br>o *AAA diameter increase, defined as > 5 mm increase in maximum diameter as measured on CT scan (or MRA/MRI ) at 12-month follow-up as compared to 1-month imaging*<br>o *Types I and III endoleaks at 12-month follow-up including those* |

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| | *requiring intervention through 12 months*<br>○ *Aneurysm rupture within 365 days*<br>○ *Conversion to surgery within 365 days*<br>○ *Stent graft migration resulting in a serious adverse event or requiring secondary intervention through 12 months*<br>○ *Stent graft occlusion through 12 months* |
| **Secondary Endpoints** | The following secondary endpoints will be evaluated:<br>• All cause-mortality within 30, 183, and 365 days<br>• Aneurysm-related mortality within 30, 183, and 365 days<br>• Secondary procedures to correct Type I and III endoleaks within 183 and 365 days<br>• Secondary procedures within 183 and 365-days<br>• Serious adverse events within 30, 183, and 365 days<br>• Conversion to open surgery within 183 and 365 days<br>• Aneurysm rupture within 183 and 365 days<br>• Major adverse events within 183 and 365 days<br>• Stent graft migration at 6- and 12-month follow-up visits (as compared to 1-month imaging)<br>• Aneurysm expansion >5 mm at 6- and 12-month follow-up visits (as compared to 1-month imaging)<br>• All endoleaks based on imaging findings at 1-, 6-, and 12-month follow-up visits<br>• Stent graft occlusions based on imaging findings through 1-, 6- and 12 months<br>• Device deficiencies based on imaging findings through 6 and 12 months |
| [redacted] | [redacted] |
| **Subject Population** | Subject population will include subjects diagnosed with an infrarenal abdominal aortic or aortoiliac aneurysm who are considered candidates for endovascular repair, and who meet the Inclusion/Exclusion Criteria for the Endurant Evo US Clinical Trial. |
| **Number of Subjects** | Globally, a total of 140 subjects will be concurrently enrolled in the United States and outside the United States to support the primary endpoints[1]. Up to 50% of subject data used to support PMA approval may come from subjects enrolled at sites outside of the US under a separate CE Mark study protocol; called the |

[1] A minimum of 50 subjects will be enrolled with the high neck angulation indication (defined as proximal neck length ≥15 mm, infrarenal neck angulation >60° and ≤75° and suprarenal neck angulation ≤60°). If a minimum of 50 subjects are not enrolled as part of the first 140 subject cohort, Medtronic will continue enrollment for the high angulation indication but submit the PMA application to obtain approval for the 60° angulation indication with the 140 subject cohort data. A minimum of 70 subjects enrolled in the study will have percutaneous access.

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| | Endurant Evo International Clinical Trial protocol. The Endurant Evo International Clinical Trial protocol and Endurant Evo US Clinical Trial protocol will be identical with respect to the inclusion/exclusion criteria, and follow up data collection.<br><br>Given the Unanticipated Adverse Device Effects (UADEs) that have occurred within the Endurant Evo study (transition stent fracture, partial suprarenal stent detachment, and suprarenal stent fracture), enrollment was terminated. Total global enrollment, upon termination, was 139 subjects. This includes 70 subjects enrolled in the United States and 69 enrolled outside the United States. |
| **Number of Sites** | The Endurant Evo Global Clinical program will be conducted at up to 30 sites worldwide with up to 20 sites participating under the Endurant Evo US Clinical trial protocol in the United States and with approximately 10 sites participating under the Endurant Evo International Clinical trial protocol outside the Unites States. |
| **Follow-up Schedule** | Subjects will have required follow-up visits at the following time points:<br>1. 1 month following the index procedure<br>2. 6 months following the index procedure<br>3. 12 months following the index procedure<br>4. Annually until 5 years following the index procedure<br>[redacted] |
| **Coordinating Principal Investigators** | [redacted] |
| **Indications for Use** | The Endurant Evo bifurcated stent graft is indicated for the endovascular treatment of infrarenal abdominal aortic or aortoiliac aneurysms. The Endurant Evo aorto-uni-iliac (AUI) stent graft is indicated for the endovascular treatment of infrarenal abdominal aortic or aortoiliac aneurysms in subjects whose anatomy does not allow the use of a bifurcated stent graft. The Endurant Evo AAA stent graft system is indicated for use in subjects with the following characteristics:<br>• adequate iliac or femoral access that is compatible with vascular access techniques (femoral cutdown or percutaneous), devices, and accessories<br>• proximal neck length of<br>  • ≥10 mm and infrarenal neck angulation of ≤60° and suprarenal neck angulation of ≤45°, or<br>  • ≥15 mm and infrarenal neck angulation of ≤75° and suprarenal neck angulation of ≤60°<br>• aortic neck diameters with a range of 18 mm to 32 mm<br>• distal fixation lengths of ≥20 mm<br>• iliac diameters with a range of 7 mm to 25 mm<br>• morphology suitable for aneurysm repair<br>**Note:** Proximal neck length refers to minimum seal zone. |
| **Inclusion Criteria** | Candidates for the Endurant Evo US Clinical trial must be appropriate subjects for endovascular repair of infrarenal abdominal aortic aneurysms or aortoiliac aneurysms (evidenced by screening contrast-enhanced CT or MRA) and have |

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| | to fulfill all of the following inclusion criteria to be eligible for enrollment in the study:<br><br>1) Subject is ≥ 18 years old<br>2) Subject understands and voluntarily has signed and dated the Informed Consent approved by the Sponsor and by the Ethics Committee/Institutional Review Board.<br>3) Subject is able and willing to comply with the protocol and to adhere to the follow-up requirements<br>4) Subject is a suitable candidate for elective surgical repair of AAA as evaluated by American Society of Anesthesiologists (ASA) Physical Status Classification System I, II, or III<br>5) Subject has an infrarenal abdominal aortic or aortoiliac aneurysm characterized by one or more of the following:<br>a) Aneurysm is > 5 cm in diameter (diameter measured is perpendicular to the line of flow)<br>b) Aneurysm is 4 – 5 cm in diameter and has increased in size ≥ 0.5 cm within the previous 6 months<br>6) Subject meets all the following anatomical criteria as demonstrated on contrast-enhanced CT or MRA imaging:<br>a) Proximal neck length of ≥ 10 mm with ≤ 60° infrarenal and ≤ 45° suprarenal neck angulation or proximal neck length of ≥ 15 mm with ≤ 75° infrarenal and ≤ 60° suprarenal neck angulation<br>b) Subject has vascular dimensions, e.g., aortic and iliac diameters, lengths from renal arteries to iliac bifurcation and hypogastric arteries, in the range of sizes available for the Endurant Evo AAA stent graft system (measured intima to intima) and within the sizing recommendations (refer to Endurant Evo AAA stent graft system Instructions for Use (IFU))<br>c) Subject has a proximal aortic neck diameter ≥18 mm and ≤32 mm<br>d) The distal fixation center of the iliac arteries must have a diameter ≥7 mm and ≤ 25 mm bilaterally for the bifur and unilaterally for the AUI<br>e) Subject has documented imaging evidence of at least one patent iliac and one femoral artery, or can tolerate a vascular conduit that allows introduction of the Endurant Evo AAA stent graft system<br>f) Subject has distal non-aneurysmal iliac (cylindrical) fixation length ≥ 20 mm bilaterally for the bifur and unilaterally for the AUI |
| **Exclusion Criteria** | Candidates who meet any of the following exclusion criteria will not be eligible for enrollment in the study:<br><br>1) Subject has a life expectancy ≤ 1 year<br>2) Subject is participating in another investigational drug or device study which would interfere with the endpoints and follow-ups of this study<br>3) Subject is pregnant<br>4) Subject has an aneurysm that is:<br>a) Suprarenal/ pararenal/ juxtarenal<br>b) Isolated ilio-femoral<br>c) Mycotic<br>d) Inflammatory<br>e) Pseudoaneurysm<br>f) Dissecting<br>g) Ruptured<br>h) Leaking but not ruptured<br>5) Subject requires emergent aneurysm treatment<br>6) Subject has a known, untreated thoracic aneurysm >4.5 cm in diameter at |

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| | time of screening<br>7) Subject has been previously treated for an abdominal aortic aneurysm<br>8) Subject has a history of bleeding diathesis or coagulopathy<br>9) Subject has had or plans to have an unrelated major surgical or interventional procedure within 1 month before or after implantation of the Endurant Evo AAA stent graft<br>10) Subject has had a myocardial infarction (MI) or cerebral vascular accident (CVA) within 3 months prior to implantation of the Endurant Evo AAA stent graft<br>11) Subject has a conical neck defined as a >4 mm distal increase from the lowest renal artery over a 10 mm length<br>12) Subject has a known allergy or intolerance to the device materials<br>13) Subject has a known hypersensitivity or contraindication to anticoagulants, antiplatelets, or contrast media, which is not amenable to pre-treatment<br>14) Subject has significant aortic thrombus and/or calcification at either the proximal or distal attachment centers that would compromise fixation and seal of the device at the discretion of the investigator<br>15) Subject has ectatic iliac arteries requiring bilateral exclusion of hypogastric blood flow<br>16) Subject whose arterial access site is not anticipated to accommodate the diameter of the Endurant Evo AAA delivery system (13F-17F) due to vessel size, calcification, or tortuosity<br>17) Subject is morbidly obese or has other documented clinical conditions that severely inhibit radiographic visualization of the aorta at the discretion of the investigator<br>18) Subject has active infection at the time of the index procedure documented by e.g. pain, fever, drainage, positive culture and/or leukocytosis considered to be clinically significant per investigator discretion<br>19) Subject has congenital degenerative collagen disease, e.g., Marfan's Syndrome<br>20) Subject has a creatinine level >2.00 mg/dl (or >176.8 μmol/L)<br>21) Subject is on dialysis |
| **Study Success Criteria** | Study success is defined as rejecting the null hypothesis for the primary safety endpoint test (≥20%), with a condition upon rejecting the null hypothesis for the post-market primary effectiveness test (≤80%). |
| **Analysis Sets** | The primary analysis set will consist of the Intent-to-Treat (ITT) population. This analysis set is defined as all subjects who were enrolled.<br><br>A secondary analysis set will be the Per-Protocol population. This analysis set is comprised of all ITT subjects who met inclusion and exclusion criteria, received the test device, and completed 12-month follow-up (including death but excluding withdrawal or lost to follow-up subjects within the 12-month follow-up period). |
| **Data Oversight** | A Data Monitoring Committee, Clinical Events Committee, and imaging core Lab will be established to independently evaluate subject health status, device performance, and identify any safety concerns regarding subjects' well-being.<br>Contact details of the committees and the Core Lab will be available in the investigational site file. |

# B GENERAL INFORMATION

## B.1 Introduction

*Background*

Abdominal aortic aneurysms (AAA) occur in approximately 5% of the general population as estimated by a systematic literature survey of 56 epidemiological studies.[1] This estimate is similar to that observed in an autopsy report from Malmo Sweden, where AAA were found in 4.7% of men and 1.2% of women between 65 and 74 years of age.[2] The prevalence is greater in males (6.0%) compared with females (1.6%) and aneurysms are found more frequently in western countries than in Asia. Risk factors for AAA include advanced age, smoking, family history of AAA, hypertension, atherosclerosis, and hyperlipidemia. The female gender and diabetes were associated with a lower prevalence of AAA.[3]

Aneurysms are prophylactically treated to prevent premature death from rupture. More than one-third of patients with ruptured aneurysms succumb from the event; a proportion that has not decreased appreciably over the last several decades.[4] By contrast, elective treatment of AAA prior to rupture is associated with a perioperative mortality rate below 3%. For this reason, AAA are best managed electively, prior to rupture. Screening tests are recommended in patients at risk for AAA, usually with an abdominal ultrasound imaging study. When an AAA is identified, the clinician's decision to repair the aneurysm rests on assessing the risk of rupture compared with the risk of the repair procedure itself. In this regard, the diameter of the AAA is the only consistent predictor of rupture. As such, patients with AAA greater than 50 mm in diameter are usually recommended for treatment while observation with regular imaging studies is advisable for those with smaller aneurysms[5] The size threshold is reduced in women, since the normal aorta is smaller in the female gender. The presence of symptoms from an aneurysm, rapid enlargement of the aneurysm, saccular aneurysm configuration, or the distal embolization of aneurysm contents are each considered indications for repair, irrespective of sac diameter. Lastly, a saccular aneurysm configuration is thought to be more prone to rupture and the threshold for AAA repair is lowered when saccular morphology is encountered[6].

There are two general methods for repair of an AAA; traditional open surgical repair and endovascular repair. Traditional open surgical repair has been the standard technique for over six decades.[7,8] Open repair is performed through a transperitoneal or retroperitoneal incision; sewing a prosthetic graft to the aorta above and below the aneurysm. While durable, open repair is associated with a significant risk of perioperative complications. The risk is particularly high in the elderly and in those with multiple medical comorbidities; the population who characteristically develop AAA. The Lifeline registry documented postoperative respiratory failure in 4.3%, myocardial infarction in 4.0%, and renal failure in 2.5% within 30 days of open surgical AAA repair.[9]

Endovascular aneurysm repair (EVAR) is the second general technique for aneurysm repair, first described by Volodos in 1986[10] and first successfully performed by Parodi in 1990.[11] The objective of EVAR is to repair the aneurysm through the trans-vascular insertion of an endograft. EVAR has been shown to reduce 30-day and in-hospital mortality, blood transfusions, mechanical ventilation, and ICU and hospital length of stay compared to open surgery.[12] Current endografts, while much improved over earlier devices, still suffer from some shortcomings. Many of the shortcomings of prior designs have been remediated with more durable materials, better stent architecture, and improved manufacturing processes. However, hostile proximal neck anatomies and poor quality access vessels still exclude EVAR as an option for many patients. Anatomical characteristics such as limited proximal aortic neck lengths, severe infrarenal neck angulation, and narrow, tortuous and/or calcified iliac arteries have been identified as risk factors that can limit EVAR success rates and are associated with increased rates of secondary interventions.[13-18] Complications associated with hostile proximal neck anatomy include type I endoleaks and graft migration.[14] Challenging iliac access vessels can hinder placement accuracy resulting in inadequate distal seal zones[16]. Access related complications remain a common cause for conversion to open surgery.[14]

Newer devices must address these previous endograft shortcomings if the applicability and the durability of endovascular repair are to be improved. Engineering of newer device iterations must

address interactions between design elements. For instance, lowering the profile of a device with newer sutures, fabrics, stents and assembly methods must also consider the effect such changes will have on one another; both during deployment as well as over long-term follow-up.

Medtronic's next generation AAA stent graft system on the Endurant product platform is the Endurant™ Evo Abdominal Aortic Aneurysm (AAA) stent graft system. The Endurant Evo AAA stent graft system was designed to further expand EVAR applicability and improve access in patients with challenging anatomies. Key design targets for Endurant Evo include the following:

- Introduction of a lower profile delivery system to allow treatment of patients with challenging anatomies, expand overall patient applicability, and improve procedural ease of use of the system.
- Graft flexibility and limb design optimization to improve conformability in challenging anatomies.
- Introduction of a 3-piece modular system (similar to Endurant IIs), which is engineered to help with placement accuracy by allowing bilateral device length adjustment during deployment and also aids the physicians in better inventory management.
- Enhanced delivery system ergonomic features to improve ease of use.

These enhancements were incorporated in the Endurant Evo AAA stent graft design with an expressed focus on maintaining the high durability and high performance standards established previously in the Endurant family. Scientific literature discussing the clinical performance of the Endurant/Endurant II device documents excellent early and late results. The relatively low rate of device-related complications has the potential to be reduced further with incremental design modifications. Based on the existing scientific literature on Endurant/ Endurant II three primary areas of design change of the Endurant Evo AAA stent graft system cannot be fully evaluated; lower profile, helical limb stent graft optimization, delivery system enhancements.

While these performance/design features are well understood technically and have been comprehensively analyzed/tested through preclinical testing (bench and animal), residual risks associated with the overall performance of the Endurant Evo AAA stent graft system will be confirmed in a clinical investigation designed to evaluate system performance. Therefore, the Endurant Evo Clinical Program composed of the Endurant Evo US Clinical Trial and the Endurant Evo International Clinical Trial were designed to evaluate the safety and effectiveness of the device in subjects who are candidates for endovascular repair of infrarenal AAA or aortoiliac aneurysms. Trial endpoints are described in more detail in Section C 2.

Literature review and pre-clinical testing will be provided in the Report of Prior Investigations.

## B.2 Device Information

### *B.2.1 Device Description*

The Endurant Evo Abdominal Aortic Aneurysm (AAA) stent graft system (manufactured by Medtronic, Inc.) is designed for the endovascular repair of infrarenal abdominal aortic or aortoiliac aneurysms. When implanted within the target lesion, the stent graft provides a permanent, alternative conduit for blood flow within the subject's vasculature by excluding the lesion from blood flow and pressure. The stent graft system is comprised of the implantable stent graft and the disposable delivery system. The stent graft is preloaded into the delivery system, which is inserted endoluminally via the femoral or iliac artery and tracked through the subject's vasculature to deliver the stent graft to the target site. Upon deployment, the stent graft self-expands to conform to the shape and size of the seal zones above and below the aneurysm.

The Endurant Evo AAA stent graft system is comprised of two primary components: the Endurant Evo stent graft and the Endurant Evo delivery system. All components of the Endurant Evo AAA stent graft system are pre-market and considered to be investigational.

*Endurant Evo Stent Graft*

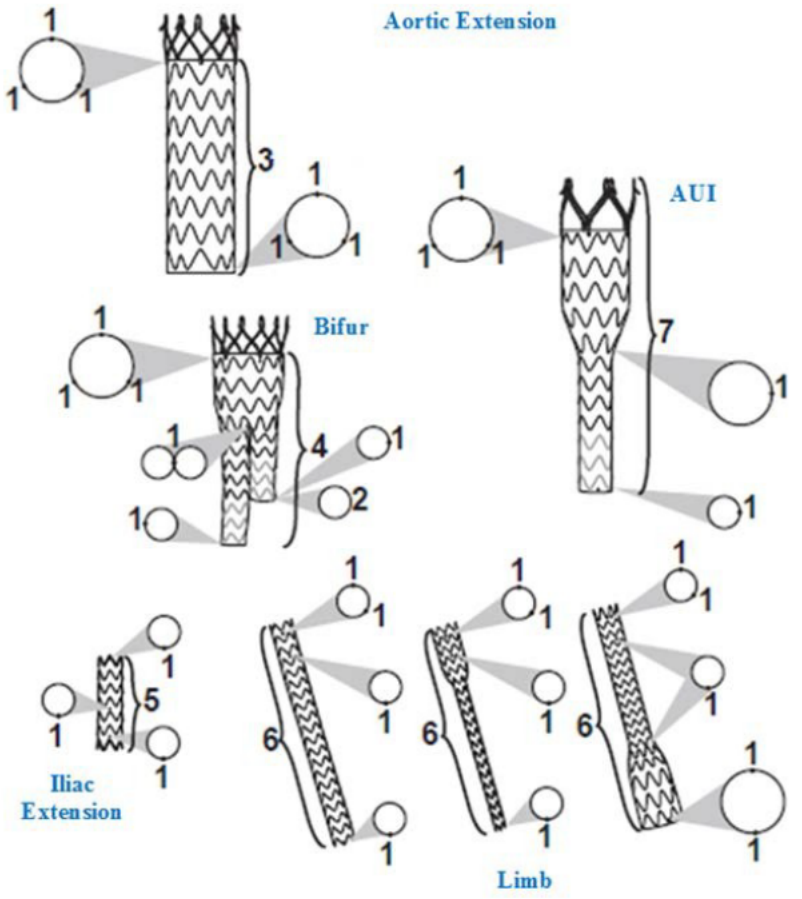
The Endurant Evo stent graft is comprised of the following stent graft configurations:

- Bifurcated component
- Limb component
- Aorto-Uni-Iliac (AUI)
- Aortic extensions
- Iliac extensions

Each stent graft component is introduced separately into the vessel and is mated in vivo to the components already in situ. All components are constructed by sewing the self-expanding nitinol stents to a fabric graft. The suprarenal stents with anchor pins on the proximal end of the bifurcated component, the AUI component and the aortic extension are laser cut from a nitinol tube and all other stents are wire-formed. The stents are formed in a ring with opposing ends being terminated together in crimp sleeves. The suprarenal and wire formed stents are sewn to the polyester (PET) graft fabric using ultra high molecular weight polyethylene (UHMWPE) suture.

The graft fabric is [redacted], then cut and seamed into the stent graft component form with PET suture and UHMWPE suture. [redacted]

Radiopaque (RO) markers are sewn onto each component of the stent graft to aid in fluoroscopic visualization and to facilitate accurate placement of each component. Endurant Evo uses three types of radiopaque markers: fold-over ("Clip") markers, tube markers, and coil markers. Clip markers are thin pieces of platinum iridium that are folded over the edge of the graft material in order to show exact location of the fabric edge. Tube markers are sectioned pieces of platinum iridium tubing. Coil marker is a coiled Platinum-Iridium wire which outlines the contralateral gate to facilitate gate cannulation. RO markers are located at the proximal and distal ends of each stent graft component, as well as at the bifurcation of the bifurcated stent grafts to help visualize the edges and locations of the stent grafts, indicate overlap distance between mating stent graft components, and indicate orientation of the contralateral gate on the bifurcated stent graft. RO markers are sewn to the graft fabric using UHMWPE suture to optimize both strength and profile. The nitinol stents may also be visualized under fluoroscopy. The Endurant Evo stent graft configurations are shown in Figure 1 below.




1. RO Marker
2. RO Gate Marker
3. Aortic Extension Configuration
4. Aortic Bifurcated Configuration
5. Iliac Extension Configuration
6. Limb Configuration
7. Aorto-Uni-Iliac Configuration

**Figure 1: Endurant Evo Stent Graft Configurations**

*Endurant Evo Delivery System*

The Endurant Evo delivery system is a single use, disposable catheter with an integrated handle designed to provide the user with accurate and controlled deployment. The catheter assembly is flexible and compatible with a 0.035" guidewire.

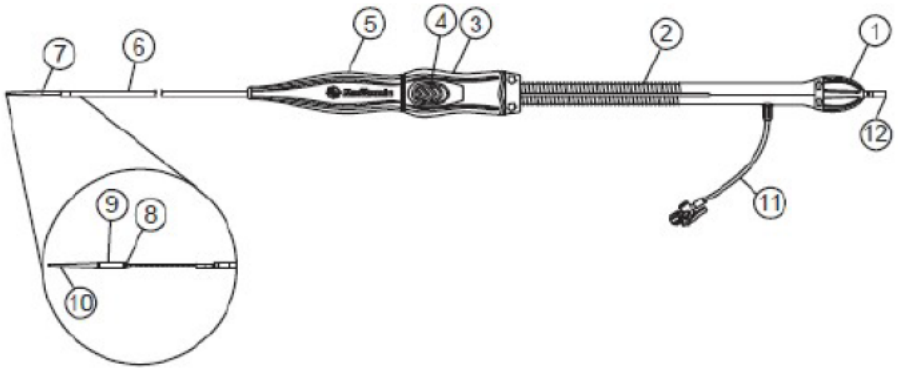
There are two kinds of Endurant Evo delivery systems:

a. Aortic delivery system, which is used to deliver the bifurcated, AUI, and aortic extension components.
b. The Iliac delivery system, which is used to deliver the limb and iliac extension components.

*Aortic Delivery System*

The working length of the aortic delivery system is 57 ± 2cm. The aortic delivery system is constructed of four concentric single lumen shafts (an outer polymer graft cover with a hydrophilic coating, a heat shrink covered laser cut stainless steel spindle-tube shaft, a polymer middle member shaft, and a nitinol guidewire tube lumen inner member). [redacted]. The aortic delivery system is used to deliver the bifurcated, AUI, and aortic extension stent graft components. Figure 2 provides a

pictorial reference of the Endurant Evo aortic delivery system.



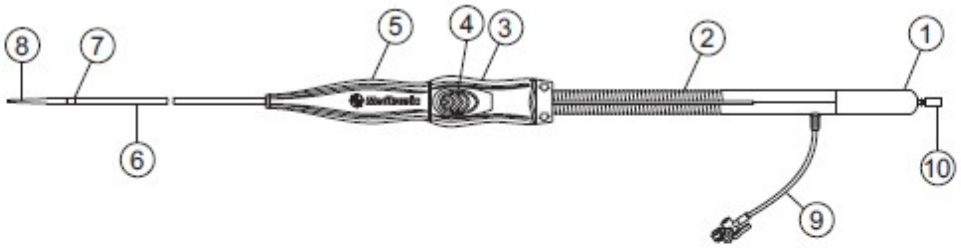

1. Rear Grip
2. Screw Gear
3. Retractor Handle
4. Retractor Trigger
5. Front Grip
6. Graft Cover
7. RO Marker
8. Spindle
9. Sleeve
10. Tapered Tip
11. Sideport Extension
12. Rear Luer

**Figure 2: Endurant Evo Aortic Delivery System**

The atraumatic polymeric aortic tapered tip is overmolded on the distal end of the nitinol guidewire tube to facilitate tracking through tortuous and calcified vessels. Attached to the proximal end of the tapered tip is a metallic sleeve that holds the suprarenal stent constrained on the spindle. The spindle is a polyether ether ketone (PEEK) overmold on the distal end of the spindle-tube to hold the proximal end of the suprarenal stent axially stationary before release. The aortic tapered tip, [redacted], and the distal end of the graft cover are radiopaque and aid in fluoroscopic visualization. Hemostasis is maintained by the seals within the delivery system that are designed to help minimize blood loss during the procedure. Retraction of the graft cover while the suprarenal stent is held by the spindle and sleeve allows for accurate positioning and deployment of the body of the stent graft components.

*Iliac Delivery System*

The working length of the iliac delivery system is 57 ± 2cm. The Endurant Evo iliac delivery system (Figure 3) is constructed of four concentric single lumen shafts (an outer polymer graft cover with a hydrophilic coating, a polymer middle member shaft, [redacted], and a PEEK guidewire tube inner lumen). [redacted] A polymeric, atraumatic tapered tip is overmolded at the distal end of the PEEK guidewire tube lumen to facilitate tracking through tortuous and calcified vessels. The tapered tip, [redacted], and the distal end of the graft cover are radiopaque and aid in fluoroscopic visualization. Hemostasis is maintained by seals within the delivery system that are designed to minimize blood loss during the procedure. The deployment of the self-expanding stent graft components is facilitated by the retraction of the graft cover.




1. Rear Grip
2. Screw Gear
3. Retractor Handle
4. Retractor Trigger
5. Front Grip
6. Graft Cover
7. RO Tip
8. Tapered Tip
9. Sideport Extension
10. Rear Luer

**Figure 3: Endurant Evo Iliac Delivery System**

The Endurant Evo AAA stent graft system is an investigational class III device in all geographies and is labeled with all the required statements per geography:

- Europe: “Exclusively for clinical investigations” (including translations into local languages)
- United States: “CAUTION: Investigational Device. Limited by Federal Law (USA) to Investigational Use”

The use of the Endurant Evo AAA 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 Endurant Evo AAA stent graft system is described in Section E. 4.

## B.2.2 Indications for Use

The Endurant Evo bifurcated stent graft is indicated for the endovascular treatment of infrarenal abdominal aortic or aortoiliac aneurysms. The Endurant Evo aorto-uni-iliac (AUI) stent graft is indicated for the endovascular treatment of infrarenal abdominal aortic or aortoiliac aneurysms in subjects whose anatomy does not allow the use of a bifurcated stent graft. The Endurant Evo AAA stent graft system is indicated for use in subjects with the following characteristics:

- adequate iliac or femoral access that is compatible with vascular access techniques (femoral cutdown or percutaneous), devices, and accessories
- proximal neck length of
  - ≥10 mm and infrarenal neck angulation of ≤60° and suprarenal neck angulation of ≤45°, or
  - ≥15 mm and infrarenal neck angulation of ≤75° and suprarenal neck angulation of ≤60°
- aortic neck diameters with a range of 18 mm to 32 mm
- distal fixation lengths of ≥20 mm
- iliac diameters with a range of 7 mm to 25 mm
- morphology suitable for aneurysm repair

**Note:** Proximal neck length refers to minimum seal zone.

# C STUDY PLAN

## C.1 Study Objectives

The purpose of the Endurant Evo US Clinical Trial is to demonstrate that the Endurant Evo AAA stent graft system is safe and effective for endovascular treatment of infrarenal abdominal aortic or aortoiliac aneurysms. The clinical evidence collected as part of this trial will be used in conjunction with data collected during the concurrently enrolling Endurant Evo International Clinical Trial to support PMA Approval of the Endurant Evo AAA Stent graft system.

### *C.1.1 Primary Objectives*

The primary safety objective is to demonstrate the safety of the Endurant Evo AAA Stent graft system for the endovascular treatment of abdominal aortic or aortoiliac aneurysms. Safety will be assessed through the proportion of subjects who have a Major Adverse Events (MAE) reported within 30-days post-implantation.

The primary effectiveness objective is to demonstrate successful delivery and deployment of the Endurant Evo AAA Stent graft system with successful removal of the delivery system during the index procedure as well as the treatment success at 12 months.
(See section *C.2.1 Primary 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 and clinical utility measures.
(See section *C.2.2 Secondary Endpoints* for a detailed description of the evaluation criteria used to assess Secondary Objectives)

## C.2 Clinical Endpoints

### *C.2.1 Primary Endpoints*

#### C.2.1.1 Primary Safety Endpoint

The primary safety endpoint is defined as the proportion of subjects experiencing a MAE within 30 days post-implantation. MAEs include the occurrence of any of the following events:

- All-cause mortality
- Bowel ischemia
- Myocardial infarction
- Paraplegia
- Procedural blood loss ≥1000 cc
- Renal failure
- Respiratory failure
- Stroke

Detailed definitions of MAEs are provided in Appendix L.2.

#### C.2.1.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is defined as the proportion of subjects with both technical success at the time of index procedure and treatment success at 12 months post-implantation. Successful aneurysm treatment is achieved based on the following criteria:

- Technical success at the index procedure (as assessed intra-operatively) is defined as successful delivery and deployment of the Endurant Evo AAA Stent graft system in the planned location and with no unintentional coverage of both internal iliac arteries or any visceral aortic branches and with successful removal of the delivery system

AND

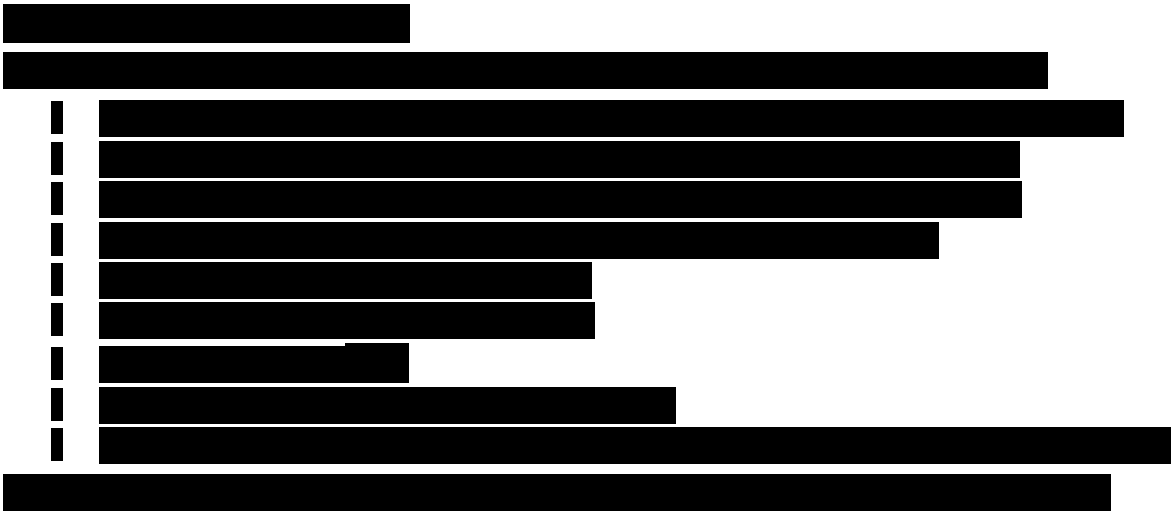
- Treatment success consisting of freedom from:
  - AAA diameter increase, defined as > 5 mm increase in maximum diameter as measured on CT scan (or MRA/MRI) at 12-month follow-up as compared to 1-month imaging
  - Types I and III endoleaks at 12-month follow-up including those requiring intervention through 12 months
  - Aneurysm rupture within 365 days
  - Conversion to surgery within 365 days
  - Stent graft migration resulting in a serious adverse event or requiring secondary intervention through 12 months
  - Stent graft occlusion through 12 months

### *C.2.2 Secondary Endpoints*

The following secondary endpoints will be evaluated:

- All cause-mortality within 30, 183, and 365 days
- Aneurysm-related mortality within 30, 183, and 365 days
- Secondary procedures to correct Type I and III endoleaks within 183 and 365 days
- Secondary procedures within 183 and 365 days
- Serious adverse events within 30, 183, and 365 days
- Conversion to open surgery within 183 and 365 days
- Aneurysm rupture within 183 and 365 days major adverse events within 183 and 365 days
- Stent graft migration at 6- and 12-month follow-up visits (as compared to 1-month imaging)
- Aneurysm expansion >5 mm at 6- and 12-month follow-up visits (as compared to 1-month imaging)
- All endoleaks based on imaging findings at 1-, 6-, and 12-month follow-up visits
- Stent graft occlusions based on imaging findings through 1-, 6- and 12 months
- Device deficiencies based on imaging findings through 6 and 12 months

Detailed definitions for secondary endpoints are provided in Appendix L.2.



[redacted]

## C.3 Study Hypothesis

The Endurant Evo US Clinical Trial will focus on balancing pre- and post-market clinical data to establish safety and effectiveness. Study success is defined as rejecting the null hypothesis for the primary safety endpoint test (≥20%), with a condition upon rejecting the null hypothesis for the post-market primary effectiveness test (≤80%). As such, the following analyses will be submitted:

- Pre-market: 30-day primary safety endpoint (hypothesis based, see H.1)
- Pre-market: 6-month effectiveness analysis (descriptive)
- Post-market: 12-month primary effectiveness endpoint (hypothesis based, see H.1)

The proposed clinical strategy described in this section will allow for appropriate evaluation of the safety and effectiveness of the Endurant Evo AAA stent graft system. Safety will be established through the hypothesis-based primary safety endpoint at 30 days. Reasonable assurance of effectiveness will be provided via the pre-market 6-month analysis and then confirmed at the 12-month post-market primary effectiveness endpoint.

## C.4 Study Population

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

## C.5 Study Design

The Endurant Evo US Clinical Trial is prospective, multi-center, pre-market, non-randomized, single-arm trial. The trial is designed to assess the clinical safety and performance of the Endurant Evo AAA Stent graft system.

Globally, a total of 140 subjects will be concurrently enrolled in the United States and outside the United States to support the primary endpoint[2]. Up to 50% of subject data used to support PMA approval may come from subjects enrolled at sites outside of the US under a separate CE Mark study protocol; the Endurant Evo International Clinical Trial protocol. The Endurant Evo International Clinical Trial protocol and Endurant Evo US Clinical Trial protocol will be identical with respect to the inclusion/exclusion criteria, and follow up data collection.

Given the UADEs that have occurred within the Endurant Evo study (transition stent fracture, partial suprarenal stent detachment, and suprarenal stent fracture), enrollment was terminated. Total global enrollment, upon termination, was 139 subjects. This includes 70 subjects enrolled in the United States and 69 enrolled outside the United States.

## C.6 Randomization and Blinding

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

## C.7 Sample Size

The sample size for the Endurant Evo global program is calculated for both the primary safety endpoint and the primary effectiveness endpoint.

It is expected that the Endurant Evo AAA stent graft system will result in a MAE rate at 10% with respect to the primary safety endpoint and 90.5% treatment success for the primary effectiveness

[2] A minimum of 50 subjects will be enrolled with the high neck angulation indication (defined as proximal neck length ≥15 mm, infrarenal neck angulation >60° and ≤75° and suprarenal neck angulation ≤60°). If a minimum of 50 subjects are not enrolled as part of the first 140 subject cohort, Medtronic will continue enrollment for the high angulation indication but submit the PMA application to obtain approval for the 60°angulation indication with the 140 subject cohort data. A minimum of 70 subjects enrolled in the study will have percutaneous access.

endpoint according to its predicates' performances shown in Table C-1.

**Table C-1: Clinical Data from Talent AAA eLPS and Endurant Studies[3]**

| Predicates | MAE within 30 Days | Successful Aneurysm Treatment at 12 Months |
|---|---|---|
| Talent AAA eLPS Arm | 11% (18/166) | 86% (107/125) |
| Endurant IDE Bifurcated Arm | 4% (6/150) | 95% (115/121) |
| Endurant IDE AUI Arm (P100021/S021) | 11% (5/44) | 97% (35/36) |

In order to pass both hypothesis tests with an overall study power of 80%, a sample size of 119 evaluable subjects will be required to pass each hypothesis with 90% statistical power (target significance level is 0.025.) To account for attrition of 15% (85% imaging compliance) at 12 months, 140 subjects will be enrolled globally to ensure at least 119 evaluable subjects. Note that a minimum of 50 subjects will be enrolled with the high neck angulation indication and a minimum of 70 subjects will be enrolled with percutaneous access[4].[4] If a minimum of 50 high angle indication subjects are not enrolled as part of the first 140 subject cohort, Medtronic will continue enrollment for the high angulation indication but submit the PMA application to obtain approval for the 60° angulation indication with the 140 subject cohort data.

At a minimum, 50% of the total global subject cohort will be enrolled in the Endurant Evo US Clinical Trial. The other subjects will be enrolled in the Endurant Evo International Clinical Trial. This trial is designed for the data to be pooled with the Endurant Evo US Clinical Trial. More details about the poolability of Endurant Evo US Clinical Trial subjects and Endurant Evo International Clinical Trial subjects can be found in H.1.

## C.8 Number of Investigational Sites and Study Duration

The Endurant Evo Global Clinical program will be conducted at up to 30 sites worldwide with up to 20 sites participating under the Endurant Evo US Clinical trial protocol in the United States and with approximately 10 sites participating under the Endurant Evo International Clinical trial protocol outside the United States. In the United States, a minimum of 70 subjects will be enrolled at up to 20 investigational sites. Investigators at any single site may not enroll more than 20% of the total global enrollment (140 subjects) in the trial.[4] Subjects will be followed for a total of 5 years. Study duration from first subject enrolled to final subject exit is expected to be 6 years.

The total enrollment period is not expected to exceed 12 months. However, if a minimum of 50 high angulation indication subjects are not enrolled as part of the first 140 subject cohort, Medtronic will submit the PMA application to obtain approval for the 60°angulation indication with the 140 subject cohort data. In this event, Medtronic will continue enrollment for the high angulation indication.

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

[3] Results are from the Talent AAA (Talent AAA Control data referenced in Endurant Clinical Study Report, Appendix 2 of M090018_M005 Clinical Module) and Endurant (P100021) PMA 90-day update submission submitted via P100021/A002. The results on successful aneurysm treatment are reported at 12 months and included all occlusions through the time period

[4] Given the UADEs that have occurred within the Endurant Evo study (transition stent fracture, partial suprarenal stent detachment, and suprarenal stent fracture), enrollment was terminated. Total global enrollment, upon termination, was 139 subjects. This includes 70 subjects enrolled in the United States and 69 enrolled outside the United States.

# D SUBJECT SELECTION

## D.1 Inclusion Criteria

Candidates for the Endurant Evo US Clinical trial must be appropriate subjects for endovascular repair of infrarenal abdominal aortic aneurysms or aortoiliac aneurysms (evidenced by screening contrast-enhanced CT or MRA) and have to fulfill all of the following inclusion criteria to be eligible for enrollment in the study:

1) Subject is ≥18 years old
2) Subject understands and voluntarily has signed and dated the Informed Consent approved by the Sponsor and by the Ethics Committee/Institutional Review Board
3) Subject is able and willing to comply with the protocol and to adhere to the follow-up requirements
4) Subject is a suitable candidate for elective surgical repair of AAA as evaluated by American Society of Anesthesiologists (ASA) Physical Status Classification System I, II, or III
5) Subject has an infrarenal abdominal aortic or aortoiliac aneurysm characterized by one or more of the following:
    a) Aneurysm is >5 cm in diameter (diameter measured is perpendicular to the line of flow)
    b) Aneurysm is 4 – 5 cm in diameter and has increased in size ≥0.5 cm within the previous 6 months
6) Subject meets all the following anatomical criteria as demonstrated on contrast-enhanced CT or MRA imaging:
    a) Proximal neck length of ≥ 10 mm with ≤ 60° infrarenal and ≤ 45° suprarenal neck angulation or Proximal neck length of ≥ 15 mm with ≤ 75° infrarenal and ≤ 60° suprarenal neck angulation
    b) Subject has vascular dimensions, e.g., aortic and iliac diameters, lengths from renal arteries to iliac bifurcation and hypogastric arteries, in the range of sizes available for the Endurant Evo AAA stent graft system (measured intima to intima) and within the sizing recommendations (refer to Endurant Evo AAA stent graft system Instructions for Use (IFU))
    c) Subject has a proximal aortic neck diameter ≥ 18 mm and ≤ 32 mm
    d) The distal fixation center of the iliac arteries must have a diameter ≥ 7 mm and ≤ 25 mm bilaterally for the bifur and unilaterally for the AUI
    e) Subject has documented imaging evidence of at least one patent iliac and one femoral artery, or can tolerate a vascular conduit that allows introduction of the Endurant Evo AAA stent graft system
    f) Subject has distal non-aneurysmal iliac (cylindrical) fixation length ≥20 mm bilateral for the bifur and unilaterally for the AUI

## D.2 Exclusion Criteria

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

1) Subject has a life expectancy ≤1 year
2) Subject is participating in another investigational drug or device study which would interfere with the endpoints and follow-ups of this study
3) Subject is pregnant
4) Subject has an aneurysm that is:
    a) Suprarenal/pararenal/juxtarenal
    b) Isolated ilio-femoral

c) Mycotic
d) Inflammatory
e) Pseudoaneurysm
f) Dissecting
g) Ruptured
h) Leaking but not ruptured

5) Subject requires emergent aneurysm treatment
6) Subject has a known, untreated thoracic aneurysm >4.5 cm in diameter at the time of screening
7) Subject has been previously treated for an abdominal aortic aneurysm
8) Subject has a history of bleeding diathesis or coagulopathy
9) Subject has had or plans to have an unrelated major surgical or interventional procedure within 1 month before or after implantation of the Endurant Evo AAA stent graft
10) Subject has had a myocardial infarction (MI) or cerebral vascular accident (CVA) within 3 months prior to implantation of the Endurant Evo AAA stent graft
11) Subject has a conical neck defined as a >4 mm distal increase from the lowest renal artery over a 10 mm length
12) Subject has a known allergy or intolerance to the device materials
13) Subject has a known hypersensitivity or contraindication to anticoagulants, antiplatelets, or contrast media, which is not amenable to pre-treatment
14) Subject has significant aortic thrombus and/or calcification at either the proximal or distal attachment centers that would compromise fixation and seal of the device at the discretion of the investigator
15) Subject has ectatic iliac arteries requiring bilateral exclusion of hypogastric blood flow
16) Subject whose arterial access site is not anticipated to accommodate the diameter of the Endurant Evo AAA stent graft delivery system (13F-17F) due to vessel size, calcification, or tortuosity
17) Subject is morbidly obese or has other documented clinical conditions that severely inhibit radiographic visualization of the aorta at the discretion of the investigator
18) Subject has active infection at the time of the index procedure documented by e.g. pain, fever, drainage, positive culture and/or leukocytosis considered to be clinically significant per investigator discretion
19) Subject has congenital degenerative collagen disease, e.g., Marfan's Syndrome
20) Subject has a creatinine level > 2.00 mg/dl (or >176.8 µmol/L)
21) Subject is on dialysis

# E STUDY PREPARATION PROCEDURES

## E.1 Investigator / Investigational 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 an abdominal stent graft
- Investigators have adequate time to follow up on the clinical study
- Investigators are willing to comply with the clinical investigation plan
- Investigators are willing to sign the appropriate clinical trial agreement
- Investigators have past experience with conducting clinical studies or appropriate training
- Investigators are familiar with FDA/ ICH-GCP requirements
- Investigators are willing to undergo auditing by sponsor or regulatory bodies
- Investigators are willing to undergo study specific training

### *E.1.2 Investigational Site Selection Criteria*

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

- Adequate staff (sub-investigator and/or research coordinator) that is accessible and has time to manage the trial and data reporting requirements
- Site personnel has demonstrated experience with conducting clinical (specifically device) trials that comply with applicable regulatory standards
- Site has sufficient annual case volume of AAA stent graft procedures
- Ability to securely store devices according to the Instructions for Use

### *E.1.3 Clinical Trial Agreement*

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

### *E.1.4 Curriculum Vitae*

A current (within 3 years) signed and dated Curriculum Vitae from all key members of the investigational site team participating in this clinical study as listed on the Delegation of Authority Form shall be obtained, evidencing the required qualifications, including the year and where obtained, and including their current position at the investigational site.

The signature on the CV must be dated within 3 years prior to the date of activation of the investigational site.

## E.2 Ethics

### *E.2.1 EC/IRB Approval*

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

### *E.2.2 Informed Consent Process*

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

In order to ensure the subject has sufficient time to review the materials, prior to the consent discussion, the subject should receive the EC/IRB approved Informed Consent Form. During the consent discussion the investigator or his/her authorized designee must fully inform the subject of all aspects of the clinical study that are relevant to the subject's decision to participate in the clinical study. If a subject is unable to read and/ or write, an impartial witness must be present during the entire informed consent discussion. All items addressed in the Informed Consent Form must be explained. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

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

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

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

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

### *E.2.3 Revisions in Informed Consent Form*

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

If new information becomes available that can significantly affect the subject's future health and

medical care, Medtronic will revise the written Informed Consent Form. The revised information will be sent to the investigator for approval by the EC/IRB. After approval by the EC/IRB, if relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

### *E.2.4 Regulatory Submission*

In countries where submission to the regulatory authority is required per local law, no subjects will be enrolled in the clinical study until the particular regulatory authority has approved the current clinical investigation plan of the clinical study and other documents as required according to the local requirements.

If the regulatory authority imposes any additional requirements (e.g., safety reports, progress reports) Medtronic will prepare the required documents and send them to the respective authority. Other documents that are referred to in this clinical investigation plan are listed below and will be made available upon request:

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

## E.3 Regulatory Compliance

The Endurant Evo US Clinical Trial will be conducted under an FDA Investigational Device Exemption (IDE) in compliance with the Declaration of Helsinki (October 2013), ISO 14155:2011 3.1, 3.15, 3.2, 3.36, 3.37, 3.42 and 21 CFR Parts 11, 50, 54, 56, and 812.

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

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

## E. 4 Training Requirements

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

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

Also after initial training, Medtronic will provide training to other clinical site study team members. Once the primary endpoint has been reached for all subjects, qualified site personnel 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

Medtronic will provide study materials to the site after approval of the site for participation. Before a study site can enroll a subject or have access to the electronic data capture (EDC) system, the

investigator must be in receipt of a “Go letter” (this may be an email, fax or other written communication means) from Medtronic.

## E. 6 Study Device/Product Traceability

### *E.6.1 Supply of Investigational Devices/Products*

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

### *E.6.2 Storage and Handling of Investigational Devices/Products*

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

### *E.6.3 Device Explant and Return Procedures/Products*

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

### *E.6.4 Device/Product Disposition Requirements*

Investigational devices/products will be traced during the clinical study by assigning unique identifiers to each device/product. The investigator is responsible for maintenance of a Device Disposition 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 original Device Disposition Log.

# F STUDY METHODS

## F.1 Point of Enrollment

Pre Screening:

Investigators will assess potential subjects with an infrarenal abdominal aortic or aortoiliac aneurysm for their suitability for enrollment in the trial. Initial subject eligibility will be determined by the investigator based upon review of their medical history, disease progress and anatomic suitability for inclusion in the trial as evidenced on screening contrast-enhanced CT/MRA. If the subject appears to meet the eligibility criteria, then the investigator will discuss the study with the potential subject and provide information related to the potential risks and benefits and required follow-up procedures per the informed consent process.

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

- Pregnancy test (for female subjects of childbearing potential). Test must be completed at the time of screening (within 45 days the index procedure). Results must be negative.
- Screening CT or MR with contrast (2 cm above the origin of the celiac artery through the bifurcation of the femoral arteries) (completed within 6 months prior to the index procedure).
- Laboratory tests (completed within 45 days prior to the index procedure) including serum creatinine (required for all subjects) and INR (only required for subjects taking Warfarin preoperatively).

Screening/Baseline Assessments:

After the subject voluntarily has signed and dated the Informed Consent Form, the subject will be considered a study candidate. If a subject does not sign the Informed Consent Form, then no further study specific screening procedures can occur.
Collection of screening and baseline information will take place only after the subject has given voluntary, documented informed consent and will include the following:

- Subject demographics
- Medical history
- Concomitant medication
- Current health status
- Risk factors
- ASA Physical Status Classification
- Laboratory analyses (serum creatinine (required for all subjects), INR (only required for subjects taking Warfarin preoperatively))
- EQ5D Questionnaire

Screening CT/MRA images will be sent to the Core Lab to assess the anatomical inclusion/exclusion requirements. An Independent Physician Reviewer (IPR) will review screening CT/MRA images to determine eligibility. Approval by the IPR must be obtained prior to a subject's enrollment 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 enrollment. Subjects that are not approved by the IPR are considered screen failures and will not be enrolled in the study.

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

Enrollment:

Those subjects who sign and date the informed consent document, meet all of the study eligibility criteria, and are approved by the IPR will be eligible for enrollment into the Endurant Evo US Clinical Trial. The subject will be considered to be enrolled when arterial access has been established with an attempt to introduce the Endurant Evo AAA stent graft.

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

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

## F.2 Implant and Follow up

### *F.2.1 Index Procedure*

All investigators will read, understand and be trained to the Endurant Evo AAA stent graft system Instructions for Use (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.

Identification and/or serial numbers for all investigational components of the Endurant Evo AAA stent graft system used or opened during the index procedure will be recorded.

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

F.2.1.2 Treatment Failure

Inability to implant the Endurant Evo AAA 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 through the 1-month follow-up time point and then exited from the study.

If a primary conversion to open repair is required during the index procedure, then the subject will be followed for 1 month, at which time the subject will be exited from the study.

After exiting the study, subjects will be followed as per their institutional standard of care.

### *F.2.2 Hospital Discharge*

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

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

### *F.2.3 Follow-Up Visits and Procedures*

Each subject will have required post-implantation follow-up visits at 30-days, 6-month, 12-months, and annually thereafter, for a total of 5 years from index procedure. Follow-up visits and associated timeframe windows are summarized in Table F-1. Given the UADEs that have occurred within the Endurant Evo study, the DMC has made additional imaging surveillance recommendations, beyond the required follow-up in the protocol. The additional imaging surveillance recommendations are provided, under separate cover, in the most recent DMC Surveillance and Management letter that has been provided to each investigational site.

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

| Follow-Up Visit | Window Start Day | Target Day | Window Close Day |
|---|---|---|---|
| 1 Month (± 15 days) | 15 | 30 | 45 |
| 6 Month (± 30 days) | 153 | 183 | 213 |
| 12 Months (-30/+56 days) | 335 | 365 | 421 |
| 24 Months (±56 days) | 675 | 731 | 787 |
| 36 Months (±56 days) | 1040 | 1096 | 1152 |
| 48 Months (±56 days) | 1405 | 1461 | 1517 |
| 60 Months (±56 days) | 1770 | 1826 | 1882 |

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

- Physical Exam (to be reported in FUP eCRF until 24 months only)
- CT/MR with contrast and non-contrast (2 cm above the origin of the celiac artery through the bifurcation of the femoral arteries)
- Abdominal X-ray (4-view, KUB)
- EQ5D questionnaire (until 12 months F/U only)
- Adverse event assessment
- Concomitant Medication (to be reported in FUP eCRF until 24 months only)

If a CT/MR is acquired at discharge (or before Day 15) due to medical necessity, or at the discretion of the investigator, it may be used to meet the 1-month follow-up visit CT/MR requirement and, acquisition of an additional 1-month CT/MR with contrast would not be required.

Abdominal X-rays should be completed via a four-view kidney, ureter, bladder (KUB) X-ray. Posterior/anterior (PA) and lateral images are recommended for visualization of the stent graft. Ensure the entire device is captured on images for assessment.

If conversion to open repair is required during the follow-up period, then the subject will be followed for 30 days after the conversion, at which time the subject will be exited from the study. Please refer to Device Explant and Returned Product Instructions, located in L.4 of the protocol.

## F.3 Data Collection Requirements

Clinical data will be collected preoperatively to establish eligibility, at baseline, during the index procedure, throughout the hospital stay, and postoperatively at the required (and any interim imaging) follow-up visits described in Section F.2. The data collection schedule is summarized in Table F-2. Imaging source data will be sent to the Core Lab for analysis up to the 60-month follow-up visit. Any interim imaging of the stent graft region but not linked to a study visit should be sent to the Core Lab (e.g. imaging performed as standard of care beyond the protocol required time points and/or when performed further to any issue observed at previous imaging Follow-up). This also includes interim imaging performed, as recommended per the most recent DMC Surveillance and Management letter, All images taken from the stent graft region must be assessed by the site. Any findings that meet the requirements in the flowchart (Appendix L.8) must be reported on the applicable eCRF.

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

## Table F-2: Data Collection Schedule

| DATA | Screening/ Baseline | Index Procedure | Hospital Discharge | 1-Mo. F/U (±15 days) | 6-Mo. F/U (±30 days) | 12-Mo. F/U[e] (-30/+56 days) | 2 Yr. F/U[e] (±56 days) | 3-5 Yr. F/U[e] (±56 days) |
|---|---|---|---|---|---|---|---|---|
| Informed consent | ✓ | | | | | | | |
| Inclusion / Exclusion criteria | ✓ | | | | | | | |
| Physical examination | ✓ | | | ✓ | ✓ | ✓ | ✓ | |
| Medical history | ✓ | | | | | | | |
| Current health status and risk factors | ✓ | | | | | | | |
| Laboratory tests at screening: Creatinine, INR[d] | ✓ | | | | | | | |
| Device and procedure information | | ✓ | | | | | | |
| Implant adjunctive procedures | | ✓ | | | | | | |
| Hospital discharge information | | | ✓ | | | | | |
| Medications | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | |
| Adverse event assessment | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| EQ5D questionnaire | ✓ | | | ✓ | ✓ | ✓ | | |
| **IMAGING** | | | | | | | | |
| CT/MR (2 cm above origin of celiac artery through bifurcation of femoral arteries)[c] | ✓ | | | ✓[a, b] | ✓[a] | ✓[a] | ✓[a] | ✓[a,f] |
| Abdominal X-Ray (4-view, KUB) | | | | ✓ | ✓ | ✓ | ✓ | ✓[f] |

[a] A CT/MR with contrast and non-contrast is required at each follow-up visit. If a subject is unable to tolerate a CT/MR with contrast due to renal insufficiency or physician discretion, a CT/MR without contrast + duplex ultrasound is the preferred alternative imaging modality and should be performed. If the preferred alternative imaging modality is not poss ble, a duplex ultrasound + 4-view X-ray should be performed to assess the aneurysm and stent graft integrity.

[b] If a CT/MR with contrast is acquired at discharge (or before Day15) due to medical necessity or at the discretion of the investigator, it may be used to meet the 1-month follow-up visit CT/MR
requirement and acquisition of an additional 1-month CT/MR with contrast would not be required

[c] CT evaluation may include "3-phase technique", volume studies, 3-D reconstruction, or computer-aided measurements

[d] INR only required for subjects taking Warfarin preoperatively

[e] Given the UADEs that have occurred within the Endurant Evo study, the DMC has made additional imaging surveillance recommendations, beyond the required follow-up in the protocol. The additional imaging surveillance recommendations are provided, under separate cover, in the most recent DMC Surveillance and Management letter that has been provided to each investigational site.

[f] All images (routine & interim) performed 3-5 years will be required to be submitted to the Core Lab for evaluation. Sites will continue to review images for clinical evaluation and detection of device deficiencies in accordance with Appendix L.8, but will not be required to complete imaging eCRF.

## F.4 Role of the Sponsor Representatives

Sponsor representatives may provide support as required for the study, including technical support during implantation. The sponsor representative is an experienced expert of device sizing, placement and the technical features of the device and will advise the implanting physician during the implant procedure if needed. The sponsor representative will not be involved actively during the placement and deployment of the Endurant Evo AAA stent graft system.

## F.5 Source Documents

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

Examples of these original documents and data records include, but are not limited to: hospital record (paper and electronic, as applicable), subject's screening documentation, recording media such as CD, DVD, CT or other imaging reports, laboratory reports, device accountability records, worksheets and subject files at other departments. Where paper notes and worksheets are retained, these shall be signed and dated by the member of the investigational site team. Where copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by a member of the investigational site team with a statement that it is a true reproduction of the original source document.

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

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

## F.6 Adverse Events

For the purpose of this clinical investigation Medtronic will define and classify the following events per ISO14155:2011 (followed for definitions of Adverse Events only) and Title 21 CFR part 812.3.

Adverse event reporting for the remaining follow up (3-5 years) will focus on the reporting of the below listed events:

- Adverse events with a possible relationship to the aneurysm (Excluding aneurysms in anatomic areas other than the Endurant grafted segment)
- Adverse events with a possible relationship to the device
- Adverse events with a possible relationship to the procedure
- Adverse events leading to subject's death

Secondary procedures performed as a result of any of the above adverse events must be reported on the respective Adverse Event form. Please see guidance for reporting of adverse vents following image review in Appendix L.8.

All adverse events that meet the study definitions will be reported to the sponsor and documented on the Adverse Event eCRF and in the subject's medical records.
Clinical events that are inherent to a surgical procedure and expected to occur in the majority of subjects for a projected duration may be considered unavoidable. Such events include, but are not limited to, those listed in Table F-3. These events should not be reported as adverse events during this study.

**Table F-3: Expected and Un-reportable Adverse Events Related to a Surgical Procedure**

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

### *F.6.1 Definitions / Classifications*

**Adverse Event (AE):** *(ISO14155:2011 3.2)*
Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

*NOTE 1:* This definition includes events related to the investigational medical device.

*NOTE 2:* This definition includes events related to the procedures involved.

*NOTE 3:* For users or other persons, this definition is restricted to events related to investigational medical devices.

**Adverse Device Effect (ADE):** *(ISO14155:2011 3.1)*
Adverse event related to the use of an investigational medical device.

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

*NOTE 2:* This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

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

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

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

**Serious Adverse Device Effect (SADE):** *(ISO 14155:2011 3.36)*
Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

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

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

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

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

performance.

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

### *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.. 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.

Please see guidance for reporting of Adverse Events following image review in Appendix L.8.

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

### *F.6.3 Recording and Reporting of Device Deficiencies*

Device Deficiency information will be collected throughout the study and reported to Medtronic. Device Deficiencies should be reported on a Device Deficiency Form in the eCRF. In case the eCRF is not available the Device Deficiency form needs to be completed manually and must be sent to Medtronic. Contact details are given in the investigational site file. The investigator is responsible for reporting all Device Deficiencies to Medtronic.

Please see guidance for reporting of Device Deficiency following image review in Appendix L.8.

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

**Table F-4: Adverse Event Reporting Requirements from Investigator to Medtronic**

| | |
|---|---|
| **Serious Adverse Device Effects (SADE), including Unanticipated Serious Adverse Device Effect (USADE):** | Immediately (but no later than 3 calendar days) after the investigator first learns of the event or of new information in relation with an already reported event. |
| **Unanticipated Adverse Device Effect (UADE)** | Immediately (but no later than 3 calendar days) after the investigator first learns of the event or of new information in relation with an already reported event. |

| | |
|---|---|
| **Serious Adverse Events (SAE)** | Immediately (but no later than 3 calendar days) after the investigator first learns of the event or of new information in relation with an already reported event. |
| **Adverse Device Effects (ADE)** | Immediately (but no later than 3 calendar days) after the investigator first learns of the event. |
| **All other AEs** | Submit in a timely manner after the investigator first learns of the event. |
| **Device Deficiency (with SAE potential)** | Immediately (but no later than 3 calendar days) after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency. |
| **All other Device Deficiencies** | Submit in a timely manner after the investigator first learns of the deficiency. |

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

### *F.6.5 Clinical Event Committee*

A clinical event committee (CEC) will be established. The CEC is an independent committee made up of clinicians (interventional and non-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 major adverse events (except procedural blood loss), unanticipated adverse device effects, and all deaths that occur throughout the conduct of the clinical trial. A charter will be developed that will detail the criteria for selected complications and clinical events that need to be adjudicated as well as the CEC composition, duties, procedures and adjudication rules and meeting frequency.

### *F.6.6 Emergency Contact Details in Case of Serious AEs*

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

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

## F.7 Subject accountability

Every subject should be encouraged to remain in the study until they have completed the required follow up per the study protocol. If the subject discontinues prematurely from the study (e.g. withdrawal of the consent, lost to follow-up), the reason for discontinuation must be documented in the subject's hospital record and documented on the appropriate eCRF. Subjects will not be replaced in case of premature study discontinuation.

### *F.7.1 Criteria and Procedures for Exit from Study*

The Study Exit eCRF should be completed after the 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
- Subject has conversion to open repair
- Other (specify).

### *F.7.2 Study Withdrawal*

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

### *F.7.3 Missed Follow-up*

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

### *F.7.4 Lost-to-Follow-up*

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

### *F.7.5 Conversion to Open Repair*

If a primary conversion to open repair is required during the index procedure, then the subject will be followed for 1 month, at which time the subject will be exited from the study.
If a secondary conversion to open repair is required during the follow-up period, then the subject will be followed for 30 days after the conversion, at which time the subject will be exited from the study.

### *F.7.6 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 *Management of Abdominal Aortic Aneurysms Clinical Practice Guidelines of the European Society for Vascular Surgery*[19] or *Society for Vascular Surgery practice guidelines for the care of patients with an abdominal aortic aneurysm*[20].

## F.8 Study/Protocol Deviations and CIP Changes

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

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

### *F.8.1 Request for Approval of Study Deviations*

The investigator shall obtain documented approval from Medtronic before implementation, for any change or deviation from the clinical investigation plan. In case of study deviations that can affect the subject's rights, safety or well-being or the scientific integrity of the clinical study, approval from the EC/IRB and regulatory authority must also be obtained before implementation. The investigator shall timely contact the Clinical Study Manager for review of the proposed change/deviation.
Prior approval is not always realistic in situations where unforeseen circumstances are beyond the investigator's control. However, also in these cases, the event is considered a deviation, and shall be reported.

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

### *F.8.2 Reporting Requirements for Study Deviations*

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), such as those included in, but not limited to, the list below. Repetitive or serious investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases freeze enrollment or ultimately terminate the investigator's participation in the clinical study:

- Non-compliance to obtain subject's informed consent
- Non-compliance to the inclusion/exclusion criteria
- Failure to follow subjects per scheduled follow-ups
- Failure to follow-up with findings on monitoring reports
- IRB/ EC approval expiration
- IRB/ 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 site-specific reports to the investigators on a periodic basis summarizing information on deviations that occurred at the investigational site.

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

### *F.8.3 Amendments to the Clinical Investigation Plan*

The investigator can propose any appropriate modification(s) of the clinical investigation plan or investigational device or investigational device use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic will submit any significant amendment to the clinical investigation plan, including a justification for this amendment, to the appropriate regulatory authorities and to the investigators to obtain approval from their EC/IRB. The investigator will only implement the amendment after approval of the EC/IRB, regulatory authority and Sponsor. Administrative amendments to the clinical investigation plan will be submitted to the EC/IRB for notification. Furthermore investigators shall sign any approved amendment of the clinical investigation plan, if required per local regulation.

# 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 eCRFs and in all other required reports. Data reported on the eCRFs 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 or co-investigator, and filed in the subject's medical file.

Only authorized persons can complete eCRFs. The investigator (physicians only) shall sign eCRFs as specified on the Delegated Tasks List/ Delegation of Authority Form included in the Investigator Site File.

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

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 or designee 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.

On-site monitoring visits will be conducted at the start and during 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.

In-person monitoring visits will be replaced by telephone and email contact to the sites by the study team. The sponsor monitoring phone calls will include an assessment of the source documents to assure completeness of image submissions and event reporting and an assessment of the essential documents. In particular, the focus of these calls will be to ensure that safety data is entered and to verify that all relevant events are reported. Site monitoring visits will be requested by the Sponsor if a concern arises with regards to compliance or data integrity.

### *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 personnel or designee(s) and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the eCRF. 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 investigational 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 investigational sites. Any regulatory authority inspection announcements shall be forwarded immediately to the Clinical Study Manager.

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

## G.3 Study Suspension or Early Termination

### *G.3.1 Early Study Suspension or Termination*

Medtronic or regulatory authority may decide to suspend or early 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 study objectives or statistical endpoints). If the clinical study is terminated early or suspended, Medtronic shall promptly inform the investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC/IRB and the study subjects.

### *G.3.2 Early Investigation Site Suspension or Termination*

Medtronic, EC/IRB, or regulatory authority may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing EC/IRB, non-compliance to the Clinical Investigation Plan or lack of enrollment).

If an investigation site is suspended or prematurely terminated:

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

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

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

### *G.3.3 Subject Follow-up in Case of Termination*

If the study is terminated early, subjects will be followed as per routine standard of care by the investigational site or a treating physician which might be in line with the guidelines described in the *Management of Abdominal Aortic Aneurysms Clinical Practice Guidelines of the European Society for Vascular Surgery*[19] or *Society for Vascular Surgery practice guidelines for the care of patients with an abdominal aortic aneurysm*[20].

## G.4 Study Close Out

Prior to completion of study close out, all data must be entered and approved in the EDC system. Medtronic and/or its designees will notify the site of the intention to close the study. Remote study close out visits may be performed. The intent of these visits will be to assuring that the investigator's regulatory files are up to date and complete and that any outstanding issues from previous visits have been resolved. Medtronic will notify and inform the site(s) that all requirements have been met with a study closure letter.
If required, EC/IRB and/or regulatory authority will be informed by Medtronic about the study close out.

# H DATA ANALYSIS AND REPORTING

Any deviations from this section will be described and justified in the final clinical study report, as appropriate.

## H.1 Analysis of Clinical Data

All observations will be analyzed descriptively. In general, qualitative parameters will be described by their distribution frequencies; quantitative parameters will be described by their mean, standard deviation, minimum, maximum, median, and number of subjects with assessable data.
The survival from all-cause mortality over one year time or longer will be described by the Kaplan-Meier survival curve and the associated Kaplan-Meier estimate will be calculated along with its standard error using the Greenwood method.

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

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

**Table H-1: Time Windows for Statistical Analyses**

| Study Visit | Target Day | Time Window |
|---|---|---|
| Implant | Day 0 | Day 0 |
| 1 Month | Day 30 | 1 – 90 days |
| 6 Months | Day 183 | 91 – 304 days |
| 12 Months | Day 365 | 305 – 548 days |
| 2 Year | Day 731 | 549 – 913 days |
| 3 Year | Day 1096 | 914 – 1278 days |
| 4 Year | Day 1461 | 1279 – 1644 days |
| 5 Year | Day 1826 | 1645 – 2009 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.

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.

*Statistical Hypothesis:*

The primary safety endpoint will be tested against a predetermined safety Performance Goal (PG) using the following statistical hypotheses:

$H_0$: $p \geq 20\%$ vs. $H_1$: $p < 20\%$

where *p* is the proportion of subjects experiencing a MAE within 30 days of the index procedure in the target population of subjects treated with the Endurant Evo AAA Stent graft system and 20% is the safety PG.

The primary effectiveness endpoint will be tested against a predetermined effectiveness PG using following statistical hypotheses:

$H_0$: $q \leq 80\%$ vs. $H_1$: $q > 80\%$

where *q* is the proportion of subjects who have a successful aneurysm treatment in the target population of subjects treated with the Endurant Evo AAA Stent graft system and 80% is the effectiveness PG.

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

Both safety and effectiveness endpoints are dichotomous study outcomes; hence, an exact method based on the binomial distribution will be used for the hypothesis testing.

Subset analyses by-sex, by-race (based on subjects enrolled in the US only, since collection of race and ethnicity data may not be allowed outside the US as per local law and regulation), and by-region/study site will be performed on the primary safety and effectiveness endpoints using descriptive statistics and reviewed for clinical significant difference. Sensitivity analysis using tipping point method may be performed, as needed, to assess the impact of missing data.

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

*Analysis Sets:*

The primary analysis set will consist of the Intent-to-Treat (ITT) population. This analysis set is defined as all subjects who were enrolled. Subjects will be considered as enrolled in the study as described in section F.1.

A secondary analysis set will be the Per-Protocol population. This analysis set is comprised of all ITT subjects who met inclusion and exclusion criteria, received the test device, and completed 12-month follow-up (including death but excluding withdrawal or lost to follow-up subjects within the 12-month follow-up period).

[redacted]

*Long Term Follow- up:*

Subjects will be followed for a total of 5 years from index procedure.

*Poolability of the Data:*

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

Physician Reviewer (IPR) and core imaging laboratory.

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

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

## H.2 Publication Policy

Publications and presentations referring to this clinical study will be coordinated by Medtronic to allow the use of all available data. The following publication policy will have to be adhered to by all participating investigational 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 investigational site may access and use the data provided by itself for scientific publications following prior approval by Medtronic.

Pooling data from several investigational 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. Participating subjects will not be identified by name in any published reports about the clinical study.

# I STUDY MANAGEMENT

## I.1 Study Contact

The study is sponsored by Medtronic Aortic,Peripheral and Venous. 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 and non-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.

The responsibility of the DMC is to evaluate safety data during the course of the study and to advise Medtronic about the continuing safety of the study, in order to ensure the well-being of the current participants and those yet to be enrolled as well as the continuing validity and scientific merit of the study. The DMC will review the study data after all subjects have reached the 1-month follow-up time point but might also be reviewed earlier. Thereafter, the study data will be reviewed on a periodic basis as defined in the DMC Charter.

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

### *I.2.3 Publication Committee*

A publication committee will not be established for the Endurant Evo 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
- 1 copy of the Instructions for Use
- Medtronic and EC/IRB approved Informed Consent Form
- Regulatory authority approval or notification
- Fully signed Clinical Trial Agreement and confidentiality agreement (if not included in the Clinical Trial Agreement)
- Financial disclosures
- Completed Delegation of Authority Form and Curriculum Vitae of all investigational site personnel
- Training documentation of all investigation site personnel

- Relevant communications
- Subject screening log and/or subject identification log
- Signed, dated, and fully executed Informed Consent Forms
- Fully executed eCRFs and corrections (in the EDC)
- Reports of Adverse Events and Device Deficiencies
- Device accountability records
- IRB/EC correspondence

### *I.3.2 Investigator Reporting Responsibilities*

**Table I-1: Investigator Reporting Responsibilities**

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

### *I.3.3 Sponsor Records*

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

- All essential study documents and correspondence that pertains to the clinical study
- CIP and, if applicable, any amendments
- 1 copy of the Instructions for Use
- Sample of labeling attached to the investigational device
- Curriculum Vitae of investigators and investigational site personnel
- Delegation of Authority Form and training records of investigators and investigational site personnel
- EC/IRB approvals/notifications/communication and regulatory approvals/notifications/ communication
- Signed Clinical Trial Agreements and signed agreements with third parties

- Shipping records for investigational devices and clinical-investigation related documents and materials
- Medtronic and EC/IRB approved Informed Consent Forms
- Site qualification reports, site initiation reports and monitoring visit reports
- Adverse event and Device Deficiency reports
- Financial disclosure information
- Fully executed eCRFs and corrections

### *I.3.4 Sponsor Reporting Responsibilities*

**Table I-2: Sponsor Reporting Responsibilities**

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

### *I.3.5 Record Retention*

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

## I.4 Miscellaneous

### *I.4.1 Insurance*

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

### *I.4.2 Subject Reimbursement and Indemnification*

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

### *I.4.3 Subject Confidentiality*

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

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

# J RISKS AND BENEFITS

## J.1 Potential Risks

Appendix L.3 shows a list of potential adverse events that may be associated with use of the Endurant Evo AAA stent graft system. The occurrence of the listed complications may lead to a repeat endovascular intervention and/or open surgical repair. Since the Endurant Evo AAA stent graft system is an investigational device, all risks may not be known. Risk mitigation activities were performed during development and design verification tests of the device. Activities intended to minimize risks during the conduct of the clinical trial include the following:

- Investigator and study personnel will be trained to the design of the Endurant Evo AAA stent graft system, its application, and preclinical results.
- Eligibility criteria and screening procedures will be followed to ensure that appropriate subjects are enrolled.
- Investigator will adhere to the Endurant Evo AAA stent graft system IFU packaged with the device.
- 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 imaging Core Lab will be established to independently evaluate subject health status, device performance, and identify any safety concerns regarding subjects' well-being.

If a woman is pregnant or becomes pregnant, implantation of the trial device may involve risks to the embryo or fetus that are unknown at this time. Therefore, pregnant women will be excluded from the study. If a female subject becomes pregnant during the conduct of this clinical research study they need to inform the investigational site immediately.

The risks will be continuously monitored, assessed and documented by the investigator. Any unanticipated or unforeseen complications will be reported by the investigator (or authorized designee) to the IRB/ EC and to Medtronic. Medtronic will in turn report any necessary findings to the appropriate regulatory agencies in each of the respective geographies.

## J.2 Potential Benefits

The potential benefits of the Endurant Evo AAA 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. Endovascular treatment of AAA has been shown to be an effective, less invasive procedure that may result in a reduced rate of early mortality and comorbidities associated with open surgical repair[12,21,22]. Stent graft repair also provides a treatment option for subjects who would not otherwise be eligible for surgical repair. Additional potential benefits include the following:

- Reduced operating room and anesthesia time
- Reduced requirement for blood transfusions
- Shorter time in intensive care

- Shorter length of hospital stay
- Shorter recovery time and return to activities of daily living
- Reduced access complications
- Ability to treat subjects with smaller iliac anatomy
- Ability to use percutaneous access for treatment

## J.3 Risk-to-Benefit Rationale

The benefits and risks associated with Medtronic's AAA stent grafts are well-characterized through robust history of testing and successful clinical results. The Endurant Evo AAA stent graft system is Medtronic's fourth generation AAA 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 AAA endovascular stent grafts can be performed safely, and that these devices provide benefits over surgical repair.

Potential risks with this study are minimized by selecting qualified investigators, careful assessment of each subject prior to, during and after implantation. Medtronic has minimized the 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. However, to date, the UADE (transition stent fractures, partial suprarenal stent detachment, suprarenal stent fracture, and suprarenal anchoring pin fracture) observations reported have indicated that the Endurant Evo AAA stent graft system has associated risks with higher rates when compared to the associated risks of other commercially available devices.

Because of these findings, there are risks associated with this trial which are worse than the risks normally associated with the use of the predicate device or other commercially available devices. Therefore, enrollment in the clinical study has been terminated and follow-up for the enrolled subjects will continue.

Risk management for the Endurant Evo AAA stent graft system is performed in accordance with EN 14971:2012.

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# L APPENDICES

## L.1 Abbreviations

| | |
|---|---|
| AAA | Abdominal aortic aneurysm |
| ADE | Adverse Device Effect |
| AE | Adverse event |
| ASA | American Society of Anesthesiologists |
| ASADE | Anticipated serious adverse device effect |
| AUI | Aorto-uni-iliac |
| CEC | Clinical Event Committee |
| CIP | Clinical Investigation Plan |
| CRF | Case Report Form |
| CT | Computed Tomography |
| CVA | Cerebral Vascular Incident |
| DD | Device Deficiency |
| DMC | Data Monitoring Committee |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Form |
| EVAR | Endovascular Aneurysm Repair |
| FDA | Food and Drug Administration |
| F/U | Follow-up |
| ICH-GCP | International Conference on Harmonization – Good Clinical Practice |
| ICU | Intensive Care Unit |
| IDE | Investigational Device Exemption |
| IFU | Instructions for Use |
| INR | International Normalized Ratio |
| IPR | Independent physician reviewer |
| IRB | Institutional Review Board |
| ISO | International Organization for Standardization |
| KUB | Kidney, Ureter, Bladder |
| MAE | Major Adverse Event |
| MI | Myocardial Infarction |
| MRA | Magnetic Resonance Angiography |
| MRI | Magnetic Resonance Imaging |
| PET | Polyethylene terephthalate |
| PMA | Premarket Approval |
| OD | Outer Diameter |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SOP | Standard operating procedure |
| UADE | Unanticipated Adverse Device Effect USADE Unanticipated Serious Adverse Device Effect |
| WBC | White Blood Cell |

## L.2 Definitions

| Major Adverse Events (MAEs) | Definition |
|---|---|
| All-Cause Mortality | Death from any cause. |
| Bowel Ischemia | Bloody diarrhea with confirmation via colonoscopy of ischemia or the operative or postmortem demonstration of ischemic changes in the large or small intestine and requires surgical intervention. |
| Myocardial Infarction | Evidenced on 2 of the 3 following conditions: new clinical symptoms suggesting MI, changes on ECG consistent with MI, and elevated CK > 2 times the upper normal limit (per the normal ranges of the institution). |
| Paraplegia | Complete loss of motor function in the lower extremities occurring intra- or postoperatively and persisting >1 month. |
| Procedural Blood Loss ≥ 1000 cc | A blood loss ≥ 1000 cc occurring before the subject leaves the operating room. |
| Renal Failure | Failure of renal function requiring dialysis. |
| Respiratory Failure | Need for mechanical ventilation for > 24 hours postoperatively, or re-intubation for any reason. |
| Stroke | Development of a new neurological deficit that persists > 24 hours, or worsening of previous neurological symptoms that persist > 24 hours and classified as stroke by a physician. |

| Secondary Endpoints: | Definition |
|---|---|
| Aneurysm-Related Mortality | Aneurysm-related mortality is defined as death from rupture of the abdominal aortic aneurysm or from any initial or secondary procedure intended to treat the AAA. If a death occurred within 30 days of any procedures intended to treat the AAA, then it is presumed to be aneurysm-related unless there is evidence to the contrary. Deaths that occurred after 30 days of any procedures intended to treat the AAA that are procedure-related should be aneurysm-related.<br><br>*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 Endurant Evo AAA stent graft system.* |
| Stent Graft Migration | Stent graft migration can be attributed to migration of the main body stent graft or migration of a stent graft limb/extension.<br>**Main body stent graft migration** is defined as evidence of movement of the main body stent graft relative to fixed anatomic landmarks, which is not due to remodeling of the subject's vasculature. Proximal migration is observed when the stent graft completely covers a renal artery or movement is > 10 mm. Distal migration is observed when the stent graft moves > 10 mm distally relative to fixed anatomic landmarks.<br>**Stent graft limb/extension migration** is defined as evidence of movement of the stent graft limbs/extensions relative to fixed anatomic landmarks, which is not due to remodeling of the subject's vasculature. Proximal migration is observed when the distal part of the stent graft limb/extension moves > 10 mm proximally. Distal migration is observed when the distal part of the stent graft limb/extension moves > 10 mm distally or completely covers the internal iliac artery. |
| Secondary Procedures | A secondary procedure is defined as any **endovascular** or **surgical** |
| | procedure performed following the completion of the operative initial |

| Secondary Endpoints: | Definition |
|---|---|
| | implantation procedure (thus on subsequent occasion after final closure of the last artery access site) which involves the targeted vascular segment treated by the Endurant Evo AAA stent graft system, including access sites and bypasses of the targeted vascular segment in which there is either manipulation of the implanted Endurant Evo stent graft or implantation of any additional devices. *(Procedures related to complications due to the use of a closure device are excluded from this definition)* |
| Aneurysm Expansion | Aneurysm maximum diameter increase >5 mm as compared to the 1- month contrast enhanced imaging measurements. |
| Aneurysm Rupture | Rupture or perforation of the targeted abdominal aneurysmal sac as detected by angiography, CT scan, and/or direct observation at surgery or autopsy.<br>Aneurysm rupture should be reported as either procedure-related aneurysm rupture, (i.e., perforation of the aneurysm during the course of the implantation procedure), or as a late aneurysm rupture that follows device deployment.<br>*Excluded are aneurysms in anatomic areas other than the targeted segment treated by the Endurant Evo AAA Stent graft system.* |
| Conversion to Open Surgery | Conversion of the endovascular procedure to an open procedure required at the time of the index procedure (primary conversion) or at a time beyond the initial endovascular procedure (secondary conversion). |
| Major Adverse Events | Major Adverse Events include the occurrence of any of the following:<br>• All-cause Mortality<br>• Bowel Ischemia<br>• Myocardial Infarction<br>• Paraplegia<br>• Procedural Blood Loss ≥1000 cc<br>• Renal Failure<br>• Respiratory Failure<br>• Stroke |
| Stent Graft Occlusion | Defined as a 100% blockage of the lumen diameter of any implanted the stent graft component(s) as evidenced by CT, angiography, ultrasound, or other appropriate imaging modality, and/or operative or pathological analysis. |
| Endoleak | Defined by the presence of contrast-enhanced blood outside the lumen of the endoluminal graft but within the aneurysm sac.<br><br>**Type I** - Endoleak resulting from an incomplete seal of the endograft proximally or distally; the endoleak is in continuity with the proximal anchoring site (proximal endoleak) or the distal anchoring site (distal endoleak) of the device reaching the aneurysm sac.<br>Type I a - Leak at the proximal graft attachment site<br>Type I b - Leak at the distal graft attachment site.<br>Type I c - Leak around an occluding plug<br><br>**Type II** - Endoleak resulting from a collateral vessel entering the aneurysmal sac resulting in retrograde filling (e.g. inferior mesenteric, middle sacral, hypogastric, accessory renal or lumbar arteries).<br><br>**Type III** - Endoleak resulting from a defect of fabric or between the segments of the modular graft (junctional endoleak).<br>Type III a – Endoleak between the segments of the modular graft (junctional endoleak).<br>Type III b – Endoleak in the mid-graft region due to the defect of fabric. |

| Secondary Endpoints: | Definition |
|---|---|
| | **Type IV** - Transgraft leak due to fabric porosity within 30 days after index procedure.<br><br>**Type V** - Aneurysm enlargement in the absence of any demonstrable perfusion of the aneurysmal sac.<br><br>**Type undetermined** - Endoleak of undefined origin. |

| Device Deficiency | Definition |
|---|---|
| Anchoring Pin Fracture | Fracture or breakage of the anchoring pin. |
| Anchoring Pin Detachment From Aorta | Detachment of the anchoring pin that secures the stent graft to the aorta. |
| Suprarenal Bare Stent Fracture | Fracture or breakage of the suprarenal bare stent. |
| Stent Graft Wireform Fracture | Fracture or breakage in stent graft wireform. |
| Stent Graft Wire Detachment From Fabric | Detachment of the Stent Graft Wire from the fabric. |
| Suprarenal Bare Stent Detachment from Fabric | Detachment of the Suprarenal Bare Stent from the fabric. |
| Stent Graft Dilatation | Graft dilatation >50% of the manufacturer's labeled diameter as determined by CT scan, angiography, and/or direct observation at surgery or autopsy. |
| Stent Graft Extrusion or Erosion | Extrusion or erosion of the metal frame through the full thickness of the vessel wall as determined by CT, angiography, and/or direct observation at surgery or autopsy. |
| Stent Graft Twisting | Stent Graft obstruction in the vertical plane as determined by CT scan or angiography resulting in an unintentional obstruction (>50%) of blood flow through the vascular lumen and not caused by anatomy of the vessel wall. |
| Stent Graft Kinking | Stent Graft obstruction in the horizontal plane as determined by CT scan or angiography resulting in an unintentional obstruction (>50%) of blood flow through the vascular lumen and not caused by anatomy of the vessel wall. |
| 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. |

| Additional Definitions | Definition |
|---|---|
| Stent Graft Stenosis | Hemodynamically significant (>50%) reduction in the diameter of the stent graft lumen as compared to the reference diameter and not caused by anatomy of the vessel wall. |
| Stent Graft Infection | The development of a perigraft infection confirmed by direct examination, CT, and/or perigraft aspiration. |
| Technical Success | Successful delivery and deployment of the stent graft (assessed intra-operatively) in the planned location and with no unintentional coverage of internal iliac arteries or any visceral aortic branches and with the removal of the delivery system. |

## L.3 Potential Adverse Events

Adverse events that may occur related to the index procedure and/ or device or that require intervention include, but are not limited to, the following:

- amputation
- anesthetic complications and subsequent attendant problems (e.g., aspiration)
- aneurysm enlargement
- aneurysm rupture and death
- aortic damage, including perforation, dissection, bleeding, rupture, and death
- arterial or venous thrombosis or pseudoaneurysm
- arteriovenous fistula
- bleeding, hematoma, or coagulopathy
- bowel complications (e.g., ileus, transient ischemia, infarction, necrosis)
- cardiac complications and subsequent attendant problems (e.g., arrhythmia, myocardial infarction, congestive heart failure, hypotension, hypertension)
- claudication (e.g., buttock, lower limb)
- death
- edema
- embolization (micro and macro) with ischemia (transient or permanent) or infarction
- endoleak
- femoral-femoral artery bypass thrombosis
- fever and localized inflammation
- genitourinary complications and related problems (e.g., ischemia, erosion, fistula, incontinence, hematuria, infection)
- hepatic failure
- impotence
- infection of the aneurysm or device access site, including abscess formation, transient fever, and pain
- lymphatic complications and related problems (e.g., lymph fistula)
- neurologic local or systemic complications and related problems (e.g., confusion, stroke, transient ischemic attack, paraplegia, paraparesis, paralysis)
- occlusion of device or native vessel
- pulmonary complications and subsequent attendant problems
- renal complications and related problems (e.g., artery occlusion, contrast toxicity, insufficiency, failure)
- stent graft: improper placement, incomplete deployment, migration, suture break, occlusion, infection, stent fracture, graft twisting or kinking, insertion and removal difficulties, graft material wear, dilatation, erosion, puncture, and perigraft flow
- surgical conversion to open repair
- vascular access site complications, including infection, pain, hematoma, pseudoaneurysm, arteriovenous fistula, dissection
- vascular spasm or vascular trauma (e.g., iliofemoral vessel dissection, bleeding, rupture, death)
- vessel damage
- wound complications and related problems (e.g., dehiscence, infection, hematoma, seroma, cellulitis)

## L.4 Device Explant and Returned Product Instructions

### EXPLANT AND AUTOPSY PROCEDURE FOR ENDOVASCULAR PATIENTS

### SURGEON AND SITE RESPONSIBILITY

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

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

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

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

- Particular care should be taken to avoid applying force, traction, or torsion to the stent graft during the explant.
- Care should be exercised to avoid excessive manipulation with metallic instruments at the proximal and distal fixation sites whenever possible.
- Stent graft or post mortem specimen should be placed in formalin as is. Do not attempt to clean or remove organic debris.

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

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

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

**EXPLANT RETURN INSTRUCTIONS**

1.0 Complete the following forms:

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

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

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

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

- Place the explanted device and any associated organic tissue into the labeled inner plastic container in a 10% neutral buffered formalin (3.7-4% Formaldehyde) solution to maintain tissue integrity. **(To be completed by hospital staff only)**

  Note: Any specimen too large for the provided inner container may be sent in any securely closed container and placed with provided packing in the metal container and box.
- Seal the plastic container with red tape (provided in kit). The tape should be stretched clockwise around the cap and the container. Place plastic container into the absorbent bag.
- Place the absorbent bag (with plastic container) inside the labeled metal container. Fold the top flaps of the absorbent lining over the top of the plastic container and secure the bag with a twist tie or cable tie (provided in kit). Place lid on metal can and seal with the locking ring provided. Place the can into the inner partition of the cardboard box, and push in the corner tabs on the top of the partition to retain the can.
- Place the completed **Explant Procedure Observation Form**, implant and explant operative reports, and any radiology follow-up reports (if available), inside the moisture-resistant plastic bag provided, and place into the box.

  Note: A Record of Disclosure of Health Information for Public Purposes is included for your convenience and can be placed in the patients file.

  Securely seal the box with clear tape (provided in kit). Affix the shipping airbill to the outside of the box.
- Arrange for pickup from Shipping Company.

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

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

# EXPLANT PROCEDURE OBSERVATION FORM

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

**IMPLANT INFORMATION**
Date of Implant: /_ /_____
Implanting Physician: _____
Implanting Hospital Name: _____
City and State:_____
Country: _____

**EXPLANT INFORMATION**
Date of Explant/Autopsy: / /_____
Explanting Physician: _____
Name of Hospital: _____
Address: _____
City and State: _____
Country: _____
Telephone: (___)_____

**REASON FOR EXPLANT**

_____

_____

_____

⌋ Planned Surgical Conversion
⌋ Emergent Conversion
⌋ Autopsy Date of Death:____/___/____

Remarks about procedure: _____

_____

_____

_____

_____

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

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

Comments _____

_____

Successful Surgical Conversion: Δ Yes Δ No

Patient Outcome: Δ Alive Δ Expired

## EXPLANTED DEVICE INFORMATION

| DEVICE | CATALOG NUMBER | LOT NUMBER |
|---|---|---|
| Bifurcated Body<br>⌋ Distal Left<br>⌋ Distal Right | | |
| Contralateral Limb | | |
| Iliac Extension<br>⌋ Left<br>⌋ Right | | |
| Iliac Extension<br>⌋ Left<br>⌋ Right | | |
| Iliac Extension<br>⌋ Left<br>⌋ Right | | |
| Aortic Cuff | | |
| AUI<br>⌋ Distal Left<br>⌋ Distal Right | | |
| Thoracic, Proximal Main | | |
| Thoracic, Distal Main | | |
| Thoracic, Distal Main | | |
| Thoracic, Proximal Extension | | |
| Thoracic, Distal Extension | | |
| Other (Specify) | | |

Additional Comments

Form completed by: _____

Title: _____

Date: _____

## RECORD OF DISCLOSURE OF HEALTH INFORMATION FOR PUBLIC HEALTH PURPOSES

**To Custodian of Patient Information:** Federal privacy standards issued by the Department of Health and Human Services pursuant to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) require providers to record and, upon patient request, account for disclosures of patient information for public health purposes (except where disclosed pursuant to patient authorization or as part of a limited data set) (45 C.F.R. § 164.528(a)). This Record of Disclosure may be appended to the medical record to facilitate an accounting of disclosures.

The information you are providing to Medtronic Vascular as described below, is necessary for Medtronic Vascular to meet our government obligations regarding safety, effectiveness and quality, and is a public health disclosure under Section 164.512(b)(1)(iii) of the HIPAA Privacy Rule.

**Date of Disclosure:**

**Recipient and Contact Information:**

Medtronic Vascular
Quality Assurance
Department 3576 Unocal
Place
Santa Rosa, California

95403 707-591-7672

**Description of Patient Information Disclosed:**

*Examples of descriptions to be written here include:*

- *Information regarding the functioning of the patient's AneuRx or Talent Stent Graft*
- Implant Operative Report, the Explant Operative Report, and surveillance radiology reports

**Purpose of Disclosure:**

*The following language can be used on all Records of Disclosures:*

*"For public health activities and purposes under Section 164.512(b)(1)(iii) of the HIPAA Privacy Rule, i.e. activities related to the quality, safety or effectiveness of FDA-regulated products or activities for which [Medtronic/Medtronic business unit] is responsible."*

## L.5 Informed Consent Template

**THE INFORMED CONSENT TEMPLATE HAS BEEN REMOVED AS AN ATTACHMENT TO THE PROTOCOL AND WILL BE VERSION CONTROLLED AS AN INDEPENDENT DOCUMENT.**

## L.6 Imaging Technique and Sensitivity

| Anatomy/ Stent Graft Issue Detected | CT with contrast | CT without contrast | MRA | MRI | Abdominal X- ray | Duplex CDUS (Ultrasound) | Angiogram/ Aortagram, and Arteriogram |
|---|---|---|---|---|---|---|---|
| AAA Diameter and Length | 1 | 2 | 1 | 2 | 4 | 3 | 3 |
| Stent graft migration | 1 | 2 | 1 | 2 | 3 | 4 | 2-3 |
| Stent graft fracture | 2 | 3 | 2 | 3 | 1 | 4 | 2-3 |
| Stent graft kinking | 2 | 3 | 2 | 3 | 1 | 4 | 2-3 |
| Stent graft twisting | 2 | 3 | 2 | 3 | 1 | 4 | 2-3 |
| Stent graft patency | 1 | 4 | 1 | 4 | 4 | 2 | 2-3 |
| Endoleaks | 1 | 4 | 1 | 4 | 4 | 2 | 2-3 |
| Occlusion | 1 | 4 | 1 | 4 | 4 | 2 | 2-3 |
| Stenosis | 1 | 4 | 1 | 4 | 4 | 2-3 | 2-3 |
| Stent Graft Fabric Defect | 1 | 4 | 1 | 4 | 4 | 4 | 2-3 |
| 1= Highly visible | 2 = visible | 3 = Not very visible (potential artifacts) | | | | 4 = Invisible | |

## L.7 Center for Medicare and Medicaid Services (CMS) IDE Study Criteria

*Beneficiaries*

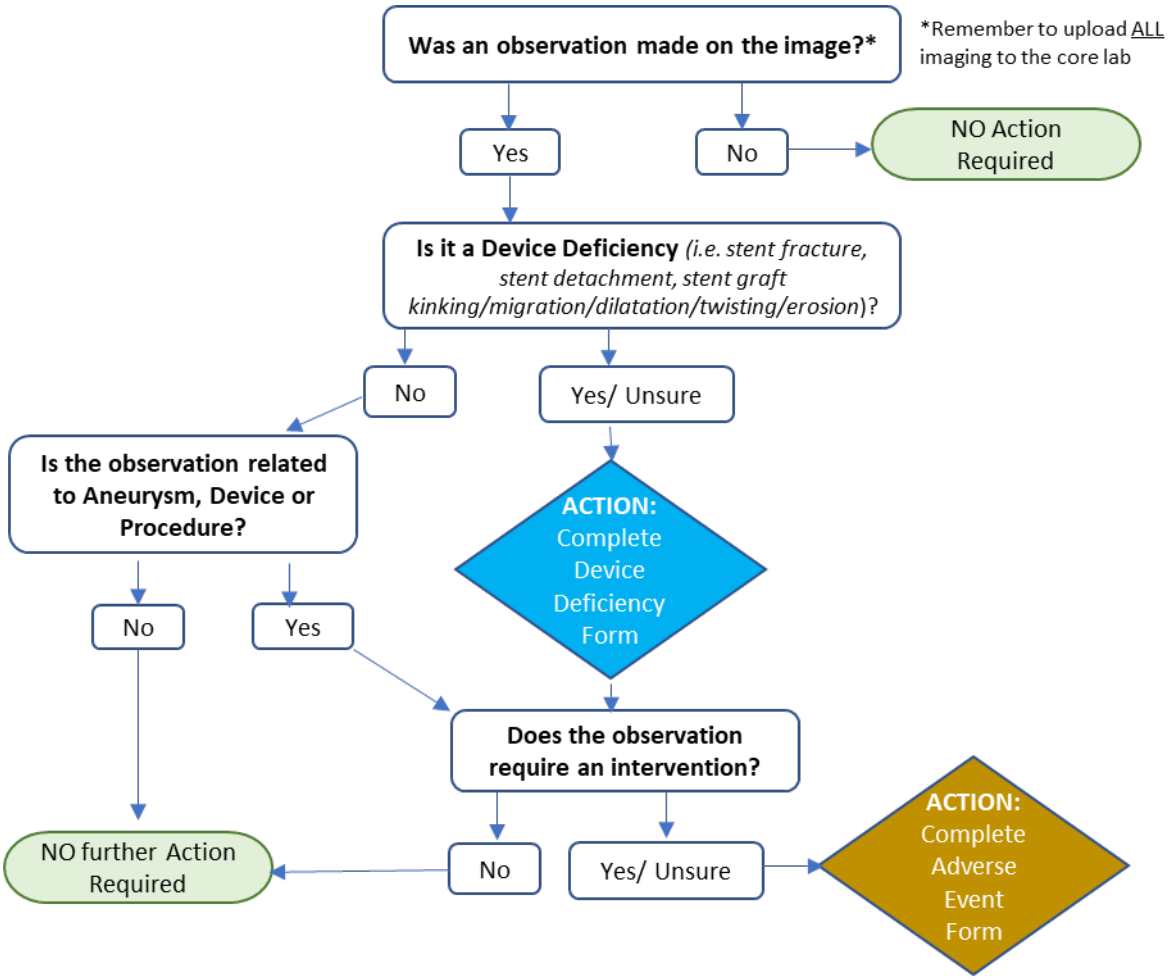
Medicare beneficiaries may be affected by the device because in 2012 more than 78% of EVAR cases were performed in Medicare beneficiaries, and 84.5% of claims with principal AAA diagnoses are age 65 or older. Study results are expected to be generalizable within the Medicare beneficiary population based on the prevalence of AAA in patients age 65 and older.

Reference: Truven Health Analytics, MarketScan Inpatient View; 2012.

*Health and Human Services (HHS) Human Subjects Protection Regulations*

All IRBs should comply with 45 CFR part 46.

## L.8 Imaging Device Assessment Reporting Decision Tree



## L.9 Overview of description of changes from CIP Version 1D to 1E with rationale

| Section | CIP Version 1D | CIP Version 1E | Rationale for change |
|---|---|---|---|
| **Throughout Document** | NA | Administrative changes | Correction of previous administrative errors and minor updates |
| **Synopsis – Coordinating Principal Investigators** | [redacted] | [redacted] | The PI address changed |
| **E.3 Regulatory Compliance** | The Endurant Evo US Clinical Trial will be conducted under an FDA Investigational Device Exemption (IDE) in compliance with ICH-GCP, ISO 14155:2011 3.1, 3.15, 3.2, 3.36, 3.37, 3.42 and 21 CFR Parts 11, 50, 54, 56, and 812. | The Endurant Evo US Clinical Trial will be conducted under an FDA Investigational Device Exemption (IDE) in compliance with the Declaration of Helsinki (October 2013) ISO 14155:2011 3.1, 3.15, 3.2, 3.36, 3.37, 3.42 and 21 CFR Parts 11, 50, 54, 56, and 812. | Updated to appropriate compliance document |
| **E.4 Training Requirements** | Also after initial training, Medtronic will provide training to other clinical site study team members. All study specific training must be documented on a formal training record that will be provided by Medtronic. | 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 site personnel 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. | As the study is in its follow up phase of the study it was deemed appropriate to allow sites to be more flexible with regards to training of new site study team members. In addition, Medtronic will remain available for site training. |
| **F.2.3 Follow-Up Visits and Procedures** | At all required follow-up visits subjects will undergo the following assessments:<br>•Physical Exam<br>•CT/MR with contrast and non-contrast (2 cm above the origin of the celiac artery through the bifurcation of the femoral arteries)<br>•Abdominal X-ray (4-view, KUB)<br>•EQ5D questionnaire (until 12 months F/U only)<br>•Adverse event assessment | At all required follow-up visits subjects will undergo the following assessments:<br>•Physical Exam (to be reported in FUP eCRF until 24 months only)<br>•CT/MR with contrast and non-contrast (2 cm above the origin of the celiac artery through the bifurcation of the femoral arteries)<br>•Abdominal X-ray (4-view, KUB)<br>•EQ5D questionnaire (until 12 months F/U only)<br>•Adverse event assessment<br>•Concomitant Medication (to be reported in FUP eCRF until 24 months only) | Clinical assessments remain to be done as per site standard of care but it is no longer required to report data from the physical exam and data from concomitant medications from 2 year follow up till the end of the study.<br>In case of medications administrated for reportable adverse events the medications should be added in the description of the event if relevant |

| | | | |
|---|---|---|---|
| | •Concomitant Medication | | |
| **F.3 Data Collection Requirements** | Imaging source data will be sent to a Core Lab for analysis up to the 60-month follow-up visit. Any interim imaging of the stent graft region but not linked to a study visit should be recorded on the Interim Image e-CRF (e.g. imaging performed as standard of care beyond the protocol required time points and/or when performed further to any issue observed at previous imaging Follow-up). Interim imaging performed, as recommended per the most recent DMC Surveillance and Management letter should also be reported on the interim imaging eCRF. | Imaging source data will be sent to ~~a~~ the Core Lab for analysis up to the 60-month follow-up visit. Any interim imaging of the stent graft region but not linked to a study visit should also be ~~recorded on the Interim Image e-CRF~~ sent to the Core Lab (e.g. imaging performed as standard of care beyond the protocol required time points and/or when performed further to any issue observed at previous imaging Follow-up). This also includes interim imaging performed as recommended per the most recent DMC Surveillance and Management letter. ~~should also be reported on the interim imaging eCRF.~~ All images taken from the stent graft region must be assessed by the site. Any findings that meet the requirements in the flowchart (Appendix L.8) must be reported on the applicable eCRF. | In protocol version D, images were analyzed by both Core Lab and sites. Moving forward, protocol version E will continue to require that the sites submit all images to the Core Lab for analysis, but the sites will not be required to report all data from imaging analysis. This is because the Core Lab will assure consistency between measurements of different sites. In addition, there is a discrepancy between the number of Device Deficiencies identified by the Core Lab and Sites. The Core Lab has proven more reliable at identifying Device Deficiencies as compared to the sites. For this reason, the Core Lab has demonstrated to be the most accurate and reliable data source for the image analysis. If in an incidental case, the site identifies a device deficiency that is not confirmed by the Core Lab, this finding will still be captured as the site continues to report such findings in the device deficiency or event eCRFs. For this reason, the decision to relieve sites from also entering this data into eCRF is not expected to affect overall data integrity. |
| **F.3 Data Collection Requirements**<br><br>Table F2 Data Collection Schedule | **Last column**<br>**2-5 Yr. F/U[e] (±56 days)**<br>• Physical examination<br>• Medications<br>• Adverse Event Assessment<br>• CT/MR (2 cm above origin of celiac artery through bifurcation of | **Last column**<br>**2~~-5~~ Yr. F/U[e] (±56 days)**<br>• Physical examination<br>• Medications<br>• Adverse Event Assessment<br>• CT/MR (2 cm above origin of celiac artery through bifurcation of femoral arteries) [c]<br>• Abdominal X-Ray (4-view, KUB)<br><br>**Column added** | Changes detailed in sections F.2.3 and F.3 are implemented in table F-2: schedule of assessments |

| | | | |
|---|---|---|---|
| | femoral arteries) [c]<br>• Abdominal X-Ray (4-view, KUB) | **3-5 Yr. F/U[e] (±56 days)**<br>• Adverse Event Assessment<br>• CT/MR (2 cm above origin of celiac artery through bifurcation of femoral arteries) [c, f]<br>• Abdominal X-Ray (4-view, KUB)[f]<br><br>**Footnote added**<br>[f] All Images (routine & interim) performed 3-5 years will be required to be submitted to the Core Lab for evaluation. Sites will continue to review images for clinical evaluation and detection of device deficiencies in accordance with Appendix L.8, but will not be required to complete imaging eCRF. | |
| **F.6. Adverse Events** Recording and Reporting of Adverse Events | For the purpose of this clinical investigation Medtronic will define and classify the following events per ISO14155:2011 and Title 21 CFR part 812.3. | For the purpose of this clinical investigation Medtronic will define and classify the following events per ISO14155:2011 (followed for definitions of Adverse Events only) and Title 21 CFR part 812.3.<br>Adverse event reporting for the remaining follow up (3-5 years) will focus on the reporting of the below listed events:<br>• Adverse events with a possible relationship to the aneurysm (Excluding aneurysms in anatomic areas other than the Endurant grafted segment)<br>• Adverse events with a possible relationship to the device<br>• Adverse events with a possible relationship to the procedure<br>• Adverse events leading to subject's death<br><br>Secondary procedures performed as a result of any of the above adverse events must be reported on the respective Adverse Event form. Please see guidance for reporting of adverse events following image review in Appendix L.8. | Because the Modular PMA was withdrawn, it was decided to focus on the collection and review of safety follow-up data for which the relationship to the aneurysm, device or procedure cannot be ruled out, for the remainder of the follow up period.<br>This means that Medtronic will no longer require the reporting of events unrelated to the aneurysm, device, or procedure. This decision was deemed appropriate as the DMC has not reported any concerns with regards to events with no relationship to aneurysm, device or procedure. If a relationship cannot be ruled out, sites are requested to report the event. To aid the sites in making a decision on reporting, an additional guidance flowchart was added in the protocol. |
| **F.6.2 Adverse Events** Recording and Reporting of Adverse Events | Adverse Event (AE) information will be collected throughout the study and reported to | Adverse Event (AE) information will be collected throughout the study and reported to Medtronic on the Adverse Event eCRF. ~~All Adverse~~ | |

| | | | |
|---|---|---|---|
| | 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. | ~~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.<br>Please see guidance for reporting of Adverse Events following image review in Appendix L.8. | |
| **F.6.3 Adverse Events** Recording and Reporting of Device Deficiencies | | **added at the end of the section:**<br>Please see guidance for reporting of Device Deficiency following image review in Appendix L.8. | |
| **L.8 Imaging Device Assessment Reporting Decision Tree** | NA | **Added:**<br>Imaging Device Assessment Reporting Decision Tree. | |
| **G.2. Monitoring Procedures** | 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. | On-site monitoring visits will be conducted at the start and 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.<br>(…)<br>In-person monitoring visits will be replaced by telephone and email contact to the sites by the study team. The sponsor monitoring phone calls will include an assessment of the source documents to assure completeness of image submissions and event reporting and an assessment of the essential documents. In particular, the focus of these calls will be to ensure that safety data is entered and to verify that all relevant events are reported. Site monitoring visits will be requested by the Sponsor if a concern arises with regards to compliance or data integrity. | To further mitigate the concern that sites could underreport safety events, it is noted that the following two procedures will remain to be in place: First, all sites will still be required to submit all images to Core Lab for analysis. The Core Lab will continue to analyze all site images for potential device deficiencies or other notable findings. Second, Medtronic will continue to monitor all source data received from the sites for any potential unreported adverse events (i.e. source data from adjudicable adverse events or source data requested by the DMC). Any findings from these additional verification procedures will be addressed with the site. |

| | | | |
|---|---|---|---|
| **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. | Prior to completion of study close out, all data must be entered and ~~monitored~~ approved in the EDC system. Medtronic and/or its designees will notify the site of the intention to close the study. Remote s~~S~~tudy close out visits may be performed. ~~During these visits, the monitors will ensure that~~ The intent of these visits will be to assure that the investigator's regulatory files are up to date and complete and that any outstanding issues from previous visits have been resolved. | |
| **H.1. Analysis of Clinical Data** | PMA Submission<br>Based on the design similarities …//.... may be revisited with FDA at that time | PMA Submission<br>No analysis is scheduled related to PMA submission. Due to the UADEs, Medtronic has requested withdrawal of PMA submission, which was granted by the FDA in November 2016. | Since PMA submission was withdrawn PMA submission related analyses is no longer applicable. The text in this section was replaced to clarify why it was removed from this protocol amendment |
| **J. 3 Risk-to-benefit Rationale** | However, to date, the UADE (transition stent fractures, partial suprarenal stent detachment, and suprarenal stent fracture) observations reported have indicated that the Endurant Evo AAA stent graft system has associated risks with higher rates when compared to the associated risks of other commercially available devices. | However, to date, the UADE (transition stent fractures, partial suprarenal stent detachment, ~~and~~ suprarenal stent fracture, and suprarenal anchoring pin fracture) observations reported have indicated that the Endurant Evo AAA stent graft system has associated risks with higher rates when compared to the associated risks of other commercially available devices. | Text updated to include the new UADE, suprarenal anchoring pin fracture, to already listed UADEs in the previous version of the protocol. |
| **L.9. Overview of description of changes to for CIP Version 1D to 1E with rationale** | NA | **Added:**<br>Overview of description of changes from CIP Version 1D to 1E with rationale. | |