Original Investigational Device Exemption Application

July 28, 2017

IDE Application Title:	Proposed Single Center Investigational Device Exemption Feasibility of Endovascular Repair of Ascending Aortic Dissections
Device Names:	Medtronic Thoracic Stent Graft System
IDE Number:	G170196
Sponsor-Investigator:	William T. Brinkman, MD

Name, Address and Signature of Sponsor Investigator

William T Brinkman, MD

1100 Allied Dr. Suite 5004708 Alliance Blvd
Pavilion 1, suite 500
Plano, TX 75093
469-800-6200
469-814-4854
William.Brinkman@BSWHealth.org

Signature of Sponsor-Investigator:

_____ Date _____

Application for an Early Feasibility Physician-Sponsored Investigational Device Exemption

Study Title: Proposed Single Center Investigational Device Exemption: Feasibility of Endovascular Repair Of Ascending Aortic Dissections

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1. Cover Sheet

A. Study Title

Proposed Single Center Investigational Device Exemption: Feasibility of Endovascular Repair of Ascending Aortic Dissections.

B. Name and Address of Sponsor

The Heart Hospital Baylor Plano
Baylor Scott and White Research Institute
1100 Allied Drive
Plano, Texas 75093

C. Contact Information

i. Name: Dr. William Brinkman

ii. Telephone: (469)-800-6200

iii. Fax: (469) 814 4854

iv. Email: William. Brinkman@BSWHealth.org

v. Additional Contacts:

Name: Dr. J. Michael DiMaio
Telephone: (469)-800-6200
Fax: (469)-814-4854
Email: Michael.DiMaio@bswhealth.org

Name: Megan White
Telephone: (469)-814-4181
Fax: (469)-814-4854
Email: Megan.White1@bswhealth.org

D. Investigational Device

i. Medtronic Thoracic Stent Graft System

ii. Device Manufacturer Contact:

Simona Zannetti, MD
Vice President, Clinical and Medical Affairs
Medtronic Cardiovascular
Address: 3576 Unocal Place
Santa Rosa, CA 95403
Telephone: (707) 591-2622
Email: simona.zannetti@medtronic.com

E. Intended Use

i. The Medtronic Thoracic Stent Graft System is intended for endovascular repair of the Type A Thoracic Aortic Dissection, Retrograde Type A Thoracic Aortic Dissection (without involvement of the Aortic Valve).

ii. Location of treatment will be the area between the Sinus of Valsalva and the innominate artery orifice.

iii. High risk subjects having appropriate anatomy will be enrolled in the study.

iv. Anatomical Limitations:

- The proximal landing zone will allow placement of the statement of the stent graft as to not inhibit valvular function, occlude a coronary ostium or proximal bypass graft;
- Distal landing zone must allow for continued perfusion of critical cerebral vessels;
- Ascending aorta between 28-44 mm in diameter

F. Study Monitor

Kristen Lyons
Baylor Scott & White Research Institute
2001 Bryan Street Suite 2200
Dallas, Texas 75201

2.1 Report of Prior Investigations (21 CFR 812.27)

2.1.1 Background

Cardiovascular disease management continues to develop gradually as its occurrence is a leading cause of death in many Western societies. There has been enhanced awareness of the spectrum of acute and chronic aortic syndromes due to improved diagnostic imaging modalities combined with longer life expectancy and exposure to high blood pressure. Vascular diseases of the aorta have been associated with very high mortality and morbidity. In the ascending aorta, the disease entails a variety of pathologies such as fusiform and saccular aneurysms, pseudoaneurysms, aortic transection, penetrating aortic ulcers, intramural hematoma, and acute and chronic aortic dissection. However, in the current iteration of this protocol we will only address dissections.

Aortic dissection involves a progressive tear in the aortic wall. The intima or inner lining of the aorta tears resulting in propagation of blood within the media or middle layer with multiple reentry sites, usually distally, but sometimes retrograde. Aortic dissections are classified as Stanford Type A or B depending on the location of the entry tear. Type A dissection starts in the ascending part of the aorta and usually expands to more distal portions of thoracic aorta. Type B dissection begins in the descending thoracic aorta and usually moves towards the abdominal aorta. In certain circumstances, Type B dissections can also propagate toward the heart.(ref #3) The standard treatment of thoracic aortic dissection has either been medical management or an open surgical procedure, depending upon the patient's clinical presentation. For patients with type A aortic dissection (involving the ascending aorta), surgical repair remains the gold standard as it offers significant survival advantage and improved quality of life. This entails heart-lung machine-assisted replacement of the ascending aorta (with or without aortic valve replacement). All of these operations require cardiac arrest and aortic cross-clamping with extracorporeal circulation. When the distal ascending aorta is involved, frequently the patients will require hypothermic circulatory arrest in order to replace the aortic arch. Due to the invasive nature of these operations and associated morbidity and mortality, they are offered only to about 50% of patients who are deemed reasonable operative risk, and average early (30-day) survival with surgical repair is 85%. (ref #4,5,6,7)

Many patients however, are extreme high-risk or non-surgical candidates due to comorbid conditions. Some of the elderly patients may have concomitant valvular heart disease — mostly calcific aortic valve stenosis. Treatment options for the non-surgical patient population are very limited. Anti-impulsive/antihypertensive therapy and other adjunct pharmacotherapy are the only available options with limited results. There are currently no transcatheter treatment options for this patient cohort. The natural history of these patients with type A aortic dissection is very poor. Historically, it is 1% mortality per hour for the first 48 hours with overall 10% survival at one month. Recent studies

reveal a better outcome. Currently, the patients with type A aortic dissection have 50% survival in the first month if no surgery is offered. (ref #11,12)

The success of endovascular stent graft repair of abdominal aortic aneurysms (AAA) has led to the application of these devices for the management of thoracic aortic diseases, including thoracic aortic aneurysms (TAA), acute and chronic Type B dissection, intramural hematoma, penetrating ulcer, traumatic injury, mycotic aneurysms and anastomotic aneurysms. (ref #13-28) This type of procedure offers an alternative method of treatment that is less invasive, less expensive, and less risky than standard operative repair. (ref #29) For these reasons, they are beneficial for the high risk or nonsurgical patients. Endovascular repair of thoracic aortic pathology involves a transfemoral or iliac introduction of a metallic stent coupled with a vascular graft. When the stent graft device is deployed and expanded within the diseased blood vessel, it creates a new aortic lumen for blood flow thereby excluding the lesion from blood flow while maintaining perfusion to the lower limbs.

The concept of endovascular stent grafting in thoracic dissections was described in research articles published in 1999 by Nienaber and coworkers and Dake and co-authors. (ref #26,27) They and others have reported preliminary results of both elective and emergency endoluminal treatment of acute, complicated Type B dissection with a satisfactory outcome. There have also been a number of case reports and retrospective studies that have demonstrated the feasibility of endovascular stem graft to repair descending thoracic aortic pathologies. In 2005, a retrospective study was conducted in France for all patients treated with a stent graft for thoracic aortic disease from 1999 to 2001. The results showed an acceptable post-op morbidity with 10% mortality during the first 3 months. Another study was conducted on the final and midterm results of the European experience in the endovascular treatment of thoracic disease between 2005 and 2009. The results of this RESTORE study support the safety of thoracic aortic endovascular repair in a variety of thoracic pathologies and lesions in different aortic and anatomic locations. Of the 304 patients treated, all-cause mortality at 1 month was 7.2% and perioperative stroke and paraplegia were 1.6% and 2%.32 In the United States, the records of 58 patients who underwent endovascular repair of their arch lesions between March 2006 and January 2010 were reviewed. The authors concluded that endografting could effectively treat aortic arch pathologies in high-risk patients with low morbidity and mortality. Thirty day mortality, stroke and spinal cord ischemia were 3.4%, 10.3%, and 3.4%.

Conventional repair of arch pathologies have a 6-20% mortality and 12% stroke rate. (ref #33) Metcalfe and coworkers also reported in 2012 a successful repair of an acute ascending aortic dissection using an endovascular stent graft that was manufactured specifically for the ascending aorta in a 68 year old female patient in Eondon. (ref #34) The patient, who was a smoker and had a history of hypertension, presented to the hospital with chest pain and was diagnosed with a type A dissection 4 days after initial presentation. She was not a candidate for open repair due to multiple comorbidities.

She was treated with a Zenith stent graft and made a successful recovery. This patient is reportedly the first patient to receive a designated stent graft for type A aortic dissection.

Off-label use of descending thoracic stent graft in the ascending aorta has been described since 2003 from outside of the United States (ref #35), while Ihnken and colleagues from Stanford reported the first off-label use in the United States in 2004. (ref #36) There are a series of case reports mostly involving high-risk patients with high-risk features or pseudoaneurysms of the ascending aorta undergoing endovascular repair. (ref #37,45)

Stenting of the ascending aorta is, as reported in the literature, technically feasible but it also presents unique challenges. These include negotiating the curvature of the aortic arch, proximal fixation close to the aortic valve and coronary ostia, distal fixation that may impinge on the innominate artery, hemodynamic forces and retrograde dissection. The major complications for this procedure include perforation of the left ventricle or massive stroke. Furthermore, the ascending aorta is on the average a centimeter larger that the descending thoracic aorta, and about one fourth in length. These anatomic characteristics of the ascending aorta have ramifications in stent graft design that should entail shorter devices with large diameter for proximal and distal landing zone fixation. In addition there is a difference in variation in the maximum and minimum size of the aorta during diastole and systole. Based on 4-dimensional evaluation of our patients, we found that the variation in size is about 10% in descending thoracic aorta while it is 15% in ascending aorta. This may have ramifications in stent graft fixation for devices with poor radial force. Both the FreeFlow and the Closed Web design of the Valiant stent graft have a strong radial force to reduce endoleak rate and potential migration in the descending aorta.

In 2015, Roselli and coworkers (ref. #46) reported clinical outcomes of a 22 patient cohort with ascending pathologies treated by an endovascular approach. Clinical events reported include: 2 early conversion to open repair; 3 strokes; 2 myocardial infarctions; 2 respiratory failure, and 3 in-hospital deaths. Median follow up in this patient cohort was 12 months and actual survival at 30 days, 1 year, and 5 years was 86%, 80%, and 75% respectively.

In 2016, Zhenjiang et al (ref. #47) reported clinical outcomes of a 15 patient cohort that underwent endovascular repair for ascending aortic dissections. Technical success was achieved in all patients with no major morbidity or deaths perioperatively. Clinical events reported include: 1 retrograde aortic dissection, 1 cardiovascular ischemia, and 1 supraventricular tachycardia. Other morbidities included perigraft endoleak, a bird-beak sign, a temporary pericardial effusion, and a left kidney atrophy. Significant enlargements of true lumens and shrinkage of false lumens and overall thoracic aorta were observed at 12 months.

In 2018, Muetterties and coworkers (ref. #48) conducted a systematic review of 46 publications regarding primary endovascular repair of the ascending aorta with 118 total patients. The most commonly treated aortic disease was type A aortic dissection (50%). Clinical events reported included: type I endoleak (18.6%), all-cause mortality (15.2%), aorta-related mortality (5%), conversion to open surgery (3.4%), and cerebrovascular complications (3.4%) with an average follow-up of 17.2 months.

In 2016, Tsilimparis and coworkers (ref. #49) retrospectively reviewed 10 patients who received the Zenith Ascend TAA Endovascular Graft for treatment of disease pathologies of the ascending aorta. All endografts were successfully deployed without intraoperative adverse events at the targeted landing zone. Clinical success in coverage of the lesions was achieved in all cases with the exception of an attempted treatment of an intraprocedural aortic valve implantation dissection that resulted in early mortality. Clinical events reported include: 1 stroke with paraplegia, 1 transient ischemic attack, 1 early evacuation of a hemopericardium, and 2 late interventions for persisting endoleaks. 30-day survival was 90%. At a mean follow-up of 10 months, three late deaths occurred, with one treatment related, as a result of graft infection.

In addition, an article was published in 2016 (ref. #50) evaluating the Valiant PS-IDE stent graft under investigation in the IDE protocol. Khonyezhad et al prospectively enrolled 6 patients at their single site and reported no early mortality and 1 late death. Other clinical events include: 1 type 1a endoleak, 1 post-operative stroke, and regression of the aortic lesions in the excluded aortic segment. There is positive remodeling of the aorta and uniform accuracy of deployment with secure fixation up to 17.5 months of follow-up.

Collectively, these studies report early outcomes following ascending endovascular treatment in patients deemed high surgical risk comparable to open repair in lower risk patients. Open surgical repair of acute Type A dissections, current gold standard treatment, is an invasive procedure with average 85% early (30-day) survival (ref 4-7). Due to invasiveness and influence of patient risk factors on outcomes, open repair is offered only to select patients. Patients deemed extreme high-risk or non-surgical candidates due to co-morbidities are routinely medically managed and the natural history of Type A dissection is poor with 50% survival in the first month if no surgery is offered (ref #11,12).

These findings lend support to the feasibility and potential life-saving benefit of endovascular intervention of ascending pathologies in patients deemed high open surgical risk with appropriate anatomy (the target population of the IDE). These articles also highlight the challenges of endovascular treatment in the ascending aorta, including the lack of devices designed for ascending use, anatomical complexity and patient selection. The intent of this IDE is to further evaluate the Medtronic Thoracic Stent Graft System as an endovascular treatment option in patients deemed high open surgical risk with appropriate anatomy.

2.1.2 Bibliography of Publications Relevant to Evaluation of Safety and Effectiveness of the Device

References Cited

1. Nienaber CA, Eagle KA. Aortic dissection: new frontiers in diagnosis and management: Part I: from etiology to diagnostic strategies. Circulation 2003 Aug 5;108(5):628-35.

2. Acierno L. The History of Cardiology. New York, NY, Parthenon Publishing Group, 1994.

3. Daily PO, Trueblood 11W, et al. Management of acute aortic dissections. Ann Thorac Surg 1970;10:237-47.

4. Lansman SL, McCullough JN, Nguyen KH, et al. Subtypes of acute aortic dissection Ann Thorac Surg 1999;67:1975-8; discussion 1979-80.

5. Fain J1, Smith JA, Miller DC, et al. Surgical management of aortic dissection during a 30-year period. Circulation 1995;92:11113-21,

6. Sinatra R, Melina G, Pulitani I, et al. Emergency operation for acute type A aortic dissection: neurologic complications and early mortality. Ann Thorac Surg 2001;71:33-8.

7. Bavaria JE, Woo YS, Hall RA, et al. Circulatory management with retrograde cerebral perfusion for acute type A aortic dissection. Circulation
1996;94:11173-6.

8. Tittle S, Lynch, Cole P, Singh H, Rizzo J, et al. Midterm follow-up of penetrating ulcer and intramural hematoma of the aorta. J Thorac Cardiovasc Surg 2002; 123:1051-105.

9. Nienaber CA, von Kodolitsch Y, Petersen B, et al. Intramural Hemorrhage of the Thoracic Aorta Diagnostic and Therapeutic Implications. Circulation 1995;92(6):1465-72.

10. Coady MA, Rizzo JA, Hammond GL, et al. Penetrating ulcer of the thoracic aorta: what is it? How do we recognize it? How do we manage its J Vasc Surg. 1998 Jun;27(6):1006-15; discussion 1015-6.

11. Hirst A, Johns V, Krime S. Dissecting aneurysm of the aorta: a review of 505 cases. Medicine 1958;37:217-79.

12. Hagan PG, Nienaber CA, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. JAMA 2000;283:897-903.

13. Doroghazi RM, Slater EE, DeSanctis RW, et al. Long-teen survival of patients with treated aortic dissection. J Am Coll Cardiol. 1984;3:1026-34.

14. Appelbaum A, Karp RB, Kirklin SW. Ascending vs descending aortic dissections. Ann Surg 1976;183:296-300.

15. Jex RK, Schaff HV, Piehler SM, et al, Early and late results following repair of dissections of the descending thoracic aorta. J Vasc Surg 1986;3:226-37.

16. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. Ann Vasc Surg 1991;5:491-9.

17. Kato N, Hirano T, Shimono T, et al. Treatment of chronic type B aortic dissection with endovascular stent-graft placement. Cardio-Vasc Intery Radiol 2000;23:60-2.

18. Yusuf SW, Baker DM, Chuter TA, et al. Transfemoral endoluminal repair of abdominal aortic aneurysm with bifurcated graft, Lancet 1994;344:650-1.

19. Moore WS, Vescera CL. Repair of abdominal aortic aneurysm by transfemoral endovascular graft placement. Ann Surg 1994;220:331-41.

20. Blum U, Langer M, Spillner G, et al. Abdominal aortic aneurysms: preliminary technical and clinical results with transfemoral placement of endovascular self-expanding stent-grafts, Radiology 1996;198:25-31.

21. Mitchell RS, Dake MD, Semba CP, et al. Endovascular stent-graft repair of thoracic aortic aneurysms. J Thorac Cardiovasc Surg 1996;111:1054-62.

22. Dake MD, Miller DC, Mitchell RS, et al. The "first generation" of endovascular stent-grafts for patients with aneurysms of the descending thoracic aorta. J Thorac Cardiovasc Surg 1998;116:689-703.

23. Kato N, Dake MD, Miller DC, et al. Traumatic thoracic aortic aneurysm: treatment with endovascular stent-grafts. Radiology 1997;205:657-62.

24. Semba CP, Sakai T, Slonim SM, et al. Mycotic aneurysms of the thoracic aorta: repair with use of endovascular stent-grafts. J Vase Intery Radiol 1998;9:33-40.

25. Sakai T, Dake MD, Semba CP, et al. Descending thoracic aortic aneurysm: thoracic CT findings after endovascular stent-graft placement. Radiology 1999;212:169-74.

26. Nienaber CA, Fattori R, Lund G, et al. Nonsurgical reconstruction of thoracic aortic dissection by stent-graft placement. N Engl .1" Med 1999;340:1539-45,

27. Dake MD, Miller DC, Semba CP, et al. Transluminal placement of endovascular stent-grafts for the treatment of descending thoracic aortic aneurysms N Engl Med 1994;331:1729-34.

28.Criado FJ, Clark NS, Barnatan MF. Stent graft repair in the aortic arch and descending thoracic aorta: a 4-year experience. J VascSurg 2002; 36 (6): 1121-8.

29. Semba CP, Dake MD. Endoluminal Stent-Grafting in the Thoracic Aorta. In Chuter TAM, Donayre CE, White RA (eds) Endoluminal Vascular Prostheses. Boston: Little, Brown and Company; 1995:153-171.

30. Dake MD, Kato N, Mitchell RS, et al. Endovascular stent-graft placement for the treatment of acute aortic dissection. N Engl J Med 1999;340:1546-52.

31. Ricco J, Cau J, Marchand, C,et al. Stent Graft repair for thoracic aortic disease: Results of an independent nationwide study in France from 199 to 2001, J Thorac Cardiovasc Surg 2006; 131:131-7.

32. Riambau V, Zipfel B, Coppi G, et al. Final operative and midterm results of the European experience in the RELAY Endovascular Registry for Thoracic Disease (RESTORE) study. J Vasc Surg 2011;53(3):565-73.

33. Murphy E, Stanley G, Lleves M, Knowles M, et al. Thoracic Endovascular Repair (TEVAR) in the Management of Aortic Arch Pathologies. Ann of Vase Surg 2012; 26 (1):55-66.

34. Metcalfe M, Karthikesalingam A, Black, S, et al. The first endovascular repair of an acute type A dissection using and endograft designed for the ascending aorta, J Vasc Surg 2012;55(1):220-2.

35. Deployment of Endograft in the Ascending Aorta to Reverse Type A Aortic Dissection; Wang et al. Asian J Surg. 2003 Apr;26(2):117-9.

36. Successful treatment of a Stanford type A dissection by percutaneous placement of a covered stent graft in the ascending aorta; Ihnken et al, J Thorac Cardiovasc Surg. 2004 Jun;127(6):1808-10.

37. Endoluminal and surgical treatment for the management of Stanford Type A aortic dissection; Zhang et al. Eur J Cardiothorac Surg. 2004 Oct;26(4):857-9.

38. Comparison of Flow Patterns in Ascending Aortic Aneurysms and Volunteers Using Four-Dimensional Magnetic Resonance Velocity Mapping; Hope et al., J Magn Reson Imaging. 2007;26:1471-1479.

39. Endovascular management of ascending aortic Pathology; Klovenbach et al. J Vase Surg. 2011;53(5):1431-7.

40. Endovascular Stent-graft Treatment of Type A Dissection: Case Report and Review of Literature; Senay et al. Eur J Vasc Endovasc Surg. 2007;34: 457e460,

41. Endovascular Management of Stanford Type A (Ascending) Aortic Dissection; Chan et al. Asian Cardiovasc Thorac Ann, 2009 Dec;17(6):566-7.
42. Treatment of Acute Type A Dissection by Percutaneous Endovascular Stent-Graft Placement; Zimpfer et al. Ann Thorac Surg. 2006 Aug;82(2):747-9.

43. Stent-Graft Repair of a Mycotic Ascending Aortic Pseudoaneurysm; Heye et al. J Vase Intery Radiol. 2006; 17:1821-1825.

44. Transapical Deployment of Endovascular Thoracic Aortic Stent Graft for an Ascending Aortic Pseudoaneurysm; Szeto et al. Ann Thorac Surg. 2010;89:616-8.

45. Endovascular Repair of Ascending Aortic Pseudoaneurysm: Technical Considerations of a Common Carotid Artery Approach Using the Zenith Aortic Cuff Endograft; Lin et al. J Endovasc Ther. 2007 Dec;14(6).794-8.

46. Roselli EE, Idrees J, Greenberg RK, Johnston DR, et al. Endovascular stent grafting for ascending aorta repair in high-risk patients. J Thorac Cardiovasc Surg. 2015;149(1):144-51.

47. Zhenjiang L, Qingsheng L, Rui F, Jian Z, et al. Outcomes of endovascular repair of ascending aortic dissection in patients unsuitable for direct surgical repair. Journal of the American College of Cardiology. 2016;68(18):1944-54.

48. Muetterties CE, Menon R, Wheatley GH. A systematic review of primary endovascular repair of the ascending aorta. J Vasc Surg. 2018;67(1):332-342.

49. Tsilimparis N, Debus ES, Oderich GS, Haulon S, Terp KA, Roeder B, et al. International experience with endovascular therapy of the ascending aorta with a dedicated endograft. J Vasc Surg. 2016;63(6)1476-82.

50. Khoynezhad A, Donayre CE, Walot I, Koopmann MC, Kopchok GE, White RA. Feasibility of endovascular repair of ascending aortic pathologies as part of an FDA-approved physician-sponsored investigational device exemption. J Vasc Surg. 2016;63(6)1483-95.

2.1.3 Summary of Safety and Effectiveness Data of the Medtronic Valiant Navion Device

Valiant Navion (approved on October 19, 2018) is Medtronic's next generation thoracic stent graft system after the commercially available Valiant Thoracic Stent Graft with the Captivia Delivery System (approved on April 1, 2011). Long term safety and effectiveness of the Valiant stent graft product line (referred to as Valiant hereafter) has been proven clinically for up to five years follow-up (VALOR II IDE study close out report, G050238/R005) and with extensive global commercial experience over 5 years. Both Valiant Navion and Valiant were evaluated and approved for indications in the descending thoracic aorta.

Medtronic's knowledge and experience with Valiant was leveraged in designing the Valiant Navion device. Valiant Navion was designed to facilitate access in patients with challenging anatomies, expand overall patient applicability, and improve procedural ease of use of the system. The Valiant Navion design modifications in comparison to Valiant are grouped into the following main categories.

- Lower profile delivery system to enhance ease of use and access
- Stent graft changes to fit it into a lower profile delivery system
- Introduction of the CoveredSeal configuration with the tip capture mechanism as the proximal or distal device

The Valiant Navion stent graft design and delivery system changes and comparison to Valiant Captivia Stent graft system are provided in Appendix 13, Table 1 and Table 2, respectively. In addition, in Appendix 13, Figure 1 and Figure 2 provide an overview of the comparison in technological characteristics between these two stent grafts in both the FreeFlo and CoveredSeal configurations, respectively.

All design changes (including the introduction of the CoveredSeal configuration with the tip capture mechanism) and device attributes incorporated within the Valiant Navion design were evaluated to ensure the device with the design modifications met the pre-established design and performance specifications and to ensure that product performance will not be negatively affected for use in the descending thoracic aorta. Additionally, the Valiant Navion device was further validated in a clinical study to confirm its safety and effectiveness for the treatment of lesions of the descending thoracic aorta. Data from pre-clinical (*in vitro* bench testing and *in vivo* animal studies) and the clinical study are publicly available through the Summary of Safety and Effectiveness Data.

The Valiant Navion™ thoracic stent graft system, in our experience, is superior to the Valiant PS-IDE stent graft in many respects. The placement of a thoracic aortic stent (TEVAR) in the proximal ascending aorta is technically demanding from a clinical and engineering viewpoint. Due to the close proximity to the coronary arteries and arch vessels leading to the brain precise deployment is critical. Our experience has shown us that a proximal constrainment (such as tip capture technology) is advantageous for satisfactory results and may be required for accurate deployment in the ascending aorta (Zone 0). First, the ubiquitous presence of tip capture technology in both the open cell proximal configurations and the closed cell proximal configurations allows for increased accuracy of deployment. Second, the shortened tip length in the Navion device allows for easier placement near the aortic valve and the sino tubular junction to avoid the critical vessels mentioned above. Third, the Navion delivery system is 10 cm longer which allows easier reach to the aortic valve through the length of the entire aorta. Finally, the Navion platform has a decreased delivery sheath diameter by 3-4 French sizes. These advances serve to decrease the risk of access vessel injury and decrease the necessity of stiff guidewire placement in the left ventricular cavity except on rare occasion. For these reasons listed above, moving forward our site will only be using the Valiant Navion device.

2.2 Reference to Medtronic MAF for Valiant Captivia PS-IDE Device

The description of the non-clinical testing that has been performed on the Valiant Captivia PS-IDE device, relevant clinical information and a table describing the purpose of each test or analysis, test results and any potential clinical significance of the results are likewise included in Medtronic's MAF-2050 in Appendix 1.

2.3 Reference to Dr. White and Dr. Khoynezhad

Please refer to Appendix 2.

2.4 Investigator Experience

Dr. Brinkman is a highly trained, experienced aortic valve and thoracic aortic surgeon. Following completion of his cardiac surgery training at Brigham and Women’s Hospital in Boston, he sought additional training in aortic surgery at the University at Pennsylvania. This additional year was under the guidance of Dr. Joseph Bavaria, who is an internationally recognized expert in open and endovascular procedures for the aorta. Dr. Brinkman is currently the Director of the Thoracic Aortic Clinic at Baylor Scott & White The Heart Hospital – Plano. Along with vascular surgeons, including Dr. Gable and Dr. Shutze, patient care is delivered in a multi-specialty manner resulting in optimal patient outcomes. Additionally, Dr. Brinkman has been active in over 20 industry-sponsored and investigator-initiated trials with endovascular devices and techniques as well as valve sparing root procedures and minimally invasive operations. Dr. Brinkman is also a member of the Society of Thoracic Surgery Aortic Task Force which oversees data on a national and international level. Notably, Dr. Brinkman has been the principal investigator for the DISSECTION trial and Valiant EVO trial. Both of these trials were important

for FDA approval of the Medtronic Valiant Captivia and Medtronic Valiant Navion devices. Baylor Scott & White The Heart Hospital – Plano performed over 300 thoracic aortic procedures last year which included open and endovascular repairs or replacements. The cardiac surgeons work as a team with the vascular surgeons to provide the maximum benefits and experience to patients undergoing thoracic endovascular procedures. They have also authored numerous manuscripts related to these issues. Below is a sampling of the literature by the investigators for reference.

1. Brinkman WT, Terramani TT, Najibi S, Weiss VJ, Salam AA, Dodson TF, Smith RB, Chaikof EL. Endovascular abdominal aortic aneurysm repair in the octogenarian. Ann Vasc Surg 2004; 18(4):401-407.

2. Chaikof EL, Lin PH, Brinkman WT, Dodson TF, Weiss VI, Lumsden AB, Terramani TT, Najibi S, Bush RE, Salam AA, Smith, III RB. Endovascular repair of abdominal aortic aneurysms: Risk stratified outcomes. Ann Surg 2002;235:833¬841.

3. Terramani TT, Brinkman WT, Najibi 5, and Chaikof EL. Complications associated with endovascular repair of abdominal aortic aneurysm. Adv Vasc Surg 2002;10:109-116,

4. Bush RI, Lin PH, Bianco CC, Lumsden AB, Terramani TT, Brinkman WT, Weiss WI, Martin LG. Endovascular aortic aneurysm repair in patients with renal dysfunction or severe contrast allergy: utility of imaging modalities without iodinated contrast. Ann Vasc Surg 2002; 16(5):537-544.

5. Lin PH, Bush RL, Chaikof EL, Chen C, Conklin B, Terramani TT, Brinkman WT, Lumsden AB. A prospective evaluation of hypogastric artery embolization in endovascular aortoiliac aneurysm repair. J Vasc Surg 2002; 36(3):500-506.

6. Brinkman WT, Szeto WY, Bavaria JE. Endovascular Therapy for the Thoracic Aorta, US Cardiology 2007-Vol. I.

7. Pochettino A, Brinkman WT, Moeller P, Szeto W, Moser W, Cornelius K, Bowen F, Woo YJ, Bavaria K. Antegrade Thoracic Stent Grafting During Repair of Acute DeBakey I Dissection Prevents Development of Thoracoabdominal Aortic Aneurysms. Ann Thoracic Surg; 2009;88:482-490,

8. Rylski B, Blanke P, Beyersdorf F, Desai ND, Milewski RK, Siepe M, Kari FA, Czemy M, Carrel T, Schlensak C, Kruger T, Mack MJ, Brinkman WT, Mohr FW, Etz CD, Luehr M, Bavaria SE. How does the ascending aorta geometry change when it dissects? J. Am Coll Cardiol 2014 Apr 8;63(13):1311-9. doi.10.1016/flacc.2013.12.028. Epub 2014 Feb 5.

9. Arsalan M, Squires JJ, Herbert MA, Brinkman WT, et al. Comparison of Outcomes of Operative Therapy for Acture Type A Aortic Dissections Provided at High Column — VS — Low Volume medical Centers in North Texas. Am J Cardiol. In Press.

10. Hybrid endovascular treatment of anomalous right subclavian artery dissection in a patient with Marian syndrome. Stanely GA, Arko FR III, Foteh MI, lessen ME, DiMaio JM. Ann Thorac Surg 2012 Aug;94(2):639-41. Doi: 10.1016/j . athoracicsur.2011 .12.082.

11. Volumetric analysis of type 13 aortic dissections treated with thoracic endovascular aortic repair. Stanley GA, Murphy EH, Knowles M, lives M, lessen ME, DiMaio JM, Modrall JG, Arko FR III. ,J Vase Surg. 2011 Oet;54(4):985-92; discussion 992. Doi: 10.1016/j.jvs.2011.03.263.

12. Technique for branched thoracic stent-graft repair of a chronic type a aortic dissection in a patient with multiple prior sternotomies. Murphy EH, Dimaio JM, lessen ME, Arko FR. J Endovasc Ther. 2011 Jun;18(3):359-64. doi: 10.1583/W¬3349.1.

13. The effects of operative indication and urgency of intervention on patient outcomes after thoracic aortic endografting. Knowles M, Murphy EH, Dimaio JM, Modrall JO, Timaran CH, lessen ME, Arko FR 3rd.J Vase Surg. 2011 Apr;53(4):926-34. doi: 10.1016/j.jvs.2010.10.052.

14. Endovascular repair of acute traumatic thoracic aortic transection with laser-assisted in-situ fenestration of a stent-graft covering the left subclavian artery. Murphy EH, Dimaio JM, Dean W, lessen ME, Arko FR.J Endovasc Ther. 2009 Aug;16(4):457-63. doi: 10.1583/09-2746.1.

15. Combined aortic debranching and thoracic endovascular aneurysm repair (TEVAR) effective but at a cost. Murphy EH, Beck AW, Clagett GP, DiMaio JM, lessen ME, Arko FR. Arch Surg. 2009 Mar;144(3)222-7. doi: 10.1001/archsurg.2009 .3.

3. Investigational Plan

3.1 Investigational Plan Synopsis

Study Title:	Proposed Single Center Investigational Device Exemption: Feasibility of Endovascular Repair of Ascending Aortic Dissections
Investigational Device:	Medtronic Thoracic Stent Graft System
Sponsor:	The Heart Hospital Baylor Plano Baylor Scott and White Research Institute
Principal Investigator and Co Investigators:	PI: William Brinkman, MD Sub-I: Dennis Gable, MD; William Shutze, MD; Katherine Harrington, MD, Justin Schaffer, MD and J. Michael DiMaio, MD
Investigational Site:	The Heart Hospital Baylor Plano 1100 Allied Drive Plano, Texas 75093
Study Purpose:	The purpose of this early feasibility study is to investigate the outcome of selected patients with ascending thoracic aortic pathologies including type A aortic dissection, who are suitable for endovascular repair with the Medtronic Thoracic Stent Graft System
Number of Subjects:	20
Study Type and Duration:	Prospective, Single Center, Non-randomized, Single arm study. The Duration of the investigation is anticipated as follows: • Time to Complete Enrollment: 5 Years • Subject follow up time: 5 years from last subject enrollment

Intended Use:	• The Medtronic Thoracic Stent Graft System is intended for endovascular repair of the Type A Thoracic Aortic Dissection, Retrograde Type A Thoracic Aortic Dissection of the Ascending Thoracic Aorta (with no involvement of the Aortic Valve) • Location of treatment will be the area between the Sinus of Valsalva and the innominate artery orifice. • High risk subjects having appropriate anatomy will be enrolled in the study. • Anatomic Limitations: ○ The proximal landing zone will allow placement of die statement of the stent graft as to not inhibit valvular function, occlude a coronary ostium or proximal bypass graft; ○ Distal landing zone must allow for continued perfusion of critical cerebral vessels; ○ Ascending aorta between 28-44 mm in diameter
Inclusion Criteria:	In order to qualify for this physician-sponsored Investigational Device Exemption, the patients would have to meet the entire entry criteria listed below, sign a consent approved by the FDA and IRB, and agrees to follow-up according to the study protocol. • Patient must have a type A thoracic aortic dissection, retrograde type A thoracic aortic dissection of the ascending thoracic aorta affecting the area between the Sinus of Valsalva and the innominate artery orifice (with no involvement of the aortic valve) and be considered a candidate for endovascular repair; ○ The proximal landing zone will allow placement of the statement of the stent graft as to not inhibit valvular function, occlude a coronary ostium or proximal bypass graft; ○ Distal landing zone must allow for continued perfusion of critical cerebral vessels; ○ Ascending aorta between 28-44 mm in diameter; ○ The patient must be high-risk surgical candidate according to the following established criteria: ASA score of IV.

Exclusion Criteria:	The following patients are excluded from this study: • Pregnant or pediatric patients (younger than 21 years of age); • Patients who have a condition that threatens to infect the stent graft/aortic valve prosthesis; • Patients with allergies to the stent graft material; • Patients or their legally authorized representative (LAR) who do not sign the informed consent; • Patients with expected survival less than one year due to a condition other than the ascending aortic
Primary Endpoint:	Primary endpoints will be early (at 30-days) and late death (at 1, 2, and 5 years), re-interventions, and surgical conversion (early or late), as well as any post-procedural stroke (early or late), ischemic or hemorrhagic events causing motoric, language or cognitive compromise.
Secondary Endpoint:	Secondary endpoints will include access vessel complications (including dissection, thrombosis, embolization), myocardial infarction, renal failure, sepsis, pulmonary failure, blood loss over 1000cc, stent graft migration, endoleaks, technical observation (including twisting, kinking, or fracture), loss of stent graft patency (occlusion), aortic valve function (AI>2+) and any malperfusion to aortic branch-vessels (diagnosed with CTA or clinical diagnosis).
Pre-Enrollment Testing:	• Physical Exam • Vital Signs • Medical History • Pregnancy Test (if applicable) • Serum Creatinine • CTA of the chest/abdomen/pelvis, Echocardiogram.
Follow up Schedule:	• Discharge • 1 Month • 6 Months • 12 Months • Annually to 5 years
Centralized Image Analysis:	Medical Data and Imaging System (M2S) • Coverage of Proximal entry tear • Aortic remodeling at 1 month, 6 month, 12 month, and annual visits up to 5 years as measured by: - Change in TL size from baseline - Change in the FL Size from baseline - Change in total ascending aortic size from baseline FL Thrombosis - Continuing or new FL perfusion

Analytical Sets:	The primary endpoint analysis set will include all enrolled subjects who had at least one study scent graft implanted. The Intent-to-Treat (ITT) analysis set will include all enrolled subjects who had an intra-arterial access procedure with intent to receive the study device.
Study Monitor:	Kristen Lyons Baylor Research Institute 2001 Bryan Street Suite 2200 Dallas, Texas 75201
Study Oversight:	A data safety monitoring committee will be used for oversight of the investigational site.

3.2 Purpose

3.2.1. Name and intended use of the device

Valiant PS-IDE Stent Graft System with the Captivia Delivery System

The first generation device used on the trial was the Medtronic Valiant PS-IDE Stent Graft System which includes a Valiant Thoracic Stent Graft, a self-expanding, tubular end prosthesis pre-loaded into the Captivia Delivery System. This device was studied by Dr. White and Dr. Khoynezhad which provided the foundation for the approval of this IDE. The Valiant PS-IDE Stent Graft is advanced to the dissection endoluminally via iliac/femoral artery introduction of the system. Upon deployment, the nitinol stent graft self-expands at the target location, where it is designed to exclude the lesion by restoring blood flow through the stent graft lumen. This device is the similar to the device is in the approved Valiant Thoracic Stent Graft System in the treatment of lesions in the descending thoracic aorta. Going forward, the Valiant Navion device will be used and may also be refered to as the Medtronic Thoracic Stent Graft System.

Valiant Navion™ thoracic stent graft system

The Valiant Navion™ thoracic stent graft system (Medtronic Thoracic Stent Graft System) is a commercially approved stent graft system designed for the endovascular repair of lesions in the descending thoracic aorta (DTA). When placed within the target lesion, the stent graft provides an alternative conduit for blood flow within the patient's vasculature by excluding the lesion from blood flow and pressure. The stent graft system is composed of 2 main components: the implantable Valiant Navion thoracic stent graft and the disposable delivery system. The stent graft is preloaded into the delivery system. The loaded delivery system is inserted endoluminally via the femoral or iliac artery and tracked through the patient's vasculature to deliver the stent graft to the target site. Upon deployment, the stent graft self-expands to conform to the shape and size of the seal zones above and below the lesion.

- For the purposes of this study, the Medtronic Thoracic Stent Graft System is intended for endovascular repair of the Type A Thoracic Aortic Dissection, Retrograde Type A Thoracic Aortic Dissection of the Ascending Thoracic Aorta (with no involvement of the Aortic Valve).
- Location of treatment will be the area between the Sinus of Valsalva and the innominate artery orifice.
- High risk subjects having appropriate anatomy will be enrolled in the study.
- Anatomic Limitations:
    - Proximal landing zone will allow placement of the statement of the stent graft as to not inhibit valvular function, occlude a coronary ostium or proximal bypass graft.
    - An entry tear will need to be at least 15 mm from the proximal and distal edge of the device

3.2.2. Objectives

The purpose of this early feasibility study is to investigate the outcome of selected patients with ascending aortic pathologies including type A aortic dissection, retrograde type A aortic

dissection. who are suitable for endovascular repair with the Medtronic Thoracic Stent Graft System We propose to study patients with dissections affecting the aorta between the Sinus of Valsalva and the innominate artery orifice (with no involvement of aortic valve). In these patients, the ascending aorta will be repaired using the stent graft. For patients with type A aortic dissection, we expect to reroute the blood to the true lumen by covering the proximal tear. In patients with retrograde type A aortic dissection, there might or might not be additional tears in the ascending aorta. If there are tears in ascending aorta, these dissections behave similarly like a type A aortic dissection, in which the all tears in the ascending aorta need to be covered. If the proximal tear is only in the descending thoracic aorta, these patients will require coverage in the ascending aorta with the stent graft along with coverage of proximal tear in the descending thoracic aorta using the Medtronic Thoracic Stent Graft System.

Patients will be selected from a high-risk surgical cohort. The total number of enrolled subjects is planned to be 20. However, we will enroll five patients at a time and evaluate outcomes prior to enrolling the second round of five patients as part of the risk mitigation strategies discussed in the Risk Analysis section of this PS-IDE in pages 36-46.

3.2.3. Duration of the investigation

Accrual of study subjects will occur over approximately 5 years with all subjects to be followed at 1 month, 6 month, and 12 month intervals post-procedure followed by annual follow-up through 5 years post implant. Per standard of care, the patients will undergo lifelong follow-up after they have completed the study.

3.3 Protocol

This study will be conducted with non-surgical or very high-risk patients who are considered suitable candidates for endoluminal repair. Adult male and female patients who fulfill the inclusion/exclusion criteria listed below are eligible for enrollment.

3.3.1. Inclusion Criteria

In order to qualify for this physician-sponsored Investigational Device Exemption, the patients would have to meet the entire entry criteria listed below, sign a consent approved by the FDA and IRB, and agrees to follow-up according to the study protocol.

1. Patient must have a type A thoracic aortic dissection, retrograde type A thoracic aortic dissection of the ascending thoracic aorta affecting the area between the Sinus of Valsalva and the innominate artery orifice (with no involvement of the aortic valve), and be considered a candidate for endovascular repair;

    1.1. The proximal landing zone will allow placement of the statement of the stent graft as to not inhibit valvular function, occlude a coronary ostium or proximal bypass graft;
    1.2. Distal landing zone must allow for continued perfusion of critical cerebral vessels;

1.3. Ascending aorta between 28-44 mm in diameter;
1.4. The patient must be high-risk surgical candidate according to the following established criteria: ASA score of IV.

3.3.2. Exclusion Criteria

The following patients are excluded from this study:

1. Pregnant or pediatric patients (younger than 21 years of age);
2. Patients who have a condition that threatens to infect the stent graft/aortic valve prosthesis;
3. Patients with allergies to the stent graft material;
4. Patients or their legally authorized representative (LAR) who does not sign the informed consent.
5. Patients with expected survival less than one year due to a condition other than the ascending aortic dissection.

3.3.3. Study Design

This early feasibility study is a prospective evaluation of patients receiving the device to determine the proportion in whom successful implantation is achieved, as indicated by exclusion of the thoracic lesion and graft patency at implant, time of discharge, and 1, 6, and 12 months, and annual visits through 5 years following implantation, and to determine the proportion of patients who die or experience adverse events during and after the implantation. Furthermore, the percentage of patients in whom technical and clinical success is achieved, will be determined. Additional endpoints include length of stay in intensive care unit following the procedure, and total length of hospital stay.

Twenty patients will be enrolled in this feasibility study. The enrollment will be performed in five-patient increments, and the results of each five-patient group will be analyzed and reported prior to enrolling further patients. This modus operandi serves as risk mitigating strategy.

3.3.4. Study Procedures

3.3.4.1 Patient Screening and Enrollment

Investigators will assess potential subjects diagnosed with Type A thoracic aortic dissection, retrograde Type A thoracic aortic dissection of the ascending thoracic aorta for their suitability for enrollment in the clinical study. If the patient appears to meet the eligibility criteria, the investigator will discuss the study with the patient and provide information relating to the potential risks and benefits, and required follow-up procedures per the informed consent process. After the patient has voluntarily signed and dated the informed consent document, the patient will be considered a study candidate. If a patient does not sign the informed consent document, then no further procedures for the clinical study will occur. Subjects who were considered for the study but do not qualify for enrollment will be documented as ineligible on the Subject Screening Log. Subjects enrolled, but with no device implant will be followed through the one-month follow-up only.

Those subjects who sign and date the informed consent document, or who have their Legally Authorized Representative sign and date the informed consent document, and meet all of the study eligibility criteria will be eligible for enrollment into the clinical study. The subject will be considered enrolled at the time the Medtronic Thoracic Stent Graft System is introduced into the arterial access vessels.

Documentation of the following will be obtained prior to the implant procedure:

- Informed consent
- Demographic data
- Medical history
- Vital signs [heart rate, blood pressure, respiratory status, pulse evaluation (Left and right Radial, Dorsalis, and/or Tibial artery)]
- Pregnancy test (females of child bearing potential)
- Clinical laboratory tests: serum creatinine
- CT of the Chest/Abdomen/Pelvis with and without contrast; MRA, may be used at the investigator's discretion.
- Echocardiogram

All subjects will undergo a neurological examination when possible depending upon the urgency of the procedure and patient availability.

3.3.4.2. Implant Procedures/Treatment

All investigators will read, understand and be trained to the Medtronic Thoracic Stent Graft System Instructions for Use (IFU) (please see Appendix 14) prior to initiation of the procedure.

The principles of endovascular repair of the type A dissections is very similar to the approach to the type B aortic dissection. The route of access is either through the iliofemoral vessels, the brachiocephalic vessels, or a transapical approach via a small left thoracotomy. Through and through true-lumen access with the guidewire is confirmed using the intravascular ultrasound (IVUS) and anatomic information obtained by pre-procedural computer tomography angiogram (CTA). The size of the stent graft is selected based on the CTA and the IVUS- interrogation. The stent graft will then be delivered and deployed in the ascending aorta using a stiff guidewire. An aortic angiogram is performed to delineate the location of the coronary arteries and the innominate artery as they relate to the true and false lumen. A dissection occurs when a tear of the intima (the inner lining) allows blood to leak into the media (middle layer). This creates two passages for blood: a true lumen, which is the normal passageway of blood, and a false lumen, the newly created passageway. The cardiac cycle will be transiently halted by administration of intravenous adenosine or rapid ventricular pacing. Both methods are well established for effectively reducing the impulsive force of the cardiac output by temporarily halting the heart rate or reducing left ventricular filling, respectively. These methods allow for controlled and precise placement of the stent graft in the desired location of interest.

The usual and customary monitoring associated with procedures for the ascending aorta and arch will be utilized. These include but are not limited to multiple invasive arterial monitoring (at

least 1 radial and 1 femoral line), Cerebral oximetry, Massimo 4 channel continuous EEG monitoring, internal jugular or subclavian venous access to allow for swan-ganz catheter.

The following events will be documented in the medical records and in the CRFs as applicable:

- General, regional, or local anesthesia will be employed during the endovascular procedure per Investigator's discretion. The method of anesthesia will be documented.
- Antibiotics will be administered per Investigator's standard regimen.
- Arterial site will be accessed per Investigator's standard method.
- Systemic heparin will be administered per the Institution's standard regimen at any time during the procedure.
- Verification of dimensions and characterization of the dissection and pertinent arteries will be conducted with an angiogram at the time of the procedure and prior to the insertion of the Medtronic Thoracic Stent Graft System. The Investigator will verify dimensions and characterizations of the subject's anatomy in relation to the Medtronic Thoracic Stent Graft System. Subjects who are found not to be candidates for Medtronic Thoracic Stent Graft System, because of findings detected during the treatment angiogram, will be documented as screen failures on the Screening Log.
- All Medtronic Thoracic Stent Graft System used for implantation and any issues related to the Medtronic Thoracic Stent Graft System will be documented in the medical chart and on the CRFs.
- Fluoroscopic guidance will be used for placement of the stent graft throughout the endovascular procedure. Total fluoroscopic time and the amount of contrast media used will be documented on the operative notes.
- Devices should be deployed following all the steps in the IFU.
- At the discretion of the Investigator, Intravascular Ultrasound (IVUS) may be used in conjunction with procedural angiography to verify the position of the proximal entry tear or luminal characteristics and to optimize implantation of the device. Additional procedures performed during the treatment will be documented on the appropriate CRFs.
- Upon completion of the procedure, a final run-off angiography will be performed to document the status of the Medtronic Thoracic Stent Graft System, the coverage of the proximal entry tear and the surrounding vasculature.
- The estimated volume of blood replaced, any technical observations and adverse events experienced during the treatment will be documented.
- The cut-down site, if necessary, will be closed as per standard of care.

3.3.4.3. Pre- Hospital Discharge

The following evaluations will take place prior to the subject's discharge from the hospital:

- CT without contrast and CTA (contrast enhanced CT) covering the length of the lesion, which may include scans of the chest, abdomen and pelvis; MRA may be used at the investigator's discretion.
    - NOTE: If the discharge occurs within the one-month follow-up window, only one set of CT/CTA images is needed.

- Vital signs [heart rate, blood pressure, respiratory status, pulse evaluation (Bilateral Radial, Dorsalis, and/or Tibial arteries where applicable.)]
- Adverse event and technical observations, evaluations, and treatments should be documented in the appropriate CRFs.
- All subjects with a history of stroke or have any post-procedural neurological deficit(s) will undergo neurological examination. A diffusion weighted MRI of the head will also be performed on these patients when clinically indicated.

3.3.4.4. Follow-up Examinations

Follow-up evaluations will be scheduled for 1 month (t 14 days), 6 months (± 60 days), 12 months (± 90 days) and annually thereafter to 5 years post implant (± 16 weeks).

The following tests and procedures will be included at each of these visits:

- Vital signs [heart rate, blood pressure, respiratory status, and pulse evaluation (Bilateral right Dorsalis, and/or Tibial artery where applicable)]
- Chest x-ray (2- or 4-view, as per standard of care).
- CT without contrast and CTA (contrast enhanced CT) covering the length of the lesion, which may include scans of the chest, abdomen and pelvis; MRA may be used at the investigator's discretion.
- Adverse event and technical observations, evaluations, and treatments should be documented in the appropriate CRFs.
- Echocardiogram at the 1 month, 12 month, and yearly visits.
- KCCQ questionnaire.

The following tests may also be ordered at the discretion of the investigator:

- Echocardiogram (after the 1 month, 12 months, and yearly follow-up)
- Diffusion weighted MRI of the head
- Neurocognitive evaluation using the NIH stroke scale
- Neuropsychological evaluation.

Per standard of care, the patients will undergo lifelong follow-up after they have completed the study. This follow-up regimen is consistent with current recommendations for patients with thoracic aortic dissections. This longitudinal imaging regimen with 3-dimensional center-of-flow reconstruction using the M2S (Lebanon, NH) or similar software will allow for morphologic changes of the aorta and structural changes of the stent graft in the long-term follow-up.

The data collection schedule is summarized in Table 1.

Table 1: Study procedures and data collection requirements

Data	Screening/ Baseline	Procedure	Pre-Hospital Discharge	1 month FU +/- 14 days	6 Month FU +/- 60 days	12 Month FU +/- 90 days	2-5 Year FU +/- 16 weeks
Informed Consent	x						
Medical History	x						
Vital Signs, Pulse	x		x	x	x	x	x
KCCQ Questionnaire	x			x	x	x	x
Pregnancy test (if applicable)	x						
Laboratory Tests Serum Creatinine	x						
CT w/out contrast & CTA/MRA	x		x	x	x	x	x
Echocardiogram	x			x		x	x
Device & Procedure Information		x					
Angiogram		x					
Chest X-Ray				x	x	x	x
Adverse Event Assessment		x	x	x	x	x	x

3.3.4.5. Unscheduled Visits

If a patient has a visit specifically associated with the treated thoracic lesion and/or the Medtronic Thoracic Stent Graft System and this visit is not within any of the protocol specified study-related visit windows, data should be recorded as appropriate on the Unscheduled Follow-Up Form.

3.3.4.6. CT/CTA Scan

Images of the CT without contrast and CTA (contrast enhanced CT) covering the length of the lesion, which may include scans of the chest, abdomen and pelvis will be submitted for evaluation through 60 months of follow-up Images at pre-procedure, pre-discharge, 1 month, 6 months, 12 months, 24 months, 36 months, 48 months and 60 months will be evaluated. In addition, any interim imaging done within one year of implantation should be evaluated if it relates to the performance of the implanted device. These data will be used for analysis of secondary observations at pre-discharge, 1 month, 6 months and 12 months. Site data will be used for reporting purposes at 24 months, 36 months, 48 months and 60 months, and submitted for central review.

The presence of the following endpoint related events would be assessed:

- Loss of stent graft patency
- FL diameter over the length of the stented segment
- TL diameter over the length of the stented segment
- Total aortic diameter
- FL thrombosis
- Changes in true and false lumen volumes over time
- Stent graft migration
- Presence and type of endoleaks
- Continuing or new false lumen (FL) perfusion

3.3.4.7. Study Deviations

Every attempt must be made to avoid deviations. All deviations are recorded on a Protocol Deviation Case Report Folio. 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. Protocol deviations will 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.

3.3.4.8. Adverse Events

Any adverse experiences reported by a subject in the study or noted by the Clinical Investigator/Sponsor, will be reported on the Post-Operative Assessment CRF. Each experience must be categorized by the Clinical Investigator/Sponsor by its degree of severity (mild - the event did not require treatment, moderate - the event was treated locally or by minimally invasive treatment, or severe - the event was fatal or resulted in permanent injury or disability), its relationship to study device and implantation procedure (not related, associated with, caused by), and whether or not the adverse experience was unanticipated. An unanticipated adverse effect as defined by the FDA is any serious adverse effect on the health and 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 (including a

supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects (Section 812.3). Refer to Appendix 2, Instructions for Use and the Study Subject Informed Consent (Appendix 4) for a listing of known events.

Adverse events are to be scored as follows:

0 = None; the event was not observed

1 = Mild; the event was observed, but no treatment was required or the event resolved without treatment

2 = Moderate; the event was treated locally or by minimally invasive means

3 = Severe/Serious; as defined below

All events scored as "3" or "severe" are considered serious adverse events (SAES) under the regulatory definition in 21 CFR 803. These events will be reported within five working days to FDA. Specifically, serious illness or injury is one that is:

- Life-threatening (or fatal),
- Results in permanent impairment of a body function or permanent damage to a body structure; or
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

The Clinical Investigator/Sponsor will report all unanticipated, device deterioration events to the FDA.

Historical data have demonstrated that several types of complications are known to occur with this procedure. These complications are described in the following sections.

Endoleaks

Immediately after placement of the Medtronic Thoracic Stent Graft System, or upon later evaluation, endoleaks may be detected. Endoleaks are considered any extravasation of contrast outside of the flow channel established by the stent-graft. For purposes of this study, endoleaks that are detected and corrected during the implantation procedure are not considered a complication of the device or procedure. However, uncorrected endoleaks that develop during implantation or endoleaks that develop after implantation are considered complications and must be reported on the Procedure or Post-Operative Assessment CRF. The type and possible cause of the endoleak should be noted on the CRF.

Table 2: Endoleak Type and Causes

Endoleak Type	Description	Probable Cause(s)	Relationship to Device
I	Attachment endoleaks (distal or proximal)	Improper graft sizing or vessel measurement	Device-related
II	Branch flow endoleaks	Inadequate identification of feeder vessels and/or graft placement	Not device-related
III	Mid-graft or modular endoleaks	Graft tears or punctures, improper docking of sections	Device-related
IV	Fabric porosity	Fabric defect	Device-related

Treatment of endoleaks is at the discretion of the Clinical Investigator/Sponsor. In general, it is recommended that endoleaks be corrected during the initial procedure unless the Clinical Investigator believes that there is a likelihood that the endoleak may spontaneously seal after a few days. The decision to intervene at later intervals will be based on the severity of the endoleak, the possible cause of the endoleak, the status of the aneurysm, and the subject's general health. Known or suspected endoleaks must be monitored carefully postoperatively with appropriate diagnostic imaging.

Attempts to correct postoperative endoleaks may be done by any of the following procedures:

- using an endovascular balloon to remodel the stent-graft near the endoleak;
- use an endovascular methodology to seal the leak;
- implanting an extension cuff over the endoleak; or surgical intervention.

Any procedure performed to correct postoperative endoleaks will be recorded on the Post-Operative Assessment CRF.

Conversion to Surgery

In some subjects there may be difficulty inserting and implanting the Medtronic Thoracic Stent Graft System during the procedure. If it is not possible to complete implantation of the device, or if peri- or post-operative complications arise that place the subject at risk, the Clinical Investigator/Sponsor may elect to convert the patient to open surgery. Alternatively, the Clinical Investigator/Sponsor may elect not to repair the dissection/hematoma, and to manage the patient with observation only. This is especially true for patients who are deemed not operative candidates. In such cases, the reason for conversion must be recorded on the Procedure CRF.

Also, as noted previously, subjects who convert to surgery or who are managed by observation will be followed in an identical manner as the other subjects. A Post- Operative Assessment CRF will be completed at 1, 6, and 12 months after the attempted implantation.

Death

Autopsies will be requested for subjects who expire following implantation of a Medtronic Thoracic Stent Graft System. If the patient or the family consents to a post- mortem exam, the device will be explanted whenever possible for examination and histological analysis. The Clinical Investigator/Sponsor will request that the explanted device be sent to the designated facility for examination and histological analysis. The Clinical Investigator/Sponsor will determine whether or not the device (or procedure) caused or contributed to the subject's death.

Other Adverse Events

The health risks associated with use of the Medtronic Thoracic Stent Graft System may be less than for conventional surgical treatment. However, as with any medical procedure, there are some risks. There is the potential for discomfort or complications resulting from the procedure and the implanted stent graft. It is hypothesized that the rate of serious adverse events in stent-graft patients will be less as compared to an expected serious adverse event rate for surgical patients.

The following is a non-exhaustive list of potential serious complications that may occur during or following implantation of the Medtronic Thoracic Stent Graft System:

- embolization that may lead to stroke, amputation, intestinal ischemia, multiple organ failure, or death;
- renal insufficiency or failure, that may necessitate dialysis;
- unsuccessful repair or early endoleak, possibly leading to rupture of the aorta and death;
- propagation of dissection into the aortic root, possibly causing acute aortic regurgitation, or coronary dissection/occlusion, both leading to shock, conversion to surgery, or death;
- delayed endoleak, possibly leading to rupture of the lesion and death;
- vessel rupture, possibly leading to shock, conversion to surgery, or death;
- migration of the device, possibly leading to rupture of the aorta, open surgery, or death;
- blood loss, possibly leading to shock or death;
- graft twisting or kinking, possibly leading to shock or death;
- infection, possibly leading to septicemia or death;
- occlusion of blood flow to the spinal cord, possibly leading to temporary or permanent paraparesis or paraplegia;

- conversion to open surgery with all the risks associated with an open surgical repair;
- myocardial infarction, arrhythmia and/or congestive heart failure possibly leading to shock or death;
- respiratory failure possibly leading to death;
- cardiac injury including perforation due to nose cone introduction;
- deformation of the sinotubular junction causing aortic valve regurgitation;
- involuntary coverage of coronaries or brachiocephalic vessel (e.g. stent graft mal deployment and/or malposition).

Similarly, there are a number of minor risks and discomforts that could result from the implant procedure or adjunctive tests/analyses. The following is a summary of those potential discomforts.

- Heart and lung testing may involve some discomfort.
- Blood collection may cause bruising and/or discomfort.
- The CT and angiography procedures may cause discomfort during scanning, but should not cause pain.
- The radiopaque dyes used during CT and angiography procedures can cause nausea, vomiting, or other reactions.
- Some pain and bruising at the site may result in the groin where the device is inserted.

3.3.4.9. Withdrawal and Lost to follow-up

Patients may be withdrawn from the study for a number of reasons. The following is a summary of the possible reasons for withdrawal:

- Subjects may voluntarily withdraw from the study. The reason for withdrawal must be documented on the Termination CRF
- After the implant procedure, some subjects may not return for follow-up visits. A minimum of three (3) attempts to contact such patients must be made. All attempts are to be documented on the Termination CRF.

In some cases, an implant procedure will be initiated (i.e., an attempt to pass or deploy the device) but is aborted prior to device deployment. Such patients maintain their enrollment status (since this is an intent-to-treat study), but need not be followed. On the other hand, if a patient is initially screened and enrolled, but no procedure is ever initiated, the patient is cancelled and his/her enrollment position is made available to another patient.

Patients who are enrolled in the study group and are converted to surgery due to peri- or post-implantation complications will be followed for a minimum of 12 months after the conversion to open repair. Conversion to surgery is documented on the Procedure CRF.

3.3.4.10 Final assessment

Patients who have completed 60 months of follow-up will continue annual follow-up examinations for life as their physician's standard of care. These follow-up visits will include a physical examination, a CT, and a plain film x-ray as defined in the Chart of Study Procedures, Subjects who received a Medtronic Thoracic Stent Graft System implant and who choose to discontinue participation in the study prior to study completion will be contacted to perform a final assessment prior to study closure. The final assessment will be recorded on Post-Operative Assessment and Termination CRFs.

A Termination Case Report Form will be completed for every subject regardless of the reason for study termination.

A chart may be found in Table 1 on page 24 indicating the times at which procedures and tests will be performed.

3.3.5. Scientific Soundness and Analysis of Data

All patients will be treated using the same inclusion/exclusion criteria and are treated under the same protocol. Standard data forms will be used to collect information about all procedures and evaluations performed, to provide comprehensive documentation of the study. Each patient will be carefully monitored following treatment at specified intervals for evaluation of adverse effects and clinical effectiveness of the device.

3.3.5.1 Description of Endpoints

Primary endpoints will be early (at 30-days) and late death (at one-, two- and five-years), re-interventions, and surgical conversion (early or late), as well as any post-procedural stroke (early or late), ischemic or hemorrhagic events causing motoric, language or cognitive compromise.

Secondary endpoints will include access vessel complications (including dissection, thrombosis, embolization), myocardial infarction, renal failure, sepsis, pulmonary failure, blood loss over 1000cc, stent graft migration, endoleaks, technical observation (including twisting, kinking, or fracture), loss of stent graft patency (occlusion), aortic valve function (AI>2+), and any malperfusion to aortic branch-vessels (diagnosed with CTA or clinical diagnosis).

3.3.5.3. Analysis of Endpoints

Data Analysis Sets

The primary endpoint analysis set will include all enrolled subjects who had at least one study stent graft implanted.

The Intent-to-Treat (ITT) analysis set will include all enrolled subjects who had an infra-arterial access procedure with intent to receive the study device. The primary endpoint will be reported for this analysis set as well.

Analysis of the Primary Endpoint

The primary endpoint will be analyzed using the exact binomial test method. The null hypothesis will be rejected if the upper limit of the one-sided 95% confidence interval on the 30 days mortality rate is less than 25%. The one-sided upper 95% confidence interval on the 30 days mortality rate will be calculated using the exact binomial test method.

The remainder of the primary endpoint will be presented and analyzed descriptively by reporting, for categorical variables, the number of known values and the percentage in each category, and for continuous variables, the number of known values, the mean, standard deviation (SD), median and the minimum and maximum number of subjects.

Analysis of the Secondary Observations

All secondary endpoints will be presented descriptively by reporting, for categorical variables the number of known values and the percentage in each category, and for continuous variables the number of known values, mean, standard deviation (SD), median, minimum and maximum of subjects meeting the endpoint.

Analysis of Baseline Variables

Baseline variables will be presented descriptively as described in the section above.

3.4 Potential Risks and Benefits

3.4.1 Potential Risks

Treatment with the Medtronic Thoracic Stent Graft System is an invasive procedure that poses significant risks to the patient. Patients participating in this trial as study patients will be exposed to such risks. These risks include:

Likely

- Bleeding during and/or after the procedure;
- Problems at the groin sites where the catheters are inserted including after the procedure are done which include:
  - Bleeding
  - Delayed wound healing
  - Wound separation
  - Wound drainage
  - Nerve injury, damage, irritation and / or pain
  - Wound infection in 1 or both groins or deep in the tissue where the catheter was placed
  - Pain caused by the implant procedure

Less likely

- New onset of pain or worsening of existing pain in buttocks and / or legs;
- Swelling of legs

Rare but serious

- Problems with blood's ability to clot;
- Injury to the blood vessel wall including separation of layers of the vessel wall;
- Tearing or rupture of the blood vessel;
- Breaking apart of plaque within the blood vessel;
- Injury to the heart and/or heart valve;
- Irritation within the blood vessel;
- Transfusion reaction
- Allergic reaction from the contrast, medication(s) and/or stent graft material; Narrowing of the blood vessel;
- Rupture of the aneurysm/dissection;
- Partial rupture of the aneurysm/dissection;
- Aneurysm/dissection expansion or pseudoaneurysm;
- Local collection of blood or fluid under the skin causing swelling and/or discoloration;
- Movement of the stent from its original site; Blockage of blood flow through the stent-graft;
- Blockage of blood flow through a blood vessel near the
- aneurysm;
- The polyester graft material may break open;
- Failure to deliver the stent-graft to correct location;
- Stent deformity;
- The stent graft may twist or kink
- The stent graft may fail to open;
- The balloon used to smooth the stent graft may break;
- Re-narrowing of the blood vessel;
- Temporary narrowing of the blood vessel;
- Ongoing leaking of blood through the graft material into the
- aneurysm;
- Ongoing leaking of blood into the aneurysm from one or more
- small vessels near the aneurysm;
- Kidney failure or insufficiency;
- Blood clots in the kidneys;
- Pneumonia and breathing problems such as lung congestion;
- Blood clots in the lungs;
- Failure of lungs to take in enough oxygen;
- Irregular heart beat;
- Chest discomfort or pain;
- Heart attack or fluid around the heart;
- Congestive heart failure (failure of the heart to adequately pump blood with resulting back-up of fluid in the veins);
- Catheter breakage;
- Breakage of the metal stent that could possibly cause a leak and may result in aneurysm growth and or rupture;
- Reaction to the medications or anesthesia;

- Decreased blood flow to the intestines;
- Bowel ischemia (temporary or permanent lack of blood flow to the intestines causing them to stop working); blockage of the bowel or death of the bowel;
- Impotence (inability of a male to have or maintain an erection);
- Nerve damage;
- Inability to tolerate food;
- Urinary tract infection;
- Infection of the stent graft causing fever;
- Staying in the hospital longer than 4 days;
- Surgery may be needed should something go wrong during the procedure;
- Failure of vital organs to function;
- Decreased blood flow to the spinal cord causing permanent or temporary paralysis (inability to move/use legs) with possible inability to control bowel and bladder function;
- Change in brain function that may cause temporary weakness and/or awareness;
- Stroke from bleeding or from a clot that forms in the brain;
- Radiation injury or injury to cell life due to therapeutic radiation;
- Death

Reproductive Risks:

Because the drugs in this study could harm an unborn baby, patients should not become pregnant while on this study. Patients should not nurse a baby while in this study.

Radiation Risks:

The following procedures completed throughout the study pose as a radiation risk to patients participating in the study:

- CT Scan of your chest, abdomen and pelvis with and without contrast
- Angiogram (x-ray) of your aorta and the arteries
- Fluoroscopy and/or Intravascular Ultrasound/IVUS (x-rays taken from inside the arteries)
- CT scan of your chest after the procedure

These risks include the potential for discomfort or complications resulting from the procedure, the implanted stent-graft as well as the patients overall participation in the study as described in Section 3.2 and 4.8.

3.4.2 Minimization of Risks

All efforts will be made to minimize the risks associated with this early feasibility study, beginning with involving the appropriate expertise and facilities as follows:

- Patient selection will involve careful review of the stated inclusion and exclusion criteria. This will include extensive screening methods that are not limited to: patient chart review, referring physician discussion, multi-disciplinary involvement to include cardiac and vascular surgery as well as cardiac anesthesia and neurology.

All personnel obtaining informed consent must have appropriate qualifications and be properly trained to the protocol as will be indicated on the Delegation of Authority and Training Logs.

- Treatment will be provided by a skilled surgical team. The treatment options for this population include open surgical procedures to include replacement of the ascending aorta and/or aortic valve which our investigators are well equipped to perform. Treatment of the ascending aorta requires a site based multidisciplinary care team with expertise in (at a minimum):
    - Thoracic endovascular repair (e.g., interventional radiologist or cardiologist, cardiovascular or vascular surgeon);
    - Cardiac surgery, with experience in ascending aortic and arch surgery;
    - Vascular surgery (i.e, experience in managing vascular complications);
    - Cardiac anesthesiology; and
    - Transesophageal ultrasound (e.g., certified cardiac anesthesiologist, dedicated cardiologist)

Our clinical center is capable and equipped to perform the full spectrum of procedures necessary for elective or emergent endovascular and any bailout operations, including conversion to open surgery, in a hybrid operating room, or in closely adjacent procedural and operating theaters. The treatment options for this population include open surgical procedures to include replacement of the ascending aorta and/or aortic valve which our investigators are well equipped to perform. In the event that the patient or LAR refuses the investigational device or the clinical team deems necessary to abort a procedure, the remaining surgical options are readily available per the PI's discretion.

Post-Procedure management will involve the usual multi-disciplinary procedures that are available at our facility including, but not limited to: invasive and imaging cardiology, diagnostic and interventional radiology, vascular and general surgery, as well as neurology and pulmonary/ critical care medicine.

Subject follow up, as outlined in Section 3.3.4.4 (Follow up Examinations), will involve experienced research staff that will be conducting study responsibility per the oversight of the PI. The imaging core lab will be used for patient safety review and measures.

Additional risk mitigation efforts are categorized below as general risk mitigation strategies and targeted risk mitigation efforts (i.e. those aimed at certain potential complications):

Table 3: Clinical Study Mitigation Strategies

Part Name	Function	Associated Failures	Functional Effect	Clinical Harm	Additional Actions Taken for Valiant Captivia PS-IDE Device and Ref. No[1]	Clinical Study Mitigation Strategies
Stent Graft	Stent graft can't be visualized	Markers Not Distinguishable Under Flouro	Inaccurate Delivery	Thrombus Formation	DV Report – 10036987DOC Sim Use Report – 10037136DOC DVT Protocol TP4370 Stent Graft Expansion Integrity, QS116313 Radiopacity of Stent Graft Marker Bands, TM115688 Deployment Test, TM112037 In-vivo Evaluation TP3689 PS274 Cadaver Study	*For all events* -Close patient follow-up for detection, treatment, and reporting of adverse events *For Dissection progression aneurysm enlargement, rupture, and endoleaks* -Completion angiogram will be performed to look for any evidence of blushing. If blushing is observed the stent may be ballooned or a cuff may be used for endoleaks and a covered stent graft may be used for endoleaks or if the original device fails -Scheduled follow-up imaging to monitor device and dissection/aneurysm -Implant additional devices (cuffs, stents) if the original device fails *For embolism, lumen obstruction, vessel occlusion, or ischemia/organ failure* -Pre-operative imaging for patient selection with appropriate anatomy
			Increased Procedure Time	Stroke		
			Endoleak Type III (acute)	Limb Ischmeia		
			Occlusion	Conversion to Vascular Bypass		
				Surgical Conversion		
				Dissection		
				Extension of Dissection		
				Vessel Perforation		
				Radiation/Contrast Media/Anesthetic overexposure		
				Death		
	Exclude False Lumen	Does Not Exclude False Lumen	Endoleak Type I (acute)	Radiation/Contrast Media/Anesthetic Overexposure	DV Report – 10036987DOC Sim Use Report – 10037136DOC DVT Protocol TP4370 – Stent Graft Expansion Integrity QSI16313 Radial Force -TP9378, Stent Graft Permeability TM00277 Deployment Test TMI 12037 Migration Force – PP8968 Stent Graft Burst Test TM116925 Stent Graft Whole Spring Fatigue TP4134	*For all events* -Close patient follow-up for detection, treatment, and reporting of adverse events -If blushing is observed the stent may be ballooned or a cuff may be used for endoleaks and a covered stent graft may be used for endoleaks or if the original device fails
			Endoleak Type III (acute)	Surgical Conversion		
			Increased procedure time			
			Occlusion	Surgical Conversion	DV Report – 10036987DOC	*For all events*

	Secure Fixaction Acute	Stent Graft Migration Acute	Endoleak Type I (acute)	Conversion to Vascular Bypass	Sim Use Report – 10037136DOC DVT Protocol TP4370 Migration Force, TM112844 Deployment Test, TM112037 Stent Graft Joint Strength TM112843 Stent Graft Spring Attachment Test TM115689 FEA Nitinal Springs DVR3178	-Close patient follow-up for detection, treatment, and reporting of adverse events *For Dissection progression aneurysm enlargement, rupture, and endoleaks* -Completion angiogram will be performed to look for any evidence of blushing. If blushing is observed the stent may be ballooned or a cuff may be used for endoleaks and a covered stent graft may be used for endoleaks or if the original device fails -Scheduled follow-up imaging to monitor device and dissection/aneurysm -Implant additional devices (cuffs, stents) if the original device fails -Pre-operative imaging for patient selection with appropriate anatomy
			Increased procedure time	Emboli		
				Stroke		
				Limb Ischemia		
				Dissection		
				Extension of Dissection		
				Radiation/Contrast Media/Anesthetic overexposure		
				Death		
				Post-Op Rupture		
				Vessel Perforation		
	Maintain Lumen	Does Not Maintain Lumen	Occlusion	Surgical Conversion	DV Report – 10036987DOC Sim Use Report – 10037136DOC Stent Graft Expansion Integrity QSI16313 Migration Force, TMI12844 Deployment Test TMI12037 Stent Graft King Radius Test Stent Graft Whole Spring Fatigue VP3153 TR4134 Graft Material and Seam Fatigue VP1965 FEA Nitinol Springs DVR3178 LPS Thoracic Stent Graft Testing, VP2615	*For all events* -Close patient follow-up for detection, treatment, and reporting of adverse events *For Dissection progression aneurysm enlargement, rupture, and endoleaks* -Completion angiogram will be performed to look for any evidence of blushing. If blushing is observed the stent may be ballooned or a cuff may be used for endoleaks and a covered stent graft may be used for endoleaks or if the original device fails -Scheduled follow-up imaging to monitor device and dissection/aneurysm -Implant additional devices (cuffs, stents) if the original device fails
			Stent Graft Kink			

	Secure Fixation – Chronic	Stent Graft Migration Chronic	Occlusion	Surgical Conversion	DV Report – 10036987DOC Sim Use Report – 10037136DOC DVT Protocol TP4370 Stent Graft Expansion Integrity QSI16313 Migration Force, TMI12844 Deployment Test TMI12037 Stent Graft Spring Attachment Test TM115689 Radial Force Test TM115686, TP9378	*For all events* -Close patient follow-up for detection, treatment, and reporting of adverse events *For Dissection progression aneurysm enlargement, rupture, and endoleaks* -Completion angiogram will be performed to look for any evidence of blushing. If blushing is observed the stent may be ballooned or a cuff may be used for endoleaks and a covered stent graft may be used for endoleaks or if the original device fails -Scheduled follow-up imaging to monitor device and dissection/aneurysm -Implant additional devices (cuffs, stents) if the original device fails
			Endoleak Type I (chronic)	Conversion to Vascular Bypass		
			Endoleak Type III (chronic)	Stroke		
				Limb Ischemia		
				Dissection		
				Extension of Dissection		
				Death		
				Post-Op Rupture		

1. Risk mitigation strategies in the table reference the Valiant Captivia PS-IDE device only. For comparison of the Valiant Captivia PS-IDE device and the Valiant Navion, refer to Appendix 13.

3.4.2.1 General risk mitigation strategies:

1. Investigators are all chosen based on experience and skills in using endoluminal aortic devices. The study site at The Heart Hospital Baylor Plano is experienced with conducting investigational and feasibility studies in endovascular procedures. In case the patient population would need open surgical conversion, the investigators will be able to offer this life-saving measure promptly. The Heart Hospital Baylor Plano has an active open-heart surgery program.

2. Appropriate risk minimization activities were performed during the development and design verification tests of the device by Medtronic Vascular.

3. Adequate informed consent will be performed by explaining to the patients the endovascular, open surgical and medical treatment options.

4. Adherence to eligibility criteria and screening procedures will ensure that appropriate patients are enrolled. Screening procedures include careful history and thorough physical examination. Only patients that meet the aforementioned inclusion criteria will be entered in the study.

5. Adherence to the Medtronic Instructions for Use packaged with the Valiant Captivia PS-IDE device (Appendix 2) and the Valiant Navion device (Appendix 14).

6. By limiting the sample size to 5 patients at a time, the investigators appropriately mitigate the risks potentially associated with an early feasibility study.

7. The subjects will be carefully and regularly monitored throughout the study period. These follow-up intervals are more frequent than the follow-up offered to patients undergoing open repair, traditional feasibility or pivotal study).

8. The investigators will evaluate the subject adverse events during the course of the study and report these on timely and periodic fashion after completion of first five subjects or within three months, whichever is the shortest interval. All serious/severe adverse events will be reported within five working days to the FDA.

9. The device performance parameters will be reported in a timely and periodic fashion which helps to determine whether the stent graft design functions as intended.

10. This ascending stent graft is used in subjects with more favorable anatomical characteristics as compared to the population enrolled with descending thoracic pathologies. The investigators expect the aortic pathologies included in this feasibility study to have a more favorable exclusion rate by TEVAR compared to cohort with ascending aortic aneurysm.

11. The placement of a thoracic aortic stent (TEVAR) in the proximal ascending aorta is technically demanding from a clinical and engineering viewpoint. Due to the close proximity to the coronary arteries and arch vessels leading to the brain precise deployment is critical. Our experience has shown us that a proximal constrainment (such as tip capture technology) is advantageous for satisfactory results and may be required for accurate deployment in the ascending aorta (Zone 0).

12. Monitoring visits will be conducted to evaluate protocol compliance and data quality.

13. 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.

3.4.2.2 Targeted risk mitigation efforts:

In this segment, targeted efforts to mitigate risk of complications are discussed. The aforementioned list of adverse events is used to discuss the appropriate mitigation strategies.

1. Plaque embolization that may lead to stroke, amputation, intestinal ischemia, multiple organ failure, or death - economy of wire and catheter manipulation in the aortic arch and the ascending aorta by an experienced investigator team should reduce the risk.

   Stroke reduction strategies: All patients will undergo a neurological exam when possible depending upon the urgency of the procedure and patient availability. If a patient has prior history of stroke, an NM stroke scale will be obtained when possible during the preoperative evaluation and prior to discharge. If there is concern about any neurological impairment, a neurology team will be involved in the care of the patient. Since the brachiocephalic vessels and calcific aortic valve are not manipulated in this feasibility study, the investigators do not recommend obtaining MRI in all patients preemptively. The investigators expect less embolic stroke with this feasibility study compared to the studies involving manipulation within the brachiocephalic arteries such as the studies involving

the left subclavian artery branch stent graft or transcatheter valve replacement, by manipulating calcific aortic stenosis.

2. Renal insufficiency or failure, that may necessitate dialysis - we will reduce the contrast to as low as possible. Many angiograms may be obtained with 50% contrast concentration Risk of embolic kidney disease is modulated as described above.

3. Unsuccessful repair or early endoleak, possibly leading to rupture of the aorta and death - ballooning of the end leaking landing zone may mitigate this risk. Addition of a larger stent graft at this location may reduce the endoleak as well. Alternatively, if the patient would need open conversion to fix any severe endoleak, the investigators would offer open repair immediately.

4. Propagation of dissection into the aortic root, possibly causing acute aortic regurgitation, or coronary dissection/occlusion, both leading to shock, conversion to surgery, or death - prompt diagnosis is paramount. This is facilitated by routine use of transesophageal echocardiogram. Immediate open surgical repair by an experienced team is key for a good outcome in this severe complication.

5. Delayed endoleak, possibly leading to rupture of the aneurysm and death; routine and close follow-up interval with various imaging techniques is key for detection of late endoleak. The repair options were discussed in #3.

6. Vessel rupture, possibly leading to shock, conversion to surgery, or death; immediate diagnosis and repair using endovascular or open techniques are key to a satisfactory outcome.

7. Migration of the device, possibly leading to rupture of the aorta, open surgery, or death — small migrations may be watched under close surveillance protocols. Other migrations may need additional stent grafting or open repair to mitigate the risk involved.

8. Blood loss, possibly leading to shock or death - this is usually promptly treated with appropriate blood product transfusion. Emergent surgery will ensure if necessary. Any injuries causing major bleeding will be addressed promptly by endovascular or open means.

9. Graft twisting or kinking, possibly leading to shock or death - most stent graft twisting and kinking warrant conservative therapy with close monitoring, while the hemodynamically significant issues will need open or endovascular options.

10. Infection, possibly leading to septicemia or death - the investigators and the OR team maintain a strict sterile field during the TEVAR procedure. Appropriate antibiotic prophylaxis is provided within an hour prior to skin incision.

11. Occlusion of blood flow to the spinal cord, possibly leading to temporary or permanent paraparesis or paraplegia - this is a rare complication for patients

with ascending aortic pathologies. The patients with evident spinal cord injury would receive an immediate spinal cord drainage catheter while the blood pressure and the hemoglobin are kept artificially high to improve perfusion pressure to the spinal cord.

12. Conversion to open surgery with all the risks associated with an open surgical repair - this may be the only reasonable option and the safest approach to mitigate certain complications.

13. Myocardial infarction, arrhythmia and/or congestive heart failure possibly leading to shock or death - having experienced anesthesiologists trained in cardiac anesthesia and transesophageal echo is helpful in diagnosing these effects promptly at our institution, and appropriate treatment is initiated that may include normotensive hemodynamics, reducing heart rate, as well as appropriate medications aspirin, nitroglycerine, amiodarone, and inotropic drips.

14. Respiratory failure possibly leading to death - this is rare with endovascular repair unless there is need for massive blood transfusion causing transfusion-associated acute lung injury (TRALI).

15. Cardiac injury including perforation due to nose cone introduction - this is a rather rare complication and mostly applies to the transcatheter valve replacement (TAVR) patients. The stent graft is introduced through the stiff guidewire that is placed in the left ventricle across the aortic valve. The nose cone does not touch the ventricles as it is significantly shorter than the left ventricular length. While there might be a small amount of acute aortic regurgitation by placing the wire in a patient without prior valve problems, it effectively eliminates any potential valve injury with the nosecone and wire piercing of the valve. The guidewire is j-tipped and pre-curved and is inserted carefully into the left ventricle so there is no piercing of the heart with the stiff wire. This is a more common complication, mostly self-limiting, and on occasion may need a pericardial hematoma drainage. Investigators may use anti-impulsive methodology similar to transcatheter valve replacement (TAVR) such as right ventricular pacing.

16. Deformation of sinotubular junction causing aortic valve regurgitation -this complication is rather rare, unless there is asymmetry in the sinotubular junction. All procedures are performed under transesophageal echo guidance. If a mild to moderate aortic regurgitation occurs, this can be frequently just monitored, as many patients live their entire life with such degree of aortic regurgitation without any significant sequelae. However, if for some rare reason, a moderate to severe aortic regurgitation occurs, this usually will require open surgical conversion.

17. Involuntary coverage of the coronary arteries — This is an extremely unlikely complication. The coronary arteries rise from the sinus of Valsalva which is

significantly larger than the ascending aorta, therefore the stent graft is very unlikely to obstruct the orifice of the coronary arteries. However, the signs of cardiac ischemia on EKG and

Transesophageal echocardiogram along with fluoroscopic findings of a very low - in the aortic root - deployed stent graft would require wither conversion to open repair or as with "high-riding" transcatheter aortic valve (TAVR), immediate cannulation and stenting of the affected coronary artery by an interventional cardiologist.

18. Involuntary coverage of the brachiocephalic (innominate) artery— This is an uncommon complication. Partial coverage of the innominate artery is frequently completely asymptomatic on neuro exam. However, if there were near-complete coverage of the innominate artery, we would immediately drop a wire down the right carotid artery down in the descending thoracic aorta and put a balloon- expandable stent in the orifice of the innominate (Snorkel method). This allows for perfusion of the innominate artery. Subsequently a carotid-carotid bypass would provide long-lasting patency and perfusion of both carotid arteries.

3.4.3. Potential Benefits

The potential benefits of the Medtronic Thoracic Stent Graft System have not been documented; however they are expected to be similar to some of the endovascular stent grafts currently in clinical use or available outside the United States. The endovascular stent graft repair procedure offers an alternative method of treatment that is potentially less invasive, less expensive, and less risky than standard operative repair.

The most superior potential benefit is that stent graft repair provides a treatment modality for many patients who otherwise would not be candidates for surgical repair because of their comorbidities. Other potential benefits include a reduction in short-term and mid-term mortality and morbidity; a reduction of risk of cardiovascular, pulmonary, neurologic and renal complications as a consequence of shorter exposure to general anesthesia, a less invasive procedure, a preservation of the distal aortic pressure due to maintenance of aortic blood flow; reduced estimated blood loss; lower post-operation complications such as paraplegia; decreased length of Intensive Care Unit and hospital stay, and shorter recuperation.

4. Device Information

Valiant Navion™ Thoracic Stent Graft System

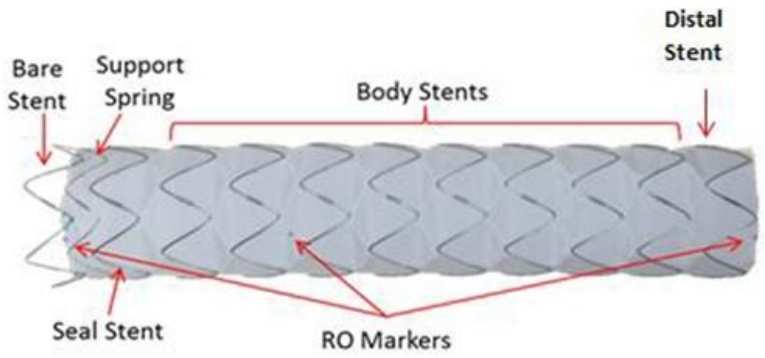
The Valiant Navion™ thoracic stent graft system is designed for the endovascular repair of lesions in the descending thoracic aorta (DTA). When placed within the target lesion, the stent graft provides an alternative conduit for blood flow within the patient's vasculature by excluding the lesion from blood flow and pressure. The stent graft system is composed of 2 main components: the implantable Valiant Navion thoracic stent graft and the disposable delivery

system. The stent graft is preloaded into the delivery system. The loaded delivery system is inserted endoluminally via the femoral or iliac artery and tracked through the patient's vasculature to deliver the stent graft to the target site. Upon deployment, the stent graft self-expands to conform to the shape and size of the seal zones above and below the lesion.

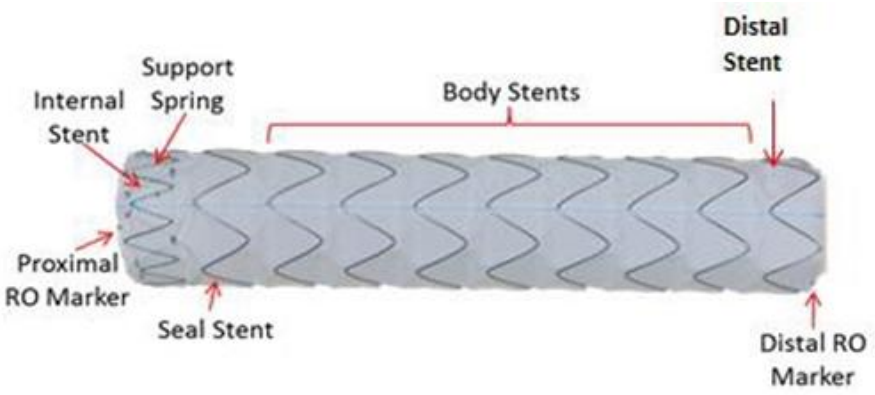
Valiant Navion thoracic stent grafts that will be used as part of this PS-IDE are available in 2 configurations: FreeFlo Straight and CoveredSeal Straight. Each stent graft configuration can be used either as a proximal or distal component; the proximal end of a FreeFlo stent graft should never be placed inside the fabric-covered section of another graft. Stent grafts are available in 18 Fr, 20 Fr, and 22 Fr delivery systems. The FreeFlo configuration includes a FreeFlo proximal end and a CoveredSeal distal end. At the proximal end, a bare stent extends past the covered portion of the stent graft to provide additional fixation while maintaining transvessel flow. The CoveredSeal configuration includes CoveredSeal proximal and distal ends. At the proximal end, an internal stent with a W-stent are covered to provide additional fixation while maintaining transvessel flow.

The Valiant Navion delivery system consists of a single-use, disposable catheter with an integrated handle, intended to provide controlled deployment. It is available in an outer diameter of 18, 20, and 22 Fr and a working length of 93 cm. The catheter assembly is flexible and exclusively compatible with a 0.035 in (0.89 mm) guidewire. A flexible tapered tip is attached to the end of the inner member and provides a smooth transition from the guidewire to the outer graft cover. The external surfaces of the tapered tip and graft cover are coated with a lubricious hydrophilic coating. Once activated with a sterile gauze saturated in saline, this coating facilitates vessel access and tracking through the anatomy. A distal RO marker indicates the graft cover edge under fluoroscopy. The flush port includes a one-way valve that prevents backflow of flush fluid and maintains hemostasis during the procedure, while allowing the delivery system to be flushed during device preparation. The stent graft is deployed by rotating or retracting the integrated slider handle. The tip capture release handle at the rear of the delivery system is unlocked and retracted to release the proximal end of the stent graft.

Valiant Navion FreeFlo Straight Configuration

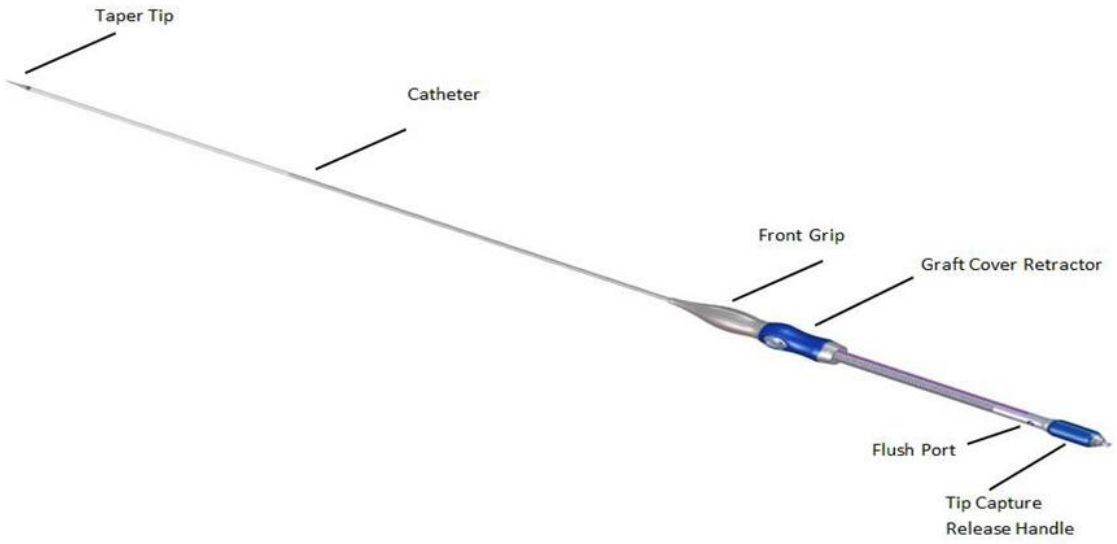


Valiant Navion CoveredSeal Straight Configuration



While not in the figure for CoveredSeal Straight, the body RO marker is at the same location and have the same configuration in both the FreeFlo and CoveredSeal configurations.

Valiant Navion Delivery System



Valiant Navion™ Thoracic Stent Graft System: **FreeFlo**

Diameter (mm)	Covered Length (mm)
20, 22, 25	96
28, 31	97
34, 37	59, 97
40, 43, 46	62, 103

Valiant Navion™ Thoracic Stent Graft System: **CoveredSea**l

Diameter (mm)	Covered Length (mm)
20, 22, 25	94
28, 31	90
34, 37	52, 90
40, 43, 46	55, 95

The Valiant Navion™ thoracic stent graft system is a commercially approved stent graft system designed for the endovascular repair of lesions in the descending thoracic aorta (DTA).

Unique challenges of stenting in the ascending aorta from literature	**Valiant Navion™ thoracic stent graft system**
Negotiating the curvature of the aortic arch	• 93cm working length • decreased delivery sheath diameter by 3-4 French sizes These advances serve to decrease the risk of access vessel injury and decrease the necessity of stiff guidewire placement in the left ventricular cavity except on rare occasion.
Proximal fixation close to the aortic valve and coronary ostia, distal fixation that may impinge on the innominate artery, hemodynamic forces and retrograde dissection	• Covered Seal with tip capture • Free flow with tip capture • Shortened tip length Allows for easier placement near the aortic valve and the sino tubular junction
The ascending aorta is on the average a centimeter larger that the descending thoracic aorta, and about one fourth in length	Size matrix up to 46mm in diameter in lengths of ~6cm and ~10cm
Difference in variation in the maximum and minimum size of the aorta during diastole and systole. Based on 4-	System has a strong radial force to reduce endoleak rate and potential migration in the descending aorta

dimensional evaluation of our patients, we found that the variation in size is about 10% in descending thoracic aorta while it is 15% in ascending aorta. This may have ramifications in stent graft fixation for devices with poor radial force	

5. Monitoring Procedures

5.1 Procedures for Monitoring

Improvement/Regulatory Specialist who is experienced in monitoring and medical device research will carry out the monitoring activities.

The purpose of the monitoring plan is to facilitate compliance with GCP guidelines (ICH E6 5.18), FDA guidelines and FDA regulations (21 CFR 812.40) which require clinical trial monitors to verify that:

- The rights and well-being of human subjects are protected.
- Reported trial data are accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol, with GCP, and with applicable regulatory requirements.

As this is a single site study, monitoring will be conducted on site at the BSW Research Institute office affiliated with The Heart Hospital Baylor Plano.

On site monitoring for this trial will support verification that:

- Appropriate FDA and IRB authorizations to conduct the research study have been obtained prior to screening and enrollment of any subjects.
- The protocol/investigational plan is being followed.
- The investigator is carrying out the agreed-upon activities and providing adequate oversight of delegated activities.
- Delegated Activities have been documented using a log to demonstrate Principal Investigator delegation to appropriate study team members. Review will also verify that activities, such as informed consent, have not been performed by individuals for whom documentation of delegation is not present.
- Informed consent has been obtained and documented in accordance with 21 CFR Parts 50 and 56 and prior to initiation of study procedures.
- Eligibility criteria are met for each subject to participate in the trial to exclude individuals for whom the investigational product may be less safe than the protocol intended and to include only subjects from the targeted study population.
- Site records are maintained, complete, and current with the progress of the trial. Records will be reviewed to confirm that Essential Documents are present and maintained.
- Subject records are maintained in a secure environment to maintain integrity and confidentiality.

    - Subject Records include documentation to support that:
        - Procedures are completed as described in Study Procedures section of the protocol related to study endpoints and completion of safety assessments
        - There is evidence of evaluation and documentation of serious adverse events, unanticipated adverse device effects, subject deaths, and withdrawals, especially when a withdrawal may be related to an adverse event
        - There is evidence of adequate Principal Investigator oversight of the study.
- eCRFs are completed and attested to by the Principal Investigator in a timely manner.
- Source data verification will be completed by comparison of the source documents to the eCRFs focusing on the elements to support confirmation of data quality for the end points and objectives as described in the protocol. These events include, but are not limited to:
    - Successful Implantation as defined in the protocol at implant time of discharge and Months 1, 6 and 12 after implantation of the graft
    - Subject Survival at time of implant, discharge, and through 60 months after implantation
    - Adverse event occurrences to support statistical analysis
    - Documentation to support determining technical and clinical success
    - Additional elements, such as: ICU Length of Stay post index procedure and total hospital length of stay

  Adverse Events, Serious Adverse Events and Unanticipated Adverse Device Effects/Events are identified and reported appropriately in a timely manner to the FDA, the IRB and the device manufacturer.

  Investigational product accountability will be completed at each visit with review of:

    - Secure location for storage and controlled access to the devices
    - Storage environment meets manufacturer guidelines
    - Investigational product tracking from receipt at the research site to disposition of each device, including but not limited to, receipt date, subject identification, specific device identification such as batch number/serial number, expiry date and disposition including Implanted, Malfunction/Returned to Manufacturer or Opened, Not Used.
    - Verification of inventory as compared to shipping/packing forms from the manufacturer/distributor.
    - Regular reports are submitted to the FDA and the IRB at least annually or as requested by either entity

  On site monitoring will be completed at regular intervals commensurate with enrollment of the first subject and completion of the index procedure. Additional visits will be completed at least every 6 to 12 weeks based on subject enrollment and study timeline status for each subject. Compliance with the study milestones for each enrolled subject will be reviewed, as well. Initial, Interim and Close Out visits will be conducted.

Detailed written reports from each monitoring visit will be provided to the Investigator and the study team within 14 business days of completion of the monitoring visit. Issues requiring immediate action will be discussed with the Principal Investigator at the time they are identified for further action. If indicated, the issues will be reported to appropriate individuals within BSW Research Institute. Copies of monitoring reports will be provided to BSW Research Institute at the time of distribution to the Principal Investigator.

5.2. Name and Address of Monitor

Monitoring functions will be conducted by Kristen Lyons, Baylor Scott & White Research Institute, 2001 Bryan Street Suite 2200, Dallas, Texas 75201.

6. Oversight

The DSMB will be responsible for assuring that research subjects are not exposed to unnecessary or unreasonable risks Ongoing responsibilities of the DSMB will be to evaluate the progress of the study, including periodic assessments of adverse events and serious adverse events The DSMB will report on the safety and scientific progress of the study.

7. Additional records and reports

Case report forms should be entered into the electronic database within 10 days after the corresponding visit. Upon request of the reviewing IRB, DSMB, or FDA, the Baylor Scott & White The Heart Hospital - Plano will provide accurate, complete, and current information about any aspect of the study.

All Unanticipated Adverse events will be reported to the IRB and FDA within 10 days of notification of event. All other adverse events and study updates will be reported at the IRB continuing review as well as the FDA annual review.

The enrollment will be performed in five-patient increments, and the results of each five-patient group will be analyzed and reported prior to enrolling further patients.

Copies of the CRFs are in Appendix 3.

8. Investigator Information

8.1. Names and addresses of Sponsor-Investigator:

William Brinkman, MD
Baylor Scott & White The Heart Hospital - Plano
1100 Allied Drive
Plano, Texas 75093

Co -Investigators

Dennis Gable, MD
Baylor Scott & White The Heart Hospital - Plano
1100 Allied Drive
Plano, Texas 75093

William Shutze, MD
Baylor Scott & White The Heart Hospital - Plano
1100 Allied Drive
Plano, Texas 75093

Katherine Harrington, MD
Baylor Scott & White The Heart Hospital - Plano

1100 Allied Drive
Plano, Texas 75093

Justin Schaffer, MD
Baylor Scott & White The Heart Hospital - Plano
1100 Allied Drive
Plano, Texas 75093

J. Michael DiMaio, MD
Baylor Scott & White The Heart Hospital - Plano
1100 Allied Drive
Plano, Texas 75093

8.2. Investigator agreement & commitment

Please refer to Appendices 6 and 7 for a sample Investigator agreement and the Investigators curriculum vitae. The investigators are not involved in an investigation or other research that was terminated.

The investigators are committed to conduct the investigation in accordance with the agreement, the investigational plan, Part 812 and other applicable FDA regulations, and the conditions of approval imposed by the reviewing IRB and FDA. They are also committed to supervise the testing of the device involving human subjects and in ensuring that the requirements for obtaining the informed consent are met. All the participating investigators have signed the agreement and no investigator will be added until the agreement is signed.

9. IRB Information

Baylor Institutional Review Board
2001 Bryan Street Suite 2200
Dallas, Texas 75201

This protocol will be reviewed by the IRB once the protocol has been approved by the FDA.

10. Sales Information

The devices will be sold according to the agreement with Medtronic to cover the cost of production of the device. The sale of devices does not constitute commercialization because it only covers the cost of device production. Subject insurance will be charged for the use of the device.

11. Labeling

Please see Appendix 3 for Instructions of Use.

12. Informed Consent

Please see Appendix 5 for a sample of the Informed Consent