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**Evaluation of the GORE® TAG® Thoracic Branch Endoprosthesis (TBE Device) in the
Treatment of Lesions of the Aortic Arch and Descending Thoracic Aorta**

Protocol Number: SSB 11-02

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W. L. Gore & Associates, Inc.
Medical Products Division



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PROTOCOL SUMMARY

Subjects enrolled on the SSB 11-02 Protocol prior to a site's IRB approval of Revision 4 should be followed under Revision 3 of the Protocol located in Appendix E (US only).

Study Summary

Study Title	Evaluation of the GORE® TAG® Thoracic Branch Endoprosthesis (TBE Device) in the Treatment of Lesions of the Aortic Arch and Descending Thoracic Aorta
Protocol Number	SSB 11-02
Revision	10
IDE or PMA Number	G130120
Sponsor	W. L. Gore & Associates, Inc. Medical Products Division 3450 W Kiltie Lane Flagstaff, AZ 86005 Telephone: 800-437-8181
Sponsor (Japan)	W. L. Gore & Associates G.K. Medical Products Division W Building, 1-8-15 Konan, Minato-ku, Tokyo 108-0075 Telephone: 81-3-6746-2562 Fax: 81-3-6746-2563
Study Design	Prospective, non-randomized, multicenter study with four independent arms consisting of a total of seven cohorts: • Zone 2 – Aneurysm, hypothesis-driven analysis • Zone 2 – Non-aneurysm aortic lesions which are anatomically suitable for treatment with the TBE Device, descriptive analysis ○ Dissection cohort ○ Traumatic Transection cohort ○ Other isolated lesion types • Zone 0/1 – Aneurysm, hypothesis-driven analysis • Zone 0/1 – Non-aneurysm aortic lesions which are anatomically suitable for treatment with the TBE Device, descriptive analysis ○ Dissection cohort ○ Other isolated lesion types
Study Objective	Determine whether the GORE® TAG® Thoracic Branch Endoprosthesis is safe and effective in treating lesions of the aortic arch and descending thoracic aorta
Study Endpoint(s)	Primary Endpoint- Zone 2 Subjects (Aneurysm Cohort) Composite of the following events from the time of enrollment through one year: • Device Technical Success • Absence of the following: ○ Aortic rupture; ○ Lesion-related mortality;



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	○ Disabling stroke; ○ Permanent paraplegia; ○ Permanent paraparesis; ○ New onset renal failure requiring permanent dialysis; ○ Additional unanticipated post-procedural surgical or interventional procedure related to the device, procedure, or withdrawal of the delivery system. Primary Endpoint- Zone 0/1 Subjects (Aneurysm Cohort) Composite of the following events from time of enrollment through one month following endovascular procedure: • Initiation of the index endovascular procedure following the debranching procedure • Device Technical Success for the index endovascular procedure • Absence of the following: ○ Aortic rupture; ○ Lesion-related mortality; ○ Disabling stroke; ○ Permanent paraplegia; ○ Permanent paraparesis; ○ New onset renal failure requiring permanent dialysis; ○ Additional unanticipated post-procedural surgical or interventional procedure related to the device, procedure, or withdrawal of the delivery system.
Subject Population	Subjects with thoracic aortic lesions which require coverage of the left subclavian artery, left common carotid artery and/or the brachiocephalic trunk/innominate artery for effective treatment.
Number of Subjects	Total Enrollment of 175-465 Subjects across four independent arms with a total of seven cohorts as follows: • Zone 2 – Aortic Aneurysm; A maximum of 115 Subjects ○ Primary Enrollment (n=85 Subjects) ○ Continued Access Enrollment (maximum 30 Subjects) • Zone 2 – Non-aneurysm aortic lesions; A maximum of 200 Subjects in all cohorts combined. ○ Dissection cohort (minimum 20 Subjects) ○ Traumatic Transection cohort (minimum 10 Subjects) ○ Other isolated lesion types • Zone 0/1 – Aortic Aneurysm; 50 Subjects • Zone 0/1 – Non-aneurysm aortic lesions; A maximum of 100 Subjects in all cohorts combined.



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	○ Dissection cohort (minimum 10 Subjects) ○ Other isolated lesion types
Number of Sites	Up to 40 sites in the U.S. (Zone 2 and Zone 0/1) and up to 5 sites in Japan (Zone 0/1).
Coordination PI	Himanshu J. Patel, M.D. Joe D. Morris Collegiate Professor of Cardiac Surgery University of Michigan Medical Center Department of Cardiac Surgery 1500 E. Medical Center Dr., 5143 CVC Ann Arbor, MI 48109-5864 Phone: (734) 615-9129 Michael Dake, M.D. UA Senior Vice President for Health Sciences Professor, Medical Imaging Professor, Surgery Professor, Medicine Health Sciences Innovation Building (HSIB) 1670 E. Drachman St. Tucson, Arizona 85721 Phone: (520) 626-1197
Expected Time to Complete Enrollment	• Zone 2 - Aortic Aneurysm Subject accrual: 18-24 months • Zone 0/1 - Aortic Aneurysm Subject accrual: 48-60 months • Follow-up – Five years from treatment date Total study duration –Ten years
Schedule of Events Zone 2 Cohorts	Screening Evaluation: (Within 30 days prior to enrollment unless otherwise noted) • Physical examination, medical history • Modified Rankin Scale • Spinal Cord Ischemia Scale • NIH Stroke Scale • Spiral Computed Tomographic Angiography (CTA) of the chest, abdomen, and pelvis (contrast only) within 90 days prior to enrollment • Serum creatinine concentration Procedure: • Endovascular repair with the TBE Device with distal extension using the Conformable GORE® TAG® Thoracic Endoprosthesis as needed • Post deployment angiogram Post Procedure: (Performed prior to discharge unless otherwise noted) • Physical examination • Modified Rankin Scale • Spinal Cord Ischemia Scale



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	• NIH Stroke Scale • In addition, NIH Stroke Scale should be performed for any Subject suspected of having a stroke event that undergoes the treating site's stroke Protocol during the study interval from the initiation of index endovascular procedure until discharge, and should be performed as soon as possible after learning of the event Follow-Up Evaluations: Intervals: 1, 6, 12, 24, 36, 48, and 60 months post-treatment • Physical examination • Modified Rankin Scale (also completed at 3 months for Subjects suspected of experiencing a stroke event through 30 days) • Spinal Cord Ischemia Scale • Spiral CTA of the chest (contrast) • NIH Stroke Scale (one month only) • Dissection Subjects only: Spiral CTA of the chest, abdomen, and pelvis (contrast) • Spiral CT of the chest (non-contrast - one month only, or if endoleak suspected) • Dissection Subjects only: Spiral CTA of the chest, abdomen, and pelvis (non-contrast - one month only, or if endoleak suspected)
Schedule of Events Zone 0/1 Cohorts	Screening Evaluation: <i>(Within 30 days prior to enrollment unless otherwise noted)</i> • Physical examination, medical history • Modified Rankin Scale • Spinal Cord Ischemia Scale • NIH Stroke Scale • Serum creatinine concentration • Spiral Computed Tomographic Angiography (CTA) of the chest, abdomen, and pelvis (contrast only) within 90 days prior to the Phase 2 procedure • Radiological Evaluation of the Head/Neck within 90 days prior to Phase 1 procedure Phase 1 Evaluation at least 24 hours but no more than 60 days following the completion of the revascularization procedure: • Physical examination • Modified Rankin Scale • Spinal Cord Ischemia Scale • In addition, NIH Stroke Scale should be performed for any Subject suspected of having a stroke event that undergoes the treating site's stroke Protocol during the study interval from the initiation of surgical



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	revascularization procedure until discharge post-index endovascular procedure, and it should be performed as soon as possible after learning of the event Phase 2 Procedure at least 24 hours but no more than 60 days following the completion of the revascularization procedure: • Endovascular repair with the TBE Device • Post deployment angiogram Post Procedure: (Performed prior to discharge unless otherwise noted) • Physical examination • Modified Rankin Scale • Spinal Cord Ischemia Scale • NIH Stroke Scale • In addition, NIH Stroke Scale should be performed for any Subject suspected of having a stroke event that undergoes the treating site's stroke Protocol during the study interval from the initiation of surgical revascularization procedure until discharge post-index endovascular procedure, and it should be performed as soon as possible after learning of the event Follow-Up Evaluations: Intervals: 1, 6, 12, 24, 36, 48, and 60 months post-treatment • Physical examination • Modified Rankin Scale (also completed at 3 months for Subjects suspected of experiencing a stroke event through 30 days) • Spinal Cord Ischemia Scale • NIH Stroke Scale (one month only) • Spiral CTA of the chest (contrast) • Dissection Subjects only: Spiral CTA of the chest, abdomen and pelvis (contrast) • Spiral CT of the chest (non-contrast – one month only, or if endoleak suspected) • Dissection Subjects only: Spiral CTA of the chest, abdomen and pelvis (non-contrast – one month only, or if endoleak suspected)
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Additional Information	Core Lab AortaCore Aortic Imaging Lab Director: Jon Matsumura, MD University of Wisconsin 600 Highland Ave., Suite H4735 Madison, WI 53792 CRO (US only) Covance, Inc. 206 Carnegie Center Princeton, NJ 08540
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LIST OF ABBREVIATIONS

AE	Adverse Event
ASA	American Society of Anesthesiologists
BCA	Brachiocephalic Artery
CDMS	Clinical Data Management System
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
cm	Centimeters
CPB	Cardiopulmonary Bypass
CRO	Contract Research Organization
CT	Computed Tomography
CTA	Computed Tomographic Angiography
CTAG	Conformable GORE® TAG® Thoracic Endoprosthesis
DDP	Data Development Plan
DHCA	Deep Hypothermic Circulatory Arrest
DSMB	Data and Safety Monitoring Board
DTA	Descending Thoracic Aorta
DTAA	Descending Thoracic Aortic Aneurysm
CRF	Case Report Form
eCRF	Electronic Case Report Form
ePTFE	Expanded Polytetrafluoroethylene
FDA	Food and Drug Administration (United States)
FEP	Fluorinated Ethylene Propylene
FET	Frozen Elephant Trunk
Fr	French (sizing)
GCP	Good Clinical Practice
HIT	Heparin-Induced Thrombocytopenia
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
LCC	Left Common Carotid Artery
LSA	Left Subclavian Artery
mm	Millimeters
MRA	Magnetic Resonance Angiography
NAL	Non-Aneurysm Lesion
PHI	Protected Health Information
PI	Principal Investigator
PMDA	The Pharmaceuticals and Medical Devices Agency
SAE	Serious Adverse Event
TAG	GORE® TAG® Thoracic Endoprosthesis
TBE	GORE® TAG® Thoracic Branch Endoprosthesis
TEVAR	Thoracic Endovascular Aortic Repair
U.S.	United States
UADE	Unanticipated Adverse Device Effect



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1.0 Introduction

1.1 Disease

A variety of pathologies can affect the thoracic aorta. These include aneurysms, dissections (including variants of dissection) and traumatic pathologies including transection.¹ Aneurysm and dissection may affect any area of the thoracic aorta, including the ascending, arch or descending, whereas traumatic transections are typically located in the descending thoracic aorta (DTA). The decision to treat thoracic aortic pathologies and the type of treatment indicated are pathology and patient dependent. Treatment options include medical management, open surgical repair, thoracic endovascular aortic repair (TEVAR) and hybrid surgery with TEVAR.

1.1.1 Thoracic Aortic Aneurysms

Aneurysms of the DTA are rare disorders (53 cases/1,000,000 population) characterized by degeneration of the aortic media resulting in weakness of the vessel wall. These aneurysms are characterized by degeneration of the aortic media resulting in weakness of the aortic wall. The natural history of DTA aneurysm is an increase in sac diameter leading to eventual rupture.² The need for surgical intervention and the type of intervention in a non-emergent setting are determined by the aortic size as well as consideration of other factors which can affect aortic growth (e.g., hypertension).² The annual risk of death, dissection and rupture is related to the size of the aorta (Figure 1). These criteria are used in establishing the threshold for intervention.

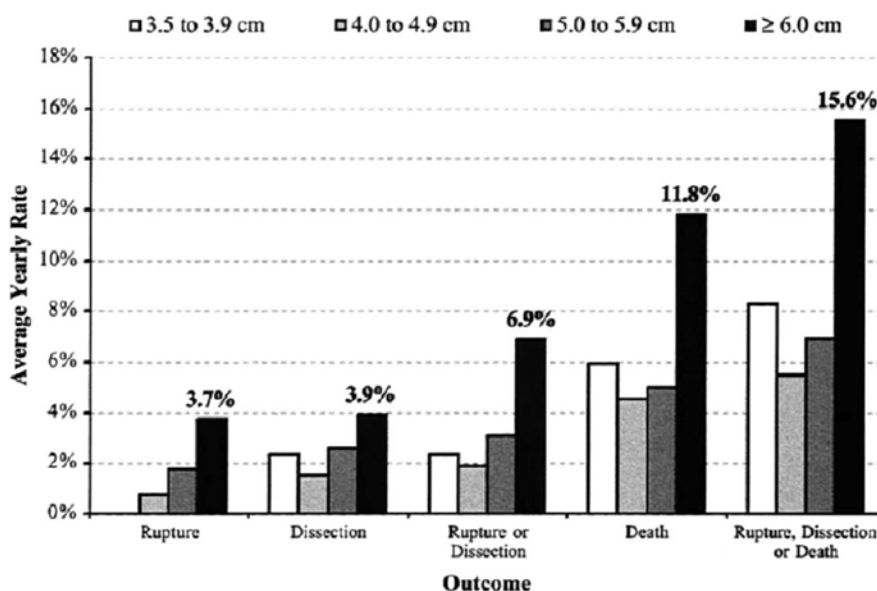


Figure 1: Relationship between Aortic Size and Risk of Rupture, Death and Dissection²



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1.1.2 Traumatic Aortic Transection

Acute aortic transection is typically associated with blunt force chest trauma and is the second leading cause of death following automobile accidents behind closed head injuries.³ Frequently, individuals sustaining aortic transection die before hospitalization.⁴ Azizzadeh and colleagues⁵ proposed a grading scale for the extent of transection based on clinical experience ranging from an intimal tear to complete rupture (**Figure 2**). SVS practice guidelines suggest serial imaging for Grade I traumatic injuries with repair indicated for types II-IV.⁴

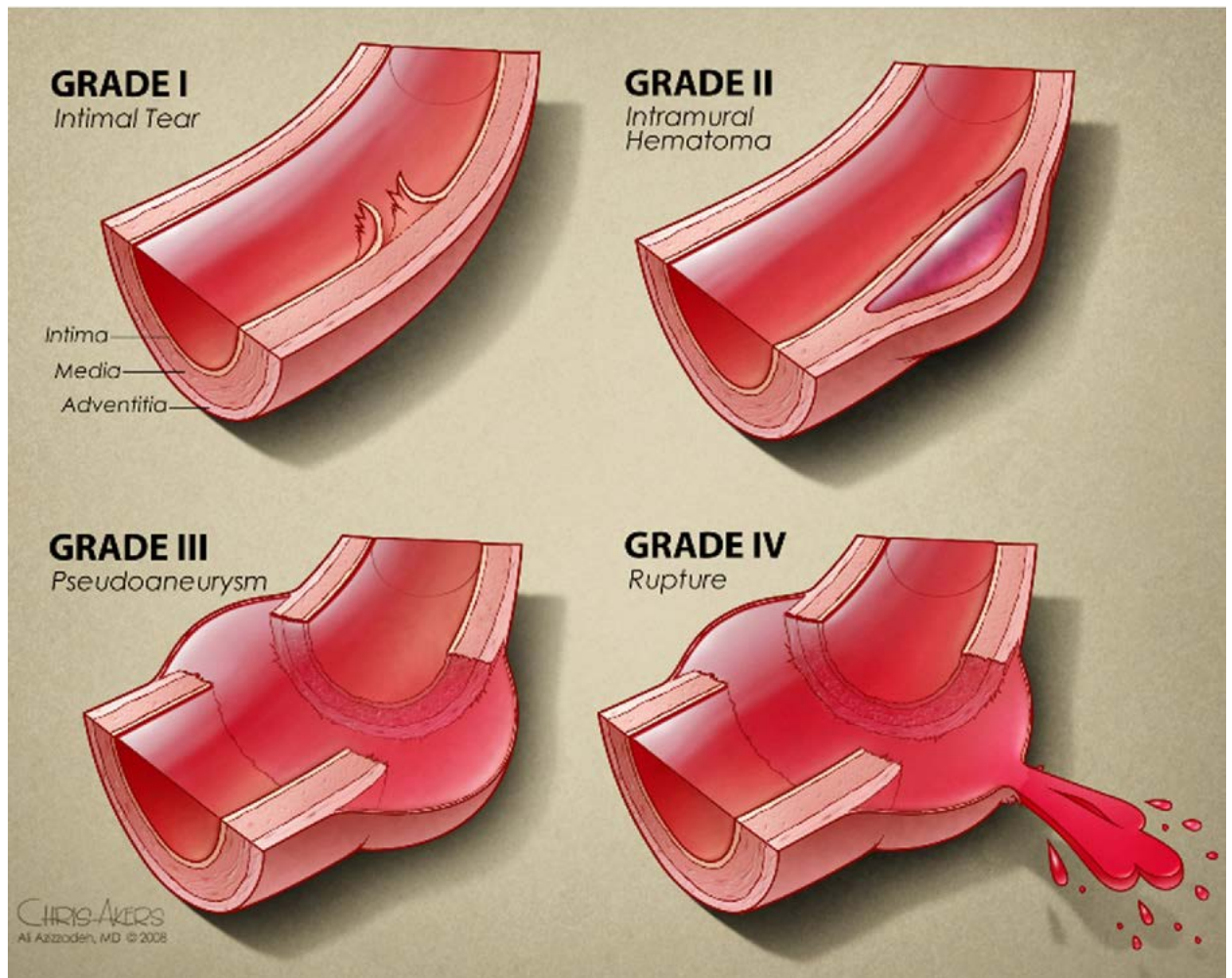


Figure 2: Classification of Traumatic Aortic Injury⁵



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1.1.3 Aortic Dissection

Aortic dissection is the most common aortic catastrophe requiring immediate surgical intervention.⁶ The exact population incidence is unknown as up to 30% of aortic dissections may not be clinically diagnosed⁷, although published figures range from 5-30 cases per 1,000,000 per year^{6, 8-10}. In addition, published figures in Japan indicate 2.62 - 5.2 cases per 100,000 per year¹¹. This injury is initiated by a tear in the aortic intima and results in a surge of blood into the aortic media, which may extend proximally or distally from the location of initial injury as it separates the intimal and adventitial layers of the aortic wall. Dissection propagation through the media results in the formation of two distinct channels of blood flow, termed true and false lumens separated by a septum composed primarily of the intimal layer of the aortic wall. Common complications associated with dissection are false lumen rupture and blood flow obstruction into branch vessels causing organ or leg malperfusion.

1.1.3.1 Aortic Dissection Classification

Aortic dissections are classified based on the time from symptom onset to dissection diagnosis. The most common classification is acute and chronic. Acute dissection is diagnosed within 14 days of symptom onset while chronic dissection is diagnosed more than 14 days after symptom onset. Dissection is anatomically classified based on location. The most common classifications, proposed by Daily and colleagues¹² and referred to as the Stanford Classification, are Type A and B. Type A dissection involves, but is not limited to, any portion of the ascending aorta. Type B dissection involves only the aorta distal to the left subclavian artery. Alternatively, the DeBakey Classification is used which classifies aortic dissection based on the location of the intimal tear and extent of dissection.¹³ A representation of these classifications is provided in **Figure 3**.

The clinical prognosis of DeBakey Type I and Type II aortic dissection is poor. Historical clinical experience suggests a high risk of immediate mortality from untreated DeBakey Type I/II aortic dissection, frequently estimated at 1-2% mortality per hour.¹⁴ As a result, primary surgical management is warranted for these patients.



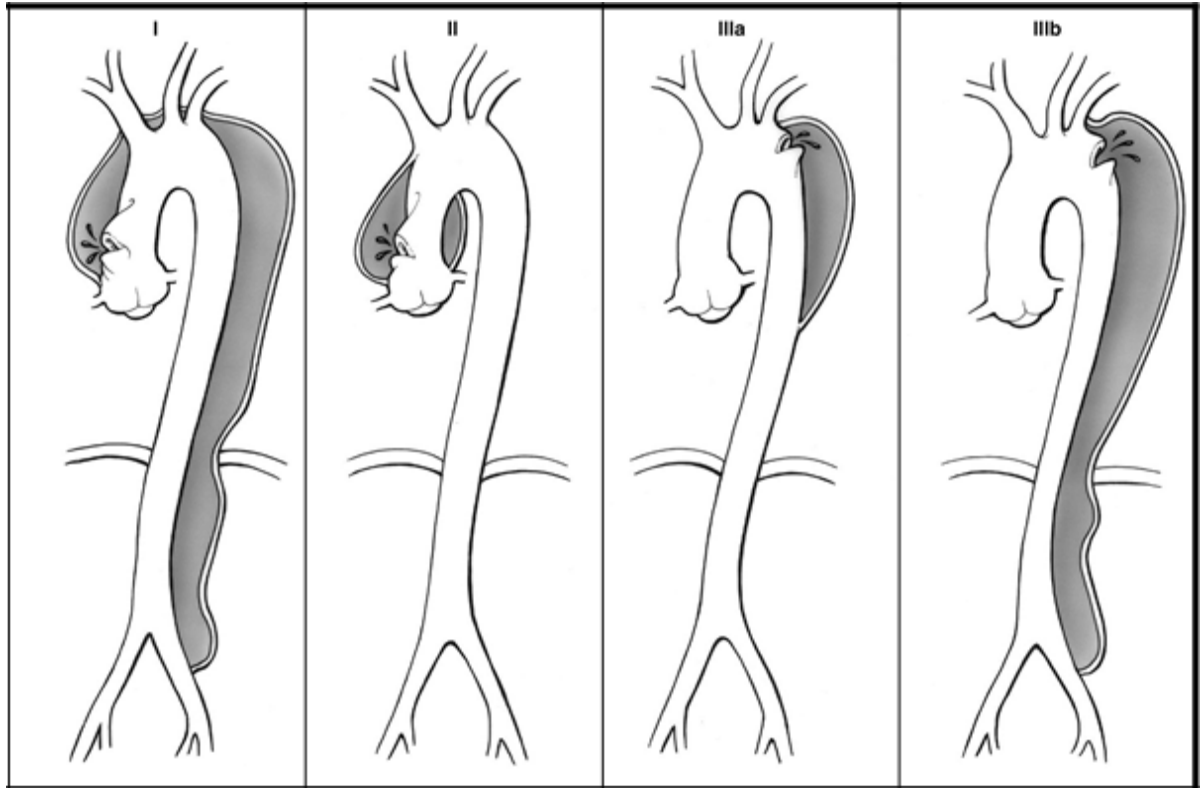


Figure 3. Aortic Dissection Classification Schema

Dissections may be further classified as uncomplicated or complicated. Patients with uncomplicated dissections generally experience symptoms of pain and / or hypertension which may be medically managed. However, these patients may ultimately require surgical interventions in the chronic phase due to aneurysmal dilatation of the false lumen or development of complications such as intractable pain.

Complicated cases are those presenting with rupture or evidence of organ or leg malperfusion; these patients require urgent intervention.^{2, 15, 16}

1.2 Historical Treatments

1.2.1 Medical Management

Medical management of thoracic aortic pathologies is considered when the benefits of surgical intervention are not clear. This may include small aneurysms (below the diameter threshold for intervention), uncomplicated Type B aortic dissections and traumatic injuries classified as small intimal disruptions or in circumstances where the concomitant injuries need to be treated before the aortic injury.

1.2.2 Open Surgical Repair

Open surgical repair for thoracic aortic pathologies remains a viable treatment option, which generally provides a durable repair of the aortic pathology. Generally speaking, open surgical repair of DTA pathologies involves a thoracotomy with surgical adjuncts such as single lung ventilation. Open surgery involving the ascending aorta and arch typically is performed via median sternotomy.



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Surgical treatment for a DTA pathology involves a thoracotomy to gain aortic exposure and replacing the aneurysm with a prosthetic vascular graft. This invasive procedure results in operative mortality of 5-10% and substantial morbidity¹⁷⁻²⁰. Surgical adjuncts such as single lung ventilation are required. These requirements inform the benefit/risk assessment for any particular patient.

For pathology involving the aortic arch, surgical approach via median sternotomy is required. These pathologies may include isolated arch aneurysm, aneurysm extending proximal into the aortic arch from the descending thoracic aorta, dissection extending proximal or distally into the aortic arch, and traumatic transection including the arch. These procedures can be technically challenging due to the need to interrupt the flow of blood to both the brain and to all downstream organs to repair the arch. The first pioneering work on aortic arch reconstruction was done by DeBakey and colleagues in 1957.²¹ This initial work yielded mortality rates exceeding 25%, with the cause of death often secondary to neurologic complications. Subsequent efforts were made to improve neuroprotection intra-operatively. Notable was the introduction of deep hypothermic circulatory arrest (DHCA) technique in 1975 by Griep and colleagues which simplified the operative approach to that currently used, and established a safe strategy for repair and neuroprotection.²² This DHCA technique was used in the influential work published in 1993 by Svensson and associates²³ reporting a study of 656 patients with much improved mortality rates of death and stroke rates of 10% and 7% respectively. Since this report, other neuroprotection techniques have evolved, including antegrade and retrograde cerebral perfusion used during DHCA, to allow for longer surgical times and repair of increasingly complex anatomy.

1.2.3 Thoracic Endovascular Repair (TEVAR)

TEVAR provides a minimally invasive treatment option for DTA pathologies. TEVAR has demonstrated benefits in clinical trials relative to open surgical repair for the treatment of DTAA including lower aneurysm-related mortality, lower morbidity, less operative blood loss, shorter intensive care unit and hospital stay, and quicker convalescence.²⁴ Additionally, the lower risk of surgical complications associated with TEVAR have led to the adoption of the procedure to treat traumatic aortic transection and Type B aortic dissection.

TEVAR involves remote access to the aortic lesion from a remote site (usually the femoral artery) and implantation of a stent graft to seal the aortic lesion from circulation. Conceptually, the application of TEVAR in DTAA and traumatic transection is similar given the presence of an isolated lesion with a proximal and distal landing zone for the device, although the patient populations and pathologic processes are different. The application of TEVAR to Type B aortic dissection is typically to seal the primary dissection entry tear, with decisions regarding the extent of aortic coverage made on a case-by-case basis, depending on complications (rupture) and chronicity (acute vs. chronic).



In the United States and Japan, TEVAR procedures are indicated for use in Zone 2 (**Figure 4**) or below. As a result of the requirement for landing zone and as physicians have encountered patients with pathology approaching the aortic arch who may otherwise be eligible for stent graft treatment, endovascular techniques have been extended to address this more challenging patient population. Most commonly, this is accomplished through the implantation of a stent graft with proximal sealing in Zone 2 (Figure 4), across the ostium of the left subclavian artery (LSA) with or without revascularization by bypass or transposition.²⁵ Although coverage of the LSA was initially reported to be a largely safe procedure,^{26, 27} not all reports are in agreement with this strategy for the management of the LSA.²⁸ Indeed, previous publications suggest that coverage of the LSA may not be a benign procedure, possibly increasing the risk of both cerebrovascular accident (CVA) and spinal cord ischemia (SCI) relative to patients without LSA coverage,^{29, 30} leading the Society for Vascular Surgery to recommend preoperative revascularization of the LSA in most cases.

In Japan, a fenestrated stent graft "Najuta Thoracic Stent Graft System" has been marketed since 2012. This device has a fenestrated graft design that allows proximal placement from Zone 0.

Due to the design of the Najuta System, there are constraints on the types of anatomy that can be treated with this device and therefore endovascular treatment options for aortic arch aneurysms involving the cervical anatomical are limited..

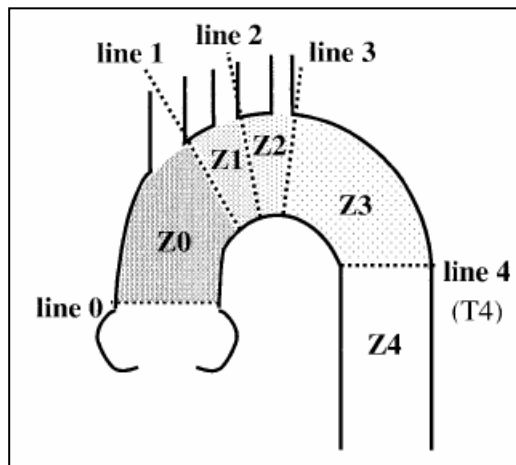


Figure 4: Anatomical Landing Zone Map for Thoracic Endovascular Stent Graft Placement²⁵

1.2.4 Hybrid TEVAR Procedures

Hybrid TEVAR procedures are operations that include an open surgical and endovascular approach. For the purposes of this document, hybrid TEVAR procedures refer to treatment of aortic arch pathologies (usually aneurysm and dissection) with proximal placement of the endovascular component in Zone 0 or 1 and a surgical component. These procedures are considered less invasive than a complete open repair of the aortic arch; however, depending on the extent of repair, large incisions are frequently required including median sternotomy and/or neck incisions such as cervicotomy or mini-thoracotomy.



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A systematic review by Cao and colleagues³¹ focused on outcomes of various hybrid procedures classified by these authors as “arch debranching”, “frozen elephant trunk” and “stented elephant trunk with endovascular repair of thoracoabdominal aorta”. Most relevant to this discussion are arch debranching procedures with proximal endovascular device placement in Zone 0-1. These particular operations involve several options for the debranching depending on the extent of the disease and considerations of individual patient anatomy.

For hybrid procedures involving device placement in Zone 1, a carotid-carotid bypass (**Figure 5**) is mandatory for stent-graft placement. Depending on the circumstance, the left subclavian may or may not be bypassed as part of this procedure. These bypass procedures can usually be performed without the need for a median sternotomy and can be accomplished through cervical incisions. In Japan, right subclavian artery-left subclavian artery-left common carotid artery bypass may also be performed for Zone 1 procedures.

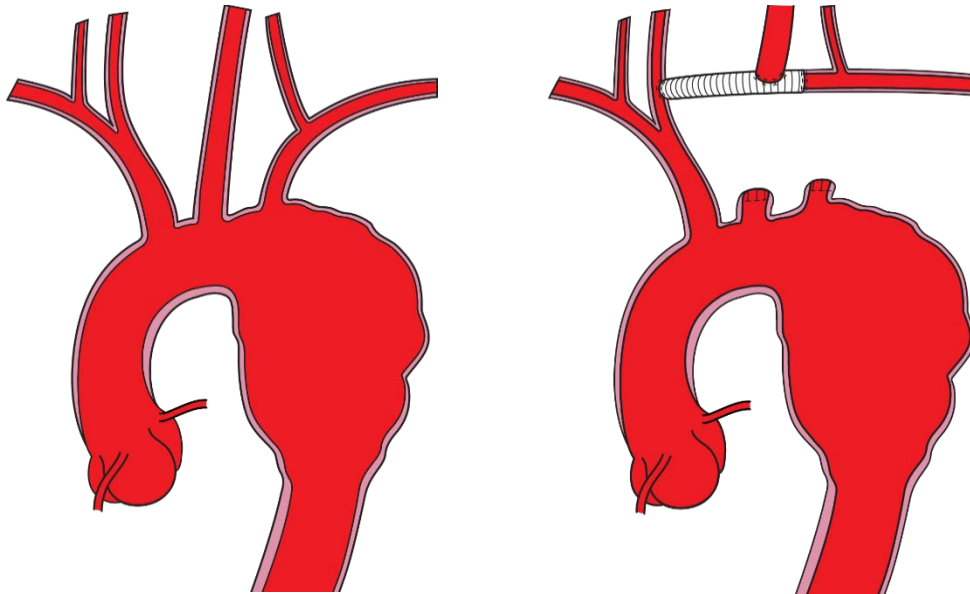


Figure 5: Representative Zone 1 Pathology (Left) with Carotid-Carotid-Subclavian Bypass (Right) and optional LSA transposition

The Cardiovascular Surgery group from the University of Pennsylvania proposed classifications for hybrid techniques involving total arch debranching or Zone 0 repair in 2009³² classified hybrid repairs as follows (**Figure 6**):

- Type I: arch debranching with adequate quality and length proximal and distal landing zones
- Type II: inadequate proximal landing zone with adequate distal aorta for landing a stent graft, and
- Type III: mega-aorta: there is no adequate suitable native proximal aorta and distal aortic landing zone is below the diaphragm.



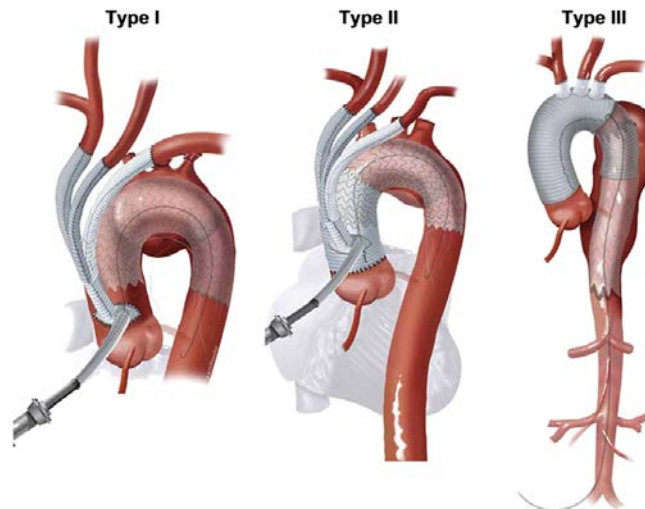


Figure 6: Zone 0 Hybrid Procedure Classification (Milewski, 2010)³³

Each of these repairs requires a proximal device placement in the ascending aorta (Zone 0), with Type I and Type II repairs confined to the thoracic aorta. The requirement for access to the ascending aorta usually requires a median sternotomy in these cases. Generally, a primary distinction between Type I and Type II is the requirement in Type II repairs for the replacement of a segment of the ascending aorta in order to create an adequate landing zone for TEVAR device placement. Depending on the circumstance, Type I repairs may require cardiopulmonary bypass (CPB), while Type II repairs always require CPB with a possible period of deep hypothermic circulatory arrest (DHCA) due to the replacement of the ascending aorta with a surgical graft.

The endovascular aspect of the hybrid procedure involves placing stent grafts to exclude the diseased segment of the aorta from circulation. This part of the procedure may be completed at the same time as the debranching, or at a later time, depending on operator preference and the clinical circumstances. In cases of Zone 0 debranching where the chest is open as part of the repair, devices may be introduced and deployed in an antegrade fashion during the debranching procedure. Otherwise, conventional access routes (e.g., femoral artery) are used to deploy the stent grafts in a typical retrograde fashion.

Another hybrid procedure reserved for patients with more extensive disease in the ascending aorta, including predominately Type A dissection³⁴, is the frozen elephant trunk (FET). This procedure requires replacement of the ascending aorta, typically involving concomitant coronary artery reimplantation and requisite CPB and DHCA. The distal repair is completed with antegrade stent-graft deployment, in a similar manner to the other described hybrid procedures.



1.3 Study Device Description

1.3.1 GORE® TAG® Thoracic Branch Endoprosthesis

The TBE Device consists of three modular components (see **Figure 7**). The two primary system components are the Aortic Component and the Side Branch (SB) Component. The trailing portion of the SB Component is deployed within a distally oriented lumen inside the Aortic component, herein referred to as the portal. The leading portion of the SB Component is deployed in the side branch vessel. This configuration enables the perfusion of a branch vessel within the intended proximal aortic sealing zone. A secondary Aortic Extender is intended to improve sealing of the Aortic Component and/or add seal length proximally within the aorta if necessary. All are delivered from a single femoral access site.

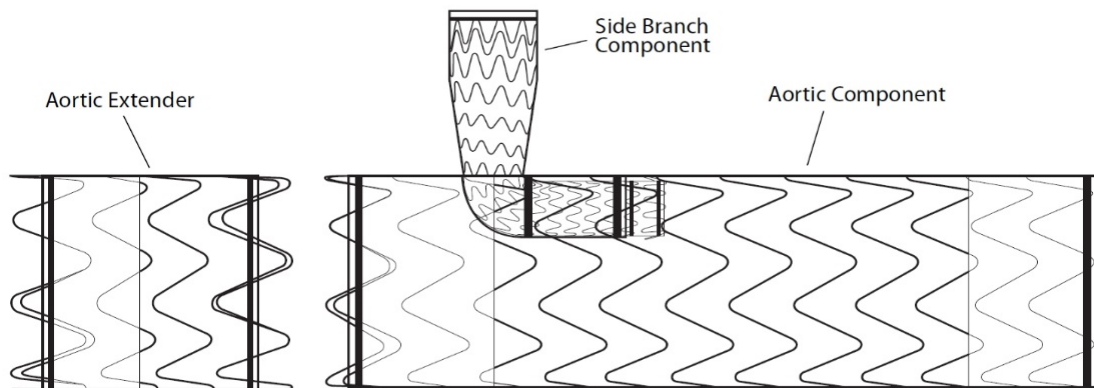


Figure 7: GORE® TAG® Thoracic Branch Endoprosthesis

1.3.2 Aortic Component

The Aortic Component (**Figure 8**) consists of an ultra-thin wall (UTW) graft supported over its entire length by a Nitinol wire-frame (stent). The UTW graft consists of an expanded polytetrafluoroethylene (ePTFE)-extruded basetube, covered with an impermeable ePTFE/FEP (fluorinated ethylene propylene) laminate, which is overwrapped with an ePTFE film. The Aortic Component contains an opening on its outer surface that extends inward to the portal, which allows for sealing and fixation of the SB Component. Embedded in both ends of the device and portal are radiopaque gold rings that provide fluoroscopic visibility. At each end of the Aortic Component are sealing cuffs bonded over the stent. This component is mounted onto a catheter delivery system. Device sizing requirements are included in **Table 1**.



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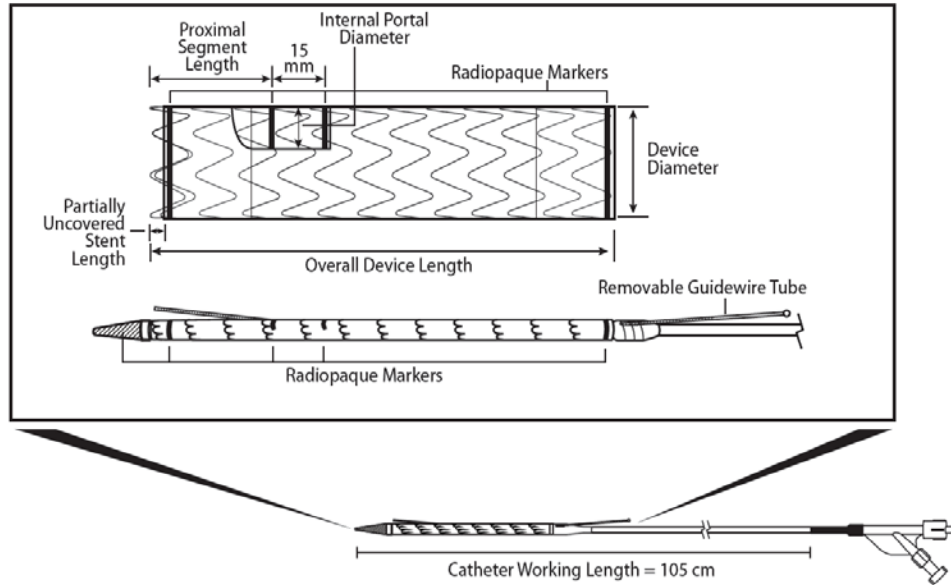


Figure 8: Aortic Component and Aortic Component Delivery System



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Table 1: Aortic Component Sizing Guide

DEVICE DIMENSIONS AND SIZING REQUIREMENTS								
CATALOGUE NUMBER	DEVICE DIAMETER (MM)	INTENDED AORTIC DIAMETERS (MM)	INTERNAL PORTAL DIAMETER (MM)	PROXIMAL SEGMENT LENGTH (MM)	PROXIMAL COVERED LENGTH (MM)	PARTIALLY UNCOVERED STENT LENGTH (MM)	OVERALL DEVICE LENGTH (CM)	GORE® DRYSEAL SHEATH SIZE (Fr)
TAC082110C	21	16 - 19.5	8	20	17	3	10	20
TAC082115C	21	16 - 19.5	8	20	17	3	15	20
TAC082120C	21	16 - 19.5	8	20	17	3	20	20
TAC082610C	26	19.5 - 24	8	20	16	4	10	20
TAC082615C	26	19.5 - 24	8	20	16	4	15	20
TAC082620C	26	19.5 - 24	8	20	16	4	20	20
TAC082810C	28	22 - 26	8	20	16	4	10	22
TAC082815C	28	22 - 26	8	20	16	4	15	22
TAC082820C	28	22 - 26	8	20	16	4	20	22
TAC083110C	31	24 - 29	8	20	16	4	10	22
TAC083115C	31	24 - 29	8	20	16	4	15	22
TAC083120C	31	24 - 29	8	20	16	4	20	22
TAC123110C	31	24 - 29	12	40	36	4	10	22
TAC123115C	31	24 - 29	12	40	36	4	15	22
TAC123120C	31	24 - 29	12	40	36	4	20	22
TAC083410C	34	27 - 32	8	20	15	5	10	24
TAC083415C	34	27 - 32	8	20	15	5	15	24
TAC083420C	34	27 - 32	8	20	15	5	20	24
TAC123410C	34	27 - 32	12	40	35	5	10	24
TAC123415C	34	27 - 32	12	40	35	5	15	24
TAC123420C	34	27 - 32	12	40	35	5	20	24
TAC083710C	37	29 - 34	8	25	20	5	10	24
TAC083715C	37	29 - 34	8	25	20	5	15	24
TAC083720C	37	29 - 34	8	25	20	5	20	24
TAC123710C	37	29 - 34	12	40	35	5	10	24
TAC123715C	37	29 - 34	12	40	35	5	15	24
TAC123720C	37	29 - 34	12	40	35	5	20	24
TAC084010C	40	31 - 37	8	25	19	6	10	26
TAC084015C	40	31 - 37	8	25	19	6	15	26
TAC084020C	40	31 - 37	8	25	19	6	20	26
TAC124010C	40	31 - 37	12	40	34	6	10	26
TAC124015C	40	31 - 37	12	40	34	6	15	26
TAC124020C	40	31 - 37	12	40	34	6	20	26
TAC084510C	45	34 - 42	8	25	18.5	6.5	10	26
TAC084515C	45	34 - 42	8	25	18.5	6.5	15	26
TAC084520C	45	34 - 42	8	25	18.5	6.5	20	26
TAC124510C	45	34 - 42	12	40	33.5	6.5	10	26
TAC124515C	45	34 - 42	12	40	33.5	6.5	15	26
TAC124520C	45	34 - 42	12	40	33.5	6.5	20	26



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1.3.3 Aortic Extender

The Aortic Extender (**Figure 9**) has a construction similar to the leading end of the Aortic Component, without the portal. Unlike the Aortic Component, only the leading end of the Aortic Extender has a sealing cuff bonded over the stent. In addition, both the leading and trailing ends of the Aortic Extender include a partially uncovered stent. This device is mounted onto a catheter delivery system. Device sizing requirements are included in Table 2.

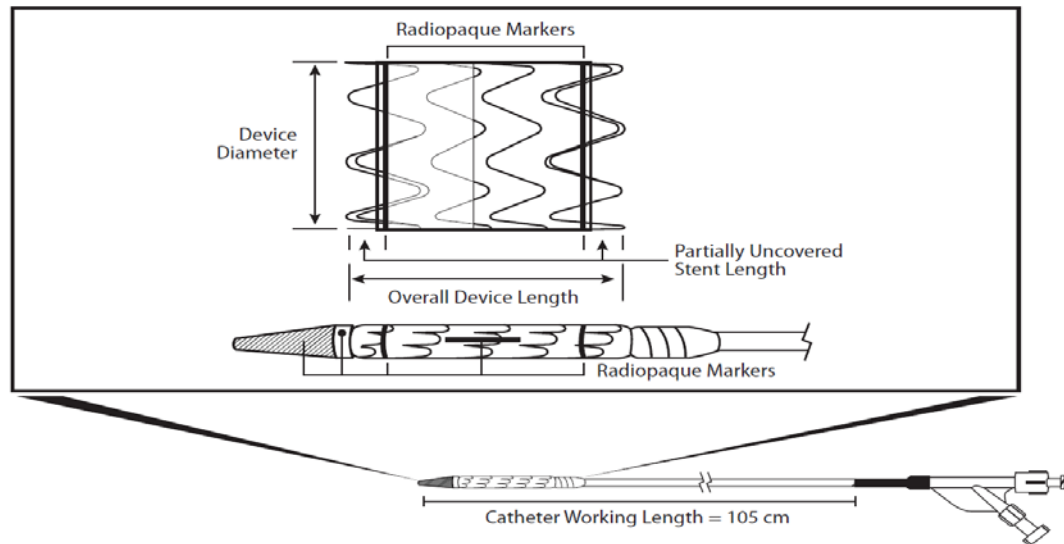


Figure 9: Aortic Extender and Aortic Extender Delivery System

Table 2: Aortic Extender Sizing Guide

DEVICE DIMENSIONS AND SIZING REQUIREMENTS					
CATALOGUE NUMBER	DEVICE DIAMETER (MM)	INTENDED AORTIC DIAMETERS (MM)	OVERALL DEVICE LENGTH (CM)	PARTIALLY UNCOVERED STENT LENGTH (MM)	GORE® DRYSEAL SHEATH SIZE (Fr)
TE2136C	21	16 - 19.5	3.6	3	20
TE2638C	26	19.5 - 24	3.8	4	20
TE2840C	28	22 - 26	4.0	4	22
TE3140C	31	24 - 29	4.0	4	22
TE3442C	34	27 - 32	4.2	5	24
TE3742C	37	29 - 34	4.2	5	24
TE4043C	40	31 - 37	4.3	6	26
TE4546C	45	34 - 42	4.6	6.5	26



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1.3.4 Side Branch Component

Similar to the Aortic Component and Aortic Extender, the SB Component (**Figure 10**) consists of a UTW graft supported over its entire length by a Nitinol wire-frame (stent). The UTW graft consists of an ePTFE-extruded basetube, covered with an impermeable ePTFE/FEP laminate, which is overwrapped with an ePTFE film. The SB Component includes the CBAS® Surface wherein the graft surface is modified with immobilized bioactive heparin. Three flared apices located near the trailing end of the device are partially unbound from the UTW. Radiopaque rings are embedded at each of the device ends and 5 mm from the trailing end. The inner radiopaque ring indicates the trailing end of the intended overlap zone of the SB Component with the Aortic Component portal. Alignment in this manner provides a sealing length of 15 mm within the portal and 5 mm of extension of the trailing end of SB Component outside the portal and within the aorta. This extension allows the SB Component flared apices to be deployed outside the portal. The diameter of the trailing portion of the SB Component is designed to be compatible with the diameter of the Aortic Component portal. The diameter of the leading portion of the SB Component may be selected such that it is compatible with the branch vessel diameter. This component is mounted onto a catheter delivery system. Device sizing requirements are included in **Table 3**.

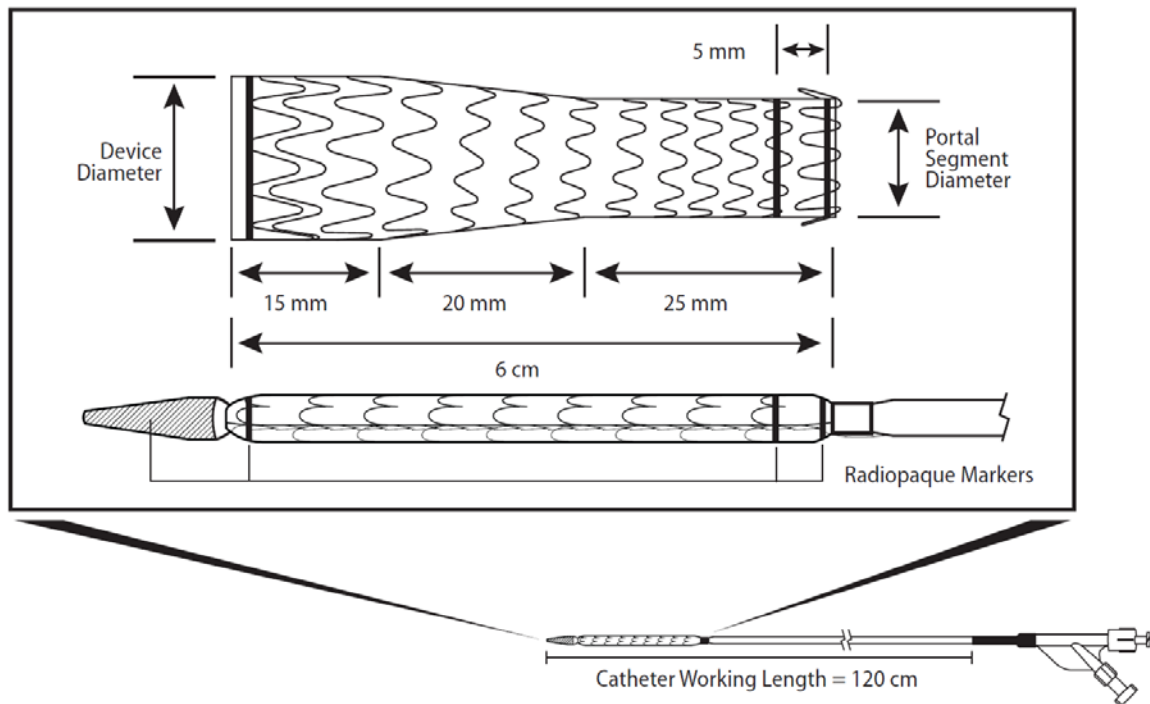


Figure 10: Side Branch Component and SB Component Delivery System



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Table 3: Side Branch Component Sizing Guide

DEVICE DIMENSIONS AND SIZING REQUIREMENTS						
CATALOGUE NUMBER	DEVICE DIAMETER (MM)	INTENDED BRANCH VESSEL DIAMETERS (MM)	PORTAL SEGMENT DIAMETER ¹ (MM)	OVERALL DEVICE LENGTH (CM)	REQUIRED BRANCH VESSEL LENGTH (CM)	GORE® DRYSEAL SHEATH SIZE (FR)
TSB080806C	8	6 - 7.5	8	6	3	14
TSB081006C	10	7.5 - 9	8	6	3	14
TSB081206C	12	9 - 11	8	6	3	14
TSB081506C	15	11 - 13	8	6	3	14
TSB121506C	15	11 - 13	12	6	2.5	14
TSB081706C	17	13 - 15	8	6	3	14
TSB121706C	17	13 - 15	12	6	2.5	14
TSB122006C	20	15 - 18	12	6	2.5	14

1. The SB component should be selected such that the Portal Segment Diameter is chosen to match the Internal Portal Diameter of the selected Aortic Component. For patients in whom the target branch vessel is the brachiocephalic artery, a Side Branch Component with a 12 mm portal segment diameter is required.

1.3.5 Delivery System

The delivery systems for the Aortic Component (**Figure 8**), the Aortic Extender (**Figure 9**), and SB Component (**Figure 10**) each consist of a dual lumen Pebax® tubing and a sewn deployment sleeve. An olive and transition longitudinally restrain and protect the endoprostheses during introduction. The olive is radiopaque to facilitate device placement. The catheter is compatible with a 0.035" guidewire. Each endoprosthesis component is constrained by a sewn deployment sleeve and is mounted on the leading end of the catheter. Pulling a deployment knob, attached to the deployment line system, unlaces the deployment sleeve and releases the self-expanding endoprosthesis. The sleeve of both the Aortic and SB Components are secured to the stent and remain implanted between the endoprosthesis and the vessel wall. The sleeve of the Aortic Extender is secured to the delivery catheter and is removed from the patient following deployment. The sleeve of the Aortic Extender includes a longitudinal radiopaque marker to allow fluoroscopic visualization during removal with the delivery catheter.



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1.3.6 Commercially Approved Devices

1.3.6.1 GORE® DrySeal Sheath

The GORE® DrySeal Sheath with Hydrophilic Coating or GORE® DrySeal Flex Introducer Sheath is intended to be inserted in the vasculature to provide a conduit for the insertion of endovascular devices while minimizing blood loss associated with such insertions. The devices consist of an introducer sheath with GORE® DrySeal Valve attached, a dilator, and a syringe. The GORE® DrySeal Sheath with Hydrophilic Coating is a polyethylene tube with a tapered leading tip and marker band incorporated within the sheath material to allow identification under fluoroscopy. The GORE® DrySeal Flex Introducer Sheath is a composite tube which consists of a flat stainless steel wire reinforced hydrophilic coated Pebax® outer tube and PTFE liner with a tapered leading tip and marker band incorporated within the sheath material to allow identification under fluoroscopy.

The sheath is attached to the GORE® DrySeal Valve, which is comprised of an outer silicone tube and an inner fluoropolymer tube. The region between the outer and inner tubes is pressurized by injecting 2.5 mL of saline into the space, using the provided syringe, during procedural preparation of the device.

The dilator has a tapered leading end and provides dilatation of the access vessel. For both the GORE® DrySeal Sheath with Hydrophilic Coating and GORE® DrySeal Flex Introducer Sheath the dilator is 0.035" guidewire compatible. The GORE® DrySeal Sheath with Hydrophilic Coating has a marker on the trailing end of the dilator that ensures correct positioning of the dilator within the sheath. For GORE® DrySeal Flex Introducer Sheath, the dilator has a locking mechanism which mates with, and secures to, the DrySeal Valve to ensure correct positioning of the dilator within the sheath.

1.3.6.2 Conformable GORE® TAG® Thoracic Endoprosthesis

The Conformable GORE® TAG® Thoracic Endoprosthesis (CTAG Device) is intended for endovascular repair of all lesions of the descending thoracic aorta, including:

- Isolated lesions (in Japan: thoracic aortic aneurysm, traumatic thoracic aortic injury) in patients who have appropriate anatomy including:
 - Adequate iliac / femoral access
 - Aortic inner diameter in the range of 16-42 mm
 - ≥ 20 mm non-aneurysmal aorta proximal and distal to the lesion
- Type B dissections in patients who have appropriate anatomy (in Japan: Complicated Stanford Type B dissections, including aneurysmal dissection, in patients who do not respond to medical therapy and have appropriate anatomy), including:
 - Adequate iliac / femoral access
 - ≥ 20 mm landing zone proximal to the primary entry tear; proximal extent of the landing zone must not be dissected
 - Diameter at proximal extent of proximal landing zone in the range of 16-42 mm



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- CTAG will be an investigational device in Japan.
The CTAG Device may be used according to its Instructions for Use (IFU) within the descending thoracic aorta as a distal extension of the Aortic Component of the TBE Device.

1.3.7 Investigational Accessory Devices

1.3.7.1 GORE® Tri-Lobe Balloon Catheter

The GORE® Tri-Lobe Balloon Catheter is intended to assist in the dilatation of self-expanding endoprostheses in large diameter vessels. The device consists of three polyurethane balloons mounted on the leading end of a multi-lumen catheter shaft. Radiopaque markers indicate the balloon edges. Each of the three inflation lumens is in communication with one of the balloons. The inflation port is in communication with all of the inflation lumens and is affixed with a luer lock. The lobed design of the balloon catheter allows for inflation without complete blockage of aortic blood flow.

Current indications for use and further testing and labeling modifications have been implemented to accommodate use with the TBE Device. No material or physical modifications were made to the currently approved balloon. For this study, the GORE® Tri-Lobe Balloon Catheter is available in two sizes, both of which are compatible with an 18 Fr sheath.



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1.4 Patient Population for Treatment with the TBE Device

1.4.1 Zone 2

Zone 2 TEVAR is an established treatment option. The CTAG Device has paved the way for broader application of TEVAR technology in the United States and Japan. Three separate clinical trials in the United States studied the application of the CTAG Device in the most common thoracic pathologies (DTAA, traumatic aortic transection and complicated type B dissection), leading to an overall indication for the CTAG Device which includes endovascular repair of all lesions of the DTA. Data collected in these trials confirmed that proximal device placement in Zone 2 is common, and more frequently observed in dissection and trauma than in DTAA (**Table 4**).

Table 4: Proximal Device Placement in CTAG Device IDE Clinical Trials

Proximal Implantation Zone	TAG 08-01 (Dissection)	TAG 08-02 (Trauma)	TAG 08-03 (DTAA)
Zone 2	36 (72.0%)	60 (59.4%)	20 (30.3%)
Zone 3 / Zone 4	14 (28.0%)	41 (40.6%)	46 (69.7%)

It is anticipated that a majority of patients with disease encroaching on Zone 2 would be candidates for treatment with the TBE Device, Subject to anatomic requirements for device placement.

1.4.2 Zone 0/1

The main pathologies with potential TBE Device applicability in Zone 0/1 are aneurysm and dissection. The TBE Device treats lesions that are distal to the proximal edge of the brachiocephalic artery (BCA) with a landing zone proximal to the BCA. Due to the necessity of a landing zone proximal to the BCA, the device is unable to treat Zone 0/1 patients with lesions of the ascending aorta. Specifically, the appropriate lesions are located in the aortic arch near the ostium of the left common carotid artery (LCC) and/or left subclavian artery (LSA) as seen in **Figure 11A**. This type of pathology requires management of the LCC and LSA (i.e., revascularization). In some cases the lesion could be distal to the LSA and require Zone 0 treatment due to lack of a proximal seal zone between the LCC and LSA or BCA and LCC (**Figure 11B**). The aortic arch usually refers to lesions or diseases that are near the BCA, LCC, and LSA. Based on these factors, the TBE Device is unable to treat all aortic arch anatomies (as seen in **Figure 11C**) since it requires the lesion to be distal to the proximal edge of the BCA to attain effective proximal seal.



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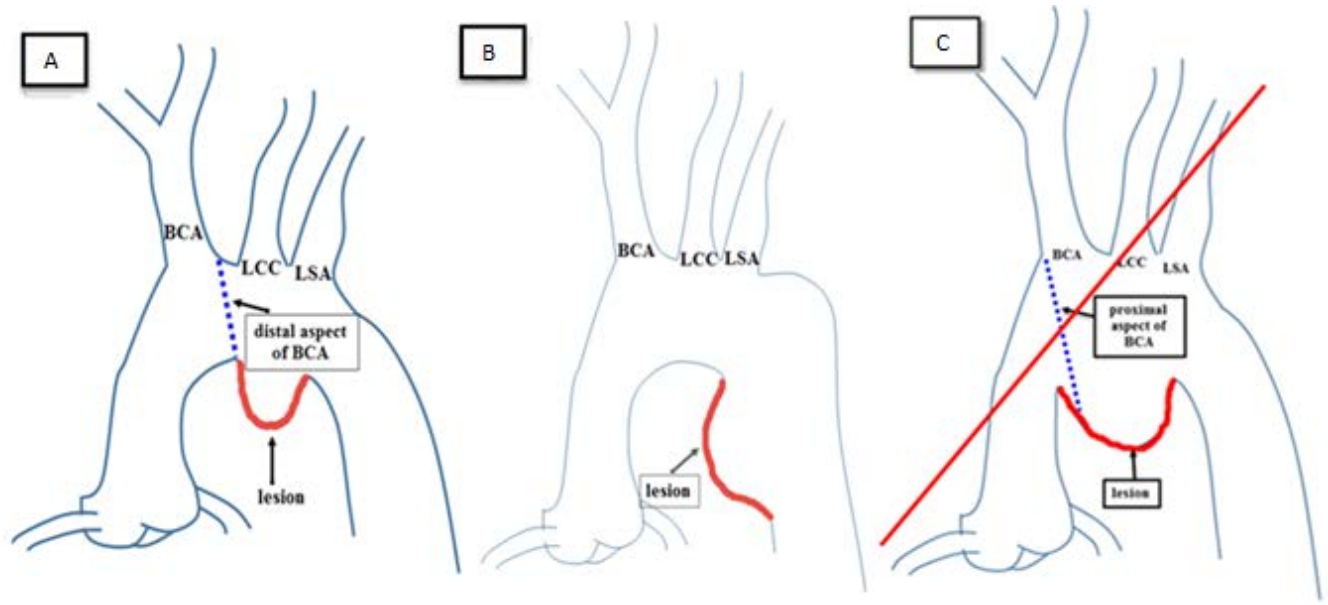


Figure 11: Representative isolated lesion (aneurysm) of the aortic arch A) distal to the BCA ostium which is suitable for TBE B) lack of a proximal seal zone between the LCC and LSA or BCA and LCC which is suitable for TBE C) proximal to the BCA ostium which is not suitable anatomy for TBE

The Zone 0/1 aneurysm patient population amenable to treatment with the TBE Device are patients with anatomies having aneurysms distal to the proximal edge of the BCA that require a seal zone proximal to the BCA in the ascending aorta (this can include a surgical graft). These patient anatomies have been referred to as “isolated arch aneurysm”, “arch aneurysm”, etc. Sood et al.³⁵ reported a 6% (137/2153 patients) occurrence of non-traumatic isolated aortic arch aneurysms at the University of Michigan over ten years with approximately 13 cases/year. The patients were treated by open (n=93) or hybrid/TEVAR repair (n=44). Therefore, the overall number of isolated arch aneurysm patients treated by endovascular repair is 2%. The University of Michigan is one of the highest thoracic treatment centers in the country and this report is likely representative of the regional incidence of this type of disease in the United States.

To estimate the overall thoracic aneurysm patient population, an estimate of 300 million people was used as the overall US patient population. In a population-based study from 1982, Bickerstaff et al.⁸ estimated an incidence of 6 new aneurysms per 100,000 people. The overall US thoracic aneurysm patient population can be estimated as 18,000. This study classified the cause of aneurysm as dissection (53%), atherosclerosis (29%), aortitis (8%), etc. Applying these historical estimates to the population at large, the annual US dissection patient population would be 9,540 patients, while the US aneurysm patient population would be 5,220 patients. Assuming the previously stated 6% estimate for “isolated arch aneurysms” and 2% for hybrid/TEVAR repair, there are approximately, 313 patients/year with 104 patients treated with endovascular or hybrid repair. Most likely not all patients are clinically or anatomically suitable for the TBE Device; during feasibility clinical trials, the anatomic screen failure rate approached 50%. Therefore, it is estimated that approximately 52



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patients per year would be potentially eligible for enrollment in a Zone 0/1 aneurysm trial for the TBE Device in the United States.

In contrast, data from the Japanese Committee for Stentgraft Management (JACSM), a patient registry in Japan that collects data on the use of thoracic stent grafts, suggests that arch aneurysm disease may be more prevalent in Japan. The data from JACSM is an unpublished, informal tabulation of the estimated number of patients with standard thoracic stent grafts implanted between 2008 and 2015 and is listed by Zone for aneurysmal disease only in Table 5.

Table 5: Number of registered patients with implanted standard thoracic stent graft by year / Zone for aneurysmal disease (unpublished JACSM data)

Year	Zone 0	Zone 1	Zone 2
2008	6	27	31
2009	18	36	134
2010	66	68	206
2011	120	166	301
2012	198	173	354
2013	158	168	363
2014	105	169	392
2015	79	133	301
Total	750	940	2,082

Those patients with devices implanted in Zone 0 or Zone 1 are assumed to have undergone hybrid TEVAR procedures; between 2011 and 2015 there were 2,278 patients registered for having Zone 0/1 stent graft placement. Applying the same assumption regarding anatomical suitability for endovascular repair with the TBE Device (50%), it is estimated that approximately 227 patients per year would be potentially eligible for enrollment in a Zone 0/1 aneurysm trial for the TBE Device in Japan.

The Zone 0/1 “de novo” dissection patient population amenable to treatment with the TBE Device are patients with anatomies having primary entry tears distal to the BCA with the most proximal extent of the landing zone in non-dissected aorta. The most common type of dissection are type A dissections (**Figure 12A**) with entry tears in the ascending and descending thoracic aorta (DTA). Primary entry tears distal to the LSA are classified type B dissections (**Figure 12B**). Since it is uncommon for the primary entry tear to be located in the aortic arch (**Figure 12C**), most dissection patients require isolated treatment of the ascending or DTA. Patient anatomies with primary entry tears in the aortic arch can be referred to as “aortic arch dissection”, “non-A-non-B aortic dissection”, “type B dissection with tear in the arch”, etc. Naturally occurring aortic arch dissections are rare. Urbanski et al.³⁶ reported 281 aortic dissections over a 12 year period, with 8 patients classified as non-A-non-B dissection, leading to an annualized rate at this TEVAR center of 0.67 patients per



year. Assuming a similar rate in a study with 20-30 overall centers, this would result in a total maximum of approximately 13-20 de novo arch dissection patients that could be treated with the TBE Device. If 50% of these patients were eligible for treatment under the study Protocol, this results in a maximum of 10 patients annually that could be treated annually with the TBE Device for de novo arch dissection.

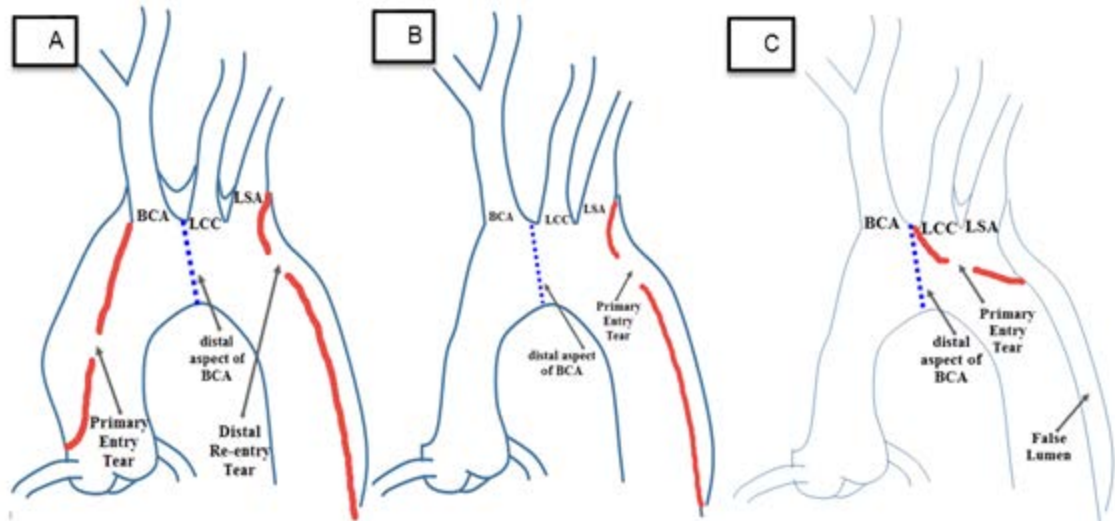


Figure 12: Types of dissection A) Type A dissection B) Type B dissection C) non-A-non-B dissection (rare)

Another potential dissection patient population amenable to treatment with the TBE Device are Type A residual dissection patients. A typical surgical repair for Type A dissection involves emergent surgical replacement of the ascending aorta. These patients ultimately may require additional intervention subsequent to the initial treatment and are therefore “residual dissection” patients.

The residual dissection may be located in the DTA (**Figure 13A**) or the arch (**Figure 13B**) and can be treated in a manner similar to de novo Type B dissection repair. The applicability of the TBE Device for these types of cases are dependent upon two factors: a) location of tear and b) configuration of the surgical graft. When the surgical graft is not seated close to the BCA, the lack of a landing zone makes the TBE Device an unsuitable option (**Figure 13C**). Roselli et al.³⁷ reported that 305 patients underwent additional interventions after initial ascending aortic dissection over 18 years which is approximately 17 patients per year. Approximately 74% of these patients required repair of the aortic arch with many of these patients requiring additional elephant trunk repair (48%), so an additional procedure was required to provide a suitable proximal landing zone for approximately half of the patients. Therefore, 6 patients per year required aortic arch intervention after Type A repair without an additional procedure to create a proximal landing zone. The Cleveland Clinic is known as the highest volume thoracic center in the world. Since TEVAR volume is generally concentrated at higher volume centers, it can be assumed that 20x the Cleveland Clinic volume is representative of the US patient population. Assuming a 50% anatomic screen failure rate, there are approximately 60 anatomically suitable patients eligible for the TBE Device annually.



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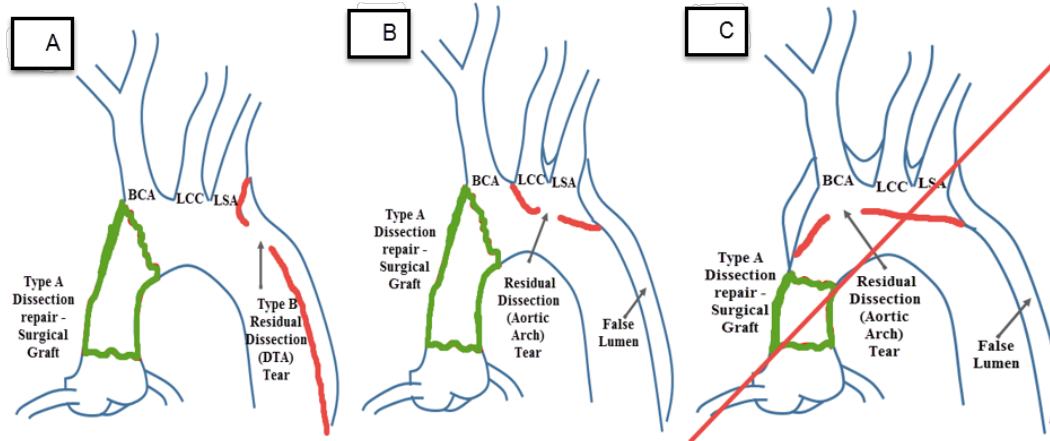


Figure 13: Types of Type A residual dissection A) Type B dissection B) Aortic arch dissection with suitable anatomy for TBE Device C) Aortic arch dissection with anatomy not suitable for TBE Device

1.5 Study Design Rationale

1.5.1 Zone 2 Patient Population

As discussed previously, Zone 2 TEVAR is an established treatment option. This patient population likely would benefit from preservation of flow into the LSA, as evidenced by the Society for Vascular Surgery recommendation for preoperative revascularization of the LSA in most cases.³⁰

Revascularization of the LSA to facilitate Zone 2 TEVAR entails some additional risks, including stroke, bleeding, and injury to the thoracic duct and left neck nerves, including the phrenic, vagus, sympathetic chain, and brachial plexus.³⁰ A completely endovascular approach that maintains perfusion to the LSA could benefit patients requiring thoracic stent graft placement in Zone 2 by obviating the need for surgical revascularization of the LSA and avoiding the risks associated with this procedure.

Given the availability of endovascular treatment options for this population, the most relevant treatment comparison for the TBE Device would be to the results from similar patient populations that have been treated endovascularly in the past for Zone 2 pathologies. The primary differences between TBE and these historical devices is the ability to perform the entire procedure with endovascular techniques, as opposed to bypass or coverage of the LSA. Therefore, for the Zone 2 aneurysm population, the study will have a planned comparison to a performance goal derived from previously conducted studies involving the CTAG and TAG Devices.

1.5.2 Zone 0/1 Patient Population

There are clear differences in the incidence, comparative surgeries and associated outcomes between Zone 2 and Zone 0/1. In general, Zone 2 patients are a larger patient population with a clear comparison for surgical repair and established, approved endovascular treatment options. The location of the disease for surgical repair has only one general surgical comparison which is a thoracotomy. The historical TAG studies have shown improved outcomes compared to thoracotomy which has led to widespread use of TEVAR as the standard of repair for Zone 2; therefore, Zone 2 studies can be conducted in standard risk patients.



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Unlike Zone 2, the location of the disease and associated surgical access sites for Zone 0/1 TBE repair lead to treatment of a lower incidence and higher risk patient population. The Zone 0/1 TBE Device was designed to treat patients with “arch disease” which can include isolated arch disease, disease of the DTA that encroaches into the arch, and previously repaired ascending disease with residual arch disease. Unfortunately, the “Zone 0 landing zone” patient population as described in the literature can include patients with ascending disease which indicates a larger patient population than the TBE Device Zone 0 patient population which requires a proximal landing zone in the ascending aorta that is not “diseased” including native aorta and surgical graft. Therefore, the Zone 0/1 TBE Device patient population has a lower incidence due to the location of disease and proximal landing zone requirements.

Not only is the disease lower incidence, but the current therapies for this smaller patient population are associated with high morbidity and mortality. As mentioned above, the Zone 0/1 TBE Device patient population are patients with “arch disease.” There are currently two main therapies available, open surgical repair and hybrid TEVAR. There are two main open surgical techniques to address this disease which are staged elephant trunk repair and bilateral thoracotomy (or the clamshell technique). Both open surgical techniques are associated with high morbidity and mortality outcomes which lead these surgeries to be labeled as “high risk” procedures. If the disease is isolated to the arch, a bilateral thoracotomy can be performed; however this is not a common procedure. If the lesion requires extensive repair of the ascending, transverse, and distal aorta a staged elephant trunk procedure is commonly performed. This procedure involves replacement of the ascending and proximal transverse aorta through a median sternotomy followed by surgical replacement of the distal transverse aorta and descending thoracic aorta through thoracotomy.

The median sternotomy is used for most cardiac procedures including valve repair, coronary bypass grafting and proximal thoracic aorta replacement. In patients undergoing arch replacement it is not uncommon for the surgical approach to be a redo sternotomy. There exists a risk inherent to a redo sternotomy. During cardiac and/or ascending and transverse arch interventions serosal injury and bleeding can occur producing cardiac adhesions between the sternum and cardiac tissues upon closure of the approach with sternal wires and healing of the sternotomy. Upon reopening of a sternotomy for further intervention, disruption and necessary breaking up of these adhesions can injure cardiac structures including the pericardium, chambers of the heart, the aorta, great vessels and previously placed conduits. This can cause severe hemorrhage and death. In a study completed in 2005³⁸, 11.3% of cardiac reinterventions had procedural complications directly attributable to the redo sternotomy.

It has been reported that any surgical approach beyond a median sternotomy for aortic arch repair, especially the bilateral thoracotomy, is a statistically significant predictor of operative and overall mortality³⁹. In a study of 200 patients by Ergin et al³⁹ the overall mortality rate was 33.3% for patients receiving non-median sternotomy to repair the distal arch and descending aorta. The distal arch and descending aorta repairs occurring through bilateral thoracotomy had a marked overall mortality rate 54.6%.



Additionally, patients with this type of disease are frequently high-risk for open surgery due to comorbid factors. This patient-specific risk is magnified by the inherent risk of surgical replacement of the aortic arch, given the need for DHCA and CPB. Though use of DHCA aids preservation of cerebral, spinal cord and end organ function, longer the duration of DHCA is correlated with higher rates of death, stroke, permanent paralysis and renal failure when used during open repair of aortic arch pathologies.⁴⁰ Patel et al reported perioperative results of 5% mortality, 4.7% stroke, 1.9% permanent dialysis, and 3.3% tracheostomy.⁴¹ In one report⁴², perioperative results were evaluated for open arch reconstruction in the Society for Thoracic Surgery database. This study reported perioperative results of 8.9% mortality, 8.4% stroke, 33% prolonged ventilation, 9% reoperation for bleeding, and 8% renal failure. Finally, a high rate (21%) of cardiac complications have been reported after these procedures.⁴²

Due to the complications associated with open surgical repair and high risk nature of these patients, the hybrid TEVAR procedure has become a standard of care for these patients. Combining open surgical and endovascular techniques, the hybrid arch repair seeks to limit operative, bypass, and circulatory arrest times by simplifying and shortening the arch repair. This is accomplished by creating proximal landing zones through less extensive surgical access sites (median sternotomy) and endovascular repair of the more difficult to access disease in the arch and descending thoracic aorta. A systemic review of hybrid procedures reported perioperative results of 9% mortality, 7% stroke rate, 5% cardiac complications, 4% pulmonary complications, and 1% renal failure.⁴³

Given the limited and high risk nature of the Zone 0/1 TBE Device patient population, it is not appropriate or feasible to randomize patients and compare to open surgery. The hybrid TEVAR technique is a more appropriate comparison due to the similarities in device requirements (proximal landing zone, endovascular repair, etc). However, the hybrid technique involves the off-label use of a TEVAR device which makes it inappropriate for a controlled clinical trial. Section 1.2.4 describes variants of the hybrid TEVAR procedure (Type I, II, and III). The patient population undergoing these operations is not necessarily homogenous which would make direct patient population comparison difficult.

For type II and III hybrid procedures, the ascending aorta and/or arch is surgically replaced which usually requires DHCA and CPB. Frozen elephant trunk (FET) procedures are categorized as type III hybrid procedures. A recent review of FET procedures³⁴ showed that CPB time, myocardial ischemia time, and circulatory arrest time strongly correlated with perioperative mortality. The same report showed moderate correlations between cerebral perfusion time and mortality; and circulatory arrest time and spinal cord injury. Even with the reduced operative, bypass and circulatory arrest times of hybrid repair, there are still complications associated with use of the adjunct procedures DHCA and CPB. The TBE Device for the treatment of Zone 0/1 patients allows for elimination of DHCA and CPB which is associated with higher morbidity and mortality. Therefore, it is clinically appropriate to study Zone 0/1 in a single arm study with comparison to hybrid repair literature.



2.0 Study Objectives

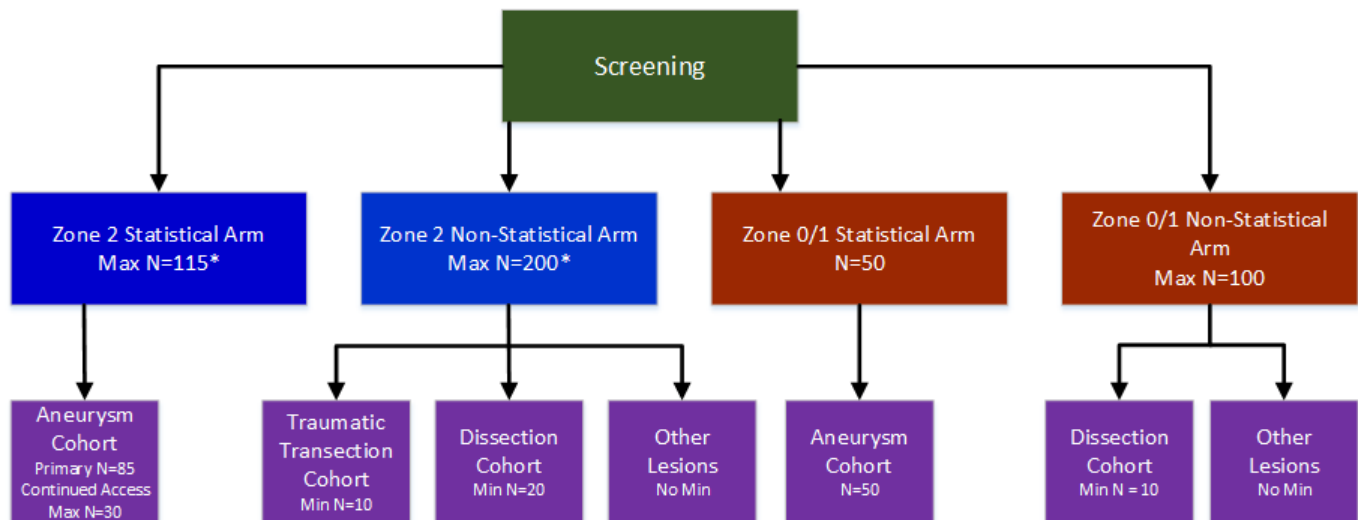
2.1 Primary Objective(s)

The primary objective of the study is to determine whether the GORE® TAG® Thoracic Branch Endoprosthesis (TBE device) is safe and effective in treating thoracic aortic pathologies. Specifically, the objective will be to perform hypothesis-driven analysis of the device's safety and effectiveness in the treatment of aortic aneurysms requiring proximal device placement in Zone 0/1 & Zone 2 of the thoracic aorta, respectively. Due to the potential applicability of the TBE Device in additional pathologic presentations, enrollment of anatomically suitable non-aneurysm patients will also be allowed to provide additional clinical data to characterize performance in these applications.

3.0 Study Design

3.1 Study Design Schema

Figure 14 illustrates the pivotal study design.



*Japan may contribute to the Zone 0/1 cohort. They will also conduct two training cases in Zone 2 Subjects which will not be included in the min and max for Zone 2 enrollment.

Figure 14: Study Design Schematic

3.2 Description of Study Design

This will be a non-randomized, multicenter, prospective study conducted at up to forty-five (45) Clinical Investigative Sites (referred to as “Sites” in the remainder of this document), with up to 40 sites in the U.S and up to 5 sites in Japan (enrolling in the Zone 0/1 arm only) with the objective of determining whether the GORE® TAG® Thoracic Branch Endoprosthesis is safe and effective in treating lesions of the aortic arch and descending thoracic aorta. A minimum of 175 and up to a total of 465 Subjects will be enrolled across four independent study arms consisting of seven cohorts as described below.

The study will consist of seven cohorts described as follows:

- Zone 2, aneurysm patients (N=115, maximum)



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- Zone 2, aneurysm patients, Primary Enrollment (N=85)
- Zone 2, aneurysm patients, Continued Access Enrollment (N=30, maximum)
- Zone 2, anatomically suitable non-aneurysm patients, descriptive analysis (N=200, maximum)
 - Dissection cohort (N=20 minimum)
 - Traumatic Transection cohort (N=10 minimum)
 - Other isolated lesion types cohort (No minimum)
- Zone 0/1, aneurysm patients, hypothesis driven (N=50, 0 up to 10 Subjects from Japan) NOTE: due to removal of the 49/53mm device sizes from this trial, any Subjects enrolled with these device sizes will not be counted as part of this N=50 enrollment and replacement Subjects will be enrolled to keep N=50.
- Zone 0/1, anatomically suitable non-aneurysm patients, descriptive analysis (N=100, maximum)
 - Dissection cohort (N=10 minimum)
 - Other isolated lesion types cohort (No minimum)

The Zone 2 aneurysm cohort will consist of 85 Subjects accrued during the Primary Enrollment period along with a maximum of 30 Subjects accrued during the Continued Access Enrollment period.

The maximum number of Subjects that may be enrolled at a single site is as follows:

- Zone 2, aneurysm patients, 17 Subjects
- Zone 0/1, aneurysm patients, 8 Subjects in US, 4 Subjects in Japan
- Zone 2 and Zone 0/1, anatomically suitable non-aneurysm patients, all cohorts, will not have a maximum per site as they are for descriptive analysis only

The anticipated accrual rate is approximately four Subjects per month for a total accrual period of approximately 18-24 months for the Zone 2 Aneurysm cohort. The anticipated accrual rate is approximately 1.2 Subjects per month for a total accrual period of approximately 48-60 months for the Zone 0/1 Aneurysm cohort. The non-statistical cohorts will continue to enroll until the maximum number of Subjects for that cohort is reached or until U.S. Regulatory approval for that indication is obtained.

The cohorts will be analyzed separately by Zone and lesion type. Analysis of each Zone, including the hypothesis-driven aneurysm cohort and the non-aneurysm cohort will be performed when 12 month follow-up for the hypothesis-driven cohort is complete. The aneurysm cohorts will be referred to as the Aneurysm Cohorts along with their respective zone for the remainder of the Protocol. The anatomically suitable non-aneurysm cohorts will be referred to as the Non-Aneurysm Lesion (NAL) Cohorts along with their respective zone for the remainder of the Protocol.

Subjects may be enrolled into the clinical study provided all inclusion and no exclusion criteria are met as specified in Section 4 for the respective study cohort into which they will be enrolled. Subjects will be evaluated through hospital discharge and return for follow-up visits at 1, 6, 12, 24, 36, 48, and 60 months post treatment.



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All enrolled Subjects regardless of study cohort will be followed after the initial treatment for five years or until termination of the trial. Total estimated duration of the study is ten years.

3.3 Study Performance Goals

3.3.1 Zone 2 Aneurysm Cohort

Historical TAG/CTAG results (TAG 99-01, TAG 03-03, TAG 04-02, TAG 05-02, TAG 08-03) were re-analyzed to determine the Zone 2 aneurysm cohort performance goal for the primary endpoint (**Table 6**). Subjects treated for DTA aneurysms with proximal device placement in Zone 2 were identified in the historical TAG/CTAG studies. Using the data to the extent possible from historical TAG/CTAG Zone 2 aneurysm studies, the primary event rate through 12 months was calculated for these Subjects applying the primary endpoint definitions planned for the prospective Zone 2 aneurysm cohort. Subjects with one or more primary endpoint events through the 12 month window (i.e. through study day 546) were counted as failures (those with >1 event counted just once as failures). Subjects without an event through 12 months had to have imaging done within the 12 month time window in order to count as successes. The percentage of TAG/CTAG Subjects successful for the primary endpoint through 1 Year was 81%. The lower bound of the 95% confidence interval on this result is 71%. However, this result did not include performance on device technical success (including patency and unanticipated additional procedure) at procedure (this was estimated to be 5-7%). Based on these results and the potential for these additional endpoint events, the performance goal was set at 64%.



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Table 6: TAG/CTAG Treatment Failure in Zone 2 Aneurysms

	Post Treatment Follow-Up Period					Total ¹ (Through 1 Month)	Total ¹ (Through 1 Year)
	Procedure	Post- Procedure	1 Month	6 Months	12 Months		
Number of Subjects	80	80	78	78	73	-	-
CT Available in Window	0	16	68	52	65	-	-
Any Event Below	6/80 (7.5%)	5/80 (6.3%)	0/78 (0.0%)	5/78 (6.4%)	0/73 (0.0%)	10/72 (13.9%)	14/75 (18.7%)
Access or Device Delivery Failure AE (Site-Reported)	-	-	-	-	-	-	-
Patency of Graft (end of index endovascular procedure) in Absence of Device Issues (Site-Reported)	-	-	-	-	-	-	-
Additional Unplanned Surgical or Interventional Procedure	1/80 (1.3%)	0/80 (0.0%)	0/78 (0.0%)	3/78 (3.8%)	0/73 (0.0%)	1/72 (1.4%)	4/75 (5.3%)
Aortic Aneurysm Rupture (Corelab or Site-Reported)	0/80 (0.0%)	0/80 (0.0%)	0/78 (0.0%)	0/78 (0.0%)	0/73 (0.0%)	0/72 (0.0%)	0/75 (0.0%)
Aortic Aneurysm Related Mortality	0/80 (0.0%)	2/80 (2.5%)	0/78 (0.0%)	3/78 (3.8%)	0/73 (0.0%)	2/72 (2.8%)	5/75 (6.7%)
Major Stroke AE ≤30 days of Procedure (Site-Reported)	6/80 (7.5%)	2/80 (2.5%)	0/78 (0.0%)	-	-	8/72 (11.1%)	8/75 (10.7%)
Major Paraplegia/Paraparesis AE ≤30 days of Procedure (Site-Reported)	0/80 (0.0%)	2/80 (2.5%)	0/78 (0.0%)	-	-	2/72 (2.8%)	2/75 (2.7%)
Major Renal Failure AE ≤30 days of Procedure (Site-Reported)	0/80 (0.0%)	0/80 (0.0%)	0/78 (0.0%)	-	-	0/72 (0.0%)	0/75 (0.0%)

¹Total (1 Month) denominator is number of Subjects with an event (exceptions indicated with a '-') anytime ≤ 59 days and/or CT available in 1 Month window (15-59). Total (1 Year) denominator is number of Subjects with an event (exceptions indicated with a '-') anytime ≤ 546 days and/or CT available in 12 Month window (243-546). Major stroke/paraplegia/paraparesis/renal failure events are only counted in the Total if ≤ 30 days from procedure.

3.3.2 Zone 0/1 Aneurysm Cohort

3.3.2.1 Background

Limited data are available to characterize the anticipated results in an exactly matched patient population similar to that which would be treated by the TBE Device in Zone 0/1. Based on clinical and technical similarity, the most relevant information that could reasonably provide a basis for comparison to the TBE Device is literature outcomes for hybrid TEVAR procedures. Hybrid TEVAR procedures are operations that include an open surgical and endovascular approach. For the purpose of this study, hybrid repair refers to treatment of aortic arch lesions (usually aneurysm and dissection) with proximal placement of the endovascular component in Zone 0 or 1 and a surgical component. These procedures are considered less invasive than a complete open repair of the aortic arch; however, depending on the extent of repair, large incisions are frequently required including median sternotomy and/or neck incisions such as cervicotomy or mini-thoracotomy.

A systematic review of arch debranching results by Cao³¹ reported outcomes of 11.9% perioperative mortality, 7.3% stroke, and 4.3% paraplegia. Notably, this review included devices placed in Zone 2, which may only require debranching of the LSA and may bias the results with a less risky patient population (Zone 2). In the same publication, frozen elephant trunk procedures were reported to have 9.8%



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perioperative mortality, 6.2% stroke and 7.9% paraplegia due to spinal cord ischemia. Similar results were reported in another meta-analysis by Tian et al³⁴, including mortality of 8.3%, stroke of 5.9% and spinal cord injury of 5.1%. Frequently, patients selected for hybrid repairs are considered high-risk for open surgical repair and/or involve emergent or urgent presentations. This report from Cao and colleagues suggested a risk of mortality in Zone 0 procedures 2.8 times greater than for Zone 1. The authors of this analysis concluded that these results are comparable with open repair procedures.

Considerations for developing the performance goal included:

- The clinical results of various treatment options for disease states that could be treated by the TBE Device when used in Zone 0/1
- The potential alternative treatment options for these disease states, and
- Matching as best as possible with the anatomic configuration of diseases that would be considered for enrollment in the present study.

As discussed in Section 1.5.2, a number of options may be considered for the patient with aortic arch disease, including open surgery. Many of these options involve the need for DHCA and CPB if replacement of the ascending aorta is required. The approaches to the open surgical procedure are not standardized. Depending on the approach and required surgical adjuncts (e.g., DHCA and CPB), these complications could include a higher risk of death, stroke, spinal cord ischemia and renal failure. It is possible that treating these patients with the TBE Device could provide an option that could lead to fewer complications than these more extensive procedures. Even in the case of hybrid TEVAR, CPB is required for operations that involve replacement of a segment of the ascending aorta to create an appropriate landing Zone (Type II hybrid procedure). These considerations led to the decision to develop a performance goal based on hybrid TEVAR since these patients are more likely to be similar to those planned for enrollment in this Protocol, especially in terms of risk stratification and the general type and location of disease being treated.

This pivotal Protocol will allow for Zone 0/1 procedures in “high risk” Subjects for open surgical repair, just as designated in the current Early Feasibility Protocol. The majority of hybrid TEVAR procedures today are performed primarily in similar high risk patient populations³¹.

3.3.2.2 Goal Derivation

A systematic literature review of hybrid repair literature was conducted.

The search terms or parameters used for the hybrid repair literature search were: ((aort* NEAR/5 arch*) AND (hybrid*) AND (revasc* OR debranch* OR transpo*) AND pd(2005-2014) AND (stent* OR "stent* graft*" OR endo*)) AND (at.exact("Article") AND la.exact("English")) Dates 2005-10/10/2014.

The literature search of publications with primary patient data in English identified 168 articles. Meta-analysis, review articles, and articles without sufficient data for analysis were excluded from the analysis (including inability to select appropriate subgroups of patients for analysis when multiple procedures were reported). Publications restricted solely to treating congenital or aberrant anatomic



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presentations (e.g., Takayasu's arteritis, Kommerell diverticulum, coarctation) were excluded; however, if these were reported in conjunction with larger series of treatments involving primarily aneurysm or dissection treatment, they were included. Additionally, a requirement for ≥ 15 cases involving device placement in Zone 0 or Zone 1 was defined. Case series from the same centers involving the same patient populations were excluded when duplication was suspected or confirmed. Publications involving only primary treatment of Type A aortic dissection were excluded; however, articles involving treatment of residual dissection from a previous repair of the ascending aorta or dissection involving the arch specifically were included. References from identified articles were also reviewed for relevant publications not included in the original search that otherwise met search criteria and an additional three publications were identified.

Overall, 23 articles with 656 total patients treated were included in the literature review analysis⁴⁴⁻⁶⁶. A majority of these articles indicated that these procedures were reserved for patients deemed "high-risk" for standard open surgical repair. This literature review encompassed results from aortic arch surgery (hybrid TEVAR) which included a mix of dissections, aneurysms and other pathologic presentations as well as surgeries that involved replacement of part of the ascending aorta to create a proximal landing zone or to treat Type A dissection in some cases. Key results that were consistently identifiable from the review included perioperative death, neurological events and spinal cord ischemia, all of which are part of the Zone 0/1 primary endpoint. The results were individually summarized (i.e., a rate for each outcome was calculated across the identified literature) and then summed up, as displayed in **Table 7**.

Table 7: Results from Literature Review of Hybrid TEVAR Procedures

Outcome	Calculated Percentage
Perioperative Death	12.5%
Neurological Event	7.6%
Spinal Cord Ischemia	3.5%
Total	23.6%

Additional events included in the primary endpoint of the Zone 0/1 statistical arm are renal failure and the components of technical success. As part of the literature review, in cases where hybrid procedures were staged (as is planned to be the case for the implantation of the TBE Device in Zone 0), inability to complete the staged procedure regardless of cause was identified in 0-5% of the cases. Renal failure was reported sparsely, however it is not possible to determine if this was not a variable assessed from publication to publication or if the actual underlying risk of renal failure is low. In selected publications identified as part of the literature review, renal failure was reported in 6-11% of patients.^{44, 46, 62} Technical success for the endovascular portion of the procedure (related to deployment accuracy, patency, etc.) is anticipated to be relatively high (>95%). At one month patency and other elements of the proposed Zone 0/1 primary endpoint (e.g., failure to complete the procedure, the



need for reintervention, open surgical conversion, etc.) is not well known at this time; however, it may be that these events occur in up to 5-10% of the treated patients. To account for these additional factors, an adjustment of 11% to the overall point estimate from the literature analysis was employed, increasing the anticipated point estimate from historical results to 34.6%.

To account for potential variability in the new study population an additional margin was incorporated. This additional adjustment to the performance goal is justified given the potential for under-reporting of key events in literature and national databases. Due to this consideration, the study performance goal for the proposed Zone 0/1 primary endpoint was set at 60%. An overall summary of the performance goal derivation is provided in **Table 8**.

Table 8: Primary Endpoint Performance Goal for Zone 0/1 Clinical Trial

Element	Percentage with Event
Literature Review Total (Death, Neurological, SCI)	23.6% (24%)
Additional Events Allocation (Renal Failure, Technical Success, etc.)	11%
Allocation for Variability	5%
Total Event Rate	40%
Performance Goal (Primary Endpoint Goal)	60%

3.4 Study Outcomes

3.4.1 Primary Endpoints

The Primary Endpoints for the two hypothesis-driven study cohorts are described below.

3.4.1.1 Zone 2 Aneurysm Cohort

The primary endpoint for the Zone 2 aneurysm cohort will be a composite of the following events through 12 months:

- Device Technical Success
- Absence of the following:
 - Aortic rupture;
 - Lesion-related mortality;
 - Disabling stroke
 - Permanent paraplegia
 - Permanent paraparesis
 - New onset renal failure requiring permanent dialysis
 - Additional unanticipated post-procedural surgical or interventional procedure related to the device, procedure, or withdrawal of the delivery system.

Definitions for these events are provided in Section 3.4.3



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3.4.1.2 Zone 0/1 Aneurysm Cohort

The primary endpoint for the Zone 0/1 aneurysm cohort will be Strategy Success.

Strategy Success (For planned staged procedures – landing zone optimization, transposition, and device placement – through one month following last planned procedure) and is defined as follows: a composite of the following events from the time of enrollment through one month following the index endovascular procedure:

- Initiation of the index endovascular procedure following the debranching procedure
- Device technical success for the index endovascular procedure
- Absence of the following :
 - Aortic rupture
 - Lesion-related mortality
 - Disabling Stroke
 - Permanent paraplegia
 - Permanent paraparesis
 - New onset renal failure requiring permanent dialysis
 - Additional unanticipated post-procedural surgical or interventional procedure related to the device, procedure, or withdrawal of the delivery system.

Definitions for these events are provided in Section 3.4.3.

3.4.2 Success Outcomes

In addition to the Primary Endpoints noted above, Procedural and Treatment Success data (aggregate and component) will be collected and analyzed for all seven study cohorts. Each component is defined in Section 3.4.3. Success Outcomes for all study cohorts will consist of the following:

Procedural Success is defined as Device Technical Success (defined in Section 3.4.3), with absence of the following events occurring from the initiation of the index endovascular procedure through one month:

- Death (Through 30 days only)
- Aortic rupture (Through 30 days only)
- Disabling stroke
- Paraplegia (Through 30 days only)
- Paraparesis (Through 30 days only)
- New onset renal failure requiring dialysis
- Additional unanticipated surgical (including conversion to open surgery) or interventional (placement of additional unanticipated endovascular devices) procedure related to the device, procedure, or withdrawal of the delivery system



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- New ischemia
- Distal device-related thromboembolic adverse event requiring intervention or surgery
- Extension of a dissection (proximally or distally) (Dissection cohorts only)
- New dissection
- Life-threatening bleed
- Myocardial infarction
- Prolonged intubation
- Laryngeal or Phrenic Nerve injury
- Renal dysfunction or volume overload requiring ultrafiltration
- Severe Heart Failure/Hypotension

Treatment Success is defined as Device Technical Success (defined in Section 3.4.3), with absence of the following events occurring from the initiation of the index endovascular procedure and at all appropriate follow-up windows:

- Aortic enlargement in the region encompassed by the initial lesion
- Aortic rupture
- Extension of a dissection (proximally or distally) (Dissection cohorts only)
- New dissection
- False lumen perfusion through the primary entry tear (Dissection cohorts only)
- False lumen perfusion through an aortic arch branch vessel (Dissection cohorts only)
- Type I or III endoleak
- Fistula formation
- Lesion-related mortality
- Loss of device integrity
- Loss of aortic or aortic branch patency
- Migration
- Disabling stroke within 30 days of the index endovascular procedure only
- Paraplegia within 30 days of the index endovascular procedure only
- Paraparesis within 30 days of the index endovascular procedure only
- New ischemia
- Additional unanticipated surgical (including conversion to open surgery) or interventional (placement of additional unanticipated endovascular devices) procedure related to the device, procedure, or withdrawal of the delivery system

In addition to the Treatment and Procedural Success outcomes the following will be collected:

- Type II or IV endoleak



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- Significant Blood Loss ($\geq 1000\text{ml}$)
- False Lumen Status in treated and untreated segments (Dissection cohorts only)
- False Lumen perfusion through a non-aortic arch branch vessel (Dissection cohorts only)

No hypothesis tests will be performed for these success outcomes measures. In addition to the outcomes described above, data comparable to the measures studied in historical TAG/CTAG trials will be collected.

3.4.3 Definitions

Primary Endpoint Event definitions are provided in **Table 9**.

Table 9: Primary Endpoint Event Definitions

Key Outcome	Definition
Device Technical Success for index endovascular procedure	• Successful access and delivery to the intended implantation site, and retrieval of the device delivery system, and; • Patency of the graft • The absence of unanticipated additional procedure related to the device, procedure, or withdrawal of the delivery system
<i>Successful access and delivery</i>	Device is successfully tracked from the access site, accurately deployed to the intended implantation site and released from the delivery catheter successfully. All delivery catheters are successfully removed from the Subject.
<i>Patency of the graft</i>	Aortic devices and side branch components are patent as assessed by angiography at the conclusion of the procedure
<i>Unanticipated additional procedure related to the device, procedure, or withdrawal of the delivery system</i>	• Additional unanticipated surgical procedure (including conversion to open surgery) related to the device (including withdrawal of the delivery system), or procedure. Anticipated or unanticipated status will be determined at the discretion of the investigator. • Additional unanticipated interventional procedure (including placement of additional unanticipated endovascular devices outside of the available TBE components [aortic component, extender, SB component and CTAG Device]) related to the device (including withdrawal of the delivery system) or procedure. Anticipated or unanticipated status will be determined at the discretion of the investigator.



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Key Outcome	Definition														
	Events can include inaccurate placement of the TBE components or improving branch patency due to device deformation resulting in additional non-TAG devices (TBE or CTAG) implanted to address vessel branch compromise. Events will not include unanticipated corrective intervention at the access site(s), lumbar drains to address spinal cord ischemia or additional non-TBE (TBE or CTAG) device intervention to address non treatment area issues (i.e. bare stent implantation to address bowel ischemia for dissection)														
Aortic Rupture	Rupture in the treated segment of the aorta verified with direct observation or CT scan														
Lesion-related Mortality	Defined as all deaths during hospitalization for index endovascular procedure and within 30 days of the index endovascular procedure or any secondary procedures due to the treated pathology, or the effectiveness of the endovascular repair (e.g., procedures to treat retrograde dissections, losses of patency, losses of device integrity, endoleaks, migrations, aortic expansions, aortic ruptures) and any deaths related to the treated pathology or endovascular graft (e.g., aneurysm rupture, retrograde dissection leading to fatal cardiac tamponade), unless evidence is available to demonstrate that the death is not lesion related.														
Disabling Stroke	Stroke will be assessed using the Modified Rankin Scale. Stroke identified as having occurred within 30 days of the index endovascular procedure, combined with MRS$\geq$2 with an increase from baseline of at least one grade due to neurological deficits at no more than 120 days post index endovascular procedure. <table border="1"> <thead> <tr> <th>Score</th><th>Status</th></tr> </thead> <tbody> <tr> <td>0</td><td>No symptoms at all</td></tr> <tr> <td>1</td><td>No significant disability despite symptoms; able to carry out all usual duties and activities</td></tr> <tr> <td>2</td><td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td></tr> <tr> <td>3</td><td>Moderate disability; requiring some help, but able to walk without assistance</td></tr> <tr> <td>4</td><td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td></tr> <tr> <td>5</td><td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td></tr> </tbody> </table>	Score	Status	0	No symptoms at all	1	No significant disability despite symptoms; able to carry out all usual duties and activities	2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance	3	Moderate disability; requiring some help, but able to walk without assistance	4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance	5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
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Key Outcome	Definition														
	<table> <tr> <td>6</td><td>Dead</td></tr> </table>	6	Dead												
6	Dead														
Permanent Paraplegia	Paraplegia secondary to Spinal Cord Ischemia identified within 30 days of the index endovascular procedure combined with Spinal Cord Ischemia scale grade = 3 at the one month follow-up visit. Paraplegia will be assessed using the following spinal cord ischemia grading system⁶⁷: <table> <tr> <th><u>Grade</u></th><th><u>Spinal Cord Ischemia Description</u></th></tr> <tr> <td>0</td><td>None</td></tr> <tr> <td>1</td><td>Resolved with minimal sensory deficit, able to walk independently</td></tr> <tr> <td>2</td><td>Minor motor deficit, able to walk with assistance or independent (implies the ability to move against gravity)</td></tr> <tr> <td>3a</td><td>Nonambulatory (wheelchair bound), able to move against gravity</td></tr> <tr> <td>3b</td><td>Nonambulatory (wheelchair bound), able to move the extremity laterally but not against gravity</td></tr> <tr> <td>3c</td><td>Nonambulatory (wheelchair bound), minimal or no movement</td></tr> </table>	<u>Grade</u>	<u>Spinal Cord Ischemia Description</u>	0	None	1	Resolved with minimal sensory deficit, able to walk independently	2	Minor motor deficit, able to walk with assistance or independent (implies the ability to move against gravity)	3a	Nonambulatory (wheelchair bound), able to move against gravity	3b	Nonambulatory (wheelchair bound), able to move the extremity laterally but not against gravity	3c	Nonambulatory (wheelchair bound), minimal or no movement
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0	None														
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3b	Nonambulatory (wheelchair bound), able to move the extremity laterally but not against gravity														
3c	Nonambulatory (wheelchair bound), minimal or no movement														
Permanent Paraparesis	Paraparesis secondary to Spinal Cord Ischemia identified within 30 days of the index endovascular procedure, combined with Spinal Cord Ischemia scale grade = 2 at the one month follow-up visit. Paraparesis will be assessed using the following spinal cord ischemia grading system⁶⁷: <table> <tr> <th><u>Grade</u></th><th><u>Spinal Cord Ischemia Description</u></th></tr> <tr> <td>0</td><td>None</td></tr> <tr> <td>1</td><td>Resolved with minimal sensory deficit, able to walk independently</td></tr> <tr> <td>2</td><td>Minor motor deficit, able to walk with assistance or independent (implies the ability to move against gravity)</td></tr> <tr> <td>3a</td><td>Nonambulatory (wheelchair bound), able to move against gravity</td></tr> <tr> <td>3b</td><td>Nonambulatory (wheelchair bound), able to move the extremity laterally but not against gravity</td></tr> <tr> <td>3c</td><td>Nonambulatory (wheelchair bound), minimal or no movement</td></tr> </table>	<u>Grade</u>	<u>Spinal Cord Ischemia Description</u>	0	None	1	Resolved with minimal sensory deficit, able to walk independently	2	Minor motor deficit, able to walk with assistance or independent (implies the ability to move against gravity)	3a	Nonambulatory (wheelchair bound), able to move against gravity	3b	Nonambulatory (wheelchair bound), able to move the extremity laterally but not against gravity	3c	Nonambulatory (wheelchair bound), minimal or no movement
<u>Grade</u>	<u>Spinal Cord Ischemia Description</u>														
0	None														
1	Resolved with minimal sensory deficit, able to walk independently														
2	Minor motor deficit, able to walk with assistance or independent (implies the ability to move against gravity)														
3a	Nonambulatory (wheelchair bound), able to move against gravity														
3b	Nonambulatory (wheelchair bound), able to move the extremity laterally but not against gravity														
3c	Nonambulatory (wheelchair bound), minimal or no movement														



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Key Outcome	Definition
Additional unanticipated post-procedural surgical or interventional procedure related to the device, procedure, or withdrawal of the delivery system	• Additional unanticipated surgical procedure (including conversion to open surgery), related to the device (including withdrawal of the delivery system) or procedure. Anticipated or unanticipated status will be determined at the discretion of the investigator. • Additional unanticipated interventional procedure related to the device or procedure. Anticipated or unanticipated status will be determined at the discretion of the investigator. ○ Events can include additional thoracic stent graft implantation due to endoleak, aortic enlargement, loss of patency, etc. or additional adjunctive procedures on the branch to improve or restore patency. ○ Events will not include unanticipated corrective intervention at the access site(s) or device intervention to address non treatment area issues (e.g., bare stent implantation to address bowel ischemia for dissection).
Initiation of the index endovascular procedure following the debranching procedure (Zone 0/1 cohorts only)	Great vessel debranching procedure is completed and Subject returns for endovascular implantation of the TBE Device, without interim death or study discontinuation.
New Onset Renal Failure Requiring Dialysis	New onset sustained renal failure identified within 30 days of the index endovascular procedure, combined with need/requirement for dialysis at the one month follow-up visit.

Success outcome definitions are provided in **Table 10**.

Table 10: Success Definitions

Key Outcome	Definition
Aortic Enlargement in the Region Encompassed by the Index Lesion	• <i>For aneurysm or other isolated lesions:</i> increase in the maximum aneurysm/lesion diameter of 5 mm or more relative to the post-operative CT scan within the one month follow-up window. • <i>For dissection:</i> increase in the maximum aortic transverse diameter within the treated area of 5 mm or more relative to the first post-operative CT scan within the Post-Procedural or one month windows.
Extension of Dissection	Proximal: False lumen propagation proximal to the originally treated aortic segment relative to the first post-operative CT scan within the Post-Procedural or one month windows. Distal: False lumen propagation distal to the originally treated aortic segment relative to the first post-operative CT scan within the Post-Procedural or one month windows.



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Key Outcome	Definition
False Lumen Perfusion through the primary intimal tear	Flow from a proximal aortic source through the primary intimal tear into the aortic false lumen (similar to a Type IA endoleak after treatment of aneurysms).
False Lumen Perfusion through an aortic arch branch vessel	Flow into the aortic false lumen via retrograde flow from aortic arch branch vessels.
False Lumen Perfusion through a non-aortic arch branch vessel	Flow into the aortic false lumen via retrograde flow from distal branch vessels in the chest (intercostals), abdomen (e.g., mesenteric, renal), or pelvis (iliac).
Loss of Aortic or Aortic Branch Patency (after the initial procedure)	No flow or contrast detected through the implanted aortic or side branch devices or distal CTAG devices after the index endovascular procedure.
Loss of Device Integrity	Defined as any of the following: • Wire fractures identified in the sealing row stents of the aortic component, branch component or aortic extender. • Transient (compression) or permanent stent-graft collapse (invagination) following complete device deployment, resulting in an overall reduction in the aortic or branch vessel luminal diameter.
Migration	Longitudinal movement of all or part of the device for a distance ≥ 10 mm, as confirmed by CT scan, relative to anatomical landmarks and device positioning at the first post-operative CT scan.
Fistula Formation	Fistula detected between the aorta and any adjacent structure associated with the area treated with the endovascular stent graft system verified with direct observation or CT scan.
New Ischemia	Clinically-reported, device-related ischemia (serious adverse event) not evident at the time of the index procedure with verified branch vessel compromise (malperfusion of organ, upper limb, or lower limb) identified on CT scan.
Type I and Type III Endoleak	• Type I endoleak is defined as a sealing failure at one of the attachment sites of the graft to the vessel wall (proximal leak, type Ia; distal, type Ib; inadequate seal at distal landing zone for side branch component, type Ic). Arterial flow therefore leaks alongside the graft and into the perigraft space. • Type IIIa endoleak is referred to flow from module disconnection, and type IIIb is flow from fabric disruption.
Type II and Type IV Endoleak	• Type II endoleak is defined as retrograde flow from branch arteries arising from the treated segment of the aorta. • Type IV endoleak is defined as flow through porous fabric.
New Dissection	• Treated Segment: A new aortic dissection entry tear within the area of the aorta treated with the endovascular stent graft



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Key Outcome	Definition						
	Untreated Aorta: A new aortic dissection entry tear outside the area of the aorta treated with the endovascular stent graft. Excludes access-related dissections.						
Renal dysfunction or volume overload requiring ultrafiltration	Renal dysfunction or volume overload that requires treatment with ultrafiltration.						
Significant Blood Loss	Blood loss ≥ 1000 ml measured during the index endovascular procedure, excluding any autologous blood transfusion or cell salvage.						
Life Threatening Bleed	Overt bleeding within 30 days plus a hemoglobin drop of ≥ 5 g/dL (provided the hemoglobin drop is related to bleeding), cardiac tamponade, bleeding after the index procedure requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid), bleeding requiring intravenous vasoactive drugs, intracranial hemorrhage and intraocular bleeding compromising vision or bleeding leading to death.						
Distal device-related thromboembolic adverse event requiring intervention or surgery	Ischemic events related to the device from tissues distal to the device implantation site sufficiently debilitating to necessitate bypass, open surgical intervention or limb amputation or leading to death.						
Myocardial infarction	Biomarker increase $> 10\times$ ULN first 72 hours or need for urgent or emergent PCI/CABG between initiation of the first procedure and 30 days, as confirmed at the one month follow-up visit.						
Prolonged intubation	Intubation duration > 1 week during the hospitalization period for the index endovascular procedure.						
Laryngeal or phrenic nerve injury	Permanent nerve damage resulting in re-intervention of a serious clinical symptomology within 30 days, as confirmed at the one month follow-up visit.						
Severe Heart Failure / Hypotension	Requiring vasopressor treatment or IV inotrope > 24 hours or mechanical circulatory support during the hospitalization period for the index endovascular procedure.						
Paraplegia and Paraparesis	For paraplegia and paraparesis events that are secondary to spinal cord ischemia identified within 30 days of the index endovascular procedure, paraplegia and paraparesis will be assessed using the following spinal cord ischemia grading system: <table> <tr> <th>Grade</th><th>Spinal Cord Ischemia Description</th></tr> <tr> <td>0</td><td>None</td></tr> <tr> <td>1</td><td>Resolved with minimal sensory deficit, able to walk independently</td></tr> </table>	Grade	Spinal Cord Ischemia Description	0	None	1	Resolved with minimal sensory deficit, able to walk independently
Grade	Spinal Cord Ischemia Description						
0	None						
1	Resolved with minimal sensory deficit, able to walk independently						



Key Outcome	Definition																
	2 Minor motor deficit, able to walk with assistance or independent (implies the ability to move against gravity) 3a Nonambulatory (wheelchair bound), able to move against gravity 3b Nonambulatory (wheelchair bound), able to move the extremity laterally but not against gravity 3c Nonambulatory (wheelchair bound), minimal or no movement • Suspected events will be adjudicated.																
Stroke	For events that do not meet the Primary Endpoint Definition in Table 9, stroke will be assessed using the Modified Rankin Scale (MRS): <table border="1"> <thead> <tr> <th>Score</th><th>Status</th></tr> </thead> <tbody> <tr> <td>0</td><td>No symptoms at all</td></tr> <tr> <td>1</td><td>No significant disability despite symptoms; able to carry out all usual duties and activities</td></tr> <tr> <td>2</td><td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td></tr> <tr> <td>3</td><td>Moderate disability; requiring some help, but able to walk without assistance</td></tr> <tr> <td>4</td><td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td></tr> <tr> <td>5</td><td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td></tr> <tr> <td>6</td><td>Dead</td></tr> </tbody> </table> • Suspected events will be adjudicated.	Score	Status	0	No symptoms at all	1	No significant disability despite symptoms; able to carry out all usual duties and activities	2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance	3	Moderate disability; requiring some help, but able to walk without assistance	4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance	5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention	6	Dead
Score	Status																
0	No symptoms at all																
1	No significant disability despite symptoms; able to carry out all usual duties and activities																
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance																
3	Moderate disability; requiring some help, but able to walk without assistance																
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance																
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention																
6	Dead																
False Lumen Status – Treated Segment	• Patent false lumen is defined as flow present throughout the aortic false lumen in the absence of evidence of thrombus <i>within the segment of the aorta initially-treated with an endovascular stent graft.</i> • Partially thrombosed false lumen is defined as clot within the aortic false lumen that has a residual patent flow channel <i>within the segment of the aorta initially-treated with an endovascular stent graft.</i> • Thrombosed false lumen is defined as complete thrombosis of the aortic false lumen within the segment of the aorta initially-treated with an endovascular stent graft.																



Key Outcome	Definition
False Lumen Status – Untreated Aorta	- Patent false lumen is defined as flow present throughout the aortic false lumen in the absence of evidence of thrombus <i>outside the segment of the aorta initially-treated with an endovascular stent graft.</i> - Partially thrombosed false lumen is defined as clot within the aortic false lumen that has a residual patent flow channel <i>outside the segment of the aorta initially- treated with an endovascular stent graft.</i> - Thrombosed false lumen is defined as complete thrombosis of the aortic false lumen <i>outside the segment of the aorta initially- treated with an endovascular stent graft.</i>

4.0 Study Population

4.1 Description of Population

The study has been designed with standard eligibility criteria to address any known or foreseeable factors that may compromise the outcome of the study or the interpretation of results. Only patients who meet all of the Inclusion Criteria and none of the Exclusion Criteria are intended to be enrolled. The enrollment of a Subject that does not meet criteria would constitute a Protocol deviation. Protocol deviations for Inclusion & Exclusion Criteria violations will be adjudicated by the Clinical Events Committee as to their severity and Major violations (as defined in Sec 6.5) will not be included in the analysis population and will be excluded.

4.1.1 Zone 2

Patients with thoracic aortic lesions of the DTA that require placement of the proximal extent of an endovascular stent graft in Zone 2 for effective treatment may be assessed for study eligibility.

4.1.2 Zone 0/1

Patients with thoracic aortic lesions of the aortic arch that require placement of the proximal extent of an endovascular stent graft in Zone 0/1 for effective treatment may be assessed for study eligibility.

4.2 Inclusion Criteria

All Subjects:

- 1) Presence of thoracic aortic pathology deemed to warrant surgical repair which requires proximal graft placement in Zone 0-2:
 - a) Aneurysms:
 - i) Fusiform aneurysm (≥ 55 mm), or
 - ii) Fusiform aneurysm (> 2 times native aortic diameter), or
 - iii) Saccular aneurysm (no diameter criteria)
 - b) Non-aneurysms
 - i) Intramural hematoma (no diameter criteria), or
 - ii) Penetrating aortic ulcer (no diameter criteria), or
 - iii) Traumatic aortic transection (no diameter criteria), or



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- iv) Other isolated lesion with non-diseased proximal and distal landing zone, or
 - v) Type B aortic dissection requiring treatment for rupture or impending rupture, malperfusion syndrome, rapid expansion, uncontrollable pain, aneurysmal dilatation or prophylactic reasons, or
 - vi) Residual aortic dissection following surgical repair of Type A aortic dissection requiring treatment. TBE implant must be at least 14 days after the surgical repair procedure.
- 2) Age ≥ 18 years at time of informed consent signature
 - 3) Subject is capable of complying with Protocol requirements, including follow-up
 - 4) Informed Consent Form (ICF) is signed by Subject or legal representative
NOTE: For Subjects less than 20 years of age enrolled at a Japanese center, the Subject's legal representative, as well as the Subject, must provide written informed consent.
 - 5) Must have appropriate proximal aortic landing zone, defined as:
 - a) Requires placement of the proximal extent of the Aortic Component in Zone 0-2 for exclusion of the lesion
 - b) Acceptable proximal landing zone outer curvature length for the required device (See **Table 1. Aortic Component Sizing Guide**)
 - c) Landing zone inner diameters between 16-42 mm in Zone 1-2 Subjects and 24-42 mm in Zone 0 Subjects
 - d) Landing zone includes either the brachiocephalic, left common carotid or left subclavian native ostium.
 - i) If the landing zone includes brachiocephalic it cannot be heavily calcified or heavily thrombosed.
 - ii) If the landing zone includes either the left common carotid or left subclavian it cannot be heavily calcified, heavily thrombosed or aneurysmal.
 - e) Dissection Patients: Primary entry tear must be distal to the target branch vessel and proximal extent of the proximal landing zone must not be dissected
 - f) For patients with prior replacement of the ascending aorta and/or aortic arch by a surgical graft, there must be at least 2 cm of landing zone proximal to the most distal anastomosis site.
 - 6) Must have appropriate target branch vessel landing zone, defined as:
 - a) Length of ≥ 3 cm proximal to first major branch vessel if using Aortic Component with 8 mm portal diameter
-or-
Length of ≥ 2.5 cm proximal to first major branch vessel if using Aortic Component with 12 mm portal diameter (required for Zone 0 Subjects)
 - b) Target branch vessel inner diameters of 6-15 mm if using Aortic Component with 8 mm portal diameter
-or-
Inner diameters of 11-18 mm if using Aortic Component with 12 mm portal diameter (required for Zone 0 Subjects)



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- c) Target branch vessel landing zone must be in native aorta that cannot be severely tortuous (i.e. vessel tortuosity that results in a 180 degree turn within the treated target branch vessel length), aneurysmal, dissected, heavily calcified, or heavily thrombosed
- 7) For patients with aneurysm/isolated lesion, must have appropriate distal aortic landing zone, defined as:
 - a) Outer curvature length must be ≥ 2 cm proximal to the celiac artery
 - b) Aortic inner diameters between 16-42 mm
 - c) Landing zone cannot be aneurysmal, heavily calcified, or heavily thrombosed
 - d) Landing zone in native aorta or previously implanted Conformable GORE® TAG® Device

Zone 0/1 Subjects Only:

- 8) Subject does not have a mechanical aortic valve
- 9) Subject is considered a high risk candidate for conventional open surgical repair at the discretion of the Investigator

4.3 Exclusion Criteria

All Subjects:

- 1) Concomitant disease of the ascending aorta or aneurysm of the abdominal aorta requiring repair
- 2) Previous endovascular repair of the ascending aorta
- 3) Previous endovascular repair of the DTA with a non-Gore device
- 4) Surgery within 30 days prior to enrollment with the exception of:
 - Surgery for Ascending Aortic Dissection and/or placement of vascular conduit for access
 - Surgery to treat any other presenting injuries in Traumatic Transection Subjects only.
- 5) Infected aorta
- 6) Life expectancy <2 years
- 7) Myocardial infarction within 6 weeks prior to treatment
- 8) Stroke within 6 weeks prior to treatment, stroke defined as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.
- 9) Patient has an active systemic infection (e.g. infection requiring treatment with parenteral anti-infective medication) that may place the patient at increased risk of endovascular infection. Patients with a chronic infection (such as HIV, Hepatitis C, etc.) that is well controlled under their current treatment regimen may be eligible.
- 10) Pregnant female at time of informed consent signature
- 11) Degenerative connective tissue disease, e.g. Marfan's or Ehler-Danlos Syndrome
- 12) Participation in another drug or medical device study within one year of study enrollment
- 13) Known history of drug abuse within one year of treatment



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- 14) Presence of protruding and/or irregular thrombus and/or atheroma in the aortic arch or ascending aorta
- 15) Tortuous or stenotic iliac and/or femoral arteries preventing introducer sheath insertion and the inability to use a conduit for vascular access
- 16) Planned coverage of celiac artery
- 17) Patient has known sensitivities or allergies to the device materials
- 18) Patient has known hypersensitivity or contraindication to anticoagulants or contrast media, which is not amenable to pre-treatment
- 19) Previous instance of Heparin Induced Thrombocytopenia type 2 (HIT-2) or known hypersensitivity to heparin
- 20) Patient with a history of a hypercoagulability disorder and/or hypercoagulability state
- 21) Diameter taper outside of the device sizing range between proximal and distal landing zones of aorta and the inability to use additional devices of different diameters to compensate for the taper
- 22) Mycotic aneurysm
- 23) Persistent refractory shock (systolic blood pressure <90 mm Hg)
- 24) Patient has body habitus or other medical condition which prevents adequate visualization of the aorta
- 25) Renal failure defined as patients with an estimated Glomerular Filtration Rate (eGFR) <30 (ml/min/1.73 m²) or currently requiring dialysis

Zone 0/1 Subjects Only:

- 26) Patient at high risk for a neurological event, e.g. stroke



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5.0 Study Procedures/Evaluations

5.1 Schedule of Events

Table 11 and **Table 12** outline the required procedures at each follow-up visit for the respective study cohorts. Detailed imaging guidelines are located in APPENDIX A: Imaging Guidelines.

Table 11: Zone 2 Subject Evaluations and Post-Treatment Follow-up Schedule

	Screening	Treatment	Discharge	1 month	6 months	12 months	24, 36, 48, and 60 months
Informed Consent	X						
Demographics and Medical History	X						
Physical examination	X		X	X	X	X	X
Modified Rankin Scale ^a	X		X	X ^b	X	X	X
Spinal Cord Ischemia Scale ^a	X		X	X	X	X	X
Brachial and Ankle Pressures (Optional)	X		X ^c	X	X	X	X
Serum Creatinine Concentration	X						
Spiral CTA (contrast) ^d	X ^e			X	X	X	X
Spiral CT (non-contrast) ^d				X			
Angiogram at Completion of Procedure		X					
NYHA Score, ASA Score	X						
ISS Score, Glasgow Coma Score (Traumatic Transection Subjects only)	X						
NIH Stroke Scale (NIHSS) ^f	X		X	X			

^a If Subject is unable to return to the site for a follow-up visit, they may be contacted by telephone to evaluate the Modified Rankin Scale and Spinal Cord Ischemia Scale.

^b For Subjects suspected of having a stroke event within 30 days following the index endovascular procedure an additional MRS score should be completed at 90 days following the suspected stroke event but no greater than 120 days post index endovascular procedure.

^c Within 48 hours of index endovascular procedure.

^d CTA of chest/abdomen/pelvis at Screening. CTA of chest at all follow-up visits, except for Dissection Subjects who must have a CTA of chest/abdomen/pelvis at all visits. Imaging Guidelines for CT are located in APPENDIX A. MRA may be used in place of CTA during follow-up if the Subject is contraindicated for CTA.

^e Screening CTA must be ≤ 90 days prior to enrollment

^f NIH Stroke Scale should be performed for all subjects during Screening, Discharge and 1 Month visits. NIHSS should also be performed for any Subject suspected of having a stroke event that undergoes the treating site's stroke Protocol during the study interval from the initiation of the index endovascular procedure until discharge. The scale should be performed as soon as possible after learning of the suspected event.



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Table 12: Zone 0/1 Subject Evaluations and Post-Treatment Follow-up Schedule

	Screening	Treatment			Discharge	1 month	6 months	12 months	24, 36, 48, and 60 months
		Phase 1 Procedure	Phase 1 Evaluation ^a	Phase 2 Procedure					
Informed Consent	X								
Demographics and Medical History	X								
Physical Examination	X		X ^b		X	X	X	X	X
Modified Rankin Scale ^c	X		X		X	X ^d	X	X	X
Spinal Cord Ischemia Scale ^c	X		X		X	X	X	X	X
Brachial and Ankle Pressures (Optional)	X		X		X ^e	X	X	X	X
Serum Creatinine Concentration	X								
Spiral CTA (contrast) ^f	X ^g					X	X	X	X
Spiral CT (non-contrast) ^f						X			
Angiogram at Completion of Procedure				X					
CTA of the Head/Neck ^h	X								
NYHA Score, ASA Score	X								
ISS Score, Glasgow Coma Score (Traumatic Transection Subjects only)	X								
NIH Stroke Scale (NIHSS) ⁱ	X				X	X			

^a Phase 1 Evaluation should be performed at least 24 hours after completion of the revascularization procedure but within 60 days post treatment

^b Subjects who are withdrawn prior to the Phase 2 Procedure should also have a Physical Exam at one month post Phase 1 procedure

^c If Subject is unable to return to the site for a follow-up visit, they may be contacted by telephone to evaluate the Modified Rankin Scale and Spinal Cord Ischemia Scale

^d For Subjects suspected of having a stroke event within 30 days following the index endovascular procedure an additional MRS score should be completed at 90 days following the suspected stroke event but no greater than 120 days post index endovascular procedure.

^e Within 48 hours of index endovascular procedure

^f CTA of chest/abdomen/pelvis at Screening. CTA of chest at all follow-up visits, except for Dissection Subjects who must have a CTA of chest/abdomen/pelvis at all visits. Imaging Guidelines for CT are located in APPENDIX A. MRA may be used in place of CTA during follow-up if the Subject is contraindicated for CTA.

^g Screening CTA must be ≤90 days prior to Phase 2 procedure.

^h Screening CTA of Head/Neck must be ≤90 days prior to Phase 1 procedure. If CT of Head/Neck is not consistent with site's standard of care then radiological modality of evaluation is at investigator discretion (Ultrasound, MR, etc.) However, imaging of head/neck vasculature is required ≤90 days prior to Phase 1 procedure.

ⁱ NIH Stroke Scale should be performed for all subjects during Screening, Discharge and 1 Month visits. NIHSS should also be performed for any Subject suspected of having a stroke event that undergoes the treating site's stroke Protocol during the study interval from the initiation of the surgical revascularization procedure until discharge post-index endovascular procedure. The scale should be performed as soon as possible after learning of the suspected event.



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MD133246 Protocol Template: Revision#: 2

Doc Type: GC

5.2 Informed Consent Process

All patients must provide informed consent prior to any study related procedures being performed. The case history (*i.e.*, source documents/Subject chart) for each Subject shall document that such informed consent was obtained. The IRB approved consent form will be signed and personally dated by the Subject or legally authorized representative, and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the Subject records. A copy of the informed consent document will be given to the Subject for their records.

The following applies only to US sites:

A Subject may be asked to have their procedure recorded. The purpose of a recorded case presentation is to increase awareness of the study for potential investigators and, if available, serve as additional training for study investigators in the safe and effective use of the TBE Device. Following the potential FDA approval of the TBE Device, recorded materials may also be used for podium presentations and for training in the safe and effective use of the TBE Device as labeled. The informed consent document and process must comply with the requirements of 21 CFR 50.20 and minimize the possibility of coercion or undue influence for Subjects who are asked to participate in a live case presentation. Subjects should be able to enroll in the study without agreeing to participate in a live/recorded case presentation.

The TBE Device is considered a significant risk device. A live/recorded case presentation for a significant risk device cannot be conducted until IRB approval is obtained, certification of IRB approval is submitted to FDA, and FDA approval is received. The sponsor must be notified and provided with all necessary documentation to complete the FDA submission and obtain approval *prior* to the live/recorded case.



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5.3 Pre-Screening / Screening

5.3.1 Screening

Figure 15 illustrates the screening process for the different study arms/cohorts:

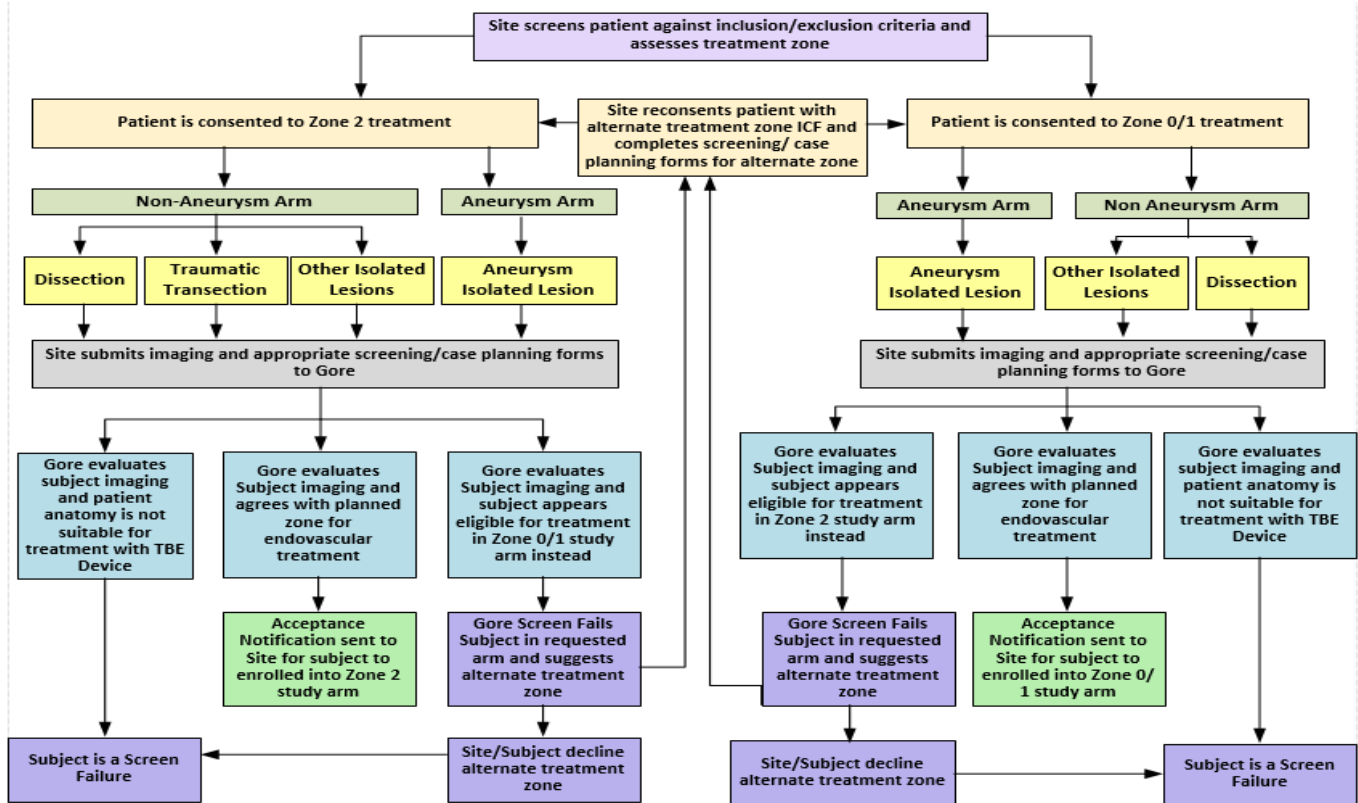


Figure 15: Pre-Screening/Screening Process

Patients will be initially screened by the Investigator, who will assess the patient as compared to the study inclusion and exclusion criteria. If the Investigator considers the patient to be eligible for enrollment into the study, the Investigator will inform the patient of his/her potential eligibility and discuss the clinical study with the patient including the risks, benefits, and required follow-up procedures.

If the patient agrees to be screened for the study, the Investigator will obtain the patient's informed consent. All patients who sign an ICF will be considered entered into the screening phase of the study.

Upon receiving consent, the Investigator will submit a Spiral Computed Tomographic Angiography (CTA) of the chest, abdomen, and pelvis, with oblique, sagittal, and coronal reconstructions to the Sponsor to confirm the required anatomic inclusion and exclusion criteria. Emergent cases (US only) for non-aneurysm lesions at sites with device consignment may be reviewed at the site by a Gore associate to confirm required anatomic inclusion and exclusion criteria prior to enrollment, however imaging must still be submitted to the Sponsor for central review even if it is following enrollment. The CTA must have been taken ≤ 90 days prior to treatment for Subjects enrolling in either of the



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Zone 2 study cohorts or taken $\leq$ 90 days prior to Phase 2 of treatment for Subjects in enrolling in either of the Zone 0/1 study cohorts. This CTA could be obtained prior to informed consent as part of the patient's standard medical care; however, informed consent is required in order to submit the CTA to the Sponsor for screening. The CTA will be used to assess the characteristics, lengths and diameters of the aneurysm, surrounding aorta, target branch vessel and other major arterial branches. Cardiac-gated CTA of the chest may be used, in which case it is preferable for prospective gating be performed in the systolic phase. (If a gated CTA of only the chest is performed, non-gated CT imaging of the abdomen and pelvis is still required.) These results should be submitted to the Sponsor as part of the pre-treatment assessment. Patients screening for the Zone 0/1 study cohorts that meet anatomical requirements as determined by the Sponsor will also be reviewed by the TBE Zone 0/1 Screening Committee (see **Section 5.3.2**).

If during the screening process it becomes apparent that a Zone 2 Subject would be more appropriately treated under the Zone 0/1 study cohort, that Subject will be considered a screen failure and should be re-consented and re-screened under the Zone 0/1 study cohort.

If the initial Sponsor review of the CTA confirms that the patient meets the Protocol anatomic requirements, the following evaluations will be conducted at the screening visit or must have been completed no more than 30 days prior to enrollment, except as noted.

- Inclusion/Exclusion criteria
- Physical examination
- Left and right brachial and ankle pressure assessments (Optional)
- Modified Rankin Scale (Appendix B)
- Spinal Cord Ischemia Scale
- NIH Stroke Scale (Appendix B)
- Demographics
- Medical history (Special attention will be given to the assessment of those risk factors listed on the case report forms (CRFs), including the assessments related to risk of coverage of the LSA)
- Classification of the Subject per the American Society of Anesthesiologists (ASA) Physical Status Clarification System and New York Heart Association (NYHA) (Appendix B)
- Serum Creatinine
- Pregnancy test (if applicable) – no more than 10 days prior to enrollment
- Radiological Evaluation of the Head/Neck, modality to be determined by the Investigator –no more than 90 days prior to enrollment (Zone 0/1 Only)
- ISS Score, Glasgow Coma Score (Traumatic Transection Subjects only) (Appendix C)
- Dissection Presentation (Dissection Subjects only)



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Further studies may be used to assess the status of the abdominal aorta, iliac and common femoral arteries and to evaluate the carotid, subclavian, vertebral, left internal mammary, intercostal, celiac, superior mesenteric and renal arteries. Subjects to be treated in the Zone 0/1 study cohort should have a radiological evaluation of the vasculature of the head and neck as well. These adjunctive studies may include angiography, intravascular ultrasound and/or duplex scans at the discretion of the Investigator and are intended for use in screening and the case planning of the surgical revascularization procedure. The Sponsor will review the CTA of the chest, abdomen, and pelvis prior to Subject enrollment into the study.

Patients who do not qualify for participation in the study based on these reviews will have the reason for exclusion documented. These patients will then be excused from further study participation and are considered screen failures.

5.3.2 TBE Zone 0/1 Screening Committee

The TBE Zone 0/1 Screening Committee will be comprised of physician consultants at study sites with previous experience using the TBE Device. The Committee will provide a clinical review for all Zone 0/1 study candidates that meet all anatomical requirements as determined by the Sponsor. The Screening Committee will review the pre-treatment CT imaging, head/neck imaging or imaging report and patient medical history (including atrial fibrillation and other comorbidities) and will make a recommendation to the Sponsor regarding whether the patient should be excluded based on high risk of adverse neurological events, e.g. stroke. The Committee can also recommend the patient be excluded based on anatomical criteria, although the Committee is not responsible for a comprehensive anatomical review. The final decision regarding any Committee recommendations with respect to anatomical and neurological risk and patient acceptance into the trial resides with the Sponsor and will be conveyed to the site.

5.4 Zone 0/1 Multi-Specialty Approach to Informed Consent and Screening

All Zone 0/1 Subjects must have a consultation with a Surgeon or other physician with experience in ascending aortic and arch surgery (such as a Cardiothoracic Surgeon in the US and a Cardiovascular Surgeon in Japan) within 90 days of enrollment. The Zone 0/1 Subject may consult with the CT Surgeon directly or the Consenting Investigator responsible for the care of the Subject may consult with the physician on behalf of the Subject and bring that information back to the Subject. This consultation will involve a discussion of other treatment options, such as open surgical repair based on the Subject's medical history and the Subject's (high) risk for open surgical repair. The Implanting Investigator responsible for the Subject must ensure that the consultation occurs prior to Subject enrollment. If the Subject consulted directly with a CT Surgeon, the Investigator is responsible for verifying the content of the consultation through a conversation with the consulting physician, if the documentation of the consultation in the Subject's medical record is not adequate. If the Consenting Investigator has experience in performing ascending arch surgery, it is not necessary for the Subject to consult with an additional surgeon.

5.5 Enrollment

5.5.1 Zone 2 Study Arm

A patient that has met the required inclusion/exclusion criteria to participate in any of the Zone 2 study cohorts will be considered as enrolled in the study when the first device delivery catheter has been introduced into the vasculature.



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The index endovascular procedure for Subjects treated for residual dissection with TBE Device placement in the LSA following surgical repair of the ascending aorta may be performed no earlier than 14 days after the ascending and/or aortic arch surgical procedure.

5.5.2 Zone 0/1 Study Arm

Subjects will be considered enrolled at the initiation of the great vessel revascularization procedure (Phase 1). A Subject will be considered to have entered the second phase of the study once a device delivery catheter has been introduced into the Subject's vasculature during the index endovascular procedure with the TBE Device (Phase 2).

The index endovascular procedure for Subjects treated for residual dissection following surgical repair of the ascending aorta may be performed no earlier than 14 days after the surgical procedure. If great vessel revascularization is required, the same requirements outlined in apply for these Subjects.

5.6 Procedure

Subjects who qualify for and are enrolled in the study will undergo planned endovascular repair of the DTA or aortic arch as appropriate dependent upon the study into which they were enrolled.

5.6.1 Zone 2 Study Arm Procedure

Procedure: Endovascular repair of the DTA may include the following:

- General, regional, or local anesthesia administration before endovascular procedure.
- Antibiotic administration.
- Systemic heparin administration, according to standard practice (if indicated).
- Spinal cord ischemia prevention techniques; e.g., cerebrospinal fluid drainage.
- Endoprosthesis introduction into the access site; e.g., iliac artery or femoral artery.
- Angiographic verification of aorta, LSA and adjacent artery characteristics performed at the time of the procedure and before endoprosthesis introduction.
- Fluoroscopic guidance used for endoprosthesis placement throughout the endovascular procedure.
- Endoprosthesis introduction and deployment.
- More than one endoprosthesis may be used to treat the aortic lesion (e.g., deployment of the TBE Device proximally with distal extension before or after using CTAG Device(s)).
- At the discretion of the Investigator, adjunct radiologic modalities may be used to assess the vasculature and to optimize prosthesis implantation.
- Angiography at the completion of the endovascular procedure to document the status of the endoprosthesis and surrounding aorta and vasculature. .

Additional information regarding the procedure can be found in the GORE® TAG® Thoracic Branch Endoprosthesis Instructions for Use.



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Post procedure:

- The TBE Device components used for implantation will be documented, as well as all CTAG Devices and accessory devices used. Issues related to any of the devices, including any accessory devices, will be documented on the appropriate CRFs.
- Additional procedures performed during the treatment (e.g., angioplasty for arterial access) will be documented on the appropriate CRFs.
- The estimated amount of total blood loss and any adverse events (AEs) experienced during the treatment will be documented.
- Procedure time, anesthesia time, and total fluoroscopic time will be documented on the appropriate CRFs.
- Physical examination
- Left and right brachial and ankle pressure assessments (within 48 hours after procedure) (Optional)
- Modified Rankin Scale (performed prior to discharge)
- Spinal Cord Ischemia Scale (performed prior to discharge)
- NIH Stroke Scale (performed prior to discharge)

For Subjects suspected of having a stroke event:

- NIH Stroke Scale should be performed for any Subject suspected of having a stroke event that undergoes the treating site's stroke Protocol during the study interval from the initiation of the index endovascular procedure until discharge. The scale should be performed as soon as possible after learning of the event
- For Subjects suspected of having a stroke event within 30 days following the index endovascular procedure an additional MRS score should be completed at 90 days following the suspected stroke event but no greater than 120 days post index endovascular procedure.

5.6.2 Zone 0/1 Study Arm Procedure

Endovascular repair of the aortic arch (Zone 0/1 Subjects) will proceed as a phased procedure and may include the following:

Phase 1 Procedure: Surgical revascularization of arch branch vessels distal to the target landing zone which may include:

- General, regional, or local anesthesia administration before the surgical procedure.
- Antibiotic administration.
- Surgical exposure and access for vessel ligation and bypass grafting or transposition.
 - The type/technique of surgical revascularization performed will be at the discretion of the Investigator.
- Systemic heparin administration, according to standard practice (if indicated).



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After the surgical procedure:

- The surgical grafts and techniques used will be documented on the appropriate CRFs.
- Additional procedures performed during the treatment will be documented on the appropriate CRFs.
- The estimated amount of total blood loss and any adverse events (AEs) experienced during the treatment will be documented.

Phase 1 Evaluation: At least 24 hours after the completion of the revascularization procedure but within 60 days post treatment, the following will be assessed:

- Physical examination
- Left and right brachial and ankle pressure assessments (Optional)
- Modified Rankin Scale
- Spinal Cord Ischemia Scale

For Subjects suspected of having a stroke event:

- NIH Stroke Scale should be performed for any Subject suspected of having a stroke event that undergoes the treating site's stroke Protocol during the study interval from the initiation of surgical revascularization procedure until discharge post-index endovascular procedure. The scale should be performed as soon as possible after learning of the event

Once the Phase I Evaluation is complete the index endovascular procedure (Phase 2) may be completed. The Phase 2 endovascular procedure must occur within 60 days of the Phase 1 revascularization procedure. If a Subject experiences a MI or stroke (defined as any neurological deficit, MRS $\geq$ 1) during or following the Phase 1 procedure then they must wait a minimum of 3 weeks prior to proceeding to the Phase 2 endovascular procedure.

Phase 2 Procedure: Within 60 days and no less than 1 day after the Phase 1 Procedure is conducted, the endovascular aortic repair with the TBE Device will occur and may include the following:

- General, regional, or local anesthesia administration before endovascular procedure.
- Antibiotic administration.
- Systemic heparin administration, according to standard practice (if indicated).
- Spinal cord ischemia prevention techniques; e.g., cerebrospinal fluid drainage.
- Endoprosthesis introduction into the access site; e.g., iliac artery or femoral artery.
- Angiographic verification of aorta, aortic branch vessels, and adjacent artery characteristics performed at the time of the procedure and before endoprosthesis introduction. Angiographic verification of patency of the Phase 1 surgical revascularization is required prior to deployment of the Aortic Component.
- Endovascular occlusion of distal vessels if needed to prevent type II endoleak.



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- Fluoroscopic guidance used for endoprosthesis placement throughout the endovascular procedure.
- Endoprosthesis introduction and deployment.
- More than one endoprosthesis may be used to treat the aortic lesion (e.g., deployment of the TBE Device proximally with distal extension before or after using CTAG Device(s)).
- At the discretion of the Investigator, adjunct modalities may be used to assess the vasculature and to optimize prosthesis implantation.
- Angiography after endoprosthesis deployment to document the status of the endoprosthesis and surrounding aorta and vasculature.

Additional information regarding the procedure can be found in the GORE® TAG® Thoracic Branch Endoprosthesis Instructions for Use.

Zone 0/1 Multi-Specialty Approach to Treatment and Post-Operative Care

A multi-specialty approach for Phase 2 treatment of Zone 0/1 Subjects is required. This includes:

- A Cardiothoracic Surgeon (or physician with experience in ascending aortic and arch surgery) and Vascular Surgeon (or physician with experience in managing vascular complications) must be present during the Phase 2 procedure or be notified of the procedure in advance and readily available should any emergent procedures be required periprocedurally.
- Cardiac Anesthesiology (or a specialty experienced in supporting ascending/aortic arch procedures and transesophageal echocardiography (TEE)) must be present during the Phase 2 procedure or be notified of the procedure in advance and readily available to provide support should any emergent procedures be required periprocedurally.

The Implanting Investigator is responsible for ensuring all specialties are readily available or present as described above. Additionally, all Phase 2 procedures must occur in an Operating Room, Hybrid Operating Room or other room that is in close proximity to a location where a Subject can be converted to open surgical repair, if needed.

Post Procedure:

- The TBE Device components used for implantation will be documented, as well as all CTAG Devices and accessory devices used. Issues related to any of the devices, including any accessory devices, will be documented on the appropriate CRFs.
- Additional procedures performed during the treatment (e.g., angioplasty for arterial access) will be documented on the appropriate CRFs.
- The estimated amount of total blood loss and any AEs experienced during the treatment will be documented on the appropriate CRFs.
- Procedure time, anesthesia time, and total fluoroscopic time will be documented on the appropriate CRFs.



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Discharge:

- Physical examination
- Left and right brachial and ankle pressure assessments (within 48 hours after procedure) (Optional)
- Modified Rankin Scale (performed prior to discharge)
- Spinal Cord Ischemia Scale (performed prior to discharge)
- NIH Stroke Scale (performed prior to discharge)

For Subjects suspected of having a stroke event:

- NIH Stroke Scale should be performed for any Subject suspected of having a stroke event that undergoes the treating site's stroke Protocol during the study interval from the initiation of surgical revascularization procedure until discharge post-index endovascular procedure. The scale should be performed as soon as possible after learning of the event.
- For Subjects suspected of having a stroke event within 30 days following the index endovascular procedure an additional MRS score should be completed at 90 days following the suspected stroke event but no greater than 120 days post index endovascular procedure.

5.7 Repeat Interventions

Additional Interventions using investigational components may be performed at the discretion of the Investigator to address clinical observations. Any additional interventions performed will be documented on electronic case report forms (eCRF). The components used as part of any additional intervention, the date of the additional intervention, and the observation(s) leading to any additional intervention will also be documented in the eCRF.

If any TBE Devices (Aortic Component, Aortic Extender, Side Branch Component) and/or CTAG Devices are used during the intervention, additional anatomical and procedural considerations may be required. Additional implant requirements are detailed in the IFUs. Reintervention narratives will be provided in the appropriate sections of the Annual Progress Report (e.g. a Zone 0 reintervention narrative for a Zone 2 Subject will be provided in both the Zone 2 and Zone 0 sections of the IDE Annual Progress Report (US only) and identified as being reported in both places).

5.8 Follow-up

Follow-up visits will be scheduled at appointed times after the date of treatment. The Sponsor recognizes that Subjects may not be able to return for follow-up visits on the exact date required. Thus, a period during which each visit is allowed, i.e. window, is provided in **Table 13** (Zone 2) and **Table 14** (Zone 0/1). Follow-up visits should include the following:

In Japan only (per PMDA requirements): After obtainment of approval for Zone 0/1 indication in Japan, "clinical trial" words and sentences in the SSB 11-02 clinical investigation plan shall be replaced with "post-market study".

- Physical examination



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- Left and right brachial and ankle pressures (Optional)
- Modified Rankin Scale (also completed at 3 months for Subjects suspected of experiencing a stroke event through 30 days)
- Spinal Cord Ischemia Scale
- NIH Stroke Scale (one month visit only)
- Spiral CTA of the chest (contrast)
- Spiral CT of the chest (non-contrast – at one month only, or if endoleak suspected)
- Dissection Subjects only: Spiral CTA of the chest, abdomen, and pelvis (contrast)
- Dissection Subjects only: Spiral CTA of the chest, abdomen, and pelvis (non-contrast – at one month only, or if endoleak suspected)

Table 13: Zone 2 Cohorts Schedule of Follow-up Visits and Time Periods

Follow-up Visit	Ideal Window (days)	Analysis Window (days)	Adverse Event Absolute Analysis Window (days)
Procedure	0	0	0
Post-Procedure	1-14	1-14	-
1 Month	23-44	15-59	1-30
6 Months	150-210	60-242	31-182
12 Months	275-455	243-546	183-365
24 Months	640-820	547-911	366-731
36 Months	1005-1185	912-1275	732-1096
48 Months	1370-1550	1276-1640	1097-1461
60 Months	1735-1915	1641-2006	1462-1826



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Table 14: Zone 0/1 Cohorts Schedule of Follow-up Visits and Time Periods

Follow-up Visit	Ideal Window (days)	Analysis Window (days)	Adverse Event Absolute Analysis Window (days)
Phase 1 Procedure: Great Vessel Revascularization	-7 up to -1 days before Phase 2 Procedure	-60 up to -1 days before Phase 2 Procedure	-60 up to -1 days before Phase 2 Procedure
Phase 1 Evaluation	-6 up to 0 days before Phase 2 Procedure*	-59 up to 0 days before Phase 2 Procedure*	-59 up to 0 days before Phase 2 Procedure*
Phase 2 Procedure: Index Endovascular Procedure	0	0	0
Post Procedure	1-14	1-14	-
1 Month	23-44	15-59	1-30
6 Months	150-210	60-242	31-182
12 Months	275-455	243-546	183-365
24 Months	640-820	547-911	366-731
36 Months	1005-1185	912-1275	732-1096
48 Months	1370-1550	1276-1640	1097-1461
60 Months	1735-1915	1641-2006	1462-1826

* Although Phase 1 Evaluation can occur on the same day as the Index Endovascular Procedure, the Phase 1 Evaluation must occur before the Index Endovascular Procedure

Follow-up visits should be scheduled within the ideal window when possible; however, any available data collected in the analysis windows will be summarized as occurring within the given window. Data collected outside the ideal window, but within the analysis window will not be considered a Protocol deviation.

5.9 Subject Withdrawal from the Study

A Subject may withdraw from the clinical study at any time and should notify the Investigator. The Investigator may also withdraw the Subject from the clinical study at any time based on his/her medical judgment.

Under no circumstances will the Investigator be expected or encouraged to enroll a Subject in the study if, based on their best medical judgment, an alternative treatment better serves the Subject or if there are doubts regarding the Subject's ability to complete the required follow-up. Enrolled Subjects who undergo a device explant will be followed for 30 days post explant, with all adverse events in that timeframe reported.

5.10 Subject Lost to Follow-Up



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The Investigator should encourage Subjects to return for all required follow-up visits. These measures are important as the clinical study objectives may not be realized if a large number of Subjects are lost to follow-up. If a Subject refuses to return a follow-up visit, the Investigator will attempt to obtain at least vital statistics.

A Subject will be considered lost to follow-up and terminated from the study once they have missed two consecutive follow-up visits within the analysis windows followed by three documented attempts by the Investigator to contact the Subject or next of kin. One of the three documented attempts must include a certified letter. In the event that the Subject is lost to follow-up, the date of discontinuation of the study will be recorded as the last contact with the Subject by the Site.

5.11 Subject Study Completion

A Subject has completed the study after finishing five years of follow-up requirements as defined in the Protocol. Any Subject that does not complete these requirements due to voluntary withdrawal, physician withdrawal, death, or any other reason will be considered a withdrawal. Subjects will not be provided with any medical care by the Sponsor after study completion or withdrawal.

5.12 Explant Procedures

The TBE Device and/or the CTAG Device may be explanted during a surgical procedure or as part of an autopsy. Sites are requested to return explanted device to the Sponsor for gross and histological evaluation. Prior to planned or potential device retrieval, contact the Gore Associate managing the study to communicate that a specimen is being retrieved from a study Subject. A specimen shipping kit will be immediately sent to the Site. The specimen kit provides specific packaging and handling instructions for the specimen and contains a shipping container.

6.0 Study Administration

6.1 Training

If a Site has no previous clinical experience with the TBE Device, the first two Subjects enrolled at that Site must be eligible for enrollment into the Zone 2 Cohort. The first case will be Subject to enhanced anatomic screening performed by the Sponsor. This enhanced screening will include, at a minimum, consideration of:

- Aortic landing zone length and integrity
- Aortic arch angulation
- Side branch landing zone length and integrity
- Side branch angulation

In order to enroll Subjects into the Zone 0/1 Cohorts (Aneurysm or NAL) a Site must have previous clinical experience with the TBE Device in no fewer than two Zone 2 cases. Japan will not contribute any Subjects to the Zone 2 Cohort, however Japan Sites will still be required to perform two Zone 2 TBE cases before they are eligible to enroll Subjects in the Zone 0/1 Cohorts (Aneurysm or NAL). These will be captured as Training cases in Japan and will be Subject to similar Informed Consent and follow-up requirements as Study Subjects, but will not be included in the Zone 2 Cohort analysis.



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Additionally, documentation of Investigator training and experience requirements must also include:

- TAG/CTAG Device certification
- Didactic presentation from a Gore product specialist or clinical specialist
- Two or more of any of the following with the TBE Device:
 - Bench top deployments
 - Pre-clinical training case in a live animal model
 - Clinical training case

6.2 Monitoring

Site monitoring for this study will be provided by Covance Inc in the US and CMIC Co., Ltd. in Japan. The Site monitors are qualified by training and experience to oversee the progress of the study at the Site and will verify that the Investigators and their staff understand and adhere to both the applicable regulatory requirements and the study Protocol. In addition, they may assist in resolution of any problems that may arise during the study.

6.2.1 Site Initiation

Site initiation will be performed to verify that each Investigator and his / her staff understands the Protocol, applicable regulations, human Subject protection requirements, and the Investigator's obligations. This visit will confirm that required documentation with the appropriate approval is in place prior to Subject enrollment.

6.2.2 Periodic Site Monitoring

Periodic Site monitoring will occur as necessary to verify continuing adequacy of facilities and adherence to the study Protocol, the GCPs, and applicable local regulations and laws that pertain to the conduct of the study. These activities will also review the CRFs and source documentation, the timely submission of accurate records to the Sponsor, and the maintenance of proper records. A report will be written following each Site visit and a follow up letter will be provided to the Site with a summary of findings. Each Site will also be visited at close-out to confirm that all documentation is complete.

6.2.3 Multi-Specialty Approach Monitoring for Zone 0/1 Subjects

For all Zone 0/1 Subjects, the site must provide evidence to the Sponsor of multi-specialty involvement in the informed consent and screening process prior to enrollment using the documentation forms provided by the Sponsor. Evidence of multi-specialty involvement in Phase 2 treatment and post-operative care must be provided within five business days of the Phase 2 procedure using the documentation forms provided by the Sponsor.



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6.3 Device Accountability and Storage

Investigational devices may only be used under the supervision of the Investigator and in strict accordance with this Protocol and applicable laws and regulations. Excluding Emergency or Compassionate Use in the U.S, devices may only be implanted in Subjects who meet the inclusion / exclusion criteria set forth in this Protocol and used only as described in this Protocol and per IFU. The Investigator or delegated site staff in charge of Device Accountability will maintain accurate, detailed records of all devices received from the Sponsor and the disposition of each device according to the instructions in the Regulatory Binder provided to all Sites. The Site will record each device used on the corresponding CRF. The Site will notify the Sponsor immediately if any devices are damaged or unaccounted for. The devices must be accessible only to the personnel involved in the study and stored in a secure location.

Upon completion or termination of the study or the Investigator's participation in the study, or at the Sponsor's request, the Site will return any remaining supply of the device to the Sponsor or dispose of the devices as directed by the Sponsor.

6.4 Core Lab

All Protocol required CTA imaging of the chest and/or chest, abdomen, and pelvis will be sent to the Core Lab via:

Medidata Medical Imaging (formerly known as Intelemage)
700 W. Pete Rose Way, Suite 436
Cincinnati, OH 45203

Medidata Medical Imaging will provide data transfer services, as well as de-identification of images sent from Sites to the Core Lab.

Analysis of pre-treatment and follow-up radiologic images will be conducted by an independent Core Lab. At a minimum, the assessment will include:

- morphology of aortic lesion, adjacent aorta, and landing zones
- device status post-implant, including Success Outcomes

Core Lab independent image analysis for this study will be provided by:

AortaCore
Aortic Imaging Lab
Director: Jon Matsumura, MD
University of Wisconsin
600 Highland Ave, Suite H4735
Madison, WI 53792



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6.5 Protocol Deviations

A Protocol deviation is defined as any change, divergence, or departure from the study design or procedures of a research Protocol. The Investigator is responsible for promptly recording and reporting Protocol deviations to the Sponsor and the reviewing IRB per IRB policy. The Sponsor will determine the effect of the Protocol deviation on the scientific soundness of the study and Subject safety and determine if additional reports or actions are required. Additional action may include Site retraining, removal of devices from the Site, and / or Site termination.

Protocol Deviations related to Inclusion/Exclusion Criteria will be adjudicated by the CEC as to their severity and are defined as follows:

Major- A deviation considered to substantially increase the risk of a Subject experiencing any primary endpoint event or success outcome event as defined in Section 3.4.

Minor- A deviation considered to have no or trivial effect on the risk of a Subject experiencing a primary endpoint or success outcome event as defined in Section 3.4.

The Investigator will not implement any changes to the Protocol without first obtaining written agreement from the Sponsor and documented approval from the IRB, except in the event of an immediate hazard(s) to a Subject. The Investigator will report the Protocol Deviation in accordance with the applicable regulations.

6.6 Protocol Amendments

The Protocol may be amended by the sponsor throughout the life of the study, as result of new findings or advisement from the applicable regulatory body or advisory committee. The investigator will obtain IRB approval on all amendments in a timely manner. The sponsor will confirm proper training of Investigator and site staff on all Protocol amendments.

6.7 Sponsor Representatives

Sponsor representatives may be present, either in-person or consulted through secure remote transmission technology (i.e. video and audio communication) using the internet, during study procedures to provide technical assistance to the Investigator in the use of the device. The activities of these Sponsor representatives will be supervised by the Investigator.

6.8 Access to Source Data/Documents

Source data are defined as all information necessary for the reconstruction and evaluation of the Clinical Investigation.

The Investigator will keep all study records, source data and investigational devices available for inspection by the Sponsor, Sponsor's monitors, IRB and regulatory authorities.

6.9 Study Records Retention



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The Investigator will maintain complete, accurate and current study records as required by applicable regulatory requirements. Records will be maintained during the study and for a minimum of two years or follow local/regional regulations after the latter of the date on which the study is terminated or completed, or the date the records are no longer required to support regulatory approval of the device. If trial follow-up is continued beyond 3 years in Japan as part of a post market clinical trial after receiving marketing approval and using the data as part of a use-results evaluation, the investigator and investigational center must retain essential documents during the period of use-results evaluation. In any event, study records will not be disposed of, nor custody of the records transferred, without prior written Sponsor approval.

Investigator records will include, but not be limited to: All correspondence with another investigator, an IRB, the Sponsor, a monitor, or Regulatory Authority, including required reports.

- Records of receipt, use or disposition of a device that relate to:
 - The type and quantity of device(s) received, the date(s) of its receipt, and lot or batch number or code mark.
 - The names of all persons who received, used, or disposed of each device.
- Records of each Subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records, including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:
 - Documents evidencing informed consent and, for any use of a device without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain the informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
 - All relevant observations, including records concerning adverse device effects (anticipated and unanticipated), the information and date and condition of each Subject upon entering, and information about relevant previous medical history and the results of all diagnostic tests.
 - A record of the exposure of each Subject to the investigational device, including the date and time of each use, and any other therapy.
- The Protocol, any amendments, and documentation of any deviations from the Protocol, including the dates and the reasons for such deviations.
- Any other records that Regulatory Authority requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.
- A certification stating that the IRB is in compliance with Regulatory Authority regulations (US only).
- A signed Investigator Agreement.
- Any other records as required by the Regulatory Authority, the IRB and the Sponsor.

The Investigator will prepare and submit the following reports:

- Withdrawal of IRB approval: The Investigator (or IRB Chairperson or Head of implementing medical institution in Japan) will report any withdrawal of approval within 5 working days after the Investigator has been notified of the withdrawal



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- Progress reports: Progress reports documenting the procedure, AEs and follow-up data concerning individual Subjects will be submitted to the Sponsor on standardized CRFs. The Investigator may also be required to submit progress reports and final reports to the IRB and to the Sponsor summarizing the Investigator's experience during the study.
- UADE Reports: UADEs shall be reported as described in Section 9.
- Protocol Deviations shall be reported as described in Section 6.
- Device Deficiencies shall be reported as described in Section 9
- Safety
- Other: Any other reports as reasonably requested by the Sponsor or required by Regulatory Authority.

6.10 Publication Plan

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry. The Sponsor will register the study and post results as required by this policy and applicable U.S. and Japan laws and regulations. It is the intent of the Sponsor that the multicenter results of this study will be submitted for publication (in a peer reviewed journal). A publications committee will be established to review the multicenter results and develop publications at the completion of the study. The timing of the multicenter publication may be dependent on regulatory submissions and approvals. Individual Sites should coordinate requests for publication through the publications committee or the Sponsor.

7.0 Data Collection and Submission

The Clinical Data Management System (CDMS) for this study will be provided by:

Medrio Inc.

345 California Street, Suite 325

San Francisco, CA 94104

7.1 Data Collection Methods

This study will report clinical data using the Medrio M-1® CDMS web-based application. The CDMS will be the database of record for the Protocol and Subject to regulatory inspections. All users will be trained to use the CDMS and will comply with study specific guidelines / instructions as well as applicable regulatory requirements.

Subject data will be collected using Protocol-specific case report forms (CRF). Site staff will enter data directly into the CRF for transmission to the Sponsor. The Sites will be notified of any significant amendments to the CRFs.

7.2 Data Clarification and Correction

Once entered, data will be evaluated to confirm that it is complete, consistent and logically sound. If changes to the data in the CDMS are required, all changes, reasons for changes, and persons making the changes will be captured in the CDMS's audit trail.

8.0 Risk Assessment

8.1 Potential Risks



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MD133246 Protocol Template: Revision#: 2

Doc Type: GC

The purpose of this study is to determine whether the GORE® TAG® Thoracic Branch Endoprosthesis is effective in treating aortic arch and descending thoracic aorta lesions. Complications associated with the use of the TBE Device in this indication may include, but are not limited to, the following:

- Access, delivery and deployment events (e.g. access failure; deployment difficulties/failures; failure to deliver the stent graft; and insertion or removal difficulty)
- Adynamic ileus
- Allergic reaction (to contrast, anti-platelet therapy, stent graft material)
- Amputation
- Anesthetic complications
- Aortic expansion, aortic rupture
- Angina
- Aortic valve injury (Zone 0/1 Subjects only)
- Atelectasis / pneumonia
- Bleeding (procedural and post-treatment)
- Bowel complications (e.g., ileus, transient ischemia, infarction, necrosis)
- Branch vessel occlusion or obstruction
- Cardiac complications (e.g., arrhythmia, myocardial infarction, congestive heart failure, hypotension or hypertension)
- Catheter breakage
- Change in mental status
- Coagulopathy
- Contrast toxicity
- Coronary artery occlusion or obstruction (Zone 0/1 Subjects only)
- Death
- Dissection, perforation, or rupture of the aortic vessel and / or surrounding vasculature
- Edema (e.g., leg)
- Embolism (micro and macro) with transient or permanent ischemia
- Endoleak
- Endoprosthesis: improper placement; incomplete deployment; migration; material failure; collapse; occlusion; infection; stent fracture; dilatation; perigraft flow
- Erectile dysfunction
- Erosion
- Extension of dissection
- Femoral neuropathy
- Fever and localized inflammation
- Fistula (e.g., aortoenteric, arteriovenous, aortoesophageal, aortobronchial)
- Genitourinary (e.g., ischemia, erosion, fistula, incontinence, hematuria, infection)
- Hematoma
- Heparin induced thrombocytopenia (HIT)



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- Infection (e.g., aneurysm, device, or access sites)
- Lymphocele / lymph fistula
- Myocardial infarction
- Neurologic damage, local or systemic (e.g., stroke, paraplegia, paraparesis)
- Nerve injury
- Persistent false lumen flow
- Peripheral malperfusion or ischemia
- Post-implant syndrome
- Prosthesis dilatation / rupture
- Prosthetic thrombosis
- Pseudoaneurysm
- Pulmonary complications (e.g., pneumonia, respiratory failure)
- Pulmonary embolism
- Radiation injury
- Renal complications (e.g., artery occlusion, contrast toxicity, insufficiency, failure)
- Reoperation
- Stenosis
- Surgical conversion
- Thrombosis
- Transient ischemic attack
- Vascular spasm
- Vascular trauma (e.g., ilio-femoral vessel dissection, bleeding, rupture)
- Wound (e.g., infection, dehiscence)

Additional potential risks associated with surgical revascularization include:

- Injury to the thoracic duct
- Injury to the neck nerves

8.2 Minimization of Risks

Potential risks associated with the use of the TBE Device may be minimized by the following activities:

- The Sponsor has performed qualification testing on the device and device components and appropriate quality control measures have been implemented into production. Investigators will be selected who are knowledgeable and experienced in aortic endovascular procedures.
- Investigators and Site personnel who have demonstrated extensive previous experience with implantation of endovascular grafts in the thoracic aorta will be selected.



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- Investigators may not enroll any Subjects prior to obtaining approval for the study from a properly constituted independent Institutional Review Board (IRB). An IRB approved informed consent form must be signed by the Subject or legally authorized representative prior to study enrollment.
- Comprehensive Site Investigator and staff training will be conducted to share information regarding design and proper use of the TBE Device and associated investigational accessory devices.
- The Site Investigator, Sub-Investigators, Clinical Study Coordinator(s) or designee at each Site will be trained to the Protocol and Subject follow-up requirements.
- Investigators will be trained to use the TBE Device in representative patient anatomy, including the performance of device deployments in simulated anatomy on the bench top.
- Each site must have previous clinical experience implanting the TBE Device in no fewer than two cases prior to enrolling Subjects in the Zone 0/1 study cohorts of this Protocol.
- An evaluation will be completed for each Subject against the inclusion/exclusion criteria before study entry to ensure the Subject's medical status and anatomic characteristics are appropriate. Screening CTs will be used to evaluate DTA and peripheral vasculature status.
- A Site initiation visit and interim Site visit(s) will be conducted as appropriate to evaluate Protocol compliance and to evaluate the data for accuracy and Subject safety.
- The first enrolled Subject at each Investigative Site with no previous TBE Device clinical experience will be Subject to enhanced screening to include:
 - Aortic landing zone length and integrity
 - Aortic arch angulation
 - Side branch landing zone length and integrity
 - Side branch angulation
- The DSMB will review aggregate safety information on a prescribed basis as specified in the DSMB Charter. This committee will operate under pre-specified procedures as outlined in the DSMB Charter and in accordance with the FDA's Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees.⁶⁸ Based on the safety data, the DSMB will make recommendations to Gore. Recommendations may include study termination, study continuation with or without major or minor modifications, temporary suspension of enrollment and / or study intervention until some uncertainty is resolved. All final decisions regarding study modifications rest with Gore.
- All Zone 0/1 Subjects must have a consultation with a Surgeon or other physician with experience in ascending aortic and arch surgery, such as a Cardiothoracic Surgeon in the US and a Cardiovascular Surgeon in Japan, directly or the Implanting Investigator will consult on the Subjects behalf to ensure that the Subject is aware of all treatment options, such as open surgical repair.
- A Cardiothoracic Surgeon (or physician with experience in ascending aortic and arch surgery) and Vascular Surgeon (or physician with experience in managing vascular complications) must be present during the Phase 2 procedure or be notified of the procedure in advance and readily available should any emergent procedures be required periprocedurally.



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- Cardiac Anesthesiology (or a specialty experienced in supporting ascending/aortic arch procedures and transesophageal echocardiography (TEE)) also must be present during the Phase 2 procedure or be notified of the procedure in advance and readily available to provide support, should any emergent procedures be required periprocedurally.
- Phase 2 procedures must occur in an Operating Room, Hybrid Operating Room or other room that is in close proximity to a location where a Subject can be converted to open surgical repair if needed.
- Antibiotic therapy may be administered to reduce infection risk.
- Heparin therapy may be administered to reduce thromboembolic risk, if appropriate.
- Protocol inclusion/exclusion criteria and follow-up schedules are designed to select appropriate Subjects and identify potential complications early. Subjects will be assessed post-procedure and subsequently on a regular basis to collect information on the Subject's status and any reportable Adverse Events.
- Subjects will be assessed post-procedure and at 1, 6, 12, 24, 36, 48, and 60 months post-treatment. Follow-up evaluations will include, but will not be limited to, physical examination and CTA of the chest. Evaluation of Subjects with aortic dissection will include CTA of the chest, abdomen, and pelvis.
- Safety and efficacy data obtained during the clinical study will be shared with the Site Investigators to aid understanding of the device and potential complications associated with its use.

8.3 Summary of Expected Benefits

The benefits of treatment with the TBE Device in aortic lesions of the aortic arch and DTA has not been documented.

Relative to open surgical repair of aortic aneurysms and non-aneurysmal lesions, repair with the TBE Device may offer the following benefits:

- A minimally invasive procedure that does not require a thoracotomy, single lung ventilation or aortic cross clamping
- Shortened procedure time
- Reduced procedural blood loss
- Reduced procedure-related morbidity incidence
- Reduced procedure-related mortality incidence
- Reduced procedure-related paraplegia
- Decreased risk of surgical incision complications

Relative to endovascular repair of DTA lesions using a non-branched endoprosthesis in Zone 2, repair with the TBE Device may offer the following benefits:

- Avoidance of complications associated with LSA coverage, including:
 - Arm weakness and/or claudication
 - Stroke
 - Spinal cord ischemia
- Avoidance of complications associated with open surgical extra-anatomic bypass or transposition of the LSA, including:



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- Shortened procedure time
- Reduced procedural blood loss
- Decreased risk of surgical incision complications

Relative to hybrid repair of aortic arch lesions using an endovascular and open-surgical technique in Zone 0/1, repair with the TBE Device may offer the following benefits:

- Shortened procedure time
- Reduced procedural blood loss
- Reduced procedure-related morbidity incidence
- Reduced surgical incisions with associated complications
- Avoidance of CPB and DHCA

9.0 Adverse Events and Safety Monitoring

Adverse Events (AEs) are defined as any untoward medical occurrences in a Subject whether device-related or not. All AEs will be recorded on the appropriate CRF and documented in the Subject's permanent medical record. The Investigator at each Site is ultimately responsible for reporting all AEs to the Sponsor, as well as to the IRB, as applicable. The Investigator is required to complete the appropriate CRFs to report each AE.

9.1 Anticipated Adverse Events

Anticipated Adverse Events are complications that are known to be associated with aneurysm and non-aneurysm lesions of the aortic arch and DTA patients undergoing treatment with the TBE Device. See Section 8, Risk Assessment.

9.1.1 Adverse Event Relationship

Each reported AE will be assessed by the Investigator for its primary suspected relationship to the device, surgical revascularization procedure, and/or endovascular procedure. It is permissible to assign multiple relationships for each reported AE.

Related to Device

The functioning or characteristics of the implanted device(s) caused or contributed to the Adverse Event. This is applicable to all components of the TBE Device (Aortic Component, Aortic Extender, Side Branch Component) as well as the CTAG Device.

Related to Surgical Revascularization Procedure

The surgical revascularization procedure (Zone 0/1 Subjects) (and not the device(s)) caused or significantly contributed to the Adverse Event.

Related to Endovascular Procedure

The endovascular procedure (and not the device(s)) caused or significantly contributed to the Adverse Event.



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Related to Device and Endovascular Procedure

The endovascular procedure as well as the device(s) caused or significantly contributed to the Adverse Event.

Unrelated to Devices and Procedures

An Adverse Event which cannot be attributed to the device(s) or procedure(s).

Unknown relationship

The relationship of the Adverse Event to the device or procedure cannot be determined.

9.1.2 Adverse Event Classification

Each AE will be assessed by the Investigator to determine if it is serious or non-serious per ISO 14155, Clinical Investigation of Medical Devices for Human Subjects- Good Clinical Practice. Second edition 2011-02-01.

Serious Adverse Event

A Serious Adverse Event (SAE) is an Adverse Event that

- led to death
- led to serious deterioration in the health of the Subject that either resulted in
 - a life threatening illness or injury, or
 - a permanent impairment of a body structure or body function, or
 - inpatient or prolonged hospitalization, or
 - medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

Non-Serious Adverse Event

Any event that does not meet the definition of serious will be classified as non-serious.

9.1.3 Adverse Event Reporting and Coding

AEs will be reported on the appropriate case report form (CRF) and documented in the Subject's permanent medical record. The Investigator at each Site is ultimately responsible for reporting AEs to the Sponsor. AE reporting from the study sites is required to be in compliance with all applicable (US and Japan) regulations. The study sites should follow the procedure outlined the AE reporting manual provided by Gore



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The following information on each reported Adverse Event will be collected:

- Adverse Event Name
- Adverse Event Onset Date
- Relationship
- Classification (Serious or Non-Serious)
- Treatment
- Outcome
- Resolution Date

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse Event submission guidelines:

- Adverse Event reporting begins once the patient is enrolled in the study. All Adverse Events should be reported from enrollment through study completion / discontinuation.
- Provide a diagnosis if possible. If unable to provide a diagnosis, report the symptoms as separate events. Adverse Events should be reported using the full name without abbreviations or narratives.
- Adverse Events with an outcome status of “Ongoing” should be assessed at each follow-up evaluation to determine if the event has resolved. Adverse Events ongoing at study completion / discontinuation should be left as “Ongoing” on the AE case report form.

9.1.4 Subject Death

Death is not an AE itself, but instead an outcome of an AE. Therefore, the cause of death, if known, should be the reported AE.

Any ongoing or unresolved AEs at the time of death will be indicated as ongoing/continuing on the CRF. Attempts should be made by the investigative Site to obtain death certificates, autopsy reports and device explants when at all possible.

9.2 Unanticipated Adverse Device Effects (UADE)

An unanticipated adverse device effect (UADE) is defined in 21 CFR 812.3(s) as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or Protocol.

The Sponsor is required to notify FDA within ten working days of becoming aware of any UADE. Similar notice will be provided to the PMDA within seven (7) calendar days of becoming aware of the event. Therefore, if a complication occurs that the Investigator believes may be a potential UADE, the Site should immediately contact the Sponsor using the contact information in the Regulatory Binder to determine reporting requirements. In addition, when there is a reason to believe a device may have malfunctioned, causing potential harm to a patient, the Site should immediately notify the Sponsor.



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The Investigator or Head of implementation medical institution (Japan only) shall submit to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than local applicable regulations permit. All UADEs must be documented by the Investigator including the date of onset, a complete description of the event, possible reason(s) for the event, severity, duration, actions taken and outcome. Copies of all supporting documents should be submitted concurrently with the appropriate CRF.

A report from the Sponsor will be submitted to the FDA or PMDA and to all reviewing IRBs, participating Investigators and Head of implementation medical institution (Japan only) local applicable regulations permit.

9.3 Device Deficiencies

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance of investigational medical device. Device deficiencies include malfunctions, use errors, or inadequate labeling. Device deficiencies may not be associated with an AE suffered by a study Subject but will need to be reported to Gore immediately upon identification by the Site. Notification to Gore will be conducted according to the instructions provided in the Regulatory Binder.

Upon receipt of a device deficiency report, Gore will review the event to determine its significance and applicability to current and future study Subjects. Applicable events will be communicated to the regulatory authority according to their requirements.

9.4 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review accumulating data on a regular basis and will advise the Sponsor regarding the continuing safety of study Subjects as well as the continuing validity and scientific merit of the study. The DSMB will be comprised of an interdisciplinary team of members with pertinent expertise in vascular or cardiothoracic surgery, as well as one biostatistician, who are not directly involved in the conduct of the study. The members will be compensated for their involvement in the DSMB, including reimbursement for reasonable travel expenses to attend meetings.

This committee will operate under pre-specified procedures as outlined in the DSMB Charter in accordance with the FDA's Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees.⁶⁸ The DSMB will be responsible for conducting periodic reviews of aggregate data on a prescribed basis. The frequency of data review and other roles and responsibilities of the DSMB will be specified in the DSMB Charter.

Based on the safety data, the DSMB will make recommendations to the Sponsor. Recommendations may include study termination, study continuation with or without major or minor modifications, temporary suspension of enrollment and / or study intervention until some uncertainty is resolved. All final decisions regarding study modifications rest with the Sponsor.

9.5 Clinical Event Committee

A Clinical Events Committee (CEC), consisting of appropriately trained Physicians with extensive relevant clinical experience, independent of the study, will adjudicate primary endpoint and success outcomes candidate events using CRF, a copy of all applicable source documents etc. The composition of the CEC membership and operating procedures for the committee are outlined in the CEC Charter. The events to be adjudicated are detailed in Appendix D.



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The CEC will also review Inclusion / Exclusion Deviations and adjudicate them as major or minor.

The members may be compensated for their involvement in the CEC, including reimbursement for reasonable travel expenses to attend meetings

10.0 Statistical Analysis

10.1 Study Hypotheses

10.1.1 Zone 2 Aneurysm Cohort

The analysis of the primary endpoint for this cohort is intended to test the hypothesis that the success exceeds the performance goal of 64%. Using the performance goal of 64% with primary endpoint success through 12 months, the following hypothesis will be tested:

$$H_0: P_{s2} \leq 0.64$$

$$H_A: P_{s2} > 0.64$$

10.1.2 Zone 0/1 Aneurysm Cohort

The analysis of the primary endpoint for this cohort is intended to test the hypothesis that the success exceeds the performance goal of 60%. Using the performance goal of 60% with primary endpoint success through one month, the following hypothesis will be tested:

$$H_0: P_{s01} \leq 0.60$$

$$H_A: P_{s01} > 0.60$$

10.2 Sample Size Determination

10.2.1 Zone 2 Aneurysm Cohort

Zone 2 aneurysm feasibility cohort data (G130120) at the time of the submitted DDP proposal was 77.8% for the proposed primary endpoint. Based on this, a true rate of 78% primary endpoint success through 12 months was assumed for the TBE Device in the Zone 2 aneurysm population.

A power analysis was performed for the Zone 2 aneurysm cohort hypothesis. Based on an assumption of a true rate of primary endpoint success for the TBE Device in the Zone 2 population of 78%, and the performance goal of 64%, a sample size of 85 Subjects is required to attain >80% power for the Zone 2 aneurysm cohort of this study. To meet the performance goal of 64%, a point estimate of > 74% primary endpoint success for at least 70 patients through 12 months is required. This allows for attrition to be up to 18%.

Additional assumptions included setting $\alpha=.05$ and power of 80%.

Sample size calculations were determined using PASS 13 one-sided exact test for one proportion.



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10.2.2 Zone 0/1 Aneurysm Cohort

Zone 0/1 aneurysm feasibility cohort data (G140060) was 80.0% for the proposed primary endpoint. However, due to possible variability, a true rate of 78% primary endpoint success through one month was assumed for the TBE Device in the Zone 0/1 population.

A power analysis was performed for the Zone 0/1 aneurysm cohort hypothesis. Based on an assumption of a true rate of primary endpoint success for the TBE Device in the Zone 0/1 population of 78%, and the performance goal of 60%, a sample size of 50 Subjects is required to attain 80% power for the Zone 0/1 aneurysm cohort of this study. To meet the performance goal of 60%, a point estimate of > 74% primary endpoint success for 50 patients through one month is required. No attrition was accounted for.

Additional assumptions included setting $\alpha=.05$ and power of 80%.

Sample size calculations were determined using PASS 13 one-sided exact test for one proportion.

10.3 Data Analysis

10.3.1 Timing of Primary Analyses

10.3.1.1 Zone 2 Aneurysm Cohort

Primary analysis timing will be dependent only on those Subjects enrolled during Primary Enrollment. The primary endpoint for the Zone 2 aneurysm cohort will be analyzed after all available Subjects meeting the analysis population criteria (as specified in Section 10.3.2.1) have completed the 12 month follow-up visit and have been in the study through 546 days. The Success Outcomes will also be analyzed at this time.

The Subjects accrued during Continued Access Enrollment will be analyzed separately from the Subjects accrued during Primary Enrollment at primary analysis. Depending on the timing of the primary analysis, continued access Subjects may not be analyzed at the time of primary analysis.

10.3.1.2 Zone 0/1 Aneurysm Cohort

The primary endpoint for the Zone 0/1 aneurysm cohort will be analyzed after all available Subjects meeting the analysis population criteria (as specified in Section 10.3.2.2) have completed the one month follow-up visit and have been in the study through 59 days. Subjects with suspected stroke primary endpoint events will need to have been in the study through 120 days before this primary endpoint analysis will be performed. This extra time is needed for these Subjects to allow for the Modified Rankin Scale to be assessed at any time during this period.

This analysis will also be repeated with 12 month results (following the same analysis population logic as that outlined for the Zone 2 aneurysm cohort in Section 10.3.2.1) with the exception that no hypothesis will be tested. The Success Outcomes will also be analyzed at this time.



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10.3.1.3 NAL Cohorts

The primary endpoint for each of the NAL cohorts will be analyzed at the same time as the Zone-respective aneurysm cohort (i.e. Zone 2 NAL cohorts will have primary analysis conducted when the Zone 2 aneurysm cohort has primary analysis conducted). This analysis may be repeated for each of the NAL cohorts at later timepoint(s). This will possibly be conducted at different times for each of the NAL cohorts. The Success Outcomes will also be analyzed at the same time as the primary endpoint for each of the cohorts.

10.3.2 Analysis Populations

10.3.2.1 Zone 2 Aneurysm Cohort

The composite primary endpoint analysis population for the Zone 2 aneurysm cohort will be among enrolled Subjects (excluding those with a CEC adjudicated 'major' inclusion/exclusion criteria violation or FDA mandated exclusion) and is outlined as follows based on events as described and defined in Section 3.4.1.1:

- Subjects with an event any time ≤ 546 days are a failure regardless of whether they had imaging in 12 month window
- Subjects that don't have imaging in the 12 month window and don't have an event ≤ 546 days are excluded
- Subjects with imaging in 12 month window and no event reported ≤ 546 days are successes
- Subjects with >1 event just count once as failures

All hypothesis testing and Primary Analysis for the PMA will be based on Zone 2 Aneurysm Subjects accrued during the Primary Enrollment Period. Zone 2 Aneurysm Subjects accrued during Continued Access Enrollment will be analyzed separately for the PMA. Continued Access Enrollment Subjects may be pooled with the Primary Enrollment Subjects in subsequent reports and/or analysis.

The analysis population for the Success Outcomes will be among enrolled Subjects (excluding those with a CEC adjudicated 'major' inclusion/exclusion criteria violation or FDA mandated exclusion). Additional analysis population details will be outlined for each of the Success Outcomes outlined in Section 3.4.2 in the Statistical Analysis Plan.



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10.3.2.2 Zone 0/1 Aneurysm Cohort

The composite primary endpoint analysis population for the Zone 0/1 aneurysm cohort will be among enrolled Subjects (excluding those with a CEC adjudicated 'major' inclusion/exclusion criteria violation or FDA mandated exclusion) and is outlined as follows based on events as described and defined in Section 3.4.1.2:

- Subjects with an event any time ≤ 59 days are a failure regardless of whether they had imaging in one month window
- Subjects that don't have imaging in the one month window and don't have an event ≤ 59 days are excluded
- Subjects with imaging in one month window and no event reported ≤ 59 days are successes
- Subjects with >1 event just count once as failures

The analysis population for the Zone 0/1 Aneurysm cohort will also exclude any Subjects treated with a 49/53mm device since those device sizes have been removed from this study. Any Subjects enrolled and treated with those device sizes will not be counted in the N=50 enrollment and replacement Subjects will be enrolled to keep N=50. These 49/53mm Subjects will be summarized separately and followed per the Protocol.

The analysis population for the Success Outcomes will be among enrolled Subjects (excluding those with a CEC adjudicated 'major' inclusion/exclusion criteria violation or FDA mandated exclusion). Additional analysis population details will be outlined for each of the Success Outcomes outlined in Section 3.4.2 in the Statistical Analysis Plan.

10.3.2.3 NAL Cohorts

The primary endpoint analysis population for each of the NAL cohorts will be among all enrolled Subjects (excluding those with a CEC adjudicated 'major' inclusion/exclusion criteria violation or FDA mandated exclusion). In addition, the primary endpoint analysis population for each cohort will follow Zone-similar logic to that written for the aneurysm cohort (as described above in Section 10.3.2.1 (Zone 2) and Section 10.3.2.2 (Zone 0/1)). However, additional analysis may be done with different analysis population criteria.

The analysis population for the Success Outcomes will be among enrolled Subjects (excluding those with a CEC adjudicated 'major' inclusion/exclusion criteria violation or FDA mandated exclusion). Additional analysis population details will be outlined for each of the Success Outcomes outlined in Section 3.4.2 in the Statistical Analysis Plan.



10.3.3 Pooling of Data

Site data will be pooled based on clinical comparability, i.e., the study Sites followed a common Protocol, the study was monitored to ensure compliance with the Protocol and applicable government regulations, and the data collection and handling procedures were the same at all study Sites. In order to justify pooling of Sites and, in the case of Zone 0/1 possibly countries (US and Japan), poolability analysis will be performed as outlined in the Statistical Analysis Plan.

10.3.4 Statistical Analysis of Primary Endpoint(s)

10.3.4.1 Zone 2 and Zone 0/1 Aneurysm Cohorts

The proportion of composite primary endpoint success (1 - composite primary endpoint failure) will be calculated for each hypothesis-driven cohort. One-sided Exact confidence intervals for binomial proportions ($\alpha=0.05$) will be constructed to test the primary endpoint hypothesis as stated for each hypothesis-driven cohort (as specified in Sections 10.1.1 and 10.1.2). The null hypothesis will be rejected if the lower bound of the 95% confidence interval estimating primary endpoint success exceeds the performance goal.

In addition, the primary endpoint data (aggregate and components) for each of these two cohorts will be summarized by statistics (count and percent).

In order to assess the impact of missing data on each of the composite primary endpoint hypothesis tests, sensitivity analyses will be performed and are outlined in the Statistical Analysis Plan.

10.3.4.2 NAL Cohorts

The primary endpoint data (aggregate and components) for each of these cohorts will be summarized by descriptive statistics (count and percent). No hypotheses will be tested.

10.3.5 Statistical Analysis of Success Outcomes

Analysis time windows will be used for the analysis of the Success Outcomes and components. Data on the Success Outcomes (aggregate and components) by each of the cohorts will be summarized by descriptive statistics (count and percent) over time.

10.4 Health Economics

Gore may use study data to develop a better understanding of the impact that the TBE Device may have on clinical practice in order to meet anticipated business needs. With consent of the Subject and approval of the supervising IRB, billing information may be collected to aid in this evaluation.



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11.0 Ethical and Regulatory Considerations

11.1 Statement of Compliance

The study will be conducted in compliance with this Protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and applicable regulatory requirements.

The following are applicable to this study:

21 CFR Part 11	Electronic Records; Electronic Signatures
21 CFR Part 50	Protection of Human Subjects
21 CFR Part 54	Financial Disclosure By Clinical Investigators
21 CFR Part 56	Institutional Review Boards
21 CFR Part 812	Investigational Device Exemptions
ICH-GCP E6	International Conference on Harmonisation Regulations Guideline For Good Clinical Practice
Japan GCP	Japanese Good Clinical Practice

11.2 Compliance Responsibilities

The Sponsor will conduct the study in accordance with all applicable regulations and laws. The Sponsor will be responsible for documenting that Investigators have the necessary skills, training and information to properly conduct the study. The Sponsor will confirm proper monitoring of the study and verify that the Site has obtained IRB approval prior to enrollment. The Sponsor will provide information to the Investigators, the reviewing IRB and the FDA/PMDA concerning the progress of and any new material information about the study.

The Investigator will conduct the study in accordance with all applicable regulations and laws, any relevant agreements, the study Protocol, and all approval conditions of the reviewing IRB and the FDA/PMDA. The Investigator will verify IRB approval is obtained prior to enrollment, maintained throughout the course of the study, and that all IRB reporting requirements are met. The Investigator is responsible for protecting the rights, safety, and welfare of Subjects under the Investigator's care and for the control of devices under investigation. The Investigator is also responsible for ensuring that informed consent is properly obtained.

11.3 Informed Consent

The Investigator shall verify that all potential Subjects for this study are provided with a consent form describing this study and sufficient information to make an informed decision about their participation.



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The formal consent of a Subject, using the IRB-approved consent form, must be obtained by the Investigator before that Subject undergoes any study-related procedure. The consent form will be signed and personally dated by the Subject or legally authorized representative, and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the Subject records. A copy of the informed consent document will be given to the Subject for his or her records. Any significant, new information which emerges while the study is in progress that may influence a Subject's willingness to continue to take part in the study will be provided to the Subject.

The Investigator shall verify that documentation of the acquisition of informed consent is recorded in each Subject's records in accordance with applicable regulations.

11.4 Independent Ethical Review

The Investigator shall not enroll any Subjects prior to obtaining approval for the study from a properly constituted independent IRB.

The Investigator will submit the Protocol, informed consent forms, other information to be provided to Subjects such as survey instruments or questionnaires, and any proposed advertising / recruitment materials, to the IRB for written approval.

11.5 Conflict of Interest

All Investigators will follow applicable laws and regulations as well as the conflict of interest policies of their Site and the reviewing IRB.

Investigators will provide the Sponsor with sufficient accurate financial disclosure information to allow the Sponsor to submit a complete and accurate certification or disclosure statement as required under 21 CFR 54, Financial Disclosure by Clinical Investigators. Investigators will promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study.

11.6 Emergency / Compassionate Use (US only)

There are circumstances where the TBE Device may provide an Investigator the ability to save a patient's life or prevent serious morbidity of which there is no reasonable alternative medical treatment available. Gore may support use of the TBE Device, in an emergency or compassionate use fashion, provided that the applicant Site provides all required information to support its use and meet all regulatory guidelines. Patients who receive the study device in this fashion will not be included in the analysis of safety or effectiveness endpoints but its use will be noted in study reports. Sites using this regulatory mechanism will be expected to meet all requirements following the procedure in terms of reporting to their IRB, Gore and hospital administration (where applicable). It will be the responsibility of the Sites to evaluate these patients and report any device events to Gore when they become aware of its occurrence.

11.7 Confidentiality

All Subject records will be kept confidential to the extent provided by applicable laws and regulations. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to medical records.

Such records may also be reviewed by the Site's IRB and other regulatory bodies such as the FDA/PMDA. The Investigator will inform the Subjects that their records will be reviewed.



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11.8 Study Discontinuation or Suspension

Enrollment into the study may be suspended by Gore at any time. The decision to suspend study-wide enrollment, along with the reason, will be communicated to study Investigators, Site IRBs and regulatory authorities. During the study-wide suspension, Sites are expected to continue safety and device evaluations per the requirements of the Protocol. If Gore wishes to resume enrollment, this will be communicated to all parties who received the suspension notice. Resumption of study enrollment activities may depend on additional IRB or regulatory authority approvals depending on study circumstance.

Sites may be individually suspended from the study due to continuing study non-compliance, repeated inclusion / exclusion violations or by an event, in Gore's judgment, that placed a study Subject at unacceptable risk. Suspension of a Site will be communicated to the Site's Principal Investigator, its IRB and corresponding regulatory authority. The removal of a Site suspension may be dependent on the successful completion of a Site compliance plan or by additional training conducted by Gore. Resumption of Site study enrollment activities may depend on additional IRB or regulatory authority approvals depending on study circumstance.

Notification of completion, termination, or discontinuation of the study will be made to the applicable regulatory agencies within 30 days of the completion, termination or discontinuation(US only). Completion of the study is defined as the point where all clinical trial Sites have had a close-out visit conducted by Gore or designee. In addition, a final report to all reviewing IRBs will be submitted within six months of completion, termination or discontinuation. Sites that have enrolled a Subject and have completed all Subject follow-up requirements are asked to keep the study active in order to receive the final study report. If Sites would like to close the study, the IRB should confirm they will allow submission of the final study report when available.

Gore may terminate or discontinue the clinical study at any point.



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12.0 References

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Appendix A: Imaging Guidelines

Computed Tomography Guidelines

Measurement technique

- Measurements according to centerline or MPR calculations are preferred over those using axial slices

CT/CTA Image Submission

- All images should be DICOM format
- Axial images only, it is NOT necessary to include any reconstructed images

CT scans should include all sequential images at the lowest possible interval and collimation. The maximum recommended interval and collimation to assure imaging will be evaluable is ≤2mm, however ≤1.25mm is preferred.



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1. Pre-Treatment (Table A1)

Experience suggests that 3D CTA reconstructions are required to accurately assess proximal neck length, diameters, and angles for thoracic endografting. These reformations should be performed using centerline reconstructions as well as in varying oblique views depending on the individual Subject anatomy.

Table A1: Pre-Treatment CT/CTA Imaging Guidelines

Start Position	<u>Pre-contrast</u> : Angle of the mandible with the head in neutral position (if performed)
End Position	<u>Arterial</u> : Angle of the mandible with the head in neutral position <u>Pre-contrast</u> : Femoral heads (if performed) <u>Arterial</u> : Femoral heads
Scan Field	Large
Field Of Vision	240 mm or as appropriate for Subject
Scan Type	Helical
Slice collimation/ thickness	≤2 mm
Reconstruction Interval	20% overlap (i.e. 0.8/1 mm, 0.4/0.5 mm or 1.6/2 mm)
Scan Delay (contrast)	Smart prep or equivalent, 3-second delay*
Kilovoltage	120 or as appropriate
Contrast Medium	Recommendation: ≥ 350 mg/ml, 70-200 ml
Contrast Medium administration	Recommendation: ≥ 4 ml/s, via right cubital vein, 18G, saline push ≥ 40 ml

2. Follow-up (Table A2)

If an endoleak is suspected, both non-contrast and arterial contrast scans should be performed. Additionally, delayed-contrast scans may be performed to further evaluate the suspected endoleak.

- For non-contrast and contrast runs, slice interval and collimation should be identical
- DO NOT change Subject orientation or re-landmark Subject between non-contrast and contrast runs



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Table A2: Follow-up CT/CTA Imaging Guidelines

Start Position	<u>Non-contrast</u> : Angle of the mandible with the head in neutral position (at 1 month or if endoleak suspected) <u>Arterial</u> : Angle of the mandible with the head in neutral position <u>Delayed-contrast, 90-120 second</u> : above the arch (if endoleak suspected)
End Position	<u>Non-contrast</u> : Superior Mesenteric Artery (at 1 month or if endoleak suspected) <u>Arterial</u> : Superior Mesenteric Artery or Femoral Heads in Dissection Subjects only <u>Delayed-Contrast, 90-120-second</u> : Superior Mesenteric Artery (if endoleak suspected)
Scan Field	Large
Field Of Vision	240 mm or as appropriate for Subject
Scan Type	Helical
Slice collimation/ thickness	≤2 mm
Reconstruction Interval	20% overlap (i.e., 0.8/1mm, 0.4/0.5 mm or 1.6/2 mm)
Scan Delay (contrast)	Smart prep or equivalent, 3-second delay
Kilovoltage	120 or as appropriate
Contrast Medium	Recommendation: ≥350 mg I/ml, 70-200 ml
Contrast Medium administration	Recommendation: ≥4 ml/s, via right cubital vein, 18G, saline push ≥40 ml



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Appendix B: Classification Scales – All Subjects (Rankin, ASA, NYHA, NIHSS)

Table B1: NYHA Functional Classification

CLASS	DESCRIPTION
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Table B2: ASA Physical Status Classification

CLASS	DESCRIPTION
I	Healthy patient
II	Mild systemic disease - no functional limitation
III	Severe systemic disease – definite functional limitation
IV	Severe systemic disease that is a constant threat to life
V	Moribund patient unlikely to survive 24 hours with or without operation

Table B3: Modified Rankin Scale

SCORE	STATUS
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead



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Table B4: NIH Stroke Scale

The NIH Stroke Scale is provided on the following pages and is also available at:
http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf



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MD133246 Protocol Template: Revision#: 2
Doc Type: GC

N I H STROKE SCALE

Patient Identification: _____

Pt. Date of Birth _____

Hospital _____

Date of Exam _____

Interval: ☐ Baseline ☐ 2 hours post treatment ☐ 24 hours post onset of symptoms $\pm$ 20 minutes ☐ 7-10 days
☐ 3 months ☐ Other _____

Time: _____ []am []pm

Person Administering Scale _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.	_____

Rev 10/1/2003



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MD133246 Protocol Template: Revision#: 2
Doc Type: GC

N I H STROKE SCALE

Patient Identification: _____

Pt. Date of Birth ____/____/____

Hospital _____ (____-____)

Date of Exam ____/____/____

Interval: ☐ Baseline ☐ 2 hours post treatment ☐ 24 hours post onset of symptoms ±20 minutes ☐ 7-10 days
☐ 3 months ☐ Other _____ (_____)

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as unstable (UN), and clearly write the explanation for this choice.	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. UN = Amputation or joint fusion, explain: _____ 5a. Left Arm _____ 5b. Right Arm _____	_____ _____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as unstable (UN), and clearly write the explanation for this choice.	0 = No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement. UN = Amputation or joint fusion, explain: _____ 6a. Left Leg _____ 6b. Right Leg _____	_____

Rev 10/1/2003



CONFIDENTIAL INFORMATION

MD133246 Protocol Template: Revision#: 2
Doc Type: GC

N I H STROKE SCALE

Patient Identification: _____

Pt. Date of Birth ____/____/____

Hospital _____ (____-____)

Date of Exam ____/____/____

Interval: ☐ Baseline ☐ 2 hours post treatment ☐ 24 hours post onset of symptoms ±20 minutes ☐ 7-10 days
☐ 3 months ☐ Other _____ (_____)

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as unstable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. UN = Amputation or joint fusion, explain: _____	_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side, or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as unstable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier, explain: _____	_____

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N I H
STROKE
SCALE

Patient Identification. _____
Pt. Date of Birth _____
Hospital _____
Date of Exam _____

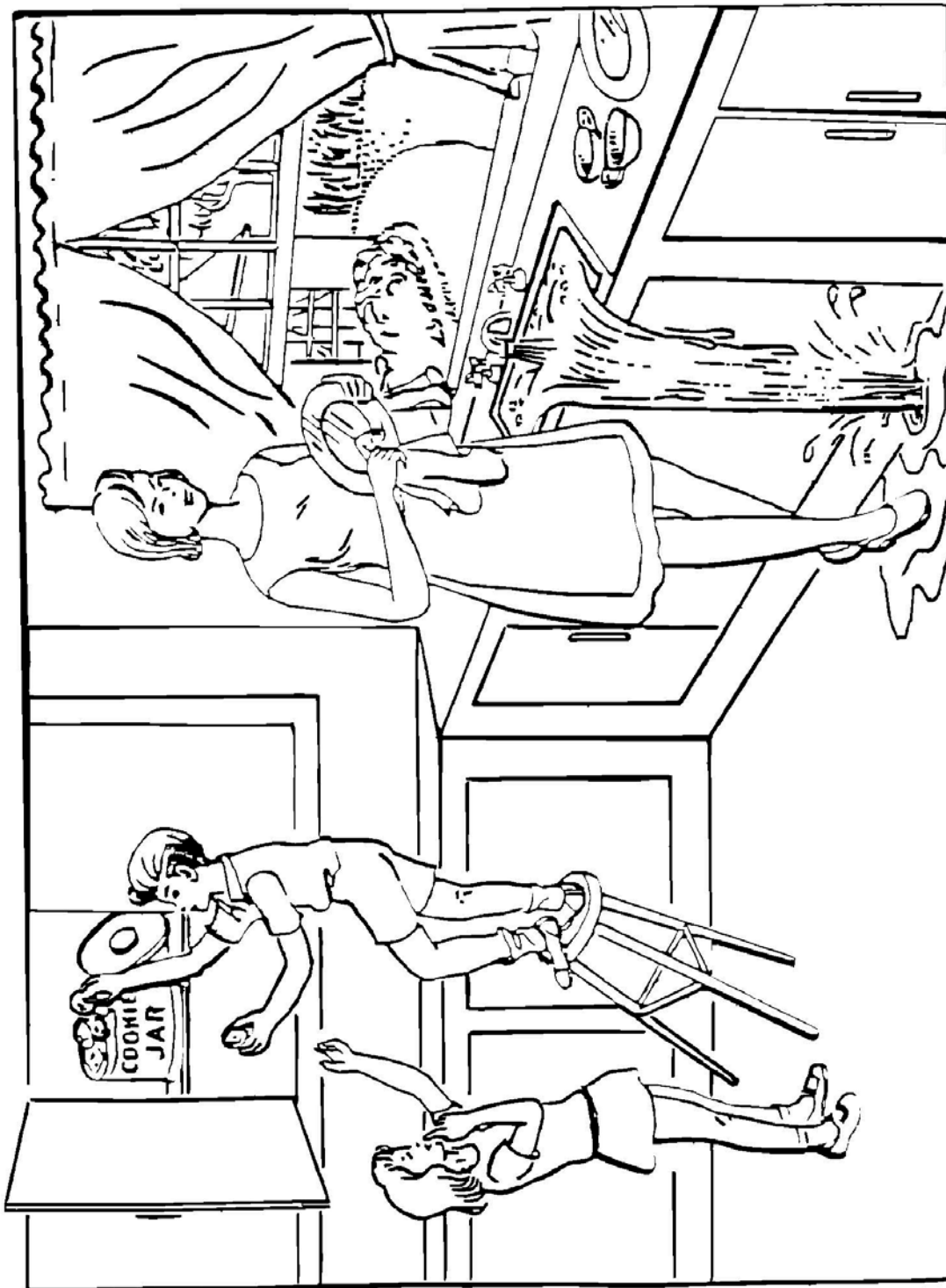
Interval: ☐ Baseline ☐ 2 hours post treatment ☐ 24 hours post onset of symptoms ±20 minutes ☐ 7-10 days
☐ 3 months ☐ Other _____

11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.	_____
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You know how.

Down to earth.

I got home from work.

**Near the table in the dining
room.**

**They heard him speak on the
radio last night.**



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MAMA
TIP – TOP
FIFTY – FIFTY
THANKS
HUCKLEBERRY
BASEBALL PLAYER



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Appendix C: Classification Scales - Traumatic Transection Subjects Only

Injury Severity Score

To calculate the Injury Severity Score (ISS), an Abbreviated Injury Scale (AIS) score (Table C1) is given to six regions of the body if injury is present (Table C2). The squares of the 3 highest AIS values are added together to determine the ISS.

Table C1: Abbreviated Injury Scale Score definitions

AIS SCORE	INJURY SEVERITY
0	None
1	Minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Unsurvivable

Table C2: Injury Severity Score Sample Calculation

REGION	AIS	EXAMPLE AIS	EXAMPLE CALCULATION
Head & Neck	1-6 (based on level of injury)	2	
Face	1-6 (based on level of injury)	2	
Chest	1-6 (based on level of injury)	5	25
Abdomen	1-6 (based on level of injury)	4	16
Extremity	1-6 (based on level of injury)	3	9
External	1-6 (based on level of injury)	1	
Injury Severity Score	0-75* (Top 3 AIS values are squared then summed)		50

* If any of the AIS scores are 6 then the ISS score is automatically 75



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Glasgow Coma Scale

To calculate the Glasgow Coma Scale Score (GCS), a Subject's eye, motor, and verbal abilities are assessed on a scale (Table C3). The eye, verbal, and motor scores are added together to yield the GCS which ranges from 3-15 (Eye + Verbal+ Motor = GCS 3-15).

Table C3: Glasgow Coma Scale Score definitions

Area Assessed	1	2	3	4	5	6
Eye Opening	No response	To pain	To speech	spontaneous	NA	NA
Verbal	No response	Incomprehensible sounds	Inappropriate words	Disoriented and converses	Oriented and converses	NA
Motor	No response to painful stimulus	Extension to painful stimulus	Flexion-abnormal to painful stimulus	Flexion-withdrawal to painful stimulus	Localizes pain to painful stimulus	Obeys verbal command



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Appendix D: Adjudication of Endpoints and Success Outcomes

The table below describes the responsible party for the determination and adjudication of each specific endpoint and success outcome described in Section 3.4 of the Protocol document.

Key Outcome	Endpoint/Outcome Determination
Device Technical Success for index endovascular procedure	<i>Composite Event - Not Applicable</i>
<i>Successful access and delivery</i>	• Site Investigator
<i>Patency of the graft</i>	• Site Investigator
<i>Unanticipated additional procedure related to the device, procedure, or withdrawal of the delivery system</i>	• Site Investigator
Aortic Rupture	• Site Reported AE followed by CEC Adjudication Or Core Lab
Lesion-related Mortality	• Site Reported AE followed by CEC Adjudication
Disabling Stroke	• Site Reported AE followed by CEC Neurologist Review and adjudication
Permanent Paraplegia	• Site Reported AE followed by CEC Adjudication
Permanent Paraparesis	• Site Reported AE followed by CEC Adjudication
Additional unanticipated post-procedural surgical or interventional procedure related to the device, procedure, or withdrawal of the delivery system	• Site Reported AE with an unanticipated post-procedural surgical or interventional procedure followed by AE adjudication by CEC.
Initiation of the index endovascular procedure following the debranching procedure (Zone 0/1 cohorts only)	• Site Reported Treatment Data
New Onset Renal Failure Requiring Dialysis	• Site Reported AE followed by CEC adjudication
Aortic Enlargement in the Region Encompassed by the Index Lesion	• Core Lab
Extension of Dissection	• Core Lab



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Key Outcome	Endpoint/Outcome Determination
False Lumen Perfusion through the primary intimal tear	Core Lab
False Lumen Perfusion through an aortic arch branch vessel	Core Lab
False Lumen Perfusion through a non-aortic arch branch vessel	Core Lab
Loss of Aortic or Aortic Branch Patency (after the initial procedure)	- Core Lab -or- - Site Reported AE with CEC Adjudication
Loss of Device Integrity	Core Lab
Migration	Core Lab
Fistula Formation	- Core Lab -or- - Site Reported AE
New Ischemia	Site Reported AE followed by CEC Adjudication
Type I-IV Endoleak	Core Lab
New Dissection	- Core Lab -or- - Site Reported AE with CEC adjudication
Renal dysfunction or volume overload requiring ultrafiltration	Site Reported AE followed by CEC Adjudication
Life Threatening Bleed	Site Reported AE followed by CEC Adjudication
Distal device-related thromboembolic adverse event requiring intervention or surgery	Site reported AE that requires intervention followed by CEC Adjudication
Myocardial infarction	Site Reported AE followed by CEC Adjudication
Prolonged intubation	Site Reported AE followed by CEC Adjudication
Laryngeal or phrenic nerve injury	Site Reported AE followed by CEC Adjudication
Severe Heart Failure / Hypotension	Site Reported AE followed by CEC Adjudication
Paraplegia / Paraparesis	Site Reported AE followed by CEC Adjudication
Stroke	Site reported AE followed by CEC Neurologist Review and Adjudication
False Lumen Status – Treated Segment	Core Lab
False Lumen Status – Untreated Aorta	Core Lab
Significant Blood Loss (≥1000mL)	Site Reported Treatment Data



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Appendix E: SSB 11-02 Protocol Revision #3



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