



<b>Study Protocol Title:</b>	<b>Prospective Investigation of The Merit WRAPSODY™ Endovascular Stent Graft for Treatment of Venous Outflow Circuit Obstruction In Hemodialysis Patients</b>
<b>Abbreviated Title:</b>	<b>WRAPSODY FIRST</b>
<b>Study Product Under Investigation:</b>	<b>Merit WRAPSODY Endovascular Stent Graft System</b>
<b>Study Protocol Number:</b>	<b>CVO-P1-18-01</b>
<b>Sponsor:</b>	<b>Merit Medical Systems, Inc.</b> [REDACTED] [REDACTED]
<b>Sponsor Contact:</b>	[REDACTED] [REDACTED]
<b>ClinicalTrials.gov Identifier:</b>	<b>NCT03644017</b>
<b>Date of Protocol:</b>	<b>October 07, 2020</b>
<b>Protocol Version:</b>	<b>Version 5.0</b>

## TABLE OF CONTENTS

Section Number	Section	Page Number
1	Introduction	3
2	Study Objectives	11
3	Subject Population	13
4	Study Design	14
5	Treatment and Assessment	15
6	Subject Completion and Withdrawal	18
7	Adverse Events	19
8	Data Monitoring Committee	23
9	Statistical Analysis	23
10	Good Clinical Practice	24
11	Informed Consent and Subject Confidentiality	25
12	Protocol Compliance	25
13	Data Recording and Retention of Study Data	26
14	References	27
Appendix A	Schedule of Study Events	29
Appendix B	Procedure for WRAPSODY Delivery	30

## 1 INTRODUCTION

### 1.1 Background

End-stage renal disease (ESRD) is a condition in which there is an irreversible decline in kidney function severe enough to be fatal in the absence of dialysis treatment or kidney transplantation. Reduction in, or absence of, kidney function leads to a host of maladaptive changes including fluid retention (extracellular volume overload), anemia, disturbances of bone and mineral metabolism, dyslipidemia, and protein energy malnutrition (Heye 2012). The incidence of end-stage renal disease in the United States increases by 5% per year, largely due to the growing prevalence of hypertension and diabetes. Currently in the US over 661,000 individuals have been diagnosed with ESRD, and of these, approximately 468,000 are receiving hemodialysis. The average cost of dialysis is \$89,000 per patient, per year, for a total cost to the US medical system of approximately \$42 billion annually, of which \$34 billion is absorbed by Medicare. Approximately 1% of the Medicare population undergoes chronic dialysis, but accounts for 7% of the Medicare budget (USRDS 2015).

Despite improvements over the past 50 years since hemodialysis became available, the mortality rate for patients with ESRD undergoing hemodialysis is 20-25% at one year, with a 5 year survival of only 35% (USRDS 2015). In part, this poor prognosis is due to the compounded impact of concurrent health conditions. Three-quarters of dialysis patients have 5 or more comorbidities, and 90% have cardiovascular disease (USRDS 2005). Hemodialysis access site and venous outflow circuit dysfunction are directly related to morbidity in this population. Inadequate dialysis can lead to cardiopulmonary decompensation, life-threatening electrolyte imbalances, and a multitude of other physiologic complications (Heye 2012). Thus, the ability to effectively complete hemodialysis treatments is critical to improving outcomes.

Vascular access for hemodialysis is achieved via arteriovenous fistula (AVF), arteriovenous graft (AVG) or central venous catheter (CVC). The National Kidney Foundation Kidney Disease Outcomes Quality

DCO20-036\_09OCT2020

Initiatives (KDOQI 2006) recommends AVF (direct surgical connection of artery to vein) as the first choice for vascular access due to longer period of patency, improved durability, and low infection rate. AVF site location in order of preference, is forearm/radiocephalic, elbow/brachiocephalic, and arm/brachiobasilic (Santoro 2014). An access in the wrist area is considered the gold standard since it is relatively simple to create, has a low incidence of complications, and if abandonment becomes necessary, it allows for more proximal future access (VAWG 2006). AVFs must be planned a minimum of a month in advance, and may take 3 months or longer to mature. This lead time can make AVFs unsuitable for patients with near term dialysis needs.

Arteriovenous grafts (AVGs) consist of a synthetic interposition between an artery and a vein and are the second choice for dialysis access. Although patency is generally of shorter duration than AVFs, AVGs may be used when autogenous options have been exhausted, or as a first line choice in patients whose superficial veins are deep in subcutaneous tissue, or those with extreme vascular fragility (Santoro 2014). Central venous catheter access is considered the third ranked choice because of the high risk of thrombosis and infection (KDOQI 2006). Use is predominantly in patients with urgent need of dialysis in which there is insufficient time to establish an AVF or AVG, or when other accesses have become dysfunctional. Avoidance of CVC use is recommended whenever possible (Fistula First, 2018).

Vascular access dysfunction, defined as low or no-flow fistulae and grafts, accounts for 20% of all hospitalizations in ESRD (Feldman 1996). Primary complications of AVFs are failure to mature and venous stenosis followed by thrombosis (Roy-Chaudhury 2006). Time from surgery to use is shorter for AVGs, but rates of stenosis, thrombosis and infection are higher (NIDDK). Stenoses for both these forms of vascular access occur at or near the anastomotic region, and involve neointimal hyperplasia, adverse vascular remodeling, and thrombosis. Although the mechanisms responsible are complex and not completely understood, factors include flow turbulence, inflammation, and a prothrombotic

environment from endothelial damage (Ocak 2013). The result to the patient is access dysfunction causing reduced blood flow, edema, pain, and neurological compromise.

Treatment of hemodialysis access site stenoses to restore adequate flow and prolong the viability of the anastomosis is performed by surgery or catheter-based interventions such as percutaneous transluminal angioplasty (PTA) or placement of a stent-graft. KDOQI guidelines recommend balloon angioplasty or surgical revision if there is a >50% decrease in luminal diameter and abnormal physical findings, or decreasing intra-anastomosis flow, or elevated static pressure within the anastomosis. If PTA fails, KDOQI guidelines state that stents may be useful (KDOQI 2006).

### **1.2 Stent Grafts For Access Circuit Revision**

Four prospective, multicenter, randomized studies conducted by Haskal, Vesely (2010; 2016), and Falk compared the performance of stent grafts (SG), percutaneous transluminal angioplasty (PTA), and bare metal stents (BMS) for treating failing or dysfunctional AVFs or AVGs. All four clinical trials demonstrated that stent grafts provided superior patency and fewer reinterventions compared to balloon angioplasty alone (Haskal 2010; Haskal 2016; Vesely 2016; Falk 2016).

In the pivotal trial of the FLAIR® Endovascular Stent Graft (Bard, Tempe AZ) 190 subjects with dialysis access graft venous anastomotic stenosis were randomized at 13 sites to PTA alone, or PTA with placement of a nitinol stent covered in carbon impregnated expanded polytetrafluoroethylene (ePTFE). The results showed statistically significantly better treatment area primary patency (TAPP) for stent grafts (SG) compared to PTA alone.

At 6 months, TAPP and access circuit primary patency (ACPP) were statistically significantly better for SG than PTA (TAPP: 51% vs 23%,  $p<.001$ ) (ACPP: 38% vs 20%,  $p=.008$ ). Freedom from reintervention at 6 months was also better in the stent graft group (32% vs 16%,  $p=.03$ ), with incidence of restenosis being higher in the PTA group (78% vs 28%,  $p<.001$ ) (Haskal 2010).

Haskal and colleagues conducted a second prospective, randomized study comparing outcomes from a stent graft (FLAIR Endovascular Stent Graft) to PTA, the RENOVA trial. This study included 270 patients with stenosis at the graft-vein anastomosis of their AVG's at 28 sites. At 12 months, the results showed statistically significantly better TAPP for the SG compared to PTA alone (47.6% vs 24.8%,  $p < .001$ ). For the same time period, ACP and index of patency function (IPF) was also better in the stent graft group (ACPP: 24% vs PTA 11%,  $p = .007$ ) (IPF: 5.2 months/intervention vs 4.4 months/intervention,  $p = .009$ ) (Haskal 2016).

At 24 months, the results continued to be statistically significantly better for the SG compared to PTA alone (TAPP: 26.9% vs 13.5%,  $p < .001$ ) (ACPP: 9.5% vs 5.5%,  $p = .01$ ) (IPF: 7.1 months/intervention vs 5.3 months/intervention). The estimated number of reinterventions before graft abandonment was 3.4 for SG subjects versus 4.3 for PTA subjects. There were no statistically significant differences in adverse events ( $p > .05$ ), except rates for restenosis requiring reintervention at 82.6% in PTA subjects vs 63.0% in SG subjects ( $p < .001$ ) (Haskal 2016).

The REVISE study was a multi-center prospective randomized trial in which 293 subjects with in-stent stenosis of the AVG venous anastomosis were randomized to receive PTA alone or PTA plus placement of the GORE® VIABAHN® Endoprosthesis with Heparin Bioactive Surface (Gore, Flagstaff AZ). The REVISE study demonstrated that the use of the VIABAHN device to treat venous anastomotic stenosis in stenosed and/or failing access grafts provided superior patency and fewer reinterventions when compared to balloon angioplasty alone (Vesely 2016). The REVISE study is the first prospective study of stent grafts for failing AVGs that included subjects with either stenotic or thrombotic hemodialysis access.

Study subjects treated with a VIABAHN device had statistically significantly better primary patency rates of the target lesion at 6 months when compared to PTA alone (51.6% vs 34.2%,  $p = .006$ ). Subjects treated with a VIABAHN stent graft also had better primary patency of the entire arteriovenous access

circuit at 6 months (41.5% vs 28.4%,  $p=.035$ ). At 24 months, there was no statistically significant difference between SG and PTA groups in the percentage of subjects with a secondary stenosis (24% vs 21%,  $p=.58$ ) (Vesely 2016).

The RESCUE study was a prospective, multicenter, randomized, concurrently controlled clinical trial designed to assess the performance of the FLUENCY® PLUS Endovascular Stent Graft (Bard, Tempe AZ) compared to PTA alone in the treatment of in-stent restenosis in the access circuit of subjects receiving hemodialysis with an AV graft or native fistula (Falk 2016).

This study showed that the stent group results were superior to PTA with respect to 6-month access circuit primary patency (ACPP) and was non-inferior to PTA with respect to safety. ACPP at 6 months was significantly higher in SG than the PTA group (18.6% vs 4.5%,  $p < .001$ ). Freedom from safety events at 30 days was comparable (SG: 96.9% vs PTA: 96.4%,  $\delta = 0.075$ ,  $p = .003$  for non-inferiority). Treatment area primary patency (TAPP) was superior for (SG) at 6 months (66.4% vs 12.3%,  $p < .001$ ). Unlike previous studies that compared SG to PTA to revise dialysis accesses, the RESCUE study included treatment of restenosis in both the peripheral and central veins (Falk 2016).

ACPP at 24 months was not statistically significantly different between the SG and PTA group (0.9 vs 0.8,  $p=ns$ ) nor were they statistically significantly different for lesions treated in the central vein, (SG: 1.1 vs PTA: 0.0,  $p=ns$ ), or peripheral vein (0.0 vs 2.0  $p=ns$ ). However, TAPP at 24 months was statistically significantly better in SG for lesions in both the central and peripheral veins (13.6 vs 4.3,  $p<.001$ ) and (16.5 vs 1.7,  $p<.001$ ), respectively (Falk 2016).

### **1.3 Thoracic Central Vein Obstruction (TCVO)**

Thoracic Central Vein Obstruction (TCVO) is a common and major complication of hemodialysis and can be caused or exacerbated by pacemaker and automatic internal cardiac defibrillator (AICD) wires, peripherally inserted central catheters, and/or a history of central venous catheter use (Agarwal 2009).

This is thought to be due to trauma and the associated inflammatory response, resulting in the formation of thrombus, intimal hyperplasia and fibrotic response (Agarwal 2015). Clinical symptoms of TCVO include edema, tenderness, pain and erythema. Thoracic central venous obstruction can lead to aneurysmal dilation and tortuosity of the arteriovenous access and/or development of enlarged venous contralaterals which divert blood flow around the obstruction. This can result in decreased blood flow and recirculation at the access site and inadequate dialysis (Kundu 2009).

First line treatment for symptomatic TCVO is percutaneous transluminal angioplasty, but neointimal hyperplasia can progress due to damage to the vessel lumen from PTA, and stenosis has been shown to progress faster after intervention (Levit 2006). The mechanism of angioplasty involves cracking and fissuring the vessel intima which can accelerate intimal hyperplasia, and recurrent lesions after PTA have been demonstrated to have a higher proliferative index than the primary lesion (Chang 2004).

Central veins are more elastic and therefore more likely to recoil after PTA than the peripheral veins, with more than 50% of central lesions showing immediate recoil (Davidson 1991). For this reason, bare metal stents have been used to achieve acceptable technical results after PTA. KDOQI Vascular Access Guidelines recommend that PTA is the first-line treatment for stenosis in the access circuit. The guidelines also suggest stent placement as a treatment option for acute elastic recoil after PTA, when a stenosis recurs within 3 months, in subjects at increased risk for surgery, or following vessel rupture (KDOQI 2000).

Stent grafts have been used to treat TCVO, but most reports cite their use within larger randomized clinical trials or in small cohort studies. In a study by Jones and colleagues, VIABAHN stent grafts were placed in the central veins of 42 subjects with stenosis that did not respond to PTA. Primary patency rates at 3, 6, 12, and 24 months were 97%, 81%, 67%, and 45%, respectively. Primary assisted patency rates at 3, 6, 12, and 24 months were 100%, 100%, 80%, and 75%. This suggests that stent grafts placed



for the treatment of central venous stenosis are an effective way to maintain luminal patency if PTA fails (Jones 2011).

As further support, in the RESCUE study summarized earlier, a subset of 73 subjects (total study n = 275) with stenoses in the central vein (n=41), subclavian vein (n=30), brachiocephalic vein (n=1), and superior vena cava (n=1) demonstrated statistically significantly better primary patency in the treatment area at 24 months for the stent graft group vs PTA (13.6% vs 4.3%,  $p < .001$ ).

To date there have been no large prospective randomized studies to investigate stent graft performance in the central veins.

Stent grafts used in central veins are the GORE VIABAHN, FLUENCY PLUS and the FLAIR Endovascular Stent Graft. Per these products' Instructions for Use, the VIABAHN stent graft is a flexible, self-expanding endoluminal endoprosthesis consisting of an expanded polytetrafluoroethylene (ePTFE) lining with an external nitinol support extending along its entire length. The FLUENCY PLUS is a flexible self-expanding vascular prosthesis comprising ePTFE encapsulating a nitinol frame work, except for 2 mm at each of the flared stent graft ends with 4 radiopaque Tantulum markers. The inner lumen of the stent graft surface is carbon impregnated. The FLAIR Endovascular Stent Graft is a flexible, self-expanding endoprosthesis comprising an expanded (ePTFE) encapsulating a nitinol stent framework. The nitinol stent, including distal and proximal ends, is encapsulated within the ePTFE and the inner lumen of the stent graft is carbon impregnated. The ePTFE outer wall of the stent graft, which contacts the AV access graft and native vein, contains cutouts which expose the nitinol stent.

#### 1.4 The WRAPSODY Stent Graft

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 2 STUDY OBJECTIVES

### 2.1 Primary Objectives

#### Safety

- Proportion of subjects without any localized or systemic safety events through 30 days that affect the access or venous outflow circuit and resulted in surgery, hospitalization, or death
  - Safety events in this calculation will not include venous outflow obstructions, which are captured in the calculation of Assisted Primary Patency of the target lesion, Assisted Primary Patency of the venous outflow circuit and Index of Patency Function

#### Effectiveness

- Proportion of subjects with Target Lesion Primary Patency at 30 days
  - Time to loss of Target Lesion Primary Patency is defined as the time interval of uninterrupted patency from initial study procedure to the next intervention performed on the target lesion or uncorrectable target lesion occlusion, whichever occurs first

### 2.2 Secondary Objectives

- Proportion of subjects with Target Lesion Primary Patency at 3, 6 and 12 months
- Proportion of subjects with Assisted Primary Patency of the target lesion at 30 days, 3, 6 and 12 months
  - Time to loss of Assisted Primary Patency of the target lesion is defined as time following study procedure until uncorrectable target lesion occlusion
- Proportion of subjects with Primary Patency of the venous outflow circuit at 30 days, 3, 6, and 12 months
  - Time to loss of Primary Patency of the venous outflow circuit is defined as the time following initial study procedure until the next venous outflow circuit intervention
- Proportion of subjects with Assisted Primary Patency of the venous outflow circuit at 30 days, 3, 6 and 12 months.

- Time to loss of Assisted Primary Patency of the venous outflow circuit is defined as the time following initial study procedure until complete access abandonment.
- Index of Patency Function at 3, 6 and 12 months, defined as time from initial study procedure to complete access abandonment divided by number of venous outflow circuit re-interventions to maintain hemodialysis
- Procedure or device related adverse events at 3, 6 and 12 months
- Clinical Success
  - The resumption of successful dialysis through existing access for at least one session following initial study procedure
- Anatomic Success
  - Less than 30% residual stenosis immediately following study procedure
- Procedural Success
  - The achievement of both clinical and anatomic success

### **2.3 Exploratory Objectives**

- Stent graft integrity (subset of subjects with thoracic central venous target lesions only)
  - Measured as freedom from stent graft fracture, defined as clear interruption of a stent strut observed in a minimum of two projections taken during the 12 Month visit or after determined by DMC/CEC examination of X-Ray images.

### 3 SUBJECT POPULATION

#### 3.1 Inclusion Criteria

1. Subject has signed informed consent
2. Subject is  $\geq 21$  years of age
3. Subject is undergoing chronic hemodialysis or other forms of renal replacement therapy including transplantation, and has one of the following being used:
  - a. AV graft placed in the arm  $\geq 30$  days prior OR
  - b. Mature fistula in the arm with at least one successful dialysis session completed
4. Angiographic evidence of (multiple stenoses may exist within the target lesion):
  - a. a lesion less than 9 cm in length in an arm or thoracic central vein, not located within the needling segment of an AVF, and ends before the superior vena cava, OR
  - b. a lesion less than 9 cm in length in an arm or thoracic central vein, not located within the needling segment of an AVG venous anastomosis, and ends before the superior vena cava
5. The target lesion has  $\geq 50\%$  stenosis
6. Subject has clinical or hemodynamic evidence of a venous outflow stenosis or obstruction
7. Full expansion of an appropriately sized standard angioplasty balloon (in the investigator's opinion) has been achieved during primary angioplasty at the target lesion prior to enrollment

#### 3.2 Exclusion Criteria

1. Subject has undergone a surgical intervention of the AVF/AVG  $\leq 30$  days from the date of the initial study procedure
2. Subject has had a previous stent or stent graft placed in the venous outflow circuit  $\leq 30$  days from the date of the initial study procedure
3. Active hemodialysis access is not in the arm
4. A pseudoaneurysm is present within the target lesion
5. Target lesion is:
  - a. in the superior vena cava
  - b. in the jugular vein
  - c. under the clavicle
  - d. requires stent graft placement across the elbow
  - e. in the needling segment of an AVF or AVG anastomosis
  - f. located within a stent
6. Lesions, other than the target lesion, in the venous outflow circuit with  $>30\%$  stenosis
  - a. Note that subjects with secondary lesions may be included IF the lesions have been treated  $> 30$  days before study procedure AND have less than 30% residual stenosis

7. Known or suspected infection of the hemodialysis access site and/or septicemia
8. Permanent pacemaker or automated implantable cardioverter defibrillator (AICD) on the side with the target lesion
9. Current central venous catheter for dialysis access
10. Uncorrectable coagulation disorders
11. Hypersensitivity to nickel titanium alloy
12. The subject is enrolled in another investigational study
13. The subject is unable or unwilling to comply with the protocol requirements
14. Life expectancy is  $\leq 12$  months
15. Subject cannot receive heparin or equivalent anticoagulant
16. Allergy to radiographic contrast material which cannot be adequately premedicated
17. Subject is pregnant, breastfeeding, or pre-menopausal and intending to become pregnant
18. Subject's access is anticipated to be abandoned within 3 months
19. Subject has a thoracic central vein obstruction that would lead to stent graft placement across the internal jugular vein
20. Subject's hemodialysis access is thrombosed
21. Active malignancy other than non-melanomatous skin cancer
22. Any other condition deemed exclusionary in the opinion of the investigator

#### 4 STUDY DESIGN

This is a phase 1 first in human study, designed to evaluate the safety and effectiveness of the WRAPSODY Stent Graft for the treatment of venous outflow circuit obstructions in the veins of the arm or thoracic central veins (brachiocephalic and/or subclavian) of subjects who receive chronic dialysis treatment for end stage renal disease.

The study will consist of a screening period in which subject eligibility will be determined. Approximately 50 subjects meeting the study entry criteria will be enrolled. Placement of the WRAPSODY stent graft will follow the procedure in Appendix B. Post study procedure subjects will have planned follow-up visits at 30 days ( $\pm 7$  days), 3, 6 and 12months ( $\pm 4$  weeks at each timepoint), and additional visits as referred by the subject's dialysis facility to assess access and venous outflow circuit patency, with revision if appropriate.

The primary study safety endpoint will be the proportion of subjects without any localized or systemic safety events through 30 days that affect the access or venous outflow circuit and resulted in surgery, hospitalization, or death. This calculation will not include venous outflow obstructions, which are

captured in the calculation of Assisted Primary Patency of the target lesion, Assisted Primary Patency of the venous outflow circuit and Index of Patency Function. Primary safety and effectiveness endpoints are at 30 days. Subjects will continue to be followed up to 12 months for supplementary information. The primary study effectiveness endpoint will be the proportion of subjects with Target Lesion Primary Patency at 30 days. Time to loss of Target Lesion Primary Patency is defined as the time interval of uninterrupted patency from initial study procedure to the next intervention performed on the target lesion or uncorrectable target lesion occlusion, whichever comes first.

## 5 TREATMENT AND ASSESSMENT

Delivery of the WRAPSODY stent graft will be according to the procedure in Appendix B.

### Visit Schedule

#### Visit 1:

- Screening
  - Informed consent
  - Eligibility criteria assessment
  - Demographics
  - Vital Signs
  - Medical History relevant to dialysis:
    - Type, location and date of all previous venous outflow circuit intervention(s)
    - Prior dialysis access type(s)
  - Location of current dialysis access (AVF/AVG)
    - For subjects with AV fistula, date fistula was first used for dialysis
    - For subject with AV graft, date of graft creation
  - Clinical reason(s) subject was referred for obstruction evaluation
  - Targeted physical exam, including at a minimum the following Clinical Indicators of Obstruction:
    - Assessment of edema in hand, arm, neck, head or trunk
    - Pain related to dialysis circuit
    - Respiratory symptoms
    - Neurological symptoms
    - Skin changes
  - Concurrent medical conditions
  - Concomitant medications

- Serum pregnancy test, if applicable
- Angiographic Imaging with location, length and percent stenosis of target lesion
- Doppler ultrasound to be performed prior to procedure
  - NOTE: A doppler ultrasound must be attempted for each subject prior to the study procedure. However, if doppler ultrasound results are unobtainable in some cases due to lesion location, this will not be considered a protocol violation.
- Study procedure (WRAPSODY Stent Graft Placement)
  - Length and diameter of stent graft
  - Percent residual stenosis
  - Doppler ultrasound post stent graft placement
    - NOTE: A doppler ultrasound must be attempted for each subject after the study procedure. However, if doppler ultrasound results are unobtainable in some cases due to lesion location, this will not be considered a protocol violation.
  - Adverse event review
  - Investigator's assessment of technical success (defined as successful deployment at intended location)
  - Procedural medications

**Visit 2: 30 days (± 7 days)**

- Targeted physical exam, including at a minimum the following Clinical Indicators of Obstruction:
  - Assessment of edema in hand, arm, neck, head or trunk
  - Pain related to dialysis circuit
  - Respiratory symptoms
  - Neurological symptoms
  - Skin changes
- Hemodialysis adequacy at the first session following the study procedure
- Adverse event review
- Interventions on venous outflow circuit since last visit
- Concomitant medications



**Visit 3: 3 months ( $\pm 4$  weeks)**

- Targeted physical exam, including at a minimum the following Clinical Indicators of Obstruction:
  - Assessment of edema in hand, arm, neck, head or trunk
  - Pain related to dialysis circuit
  - Respiratory symptoms
  - Neurological symptoms
  - Skin changes
- Adverse event review
- Interventions on venous outflow circuit since last visit
- Concomitant medications

**Visit 4: 6 months ( $\pm 4$  weeks)**

- Targeted physical exam, including at a minimum the following Clinical Indicators of Obstruction:
  - Assessment of edema in hand, arm, neck, head or trunk
  - Pain related to dialysis circuit
  - Respiratory symptoms
  - Neurological symptoms
  - Skin changes
- Adverse event review
- Interventions on venous outflow circuit since last visit
- Concomitant medications

**Visit 5: 12 months ( $\pm 8$  weeks)**

Traditional visit windows are being expanded for the 12-month visit to allow for potential impacts due to COVID-19.

- Targeted physical exam, including at a minimum the following Clinical Indicators of Obstruction:
  - Assessment of edema in hand, arm, neck, head or trunk
  - Pain related to dialysis circuit
  - Respiratory symptoms
  - Neurological symptoms
  - Skin changes
- Adverse event review
- Interventions on venous outflow circuit since last visit

- Concomitant medications
- X-rays of the treated area (subset of subjects with thoracic central venous target lesions only)
  - Minimum of two projections required to visualize WRAPSODY stent graft

**Additional visits, as needed/referred for evaluation/treatment of venous outflow dysfunction**

- Angiographic Evaluation, if medically indicated
- Clinical reason(s) subject was referred for obstruction evaluation
- Targeted physical exam, including at a minimum the following Clinical Indicators of Obstruction:
  - Assessment of edema in hand, arm, neck, head or trunk
  - Pain related to dialysis circuit
  - Respiratory symptoms
  - Neurological symptoms
  - Skin changes
- Interventions on venous outflow circuit since last visit
- Adverse event review
- Current intervention, if done, including:
  - Procedure type
  - Lesion location and length
  - % stenosis before treatment
  - % residual stenosis after treatment
- Concomitant medications
- X-rays of the treated area (subset of subjects with thoracic central venous target lesions only)
  - Subjects who were unable to have X-Rays completed at scheduled Visit 5 (12 Months) may be brought back for an additional visit to complete X-Rays after obtaining proper consent.

**6 SUBJECT COMPLETION AND WITHDRAWAL**

A subject is considered to have completed the study if he/she has had an initial study procedure and has follow-up information through 12 months.

Subjects will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw subjects from the

study for any reason. If a subject has a kidney transplant and/or current dialysis access is abandoned, he/she will be withdrawn from the study. If a subject is withdrawn from the study, the reason will be recorded on the end of study form. If a subject signs informed consent and is not enrolled in the study for any reason, the subject is a screen failure. A record of all subjects who signed an informed consent will be maintained.

Subjects will be considered lost to follow up if:

- The site has documented attempts to contact the subject at least three times without success, AND
- The site has a documented attempt to contact the subjects' dialysis center, AND
- The site has a documented attempt to contact the subjects' managing physicians

Subjects who are withdrawn from the study after completion of the study procedure for any reason will not be replaced. All subjects regardless of whether or not they complete the study, will be included in the Intent-to-Treat (ITT) population. The Sponsor may terminate the study at any time. In addition, termination or modification may be recommended for any other perceived safety concern based on clinical judgment of the Data Monitoring Committee (DMC) members.

## **7 ADVERSE EVENTS**

### **7.1 Definitions**

#### **Adverse Event (AE)**

An adverse event (AE) is any untoward medical occurrence in a subject (regardless of treatment group) that may or may not have a causal relationship with the study procedure. An AE therefore can be any unfavorable or unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or procedure, whether or not considered related to the product or procedure. A serious adverse event (SAE) is any untoward medical occurrence that meets any of the criteria for an SAE as defined below.

Subjects should be instructed to report any AE that they experience to the Investigator or Study Coordinator. Adverse events (AE) will be collected starting on the date of study procedure. AEs will be re-assessed at 30 days, 3 months, 6 months, and 12 months, and at any additional interim visit. AEs occurring during the study procedure and the protocol-defined 12 month follow-up period should be recorded on the appropriate AE CRF. It is important that the Investigators record AE terms accurately and consistently throughout the study. Wherever possible, a specific disease or syndrome should be reported

on the CRF rather than the associated individual signs and symptoms (e.g., diabetes mellitus instead of hyperglycemia). If observed or reported signs or symptoms are not considered a component of a specific disease or syndrome by the Investigator, they should be recorded as separate AEs on the CRF. For this study venous outflow obstructions will not be considered adverse events because they will be captured in the calculation of Assisted Primary Patency of the target lesion, Assisted Primary Patency of the venous outflow circuit, and Index of Patency Function.

### **Serious Adverse Event (SAE)**

A serious adverse event (SAE) is any adverse event, regardless of causality that:

- Results in death
- Is life-threatening, where life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires in-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial e.g., surgery performed earlier than planned.
- Results in persistent or significant disability/incapacity, where disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect
- Is an important medical event as defined by the Investigator. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in subject hospitalization, or the development of drug dependency or drug abuse.

Clarification should be made between the terms "serious" and "severe" since they are not interchangeable. The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious," which

is based on the subject/event outcome or action criteria described above and are usually associated with events that pose a threat to a subject's life or functioning. A severe adverse event does not need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not constitute a SAE, unless the subject would be admitted to the hospital or the event would meet any other of the criteria for seriousness. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Under this protocol, scheduled hospitalizations or elective surgical procedures will not be considered SAEs. Deaths due to renal disease progression will not be considered SAEs.

### **Unanticipated Adverse Device Effect (UADE)**

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, 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 application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

### **7.2 Adverse Event Reporting**

The Investigators are responsible for monitoring the safety of subjects who have been enrolled in this study. All adverse events (AE) considered to be related to study procedure will be followed until the event resolves or has reached a final outcome. AEs will be evaluated for severity according to the following Common Terminology Criteria for Adverse Events (CTCAE) grading scale:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

The Investigator, based on his/her clinical judgment and the following definitions, must determine the relationship of the adverse event to the device and/or procedure:

- None: The AE/SAE does not follow reasonable temporal sequence from the time of study procedure and/or does not follow a known response pattern to the study procedure and is likely to have been produced by other factors.
- Possible: The AE/SAE follows a reasonable temporal sequence from the time of study procedure, and/or follows a known response pattern to the study procedure, but could have been produced by other factors.
- Probable: The AE/SAE follows a reasonable temporal sequence from the time of study procedure, follows a known response pattern to the study procedure, and cannot reasonably have been produced by other factors.
- Definite: The AE/SAE follows a reasonable temporal sequence from the time of study procedure; follows a known response pattern to the study procedure; and cannot have been produced by other factors.

Investigators are required to document all device and/or study procedure related AEs occurring during the study commencing with the date of study procedure through the protocol defined 12 month post-treatment follow-up period, or discontinuation, death, or loss to follow-up subject. AEs that occur following the signature of informed consent but prior to treatment will not be captured.

Serious Adverse Events (SAE) that occur following the signature of the informed consent but prior to treatment will not be reported. Deaths due to disease progression will not be considered SAEs, but must be reported to the sponsor within 24 hours of site notification of the event using the electronic Death Report form.

### **7.3 Serious Adverse Event Reporting**

Any unanticipated adverse event or SAE that occurs during study procedure through the 12 month follow-up period, whether or not related to the study procedures, must be reported to the Sponsor within 24 hours of site knowledge of the event on the electronic SAE form. The SAE must be completely described on the AE CRF as well as the electronic SAE report form.

Safety Contact Information:
[REDACTED]
[REDACTED]
[REDACTED]

## 8 DATA MONITORING/CLINICAL EVENTS COMMITTEE & SAFETY STOPPING RULES

A Data Monitoring/Clinical Events Committee (DMC/CEC) will be formed consisting of at least 3 individuals with expertise and experience in clinical trials, and safety evaluations, but without direct involvement in the conduct of the study. The exact responsibilities, procedures, and guidelines used to manage the DMC/CEC are described in a separate charter.

Any SAE or UADE resulting in surgery or death will trigger a DMC/CEC meeting. The study will stop at 1 SAE or UADE unless the DMC/CEC determines that the event was not primarily due to the study device or procedure. The DMC/CEC will review and adjudicate all target lesion and access circuit interventions performed after the study procedure.

In addition, termination or modification may be recommended for any other perceived safety concern based on clinical judgment of the DMC members.

## 9 STATISTICAL ANALYSIS

### Analysis Sets

**Safety Population:** The safety population will include all enrolled subjects who received the treatment.

**Efficacy Population:** The efficacy population will include all enrolled subjects who received the treatment as specified in the protocol and met all eligibility criteria.

The primary safety endpoint is the proportion of subjects without any localized or systemic safety event through 30 days that affect the venous access circuit and resulted in surgery, hospitalization, or death. Safety events in this calculation will not include venous outflow obstructions which are captured in the calculation of assisted primary patency of the target lesion, assisted primary patency of the venous outflow circuit, and index of patency function. This is an observational study, and outcomes will be summarized, but no comparisons will be performed. Confidence intervals will be provided for all outcome calculations wherever possible.

The primary effectiveness endpoint is the proportion of subjects with target lesion Primary Patency at 30 days. Time to loss of target lesion Primary Patency is defined as the time interval of uninterrupted patency from initial study procedure to the next intervention performed on the target lesion or uncorrectable target lesion occlusion, whichever occurs first.

#### Sample Size

A sample size of approximately 50 subjects was chosen as appropriate for an initial safety and efficacy evaluation.

The primary effectiveness analyses of target lesion Primary Patency at 30 days will be summarized using number and proportion of subjects with Target Lesion Primary Patency at that timepoint.

This methodology will be repeated to test secondary endpoints, proportion of subjects with: target lesion Primary Patency at 3, 6, and 12 months; Assisted Primary Patency of target lesion at 3, 6, and 12 months; Primary Patency of the venous outflow circuit at 3, 6, and 12 months; Assisted Primary Patency of the venous outflow circuit at 3, 6, and 12 months.

The primary safety endpoint will be summarized using number and proportion of subjects without any localized or systemic safety event that affected the access or venous outflow circuit and resulted in surgery or hospitalization or death through 30 days.

A formal interim analysis will be completed when all subjects complete the 6-month visit, (Visit 4), (or discontinue prior to the 6-month visit). As the interim analysis will be the primary effectiveness analysis, no alpha adjustment for multiplicity will be applied for this interim analysis. The final analysis will be completed when all subjects complete the study (12-month visit; Visit 5).

#### 10 GOOD CLINICAL PRACTICE (GCP)

The study will be conducted in accordance with the International Conference on Harmonization (ICH) E6 for Good Clinical Practice (GCP). The Investigators will be thoroughly familiar with the appropriate use of the treatment procedure as described in the protocol. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Essential documents will be maintained for the duration of the trial and retained according to the appropriate regulations.



A Merit Medical Systems monitor, or designee, will visit the center periodically to monitor the progress of the clinical trial and review CRFs and original source documents with the study personnel to verify accuracy of data recording. Some/all of the facilities (e.g. laboratory) used in the trial may be reviewed or inspected by the Ethics Committee (EC) and/or other regulatory authorities, including the FDA.

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The EC of the clinical trial site will review and approve all appropriate study documentation in order to safeguard the rights, safety and well-being of the subjects. The study will only be conducted after EC approval has been obtained. The protocol, informed consent, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the EC by the Investigator.

## **11 INFORMED CONSENT AND SUBJECT CONFIDENTIALITY**

After the study has been fully explained, written informed consent will be obtained from the subject (or subject's legal representative) prior to any study-specific procedures being performed. The informed consent form used at the site will be approved by the EC prior to use. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

In order to maintain subject privacy all CRFs, study reports, and communications will identify the subject by the assigned study subject ID number only. The Investigator will grant monitor(s) and auditor(s) from Merit Medical Systems, or its designee, and regulatory authority(ies), including the FDA, access to the subjects' original medical records for verification of data gathered on the CRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

## **12 PROTOCOL COMPLIANCE**

The Investigators will conduct the trial in compliance with the protocol provided by Merit Medical Systems. Modifications to the protocol must not be made without agreement of the Investigator and Merit Medical Systems. Changes to the protocol potentially affecting safety or efficacy will require written EC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. Any deviations from the protocol must be captured on the electronic protocol deviation form and reported to EC and any other regulatory authorities as applicable.

Effort should be made to have subjects return to study physician office for in-person follow-up visits, but if subjects are unable or unwilling to complete visits the clinical trial site may obtain subject status information from the subject's dialysis center or other treating physician. The clinical trial site will confirm with subjects' dialysis centers whether any access or venous outflow dysfunction revisions have happened at other facilities.

### **13 DATA RECORDING AND RETENTION OF STUDY DATA**

The sponsor will provide electronic case report forms for study data recording. All trial documents must be retained for a minimum of two years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region by Merit Medical Systems. Documents must be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Merit Medical Systems, who will inform the Investigator, in writing, as to when these documents no longer need to be retained.

**14 REFERENCES**

1. Agarwal, AK. Central vein stenosis: current concepts. *Adv Chronic Kidney Dis*. 2009 Sep;16(5):360-70.
2. Agarwal A. Endovascular interventions for central vein stenosis. *Kidney Res Clin Pract* 2015; 34: 228-232.
3. Chang CJ, Ko PJ, AnHsu L, Ko YS, Ko LK, Chen CF, Huang CC, Hsu TS, Lee YS, Hwei J, SPang JH. Increased cell proliferation activity in the restenotic hemodialysis vascular access after percutaneous transluminal angioplasty: implication in prevention of restenosis. *AJKD* 2004; 43(1):74-84.
4. Davidson CJ, Newman GE, Sheikh KH, et al. Mechanisms of angioplasty in hemodialysis fistula stenosis evaluated by intravascular ultrasound. *Kidney Int* 1991; 40: 91-95.
5. Falk A, Maya ID, Yevzlin AS, RESCUE Investigators. Prospective, randomized study of an expanded polytetrafluoroethylene stent graft versus balloon angioplasty for in-stent restenosis in arteriovenous grafts and fistulae: two-year results of the RESCUE study *J Vasc Interv Radiol* 2016; 27(10):1465-1476.
6. Feldman H, Kobrin S, Wasserstein A. Hemodialysis vascular access morbidity. *J Am Soc Nephrol* 1996; 7: 523-535.
7. Fistula First Catheter Last. (2018 - ESRD NCC) Retrieved from <https://www.esrdncc.org/en/fistula-first-catheter-last/>
8. Haskal Z, Trerotola S., Dolmatch B., et al. Stent graft vs. balloon angioplasty for failing dialysis -access grafts. *N Engl J Med*. 2010; 362: 494-503.
9. Haskal Z, Saad T, Hoggard J, et al. Prospective, randomized, concurrently-controlled study of a stent graft versus balloon angioplasty for treatment of arteriovenous access graft stenosis: 2-year results of the RENOVA study. *J Vasc Interv Radiol* 2016; 27(8):1105 –1114.
10. Heye S, Maleaux G, Vaninbrookx J, et al. Factors influencing technical success and outcome of percutaneous balloon angioplasty in de novo native hemodialysis arteriovenous fistulas. *European J Radiol*. 2012; 81(9): 2298-2303.
11. Jones, R, Willis A, Jones C, et al. Long-term results of stent-graft placement to treat central venous stenosis and occlusion in hemodialysis patients with arteriovenous fistulas. *J Vasc Interv Radiol* 2011; 22:1240–1245.
12. KDOQI National Kidney Foundation Guideline 20. Clinical Practice Guidelines for Vascular Access, 2000. *Am J Kidney Dis*.
13. KDOQI National Kidney Foundation Guideline 20. Clinical Practice Guidelines for Vascular Access, 2006. *Am J Kidney Dis*.
14. Koirala N, Anvari E, McLennan G. Monitoring and surveillance of hemodialysis access. *Sem Interv Radiol* 2016; 33(1): 25-30.

15. Kundu S. Central venous obstruction management. *Semin Interv Radial* 2009; 26: 115-121.
16. Levit R, Cohen R, Kwak A, et al. Asymptomatic central venous stenosis in hemodialysis patients. *Radiology* 2006; 238: 1051-1056.
17. McLennan G. Stent and stent-graft use in arteriovenous dialysis access. *Semin Intervent Radiol* 2016; 33:10-14.
18. NIDDK, National Institute of Diabetes, Digestive and Kidney Diseases. [www.niddk.nih.gov](http://www.niddk.nih.gov). accessed Jan 15, 2017.
19. Ocak G, Rotmans J, Vossen C, et al. Type of arteriovenous vascular access and association with patency and mortality. *Nephrology* 2013; 14: 79-86.
20. Roy-Chaudhury P, Kelly B, Melhem M, et al. Vascular access in hemodialysis: issues, management and emerging concepts. *Cardiol Clin.* 2005; 23:249-273.
21. Santoro D, Benedetto F, Mondello P, et al. Vascular access for hemodialysis: current perspectives. *Internat J Nephro and Renovasc Dis* 2014; 7:281-294.
22. USRDS 2005, US Renal Data System, Annual Data Report: Atlas of end stage renal disease in the United States. Incidence and prevalence, patient characteristics. Bethesda, National Institutes of Health, National Institute of Diabetes, Digestive and Kidney Diseases.
23. USRDS 2015, US Renal Data System, Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes, Digestive and Kidney Diseases, Bethesda, MD.
24. Vascular Access 2006 Work Group (VAWG). Clinical practice guidelines for vascular access. *Am J Kidney Dis* 2006; 48 (suppl 1): s176-s247.
25. Vesely T, DaVanzo W, Behrend T, et al. Balloon angioplasty versus Viabahn stent graft for treatment of failing or thrombosed prosthetic hemodialysis grafts. *J Vasc Surg* 2016; 64: 1400-1410.

## APPENDIX A

## Schedule of Study Events

Visit Schedule	Visit 1	Visit 2 <sup>3</sup> 30 days (± 7 days)	Visit 3 <sup>3</sup> 3 Months (± 4 weeks)	Visit 4 <sup>3</sup> 6 Months (± 4 weeks)	Visit 5 <sup>3</sup> 12 Months (± 8 weeks)	Additional Visits <sup>3</sup>
Informed Consent	X					
Eligibility Criteria Assessment	X					
Demographics	X					
Vital Signs	X					
Medical History Relevant to Dialysis	X					
Current dialysis access	X					
Reason(s) for obstruction evaluation	X					X
Concurrent Medical Conditions	X					
Targeted Physical Examination (Clinical Indicators of Obstruction)	X	X	X	X	X	X
Serum Pregnancy Test (if applicable)	X					
Concomitant Medications	X	X	X	X	X	X
Angiographic Imaging	X					X <sup>2</sup>
X-rays of treatment area <sup>4</sup>					X	X <sup>5</sup>
Enrollment	X					
Stent Graft Placement	X					
Hemodialysis Assessment		X				
Adverse Event <sup>1</sup>	X	X	X	X	X	X
Interventions on access and venous outflow circuit since last visit		X	X	X	X	X
Protocol Deviation	X	X	X	X	X	X

<sup>1</sup> Adverse Events to be collected beginning at time of study procedure

<sup>2</sup> If medically indicated

<sup>3</sup> Every effort should be made to collect information by subject visit, however information may be obtained from the subject's dialysis clinic or managing physician if a visit is not possible

<sup>4</sup> X-rays of treatment area for a subset of subjects with thoracic central venous target lesions only. All potential subjects will be reconsented prior to X-Ray imaging.

<sup>5</sup> Only for those subjects with thoracic central venous target lesions who were unable to complete the x-rays at the 12-month follow up visit. X-rays are only requested at the 12-month time point or later.

APPENDIX B

Instructions for Delivery of the Merit WRAPSODY Stent Graft

[REDACTED]

- [REDACTED]  
[REDACTED]
- [REDACTED]  
[REDACTED]
- [REDACTED]  
[REDACTED]
- [REDACTED]  
[REDACTED]  
[REDACTED]
- [REDACTED]  
[REDACTED]

[REDACTED]

- [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]
- [REDACTED]  
[REDACTED]
- [REDACTED]
  - [REDACTED]  
[REDACTED]
  - [REDACTED]  
[REDACTED]  
[REDACTED]
  - [REDACTED]  
[REDACTED]
  - [REDACTED]
- [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]
- [REDACTED]  
[REDACTED]  
[REDACTED]

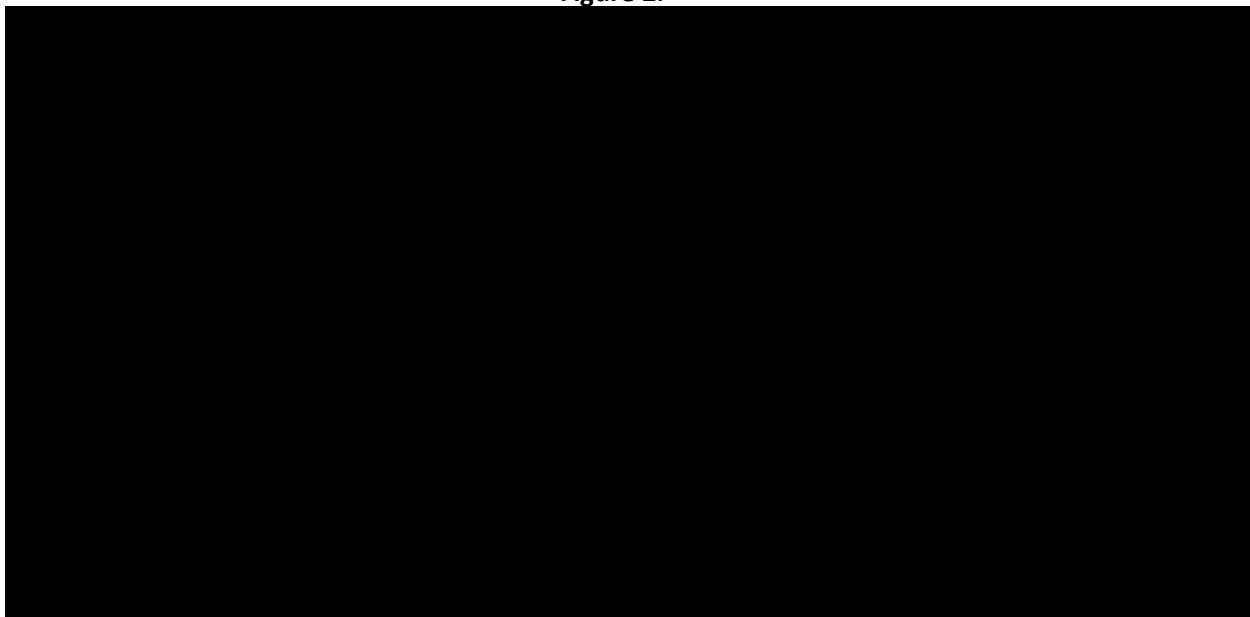
[illegible]

Response	Percentage
U.S. should take action	71%
U.S. should not take action	28%
U.S. should take action, but only if other countries do first	1%

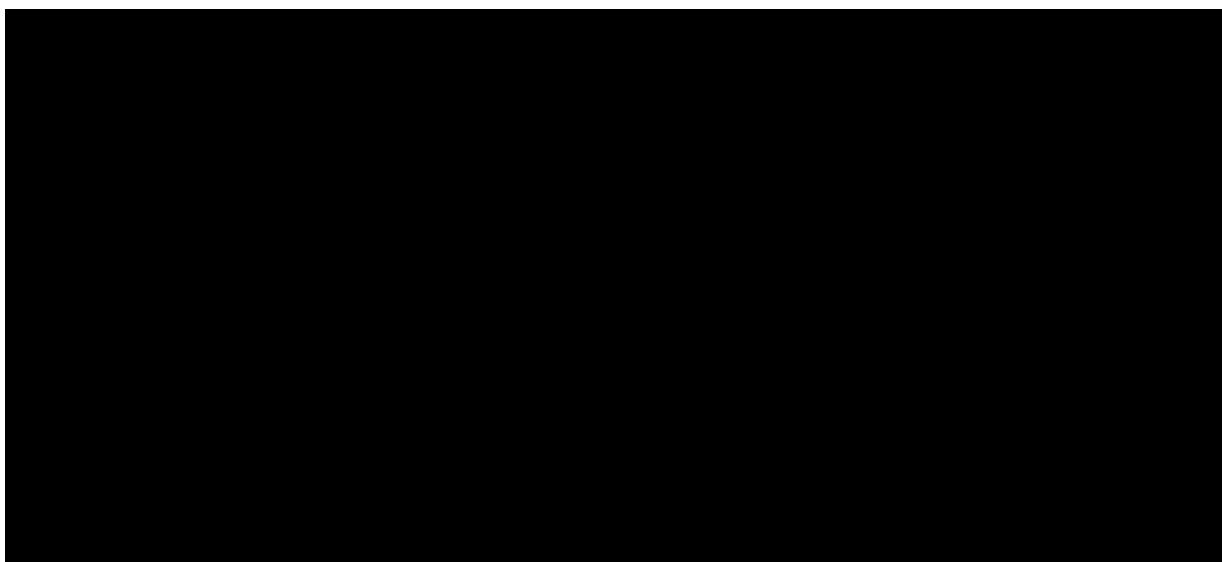
[illegible]



**Figure 2.**



**Figure 3.**



[REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]

### Table 1

Table 1