Prospective, Randomized, Controlled, Multicenter Study Comparing the Merit WRAPSODY™ Endovascular Stent Graft to Percutaneous Transluminal Angioplasty for Treatment of Venous Outflow Circuit Stenosis or Occlusion in Hemodialysis Patients

The WAVE Study

(WRAPSODY AV access Efficacy)

Protocol Number: CVO-P3-20-01
Revision: 6.0
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Sponsor:

Merit Medical Systems, Inc.

[redacted]

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INVESTIGATOR PROTOCOL SIGNATURE PAGE

STUDY TITLE:	Prospective, Randomized, Controlled, Multicenter Study Comparing the Merit WRAPSODY™ Endovascular Stent Graft to Percutaneous Transluminal Angioplasty for Treatment of Venous Outflow Circuit Stenosis or Occlusion in Hemodialysis Patients
PROTOCOL NUMBER & ISSUE:	CVO-P3-20-01 Rev. 6.0
STUDY CENTER NAME & SITE NUMBER:	_____ (Print name & number of study center)

I, the undersigned, have read and understand the protocol specified above and agree with its content. I agree to perform and conduct the Study as described in the protocol. In addition, when applicable, I agree to enlist sub-investigators who also agree to perform and conduct the Study as described in the protocol. I will provide copies of this Protocol and all pertinent information to the Study personnel under my supervision and my hospital Institutional Review Board/Ethics Committee. I will discuss this material with them and ensure they are fully informed regarding the Merit Medical Systems investigational device and the conduct of the Study according to Good Clinical Practice (GCP), Declaration of Helsinki, 21 CFR Parts 50, 54, 56 and 812, ISO 14155:2020 (OUS centers only), and any local regulations.

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SITE PI – Print Name

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SITE PI – Signature

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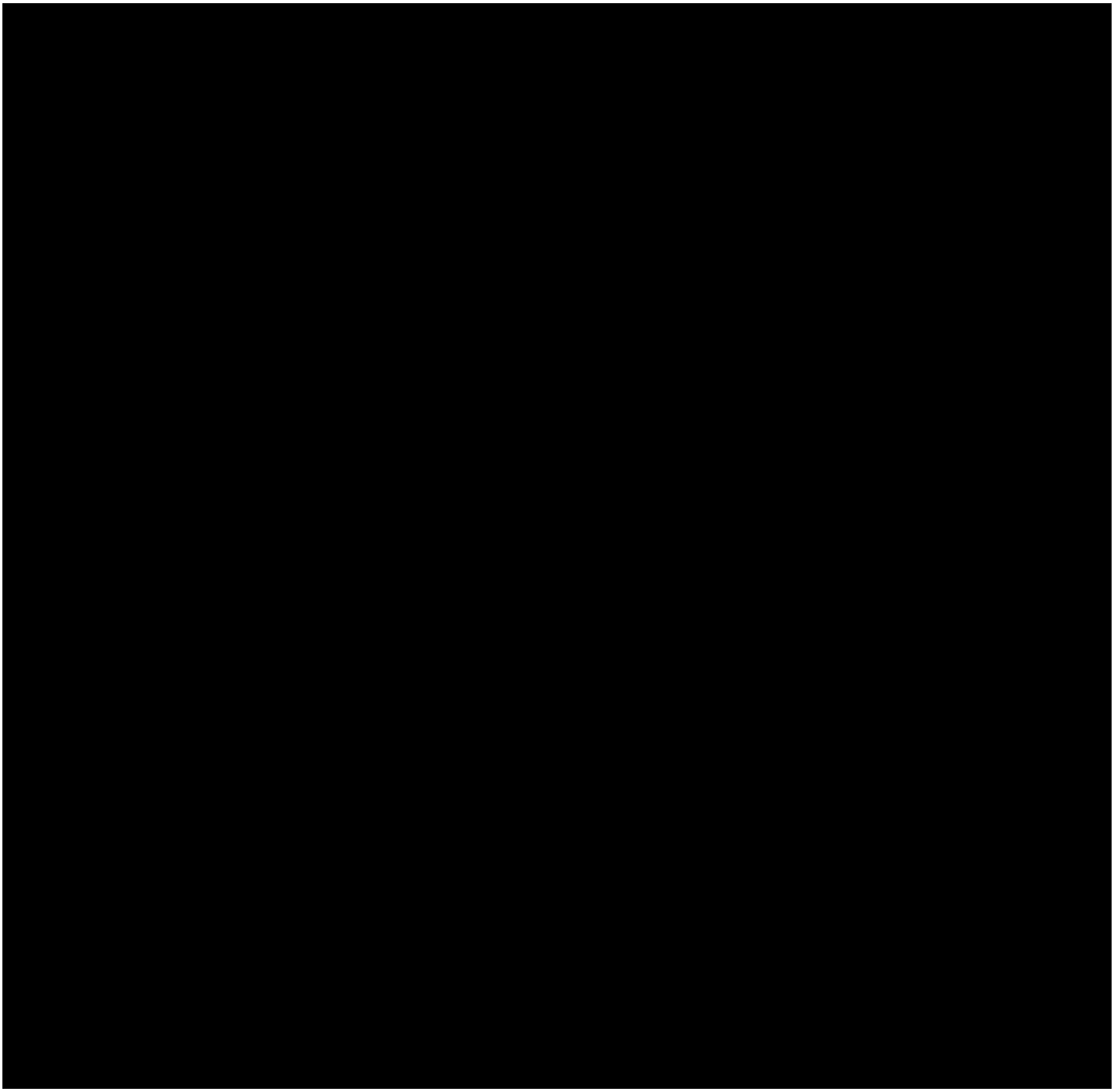

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PROTOCOL SUMMARY

Study Title:	WAVE: Prospective, Randomized, Controlled, Multicenter Study Comparing the Merit WRAPSODY™ Endovascular Stent Graft to Percutaneous Transluminal Angioplasty for Treatment of Venous Outflow Circuit Stenosis or Occlusion in Hemodialysis Patients
Study Objective:	Demonstrate the safety and efficacy of the Merit WRAPSODY Endovascular Stent Graft for treatment of stenosis or occlusion within the dialysis access outflow circuit, including: a) the peripheral veins of subjects with an arteriovenous (AV) fistula (AVF Peripheral), and b) at the venous anastomosis of subjects with a synthetic arteriovenous graft access (AVG Anastomosis) Cohort (a) will be compared to PTA. Cohort (b) will be compared to performance goals.
Study Device:	Merit WRAPSODY Endovascular Stent Graft System
Intended Use:	The Merit WRAPSODY Endovascular Stent Graft System is a flexible, self-expanding endoprosthesis indicated for use in hemodialysis patients for the treatment of stenosis or occlusion within the dialysis access outflow circuit, including stenosis or occlusion: a) in the peripheral veins of individuals with an arteriovenous (AV) fistula, and b) at the venous anastomosis of a synthetic AV graft
Study Design:	Prospective, Randomized (1:1), Controlled, Multicenter for AVF Peripheral cohort; and Prospective, Single Arm, Multicenter for the AVG Anastomosis cohort Each cohort will be analyzed separately
[redacted]	[redacted]
Estimated Enrollment:	Up to a total of 357 subjects across all cohorts. At least 60% of the subjects must come from the US for each cohort. No site may enroll more than 20% of the total population for a specific cohort.

	Cohorts: 1. Up to 244 AVF Peripheral Subjects (1:1 randomization, with approximately 122 in the study treatment and control groups) 2. Up to 113 AVG Anastomosis Subjects (no randomization, comparison to Performance Goals)
Subject Population:	The study comprises 2 independent cohorts: 1. Subjects with AVF for hemodialysis who have stenosis or occlusion of the peripheral venous outflow circuit, including the cephalic arch, 2. Subjects with AVG for hemodialysis who have stenosis or occlusion at the graft-vein anastomosis or juxta-anastomosis
Clinical Sites:	Up to a total of 50 centers with up to 15 international centers.
Study Follow-Up:	After the index procedure on Day 0, subjects shall be evaluated within the clinic at 30 days, then at months 6, 12 and 24. Telephone follow-up shall be completed at months 3, 9 and 18.
Anticipated Study Duration:	First subject enrolled (actual): March 2021 Last subject enrolled (all cohorts): December 2023 Last subject completes Month 6 Visit: June 2024 Last subject completes Month 24 Visit: January 2026
Primary Outcome Measures:	<u>Primary Safety Endpoint</u>: Proportion of subjects without any localized or systemic safety events through 30 days post-index procedure that affect the access or venous outflow circuit and resulted in reintervention, hospitalization, or death (not including stenosis or thrombosis). Endovascular procedures performed to treat safety events after the index study procedure will be considered surgeries. <u>Primary Effectiveness Endpoint</u>: Proportion of subjects with Target Lesion Primary Patency (TLPP) at 6 Months. TLPP is defined as freedom from clinically-driven target lesion revascularization (CD-TLR) or target lesion thrombosis measured through 6 months post-procedure, which is the time interval of uninterrupted patency after study procedure to the next intervention performed on the target lesion or uncorrectable target lesion occlusion.
Secondary Outcome Measures:	1. Proportion of subjects with Target Lesion Primary Patency at months 12 and 24. 2. Proportion of subjects with Assisted Target Lesion Primary Patency (aTLPP) at months 6, 12 and 24 defined as time to loss of Assisted Primary Patency of the target lesion, which is the time from post-procedure until uncorrectable target lesion occlusion. 3. Proportion of subjects with Access Circuit Primary Patency (ACPP) at months 6, 12 and 24 defined as time to loss of Primary Patency of the access circuit, which is the time post-procedure until any venous outflow circuit re-intervention, or access thrombosis or abandonment.

	4. Proportion of subjects with Post-Procedure Secondary Patency at months 6, 12 and 24 defined as the interval post-procedure until access circuit abandonment. 5. Rates of procedure- and device-related adverse events involving the access circuit at index procedure, 30 days, and months 6, 12 and 24. [redacted]
Exploratory Endpoints:	[redacted]
Inclusion Criteria:	1. Subject provides written informed consent before any study-specific investigations or procedures. 2. Subject is male or female, with an age ≥ 18 years at date of enrollment. 3. Subject is willing to undergo all follow-up assessments according to the specified schedule over 24 months. 4. Subject has a life expectancy ≥ 12 months. 5. Subject is undergoing chronic hemodialysis. 6. Subject has either a mature AVF or AVG in the arm that has been created ≥30 days prior to the index procedure and has completed at least one successful dialysis session. 7. Subject has clinical and/or hemodynamic evidence of a venous outflow obstruction or AV fistula or graft dysfunction.
Angiographic Inclusion Criteria:	[redacted]

	[redacted] 6. Target lesion reference vessel diameter is between 5.0 mm and 14.0 mm by operator's visual estimate. [redacted]
Exclusion Criteria:	[redacted] 3. Subject has a known or suspected infection of the hemodialysis access site, systemic infection and/or septicemia. [redacted] 6. Subject has a stroke diagnosis within 3 months prior to enrollment. 7. Subject has a history of unstable angina or myocardial infarction within 60 days prior to enrollment. [redacted]

	[redacted] 10. Subject is pregnant, breastfeeding, or intending to become pregnant within the next year. [redacted]
Angiographic Exclusion Criteria:	1. Target lesion is located within a stent / stent graft. [redacted]

	
Sponsor:	Merit Medical Systems, Inc., USA
Co-National Principal Investigators:	USA: Mahmood K. Razavi, MD, Orange, CA, USA EU: Robert Jones, MD, UK
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Data Safety Monitoring Board:	Yale Cardiovascular Research Group, New Haven, CT, USA
Angiographic Core Lab:	Yale Cardiovascular Research Group, New Haven, CT, USA
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1.0 INTRODUCTION AND BACKGROUND

1.1 Introduction

Merit Medical intends to conduct a prospective, multi-arm, randomized, multi-center trial (WAVE) to demonstrate the safety and effectiveness of Merit Medical's WRAPSODY Endovascular Stent Graft System. The WRAPSODY Stent Graft is a flexible, self-expanding endoprosthesis made of nitinol that is encapsulated between layers of fluoropolymer. The WRAPSODY Stent Graft is indicated for use in hemodialysis patients for the treatment of stenosis or occlusion within the dialysis access outflow circuit, including stenosis or occlusion within the peripheral veins of an arteriovenous fistula (AVF) patient, and at the venous anastomosis of synthetic AV access grafts. Up to 357 subjects will be enrolled into the WAVE Study.

1.2 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[1]. 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. In 2015, the US had over 661,000 individuals diagnosed with ESRD, and of these, approximately 468,000 were receiving hemodialysis; this increased to 726,000 diagnosed cases in 2016 with 458,000 receiving hemodialysis. The average cost of dialysis was $91,000 per patient, per year, in 2016. The total cost to the US medical system for ESRD patients is approximately $42 billion annually, of which $35.4 billion is absorbed by Medicare. Approximately 1% of the Medicare population undergoes chronic dialysis, but accounts for 7% of the Medicare budget[2,3].

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%[2]. In part, this poor prognosis is due to the compounded impact of concurrent health conditions. Three-quarters of dialysis patients have five (5) or more comorbidities, and 90% have cardiovascular disease[4]. 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[1]. Thus, the ability to effectively complete hemodialysis treatments is critical to improving outcomes.

1.3 Methods of Vascular Access for Dialysis

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 Initiatives (KDOQI)[5] 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[6]. 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[7]. 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[6]. Central venous catheter access is considered the third ranked choice because of the high risk of thrombosis and infection[5]. 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[8].

1.4 Vascular Access Dysfunction

Vascular access dysfunction, defined as low or no-flow fistulae and grafts, accounts for 20% of all hospitalizations in ESRD[9]. Primary complications of AVFs are failure to mature and venous stenosis followed by thrombosis[10]. Time from surgery to use is shorter for AVGs, but rates of stenosis, thrombosis and infection are higher[11]. Stenoses for both forms of vascular access often 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[12]. 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) and/or placement of a stent graft. KDOQI guidelines recommend balloon angioplasty or surgical revision if there is a >50% decrease in luminal diameter, abnormal physiological findings, decreasing intra-anastomosis flow, and / or elevated static pressure within the anastomosis. If PTA fails, KDOQI guidelines state that stent or stent grafts may be useful[5].

1.5 Marketed Stent Grafts for Dialysis Access Maintenance

The most frequently used covered stent grafts (SG) for treating stenoses in the dialysis access and outflow circuit are the Gore VIABAHN, BD Bard FLUENCY PLUS, BD Bard FLAIR, and BD Bard COVERA. Per the 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 framework, except for 2 mm at each of the flared stent graft ends with four (4) radiopaque tantalum 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 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. COVERA is a self-expanding endoprosthesis with a nitinol framework encapsulated by ePTFE, and a carbon-impregnated inner lumen. Radiopaque ePTFE encapsulated tantalum markers are evenly distributed around the circumference of the proximal and distal ends.

1.6 Performance of Stent Grafts for AVG Outflow Circuit Revision

Three prospective, multicenter, randomized pivotal studies have demonstrated that stent grafts provided superior patency and fewer reinterventions compared to PTA in subjects with AVG vascular access. Safety events were comparable between stent grafts (SG) and PTA in all trials.

In the pivotal trial of the FLAIR® Endovascular Stent Graft (BD Bard, Franklin Lakes, NJ, USA) 190 subjects with dialysis access graft venous anastomotic stenosis were randomized at thirteen (13) sites to PTA, or placement of a FLAIR Endovascular Stent Graft. At six (6) months, treatment area primary patency (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). There was no significant difference in the incidence of

reported adverse events between the PTA and stent graft groups except for the incidence of restenosis, which was higher with balloon angioplasty at 77% vs 40% for the stent graft (p<0.001)[13].

The REVISE study was a multi-center, prospective, randomized trial in which 293 subjects with in-stent restenosis of the AVG venous anastomosis were randomized to receive PTA or placement of the GORE® VIABAHN® Endoprosthesis with Heparin Bioactive Surface (Gore, Flagstaff, AZ, USA). REVISE was the first prospective study of stent grafts for failing AVGs that included subjects with either stenotic or thrombotic hemodialysis access. Subjects treated with a VIABAHN device had statistically significantly better rates of TLPP at six (6) months when compared to PTA (51.6% vs 34.2%, p=.006), as well as better primary patency of the entire arteriovenous access circuit at six (6) months (41.5% vs 28.4%, p=.035). There were no differences in the proportion of subjects who experienced any device, procedure, or treatment site-related adverse event, either major or minor, between the two treatment groups (p = .98). Two major adverse events occurred through 30 days in subjects treated with angioplasty[14].

The RESCUE study was a prospective, multicenter, randomized, concurrently controlled clinical trial conducted at 23 sites and designed to assess the performance of the FLUENCY® PLUS Endovascular Stent Graft (BD Bard, Franklin Lakes, NJ, USA) compared to PTA in the treatment of in-stent restenosis in the outflow circuit of subjects (N = 275) receiving hemodialysis with an AV graft or native arteriovenous fistula[15]. For the subset of subjects with AVG access (N = 61 SG, 65 PTA), the six (6) month primary patency of the target lesion was 57.4% for those who received the stent graft compared to 7.7% for the PTA cohort (p<.001), and ACPP at the same time point was also significantly higher among those with SG than PTA (20.0% vs 1.6%, p < .01). For patients with AVG access freedom from major adverse events was 100% in the SG group and 98.4% in the PTA group (p value not given). 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[15].

A fourth pivotal study, the AVeVA trial, was prospective and multicenter, but compared outcomes to a performance goal (PG) rather than having an active control. The BD Bard COVERA vascular covered stent was evaluated at 14 sites and included 110 subjects. Target lesion primary patency at six (6) months was 71% and ACPP was 40%. The proportion of subjects free from primary safety events through 30 days was 96.4%, which met the performance goal of 88% (p value=0.0021)[16].

1.7 Performance of Stent Grafts and Drug-Coated Balloons for AVF Outflow Circuit Revision

Three recent prospective, multicenter, randomized pivotal trials, one for a stent graft and two for drug-coated balloons, have been conducted to evaluate the performance for treatment of stenoses in the peripheral venous outflow of subjects with native AVFs compared to PTA. In addition, the pivotal RESCUE study[15] for FLUENCY PLUS summarized previously, included patients with AVF and treated for in-stent restenosis.

The AVeNEW pivotal study for the BD Bard COVERA stent graft included 280 subjects at 24 sites randomized to PTA or stent graft. At six (6) months, the TLPP was 78.7% for the Covera stent graft vs 47.9% for PTA (p<.001). Evaluation of the primary safety endpoint demonstrated statistically significant non-inferiority of subjects randomized to the covered stent compared to subjects treated with PTA only, at 95.0% vs 96.4% respectively (p =.0022) (product IFU).

The only other outcome data from a pivotal study for stent grafts in the treatment of outflow stenoses in patients with AVFs comes from a subset analysis in the RESCUE study for FLUENCY PLUS, summarized earlier[15]. This clinical trial included 149 patients with AVF who were treated for in-stent restenosis. Six (6) month TLPP for the Fluency Plus compared to PTA was 74.5% vs 16.2% (p<.001).

More recently, drug-coated balloons (DCB) have been studied for use in PTA, after successful pre-dilatation, for treatment of stenotic lesions of dysfunctional AVFs. The BD Bard Lutonix drug-coated

balloon catheter consists of an over-the-wire catheter with a drug-coated balloon fixed at the distal tip. The balloon is coated with a specialized formulation of paclitaxel. In the pivotal study, 285 subjects at 23 sites were randomized to receive either the Lutonix DCB or uncoated, standard PTA. Statistical significance was not met for TLPP at 71.4% vs 63.0% for the DCB and plain PTA respectively (p=.0562). The primary safety endpoint, defined as freedom from localized or systemic serious adverse events through 30 days that reasonably suggest the involvement of the AV access circuit, was statistically significant for non-inferiority (p=.0019) at 94.9% for Lutonix vs 95.5% for PTA (product IFU).

The initial results from the Medtronic IN.PACT AV drug-coated balloon pivotal trial were presented at the 2019 CIRSE conference in Barcelona. Three hundred thirty (330) subjects from 29 sites were randomized for treatment by either DCB or standard PTA. The six (6) month TLPP was 86.1% for the DCB vs 68.9% for PTA (p<.001). Safety, defined as the serious adverse event rate involving the AV access circuit through 30 days was 95.8% vs 95.6%, and was statistically significant for non-inferiority[17].

1.8 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[18]. This is thought to be due to trauma and the associated inflammatory response, resulting in the formation of thrombus, intimal hyperplasia and fibrotic response[19]. 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 collaterals which divert blood flow around the obstruction. This can result in decreased blood flow and recirculation at the access site and inadequate dialysis[20].

1.9 Treatment of Thoracic Central Vein Obstruction

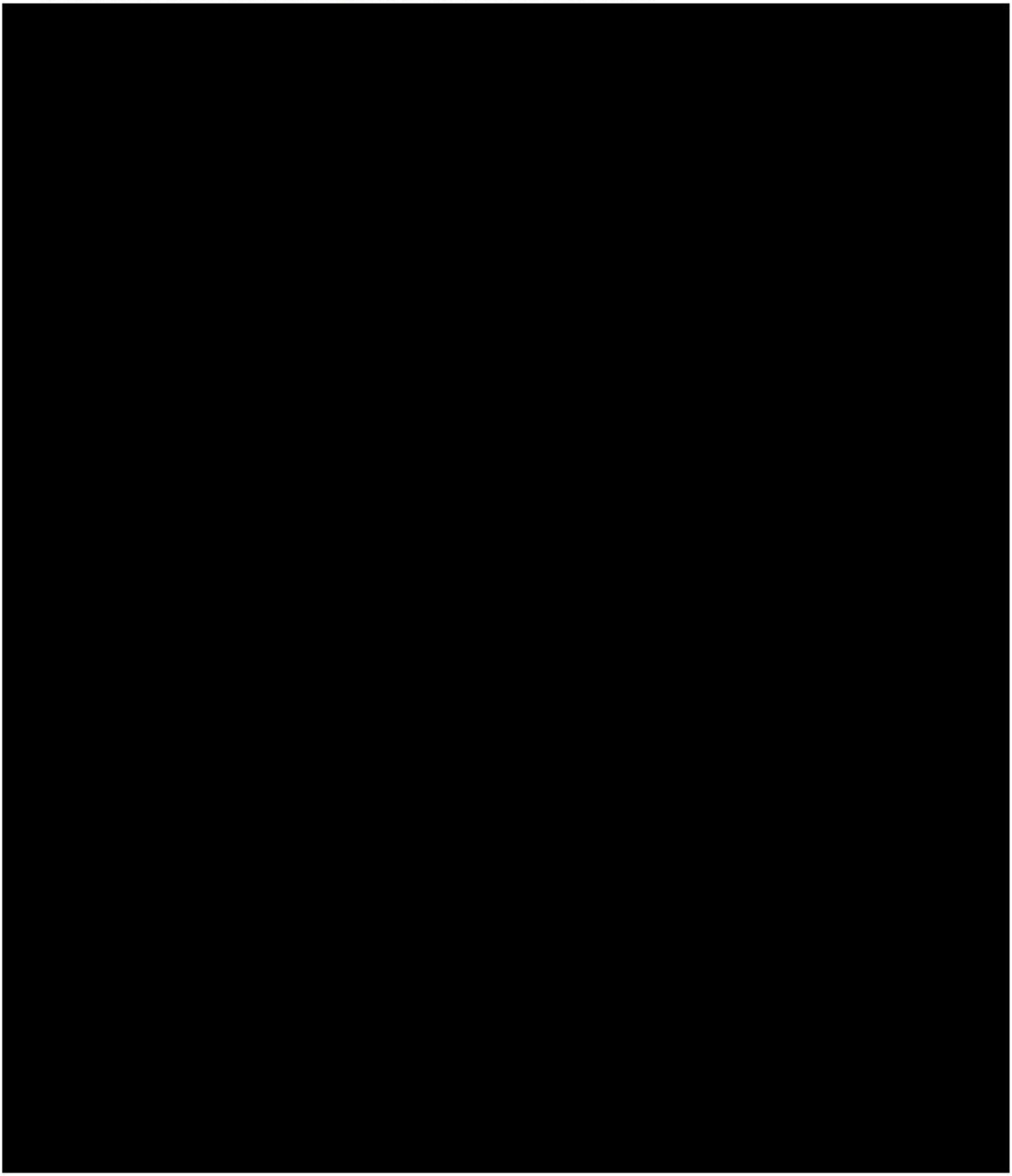
Treatment for symptomatic TCVO is PTA, but neointimal hyperplasia can progress due to damage to the vessel lumen from PTA, and stenosis has been shown to progress faster after intervention[21]. The mechanism of angioplasty involves cracking and disrupting the vessel intima, which can accelerate intimal hyperplasia. Recurrent lesions after PTA have been demonstrated to have a higher proliferative index than the primary lesion[22].

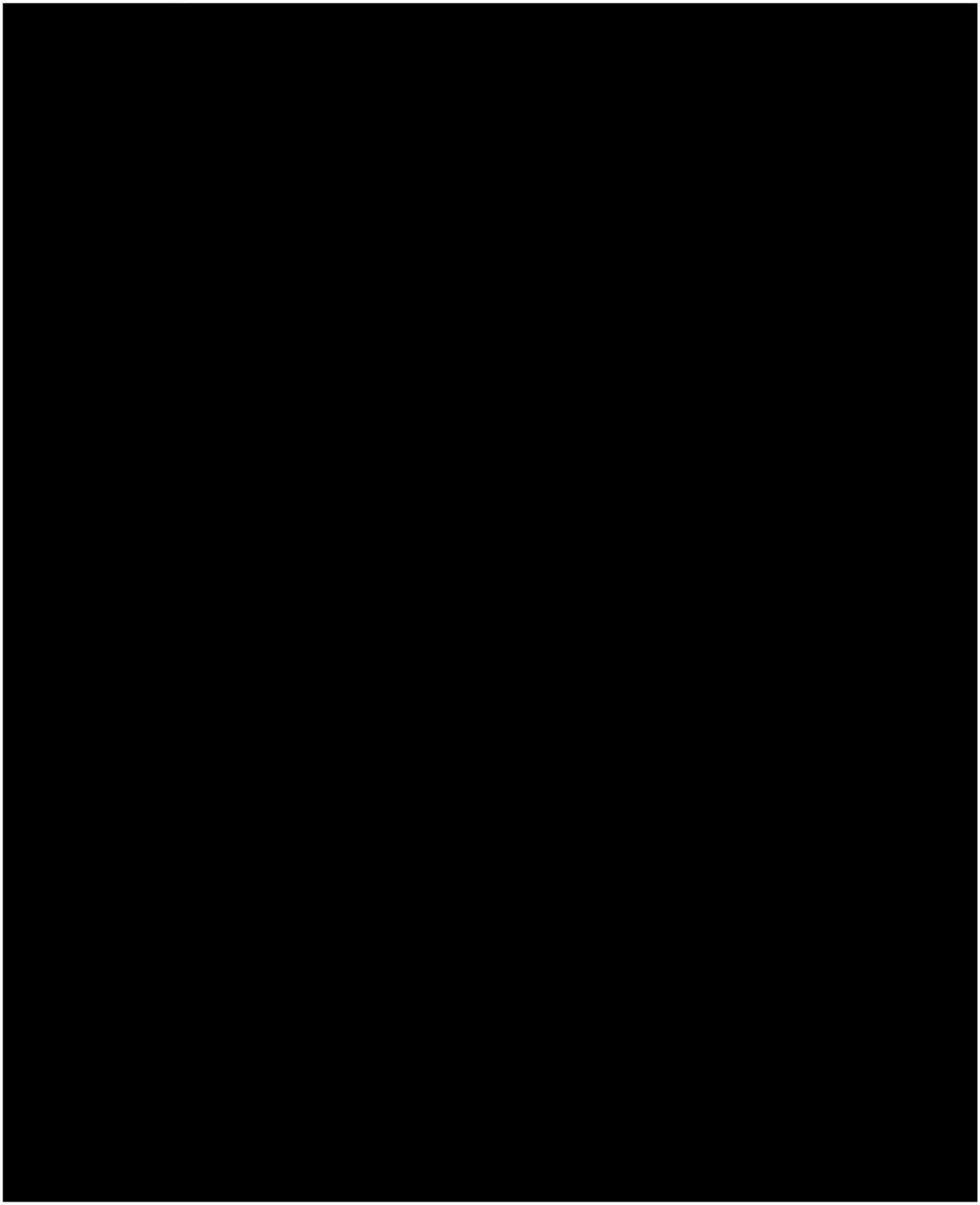
Central veins are more elastic, and therefore, more likely to recoil after PTA than the peripheral veins, with more than 50% of central lesions showing immediate recoil[23]. KDOQI guidelines suggest stent/stent graft placement as a treatment option for acute elastic recoil after PTA, when a stenosis recurs within three (3) months, in subjects at increased risk for surgery, or following vessel rupture[24].

No stent graft has been approved for treatment of thoracic central vein obstruction; consequently, there are no pivotal studies and published data on their effectiveness for this use is limited. In a cohort 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 rate at six (6) months was 81% and 67% at 12 months[25]. As further support, in the RESCUE study summarized earlier[15], a subset of 96 subjects (total study n = 275) with instent stenoses in the central veins demonstrated statistically significantly better TLPP and ACPP at six (6) months for the stent graft group compared to the PTA cohort (TLPP 63.4% vs 4.3%, p < .001; ACPP 17.5% vs 2.0, p.02). The performance of PTA is exceptionally low in these subjects, perhaps because the balloons could not be inflated sufficiently within the existing stents. It is not likely to be representative of PTA performance in native central veins; however, together, the two (2) studies above suggest that stent grafts placed for the treatment of central venous stenosis are an effective way to maintain luminal patency.

1.10 Report of Prior Investigations

The Investigator's Brochure includes a detailed description of the pre-clinical (bench and animal) testing performed with the WRAPSODY Endovascular Stent Graft System and full details on the WRAPSODY FIRST clinical study (FIRST). The Investigator's Brochure shall be provided to clinical sites if required. Summary details on the FIRST clinical investigation are provided in Section 1.11.





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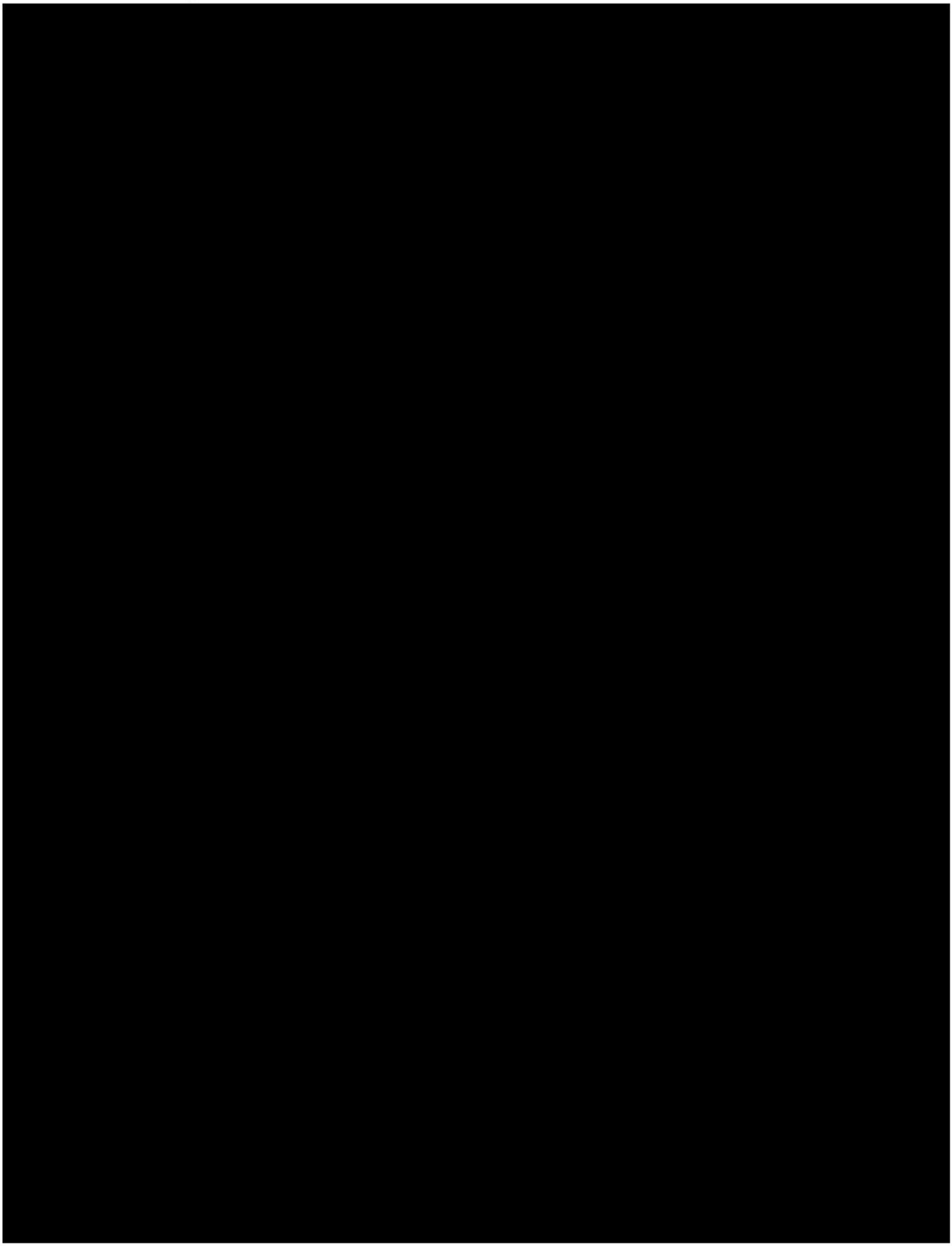

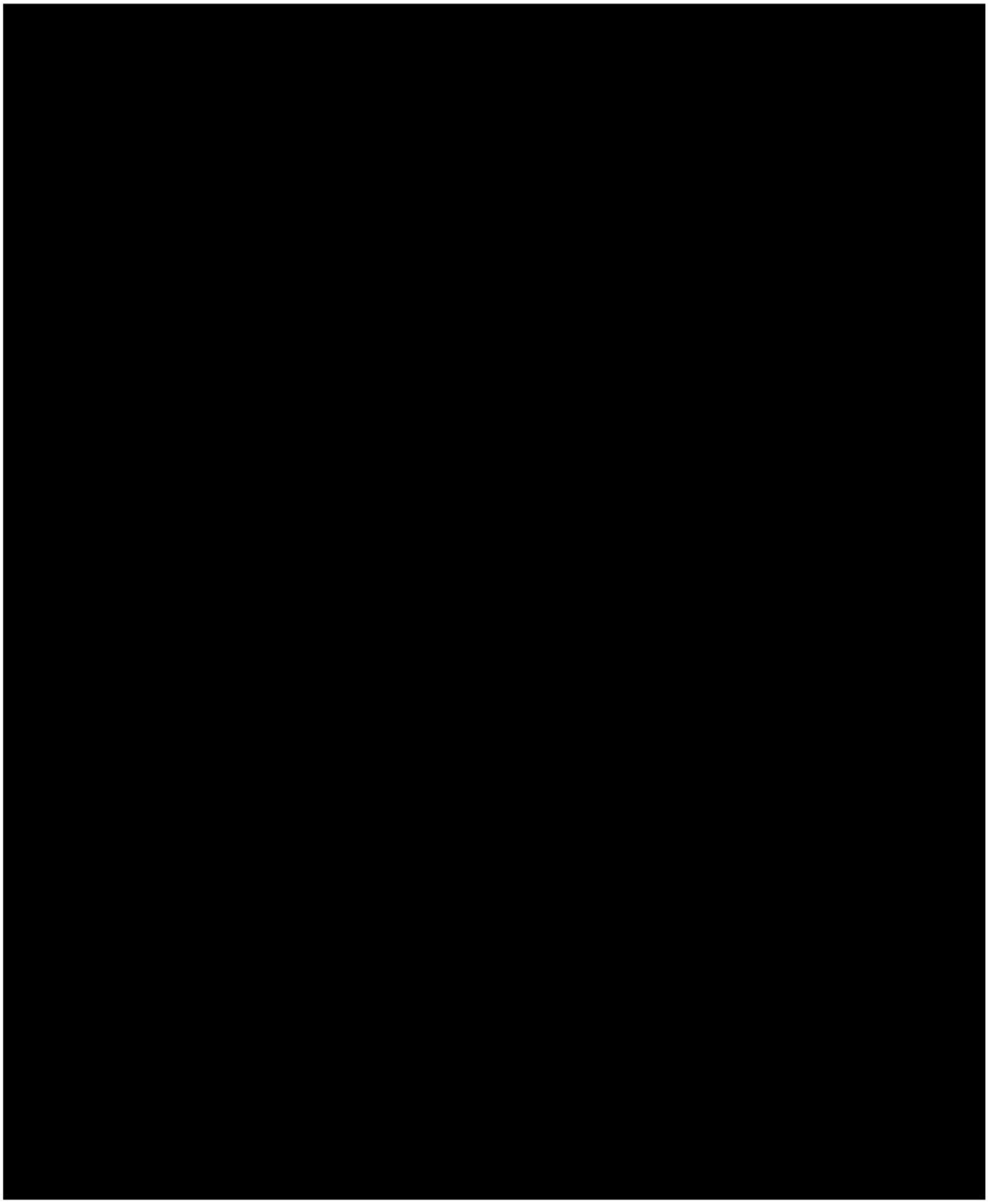

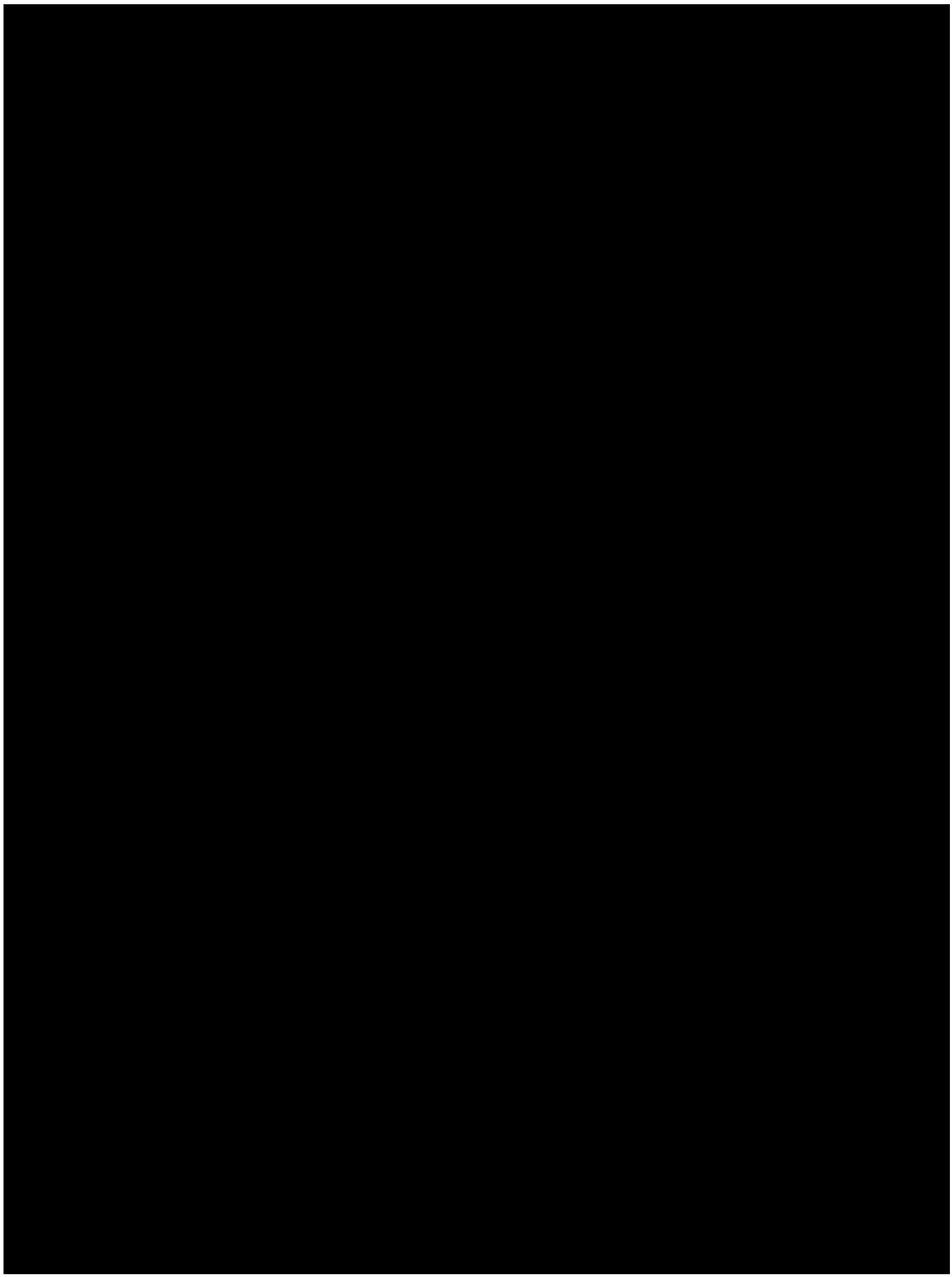

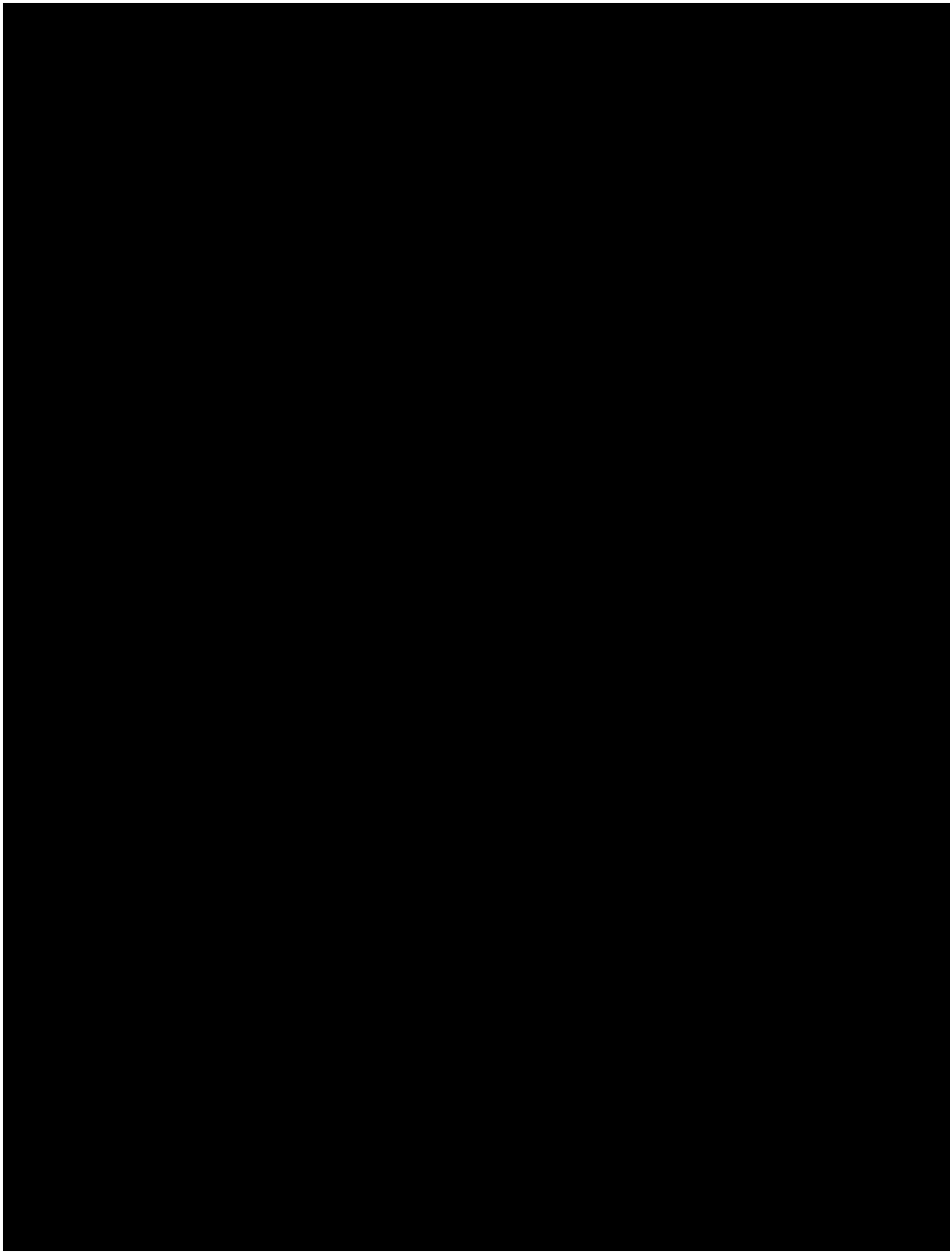

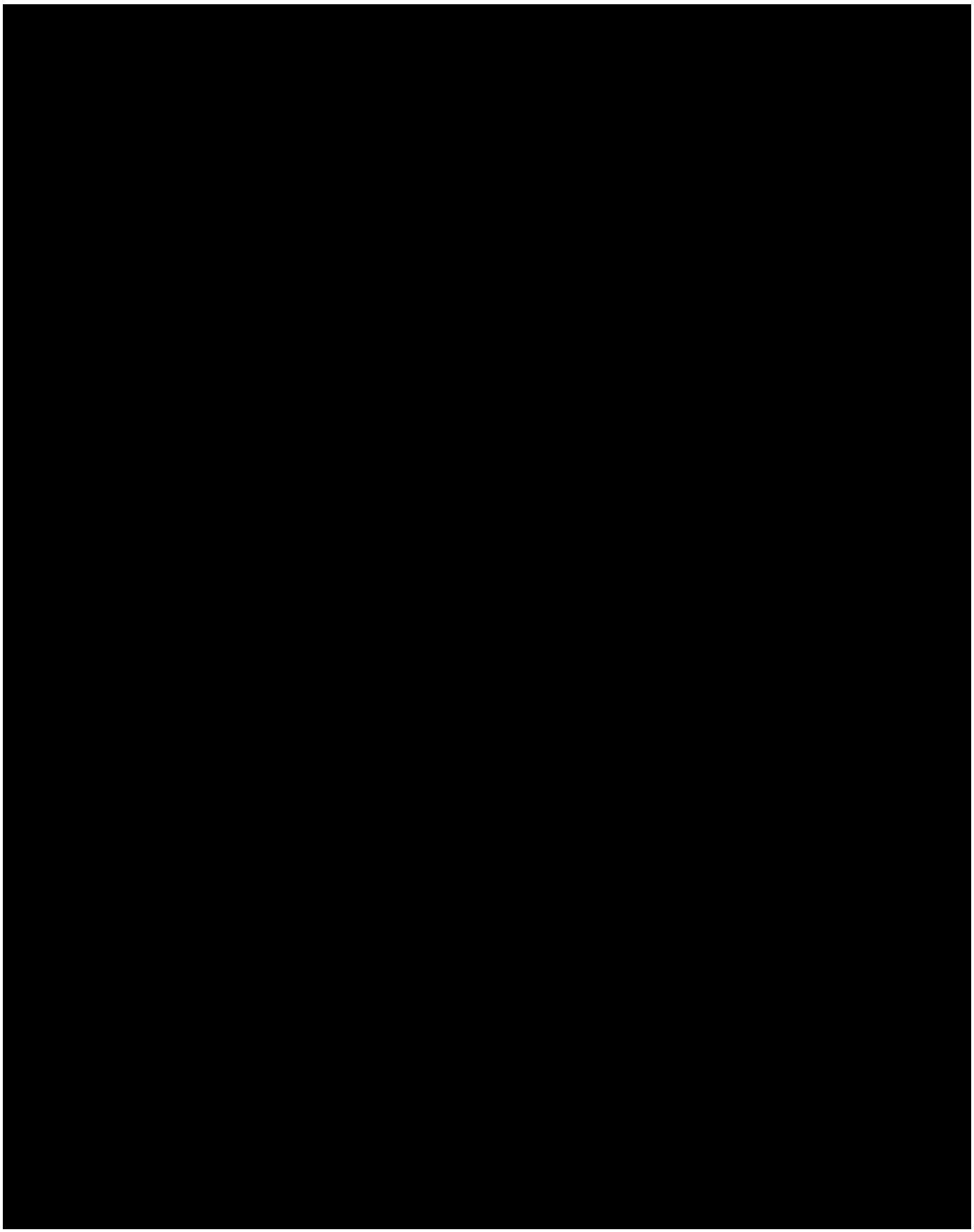

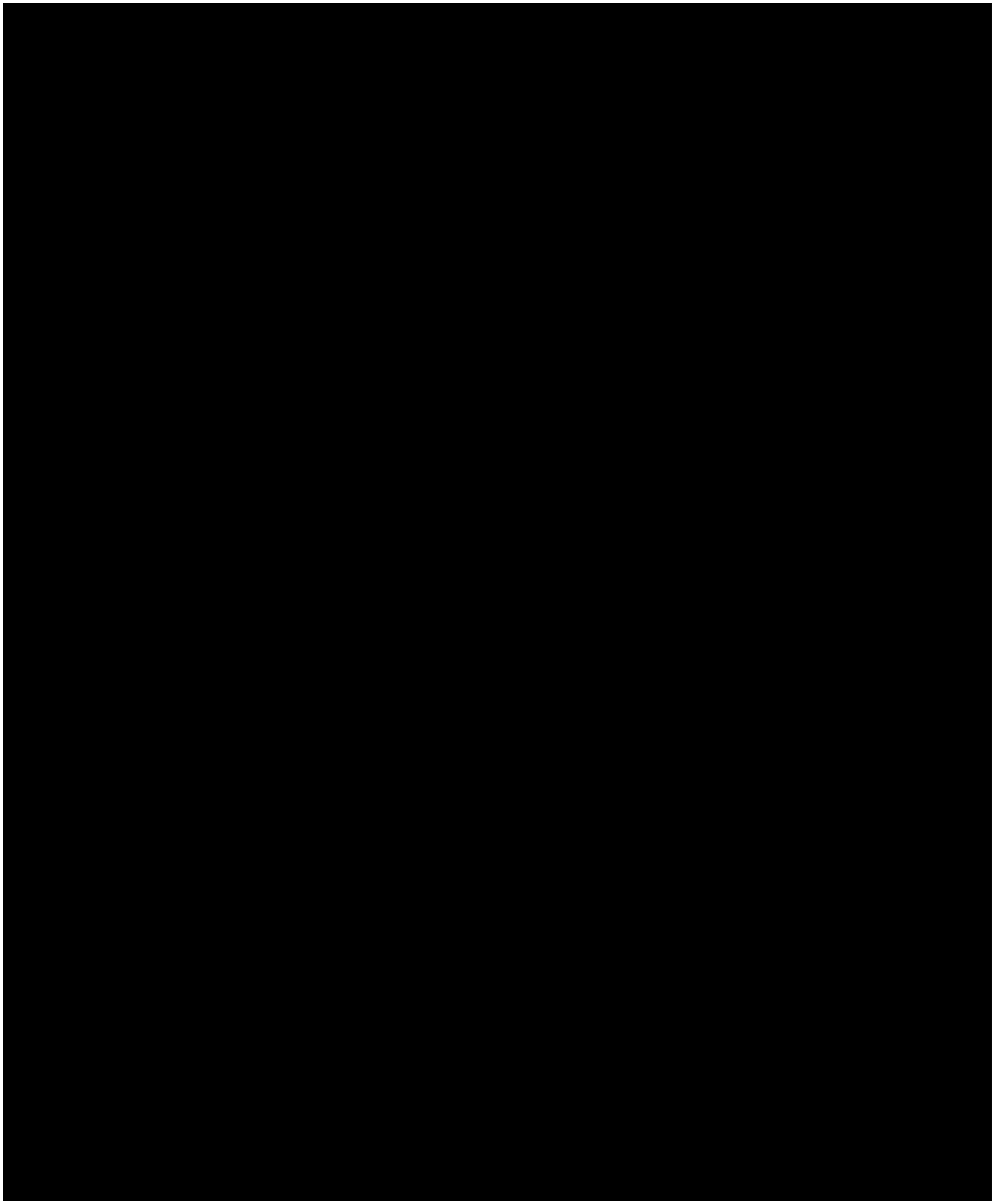

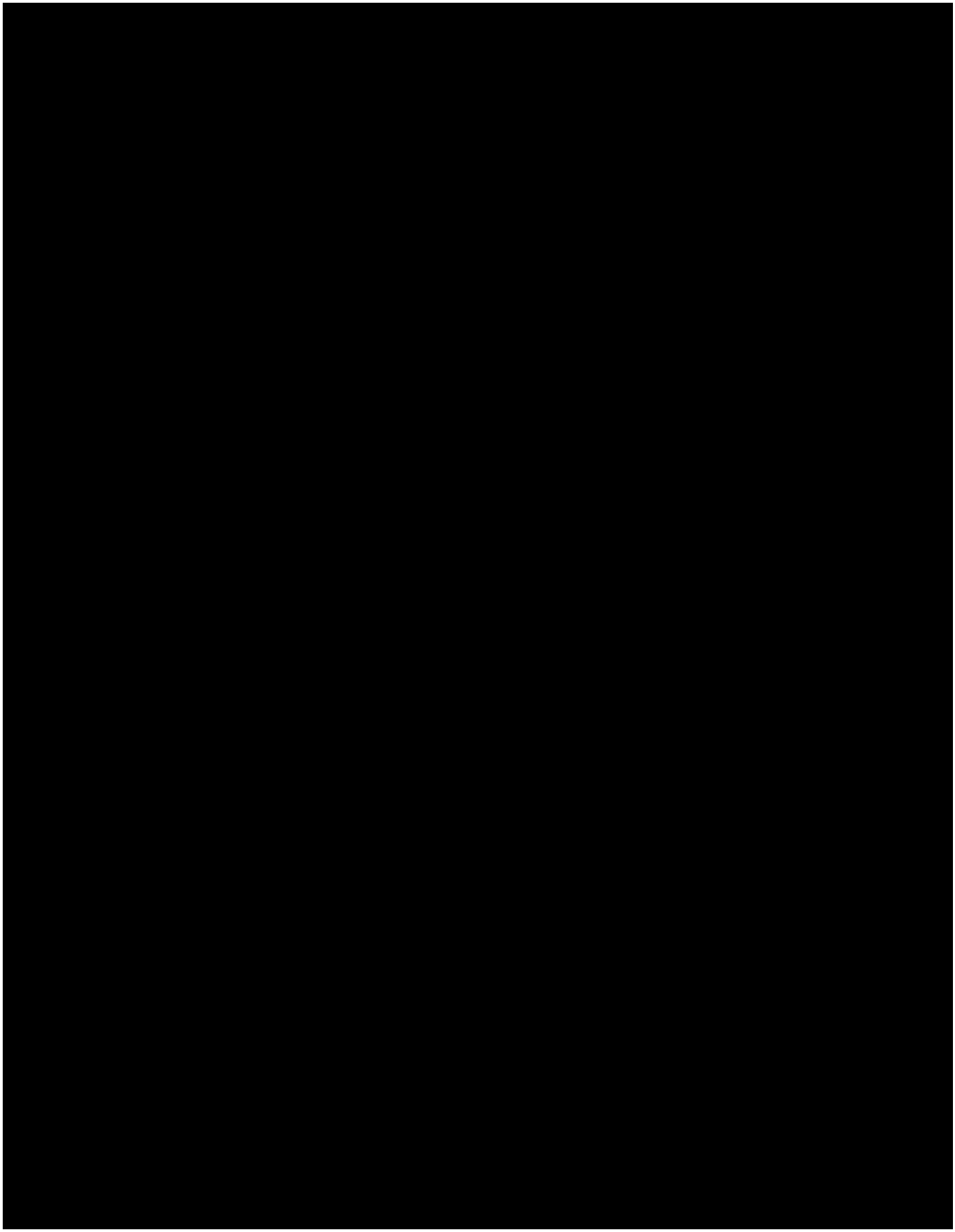

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3.0 INVESTIGATIONAL PLAN

3.1 Study Objective

To demonstrate the safety and efficacy of the Merit WRAPSODY Endovascular Stent Graft for treatment of stenosis or occlusion within the dialysis access outflow circuit, including:

a) the peripheral veins of subjects with an arteriovenous (AV) fistula (AVF Peripheral), and
b) at the venous anastomosis of subjects with a synthetic arteriovenous graft access (AVG Anastomosis).

Cohort (a) will be compared to PTA. Cohort (b) will be compared to performance goals.

3.1.1. Study Design

Prospective, Randomized (1:1), Controlled, Multi-center study for AVF Peripheral cohort in which subjects will be randomized to receive treatment with the WRAPSODY Endovascular Stent Graft System or PTA. In addition, a separate arm of the trial will include a prospective, single arm, multi-center study for the AVG anastomosis cohort in which subjects will receive treatment with the WRAPSODY Endovascular Stent Graft System.

3.1.2. Enrollment

Up to a total of 357 subjects across both cohorts allowing for a sufficient number of evaluable subjects at six (6) months. At least 60% of the subjects must come from the US for each cohort (40% OUS). No site may enroll more than 20% of the total population for a specific cohort. There are two cohorts for the trial:

1. Up to 244 AVF Peripheral Subjects (1:1 randomization, with approximately 122 in the study treatment and control groups)
2. Up to 113 AVG Anastomosis Subjects (no randomization, comparison to Performance Goal)

3.1.3. Study Population

The study comprises two (2) independent cohorts: 1) Subjects with AVF for hemodialysis who have stenosis or occlusion of the peripheral venous outflow circuit, including the cephalic arch; and 2) subjects with AVG for hemodialysis who have stenosis or occlusion at the graft-vein anastomosis or juxta-anastomosis. Juxta-anastomosis is defined as a location such that the PTA balloon or WRAPSODY Stent Graft cross the anastomosis.

3.2 Study Duration and Follow-Up

The study commenced enrollment in March 2021. Enrollment is expected to continue until December 2023, at which time it is anticipated that all cohorts would be completely enrolled. Study subjects will be required to return for clinic visits post-procedure at Day 30 (± 10 days), Month 6 (180 days ± 30 days), Month 12 (360 days ± 45 days) and Month 24 (720 days ± 75 days). Several telephone visits will be completed as well at Months 3 (90 days ± 15 days), 9 (270 days ± 30 days) and 18 (540 days ± 45 days). The 24-month visit is expected to be in the post-market surveillance phase of the study. In addition, this study shall meet the Post-Market Study requirements for CE Marking. All subjects will be followed according to the Schedule of Events in Table 9. The last follow-up visit is expected to be completed by January 2026, at the last subject's 24-month follow-up visit.

4.0 STUDY ENDPOINTS AND SUBJECT POPULATION

4.1 Primary Outcome Measures

4.1.1. Primary Safety Endpoint

The primary outcome measure for safety in the WAVE Study is proportion of subjects without any localized or systemic safety events through 30 days post-procedure that affect the access or venous outflow circuit and resulted in reintervention, hospitalization, or death (not including stenosis or thrombosis). Endovascular procedures performed to treat safety events after the index study procedure will be considered surgeries.

4.1.2. Primary Effectiveness Endpoint

The primary outcome measure for effectiveness in the WAVE Study is Target Lesion Primary Patency (TLPP) at 6 months. Target Lesion Primary Patency defined as freedom from clinically-driven target lesion revascularization (CD-TLR) or target lesion thrombosis measured through 6 months post-procedure, which is the time interval of uninterrupted patency after study procedure to the next intervention performed on the target lesion or uncorrectable target lesion occlusion.

4.2 Secondary Outcome Measures

1. Proportion of subjects with Target Lesion Primary Patency at months 12 and 24.
2. Proportion of subjects with Assisted Target Lesion Primary Patency (aTLPP) at months 6, 12 and 24 defined as time to loss of Assisted Primary Patency of the target lesion, which is the time from post-procedure until uncorrectable target lesion occlusion.
3. Proportion of subjects with Access Circuit Primary Patency (ACPP) at months 6, 12 and 24 defined as time to loss of Primary Patency of the access circuit, which is the time from post-procedure until any venous outflow circuit re-intervention, or access thrombosis or abandonment.
4. Proportion of subjects with Post-Procedure Secondary Patency at months 6, 12 and 24 defined as the interval post-procedure until access circuit abandonment.
5. Rates of procedure- and device-related adverse events involving the access circuit at index procedure, 30 days, and months 6, 12 and 24.

4.4 Eligibility Criteria

Subjects in both cohorts are required to meet ALL of the following inclusion criteria and NONE of the exclusion criteria in order to be included in this clinical trial:

4.4.1. General Inclusion Criteria

1. Subject provides written informed consent before any study-specific investigations or procedures.
2. Subject is male or female, with an age ≥ 18 years at date of enrollment.
3. Subject is willing to undergo all follow-up assessments according to the specified schedule over 24 months.
4. Subject has a life expectancy ≥ 12 months.
5. Subject is undergoing chronic hemodialysis.
6. Subject has either a mature AVF or AVG in the arm that has been created ≥30 days prior to the index procedure and has completed at least one successful dialysis session.
7. Subject has clinical and/or hemodynamic evidence of a venous outflow obstruction or AV fistula or graft dysfunction.

4.4.2. Angiographic Inclusion Criteria

[redacted]

6. Target lesion reference vessel diameter is between 5.0 mm and 14.0 mm by operator's visual estimate.

[redacted]

4.4.3. General Exclusion Criteria

[redacted]

3. Subject has a known or suspected infection of the hemodialysis access site, systemic infection and/or septicemia.

[redacted]

7. Subject has a history of unstable angina or myocardial infarction within 60 days prior to enrollment.

[redacted]

10. Subject is pregnant, breastfeeding, or intending to become pregnant within the next year.

[redacted]

4.4.4. Angiographic Exclusion Criteria

1. Target lesion is located within a stent / stent graft.

[redacted]

[redacted]

5.0 STUDY SCREENING AND ENROLLMENT

5.1 Subject Screening

All patients presenting to the institution with known arteriovenous access circuit stenosis requiring an interventional procedure shall be evaluated for eligibility and participation in the study. A member of the research team shall perform a preliminary evaluation of the potential subject's medical history and previously performed examinations to assess for initial eligibility. If the patient is willing to participate in the study, a written consent will be obtained. No study-specific requirements will be performed prior to obtaining informed consent.

5.2 Informed Consent

Written Informed Consent with the Institutional Review Board (IRB) or Ethics Committee (EC) approved consent form will be obtained for all subjects **prior** to any study-specific screening/baseline tests or procedures being performed. This does not include those procedures or tests that are obtained in the normal course of the subject's non-study related care and prior to undergoing the study procedure. The subject shall be given adequate time to read the informed consent form, have the study procedures explained, including the risks, benefits and follow-up requirements prior to signing the Informed Consent documents. All subjects providing informed consent are to receive a copy of their signed informed consent. The consent process may be obtained up to 30 days prior to index / treatment procedure.

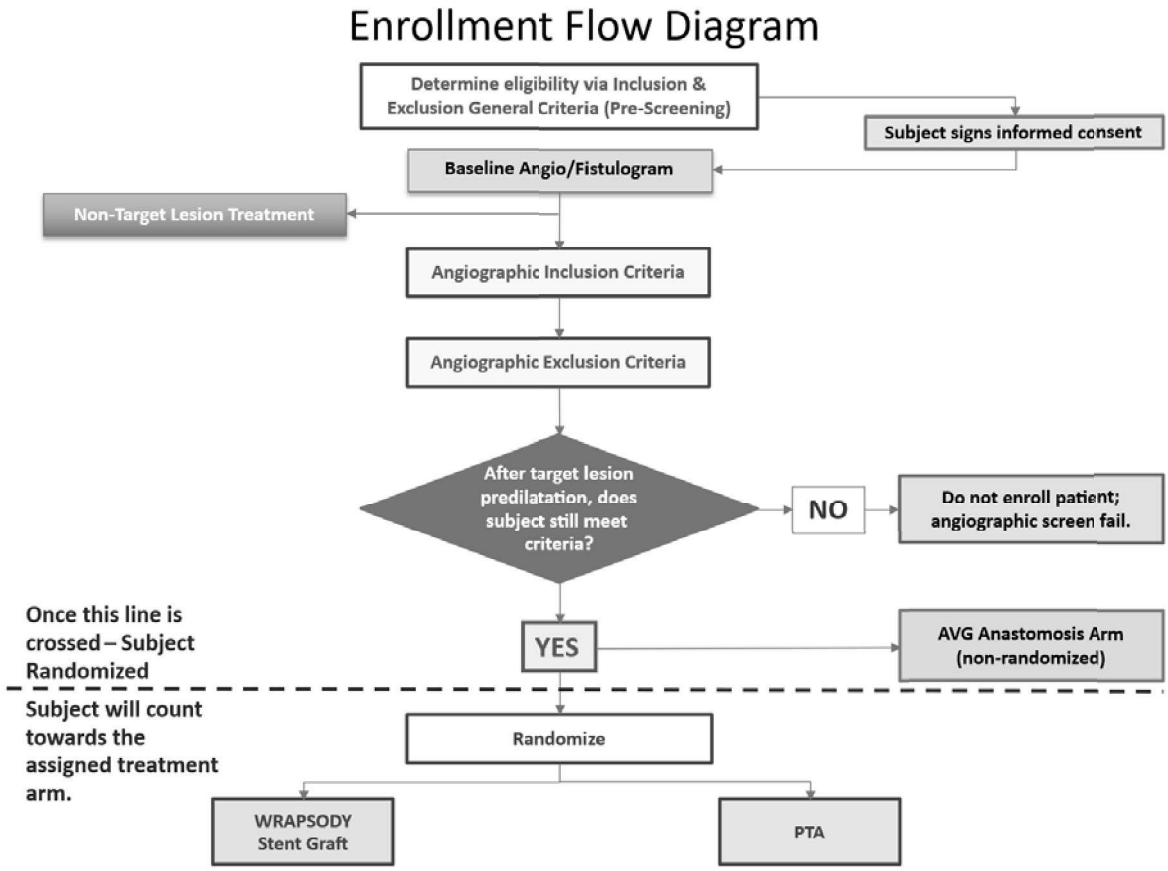
5.3 Subject Enrollment

All patients requiring an intervention due to reasons detailed in this protocol are potential study candidates and shall be screened for eligibility. Every effort will be made to ensure eligibility prior to enrollment. According to ISO 14155:2020, enrollment in the study occurs at the time of informed consent; however, for the purposes of this study, only subjects who are consented and meet all the study inclusion criteria and none of the study exclusion criteria and are treated, or treatment is attempted with the study device or randomized, will be considered enrolled into the study. Therefore, the enrollment date (Day 0) will be the date of the study index procedure; the enrollment date will not be the date of informed consent for this study. Subjects who do not meet all inclusion and exclusion criteria (e.g., including: (i) operator is unable to successfully predilate the lesion; (ii) either target reference vessel diameter or target lesion length are outside the eligible parameters, etc.) will be considered an angiographic screen failure and will not be followed in the study (no data will be collected on these subjects). Subjects in whom the WRAPSODY Endovascular Stent Graft System is inserted into the vasculature and the treatment of the target lesion is attempted, but the procedure is aborted without delivery of a stent graft, will be followed through discharge for safety only and the subject will be allowed to exit the study. No additional study required assessments shall be collected. These subjects will be replaced.

Subjects randomized to PTA who experience perforation, rupture or significant dissection requiring intervention beyond PTA (i.e., requires treatment with bare metal stent, non-study stent graft, drug-eluting balloon) will followed through discharge for safety only and the subject will be allowed to exit the study. No additional study required assessments shall be collected as the subject would not be able to be assessed for study endpoints. These subjects will be replaced.

Subjects who are enrolled and treated, but who are later discovered to not meet all of the study criteria will remain in the study and complete all of the study testing and follow-up requirements. A Protocol Deviation will be completed for study subjects who are found to be ineligible after enrollment.

Refer to Figure 6: Enrollment Diagram:



5.4 Subject Withdrawal

Subjects may withdraw at any time from the clinical trial without jeopardy or prejudice. If a subject prematurely terminates from the study, the reason for study termination will be recorded and the results will be tabulated by number and percent for each category. If termination is a result of an adverse event or death, an Adverse Event Form will also be completed. Subjects who withdraw consent after treatment will have their data evaluated until the time of their withdrawal.

The Investigator should follow all unresolved SAEs until the events are resolved, the subject is lost to follow-up, the subject has withdrawn consent, the subject completes the study, or the adverse event is otherwise explained.

All reasonable efforts will be made to obtain complete data for all subjects; however, missing observations will occur due to lost to follow-up, withdrawal, or non-adherence with required assessments. Three (3) attempts shall be made to contact subjects who do not return for study follow-up visits. The final attempt shall include a certified letter to the subject regarding study participation. If these subjects cannot be located, they will be considered lost to follow-up. If they are contacted but refuse to return for visits, they

will be considered withdrawals. If they actively request to withdraw from the study, they will be considered withdrawals. Subjects shall be encouraged to complete a final study exit visit at the time of withdrawal to assess for safety. Data collected up to the time of loss to follow-up or withdrawal will be maintained in the study database and used for analysis purposes, as appropriate. These subjects will not be replaced.

Subjects should be withdrawn from the study by the Investigator if any of the following occur as these additional treatments prevent further analysis of patency related endpoints:

- Subject proceeds to renal transplant
- Device is explanted
- Access is abandoned

Investigator may also withdraw subjects from the study for reasons other than above, where they judge this is in the subject's best interest. Data collected up to the time subject is withdrawn from the study will be maintained in the study database and used for analysis purposes, as appropriate. These subjects will not be replaced.

5.5 Anticipated Total Enrollment

Up to a total of 357 subjects shall be enrolled into the WAVE Study across both cohorts. Up to 40% of the total enrollment for each cohort may be enrolled outside of the US. No site may enroll more than 20% of the total enrollment per cohort.

6.0 STUDY PROCEDURES

6.1 Visit Schedule

Study participation will last for a total of 24 months (± 75 days). Traditional visit windows are being expanded to allow for potential impacts due to COVID-19. Subjects will be enrolled in the acute phase of the study. Study clinic visits and data collection during the acute phase will be completed at index procedure, 30 days (± 10 days), 6 months (180 days ± 30 days) and 12 months (360 days ± 45 days); telephone visits will be completed at 3 months (90 days ± 15 days), 9 months (270 days ± 30 days) and 18 months (540 days ± 45 days). A final post-market surveillance follow-up visit will be performed at 24 months (720 days ± 75 days).

A summary schedule of the required study tests and evaluations is in **Table 9**:

[redacted]

6.2 Baseline

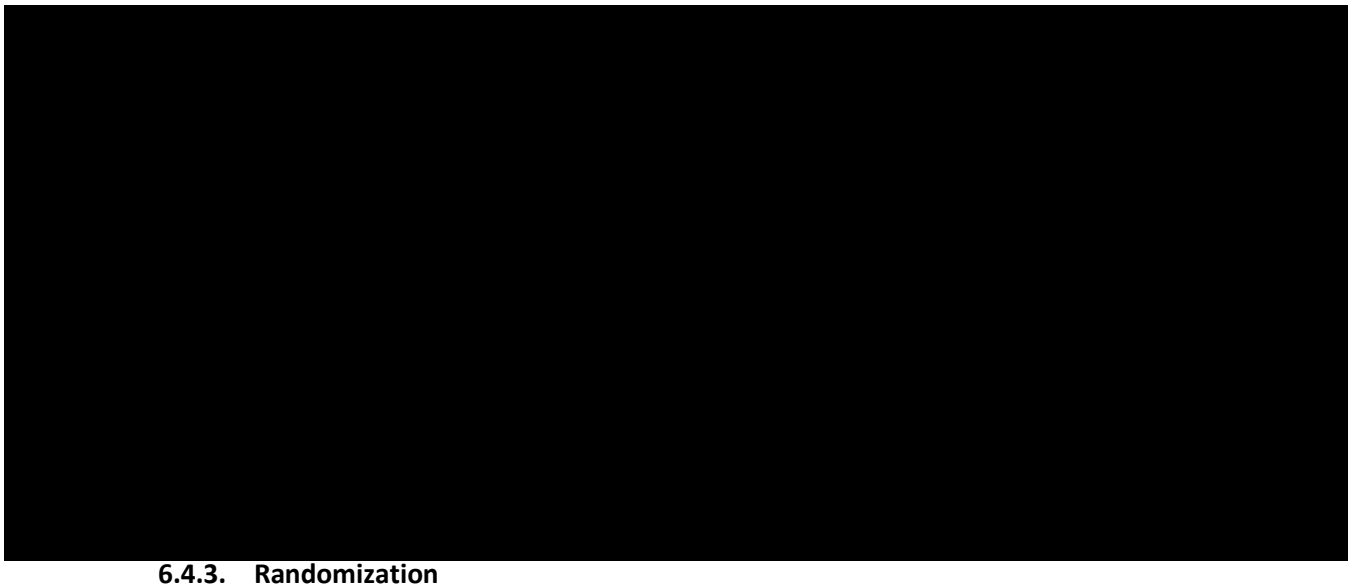
The following examinations and tests will be performed. For those study procedures that are not considered standard of care (performed only for study participation), they will be performed after the subject signs the informed consent form in order to meet **all** inclusion and **no** exclusion criteria. These examinations and tests will be used both to screen eligible subjects and provide baseline information for those subjects that meet study eligibility criteria.

All tests must be completed within the 30 days prior to undergoing the index / study procedure, except for the pregnancy test, which must be completed within 14 days of the procedure (if applicable).

- Demographic information and medical history including, but not limited to, risk factors and hemodialysis and dialysis access history:
    - Type, location and date of all previous venous outflow circuit intervention(s)
    - Prior dialysis access type(s) and location(s)
        - Location of current dialysis access, including date AVF or AVG was first used for dialysis
- Targeted physical examination, including but not limited to:
    - Height and weight
    - Vascular access circuit / fistula assessment including, but not limited to:
        - Presence / absence of steal syndrome
        - Presence / absence of thrill
        - Presence / absence of bruit
        - Presence / absence of infection
- Laboratory Assessments:
    - Urine or serum pregnancy test if female of child-bearing potential (within **14** days of procedure). NOTE: Please review your institutions standard for women of childbearing potential.

6.3 Medications

Effective anticoagulation therapy should be maintained throughout the procedure with heparin (per hospital or institutional standards) or a clinically acceptable alternative of the treating physician's choice. There is no current requirement for dual antiplatelet therapy for this therapeutic area and treatment modalities. Treatment with antiplatelet and/or anticoagulation post-procedure is per investigator discretion for the best interest and safety of the subject.



6.4.3. Randomization

Randomization will be used to reduce potential bias during data collection and evaluation of clinical endpoints in the AVF Peripheral cohort. Randomization schedules will be generated using block randomization that will control the balance of treatment groups within each site and across the study. It is not possible for treating physicians to be blinded to the treatment group. Subjects who receive a Merit WRAPSODY Stent Graft must receive a device information card to provide to health care givers in the event they undergo an MRI, so subjects cannot be blinded.

AVF Peripheral subjects will be randomized 1:1 to receive either the Merit WRAPSODY Stent Graft (SG) or PTA. AVG Anastomosis subjects will not be randomized. Once baseline angiography confirms eligibility, including confirmation of reference vessel diameter (RVD), lesion length, full expansion of the predilatation balloon, the patient is eligible to be randomized or enrolled in the AVF Anastomosis cohort.

Subjects randomized to the PTA arm (control) will undergo standard percutaneous balloon angioplasty. Subjects randomized to receive treatment with the Merit WRAPSODY Stent Graft after predilatation will undergo stent graft placement as outlined in Section 6.4.4. Only the target lesion will be treated with the WRAPSODY stent graft.

Note: Subjects in the AVG Anastomosis cohort will all receive treatment with the Merit WRAPSODY Stent Graft as this cohort is non-randomized.

6.4.3.1. Randomization Errors

Randomization was built in the EDC system with multiple safeguards to prevent randomization, including but not limited to, verification of treatment cohort (e.g., AVF, AVG anastomosis) prior to proceeding with randomization. In the event that a randomization error occurs, the subject will continue to be considered enrolled.

6.4.4. Implant Procedure

Refer to the Instructions for Use (IFU) for a description of the implant procedure. Additional data captured during the procedure include, but may not be limited to:

- Baseline angiographic criteria assessment

- Location of stent graft placement using angiographic radiopaque ruler during index procedure
- Assessment of post-stent graft implantation lumen patency via angiogram at the conclusion of the index procedure (percent angiographic stenosis and angiographic patency of ≤30% residual stenosis at target site)
- Evaluation of total procedure time
- Determination of blood loss and replacement
- Identification of technical difficulties
- Adverse event observation, evaluation, and treatment
- At the conclusion of the index procedure, a final angiographic cine showing the entire vascular access circuit is required (per Angiographic Core Lab Protocol) to assess for procedural- and/or device-related complications.

[redacted]

6.5 Day 30 Follow-Up – Clinic Visit

The following evaluations will be scheduled for **Day 30** (± 10 days) post procedure:

- Targeted physical examination, including but not limited to:
    - Physical assessment of fistula / access circuit including, but not limited to:
        - Presence / absence of steal syndrome

        - Presence / absence of thrill
        - Presence / absence of bruit
        - Presence / absence of infection
    - Dialysis status including, but not limited to:
        - Access blood flow
        - Arterial and venous pressures
        - Ipsilateral extremity edema
        - Clot aspiration during dialysis
        - Prolonged bleeding from puncture site
        - Dialysis flow rates
- Medication assessment (antiplatelets, anticoagulation medications)
- Adverse event assessment, including interventions on the venous outflow circuit

Note: In situations where investigator for the site does not oversee the subject's hemodialysis, measures shall be taken to obtain the necessary information for the applicable visits by their hemodialysis provider.

6.6 Month 3 Follow-Up – Telephone Visit

The following evaluations will be scheduled for **Month 3** (90 days ± 15 days) post procedure:

- Medication assessment (antiplatelets, anticoagulation medications)
- Adverse assessment, including interventions on the venous outflow circuit

6.7 Month 6 Follow-Up – Clinic Visit

The following evaluations will be scheduled for **Month 6** (180 days ± 30 days) post procedure:

- Targeted physical examination, including but not limited to:
    - Physical assessment of fistula / access circuit including, but not limited to:
        - Presence / absence of steal syndrome
        - Presence / absence of thrill
        - Presence / absence of bruit
        - Presence / absence of infection
    - Dialysis status including, but not limited to:
        - Access blood flow
        - Arterial and venous pressures
        - Ipsilateral extremity edema
        - Clot aspiration during dialysis
        - Prolonged bleeding from puncture site
        - Dialysis flow rates
- Medication assessment (antiplatelets, anticoagulation medications)
- Adverse assessment, including interventions on the venous outflow circuit

Note: In situations where investigator for the site does not oversee the subject's hemodialysis, measures shall be taken to obtain the necessary information for the applicable visits by their hemodialysis provider.

6.8 Month 9 Follow-Up – Telephone Visit

The following evaluations will be scheduled for **Month 9** (270 days ± 30 days) post procedure:

- Medication assessment (antiplatelets, anticoagulation medications)
- Adverse assessment, including interventions on the venous outflow circuit

6.9 Month 12 Follow-Up – Clinic Visit

The following evaluations will be scheduled for **Month 12** (360 days ± 45 days) post procedure:

- Targeted physical examination, including but not limited to:
  - Physical assessment of fistula / access circuit including but not limited to:
    - Presence / absence of steal syndrome
    - Presence / absence of thrill
    - Presence / absence of bruit
    - Presence / absence of infection
  - Dialysis status including, but not limited to:
    - Access blood flow
    - Arterial and venous pressures
    - Ipsilateral extremity edema
    - Clot aspiration during dialysis
    - Prolonged bleeding from puncture site
    - Dialysis flow rates
- Medication assessment (antiplatelets, anticoagulation medications)
- Adverse assessment, including interventions on the venous outflow circuit

Note: In situations where investigator for the site does not oversee the subject's hemodialysis, measures shall be taken to obtain the necessary information for the applicable visits by their hemodialysis provider.

6.10 Month 18 Follow-Up – Telephone Visit

The following evaluations will be scheduled for **Month 18** (540 days ± 45 days) post procedure:

- Medication assessment (antiplatelets, anticoagulation medications)
- Adverse assessment, including interventions on the venous outflow circuit

6.11 Month 24 Follow-Up – Clinic Visit (Post-Market Surveillance Phase of the Study)

The following evaluations will be scheduled for **Month 24** (720 days ± 75 days) post procedure:

- Targeted physical examination, including but not limited to:
  - Physical assessment of fistula / access circuit including, but not limited to:
    - Presence / absence of steal syndrome
    - Presence / absence of thrill
    - Presence / absence of bruit
    - Presence / absence of infection
  - Dialysis status including, but not limited to:
    - Access blood flow
    - Arterial and venous pressures
    - Ipsilateral extremity edema
    - Clot aspiration during dialysis
    - Prolonged bleeding from puncture site
    - Dialysis flow rates
- Medication assessment (antiplatelets, anticoagulation medications)
- Adverse assessment, including interventions on the venous outflow circuit

Note: In situations where investigator for the site does not oversee the subject's hemodialysis, measures shall be taken to obtain the necessary information for the applicable visits by their hemodialysis provider.

6.13 Vascular Access Interventions

In the event that a subject requires an intervention to either the target lesion or elsewhere within the access circuit, the investigational site should provide sufficient documentation regarding the clinical and physiological signs and symptoms requiring the need for interventions, including but not limited to, status of thrill, bruit, infection, decreased dialysis pump flows, limitations to effective dialysis treatment, increased venous pressures, etc. Reinterventions to the target lesion and elsewhere within the access circuit shall follow the KDOQI Guidelines (2019). Such reinterventions shall only be performed on those subjects that have a clinically relevant lesion requiring intervention for resolution of clinical symptomatology. Reinterventions on lesions that are not clinically symptomatic should be avoided until such a time that the lesion is clinically symptomatic.

Angiography should only be performed if reintervention is deemed necessary from clinical and physiological symptoms. All procedural angiograms should be recorded at the same angles and views as taken during the index procedure, where possible. All images should be taken per core laboratory manual.

7.0 ADVERSE EVENTS

All adverse events will be recorded and documented throughout the 12-month visit. Following the 12-month visit, only serious adverse events (SAE) and unanticipated adverse device effects (UADE) will be recorded and documented through the 24-month follow-up visit.

The Investigator at each participating center is ultimately responsible for reporting adverse events to the Sponsor. The adverse event electronic case report form (eCRF) provides a venue for the Investigator to record any adverse event data. The Investigator should follow all unresolved serious adverse events until the events are resolved, the subject is lost to follow-up, the subject has withdrawn consent, the subject completes the study, or the adverse event is otherwise explained.

The Sponsor shall review all adverse events for their relationship to the study device(s) and/or procedures and comparative anticipated safety event rates. The Sponsor will conduct evaluations of any unanticipated device-related event per standard operating procedures.

7.1 Adverse Event

For the purposes of this study, an adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in subjects, whether or not related to the investigational device or procedure. In addition, the definition of AE applies to any event with an onset during enrollment / index procedure or to any underlying diseases, present at baseline, that exacerbate in severity post study procedure. Therefore, an underlying disease that was present at the time of enrollment is not reported as an AE, but any increase in the severity of the underlying disease is to be reported as an AE. This definition includes events occurring during the follow-up period.

All reported AEs through 12 months must be recorded in the electronic database. Following the 12-month visit, only SAEs and UADEs will be recorded in the electronic database. A description of the event, including the start date, resolution date (or final outcome assessment date), action taken, and the outcome should be provided, along with the Investigator's assessment of the severity, seriousness, the relationship between the AE, the study device and the study procedure.

The following definitions for rating severity of adverse events will be used:

Mild: Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would generally not require medication or a medical evaluation; signs or symptoms are transient (e.g., headache treated with acetaminophen, common cold, etc. would be considered mild).

Moderate: Interferes with the subject's usual activity and/or requires symptomatic treatment.

Severe: Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

Adverse Device Effect (ADE) / Device-Related Adverse Event*:* an adverse device effect (or device-related adverse event) is defined as any untoward adverse effect when, in the judgment of the Investigator, the clinical event has a reasonable time sequence associated with use of the assigned device (e.g., WRAPSODY Endovascular Stent Graft System or standard PTA) and is unlikely to be attributed to concurrent disease or other procedures or medications. It is reasonable to believe that the device directly caused or contributed to the adverse event. A Serious Adverse Device Effect (SADE) is an event that also meets at least one of the seriousness definitions as listed in Section 7.2.

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

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

Procedure-Related Adverse Event*:* an adverse event is considered to be procedure-related when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with the assigned study procedure and is not specific to the assigned device (e.g., WRAPSODY Endovascular Stent Graft System or standard PTA) used. Other products, surgical techniques, or medications required specifically for the procedure are likely to have contributed to the occurrence of the event.

Concomitant Medication-Related Adverse Event: an adverse event is considered to be concomitant medication-related when, in the judgment of the Investigator, it is reasonable to believe that the event is

associated with concomitant medications used in conjunction with the assigned device and is not otherwise specific to the assigned device (e.g., bleeding associated with anticoagulation medication).

Pre-Existing Condition-Related Adverse Event: an adverse event is considered to be related to a pre-existing condition when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with the subject's pre-existing condition and is not specific to the device or procedure. Pre-existing conditions that are aggravated or become more severe during or after the procedure should be evaluated on a case-by-case basis to determine if the event may be more appropriately classified as device-related or procedure-related.

Unanticipated Adverse Device Effect (UADE): 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.

Merit Medical or its designee, in cooperation with the Investigator, will assess all adverse events considered to be device-related for potential reportability to the FDA and other regulatory authorities (as applicable) as an UADE.

Events Not Considered Adverse Events

For purposes of this study, the following events are not considered adverse events, because they are normally expected to occur in conjunction with endovascular procedures / post-procedure, or are associated with customary, standard care of subjects undergoing these procedures:

- Early post-operative pain (within 24 hours post-index procedure) at the access site and/or related to position on procedure table
- Post-anesthesia/conscious sedation emesis, nausea, or headache (within 24 hours post-index procedure)
- Chest pain without associated ECG changes
- Hematocrit decrease from baseline not associated with hemodynamic changes, remaining above 26% and not requiring transfusion
- Electrolyte imbalance without clinical sequelae following endovascular procedure, even if requiring correction
- Low grade temperature increase (≤38.3 °C/≤101 °F)
- Sinus bradycardia/tachycardia that does not require treatment or intervention
- Systolic or diastolic blood pressure changes that do not require treatment or intervention
- Minor dissections (Grade B or less) secondary to predilatation angioplasty
- Any pre-planned surgical procedures

This listing of events is intended to provide guidance to the investigational sites for purposes of adverse event reporting. The Investigator at the investigational site should utilize his/her own clinical judgment in evaluating adverse experiences and may decide that the above events should be reported as adverse events.

7.2 Serious Adverse Events

A serious adverse event is defined as an adverse event that:

- Led to death,
- Led to a 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 a body function, or

- in-patient hospitalization or prolongation of existing hospitalization
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function, or

- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

All Serious Adverse Events will be reported throughout the study.

NOTE: Planned hospitalization for a pre-existing condition or elective cosmetic procedures, or a procedure required by the investigational plan without serious deterioration in health, is not considered a serious adverse event.

All SAEs must be reported to the IRB / EC in accordance with IRB / EC reporting requirements and institutional policies. The Investigator will note whether the adverse event was device-related or procedure-related and the severity of the event. All SAEs must be reported by the Investigator (or designee) to the Sponsor within 24 hours of knowledge of the event, or by the end of the next working day.

7.3 Adverse Event Reporting

7.3.1. General Reporting Requirements

All serious and potentially device- and/or procedure-related adverse events must be recorded on the Adverse Event electronic CRF by the Investigator (or designee). The report should include: severity, duration, action taken, treatment outcome and relationship of the adverse experience to the study device, procedure, concomitant medications, pre-existing condition, (i.e., unrelated, related or relationship unknown).

In the case of serious adverse events, device-related adverse events, target lesion and access circuit interventions, and potential device malfunctions and failures, medical record documentation (e.g., procedure notes, operative notes, discharge summary, relevant progress notes, imaging, or lab studies) must be provided to the Sponsor or its designee as requested for safety adjudication by the Clinical Events Committee (CEC).

7.3.2. Reporting Requirements for Serious Adverse Events

All serious adverse events must be reported by the Investigator (or designee) to the Sponsor within 24 hours of knowledge of the event or by the end of the next working day. This may be done via phone, fax, email or electronic data capture for the clinical database.

The Investigator (or designee) shall send a written report including a narrative description of the serious adverse event to the Sponsor or their designee within five (5) working days of the initial report. This can also be in the form of the AE eCRF.

Any serious adverse events and all deaths regardless of cause may need to be reported to the IRB / EC per local IRB / EC requirements. It is the responsibility of the Investigator to inform their IRB / EC of these serious adverse events as required by their IRB / EC procedures and in conformance with FDA and local regulatory requirements. In addition, the investigator shall provide documentation of the IRB / EC report to Merit Medical or its designee.

All adverse events (AE) will be monitored from the time of enrollment through the 12-month assessment. SAEs and UADEs as well as vascular access circuit events will be monitored from the time of enrollment through the follow-up period for this trial (24 months). A description of the event, including the start date, resolution (or date of final outcome assessment) date, action taken, and the outcome should be provided, along with the Investigator's assessment of the relationship between the AE and SAE and the study treatment.

All AEs should be followed until the event is resolved or judged to be chronically stable. The clinical site should plan to provide relevant AE follow-up information to the Sponsor upon request.

The Sponsor or its designee will report all applicable serious adverse events as vigilance reports per MEDDEV 2.12.1, Rev 8 (2013) "Guidelines on a Medical Devices Vigilance System" and as clinical study reportable events per MEDDEV 2.7/3 "Clinical Investigations: Serious Adverse Event Reporting," MDCG 2020-10/1 "Guidance on safety reporting in clinical investigations" and EU MDR 2017/745 "The European Union Medical Device Regulation of 2017". The Sponsor will determine whether all of the local Investigators need to be informed immediately of an SAE or UADE, or whether this can be postponed until the next regularly scheduled study update.

7.3.3. Device Malfunctions and Failures

All reported device observations / performance issues, malfunctions or failures of the Merit WRAPSODY Endovascular Stent Graft System are required to be documented in the eCRF. In the event of a suspected observation or device problem, the investigational device shall be returned to the Sponsor for analysis. Potential device failures and malfunctions should also be documented in the subject's medical record. Instructions for returning the investigational device are included in the Manual of Operations Binder.

NOTE: Device failures or malfunctions are NOT to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded in the usual manner on the AE eCRF.

8.0 RISK / BENEFIT ASSESSMENT

8.1 Risks to the Subject

8.1.1. Risk Analysis

The WRAPSODY Endovascular Stent Graft System or the WAVE Study treatment procedure may result in failures or complications similar to other peripheral stents/stent grafts with similar indications for use. Prior human use and preclinical studies of the WRAPSODY Stent Graft System have not shown any additional risks. Documented risks of peripheral stents/stent grafts and/or the endovascular treatment procedure include, but are not limited to (potential risks are listed in alphabetical order and not per risk level):

- Access-site complications
- Allergic reaction to contrast media / medications
- Aneurysm
- Arteriovenous (AV) fistula
- Bleeding complications
- Cardiac arrest
- Cardiac arrhythmia
- Death
- Device embolization
- Device malfunction
- Device migration
- Device occlusion / thrombosis
- Embolism and/or vessel thrombosis
- Emergency or non-emergency access circuit intervention
- Extravasation of contrast media
- Fracture of the guide wire or any component of the device that may or may not lead to device embolism, serious injury or surgical intervention

- Hematoma
- Infection or fever
- Ischemia
- Myocardial infarction or coronary ischemia
- Neurological deficit
- Placement of a bailout stent / stent graft
- Pseudoaneurysm
- Radiation exposure
- Reaction to contrast media / medication
- Respiratory distress or failure
- Restenosis of the treated segment
- Serious injury requiring surgical intervention
- Seroma
- Stent graft compression
- Stent graft kinking
- Stent strut fracture(s)
- Stroke or TIA
- Transfusion
- Total occlusion of the vascular access circuit
- Vascular complications that may require surgical repair (conversion to open surgery)
- Vessel dissection
- Vessel perforation
- Vessel rupture
- Vessel spasm

These risks are present in any endovascular treatment procedure for which the study subjects would be indicated because of their disease, and the subject's physician will review these risks with the subject. Standard of care practice should be followed for preparing a subject for endovascular intervention, including medication and vascular access.

8.1.2. Risk Minimalization

As with any endovascular procedure, appropriate safety precautions will be followed. In addition, this protocol provides additional steps to minimize risk to study subjects. These include the following:

- **Investigator Selection**: The Investigators in this study are selected based on their experience in treating subjects with vascular access circuit dysfunction and performing endovascular treatment procedures, including stent/ stent graft placement and peripheral balloon angioplasty and the availability of appropriate resources and facilities to conduct the study.
- **Investigator Training**: Investigators will be trained in proper device operation prior to study start. Training will include didactic and hands-on training with the WRAPSODY Stent Graft System (e.g., bench-top model, animal lab training).
    - Enhanced training shall be conducted with all clinical investigators on WRAPSODY Stent Graft sizing and placement. Each investigator shall deploy a demo device prior to enrollment.
- **Subject Screening**: This protocol includes appropriate precautions in subject selection. For example, subjects with significant co-morbidities or uncontrolled cardiovascular or other disease will be excluded.

Patients who do not meet all inclusion criteria and none of the exclusion criteria, including known allergy to nickel alloy, will be excluded from this protocol per IFU Contraindications for Use.

8.2 Potential Benefits

Prior human clinical experience in a population of 46 subjects has validated that the WRAPSODY Stent Graft System can be used to safely and effectively treat stenoses and occlusions within the venous outflow circuit and graft/vein anastomosis, resulting in acute and long-term luminal patency. The WAVE Study is intended to evaluate the safety and effectiveness of the WRAPSODY Stent Graft System in a larger clinical population.

9.0 STATISTICAL ANALYSIS PLAN

This study comprises two cohorts:

1. Subjects with AVF access who have stenosis or occlusion in a peripheral vein, including the cephalic arch will undergo 1:1 randomization to the Merit WRAPSODY Stent Graft or PTA (AVF Peripheral cohort);
2. Subjects with AVG access who have stenosis or occlusion at the anastomosis or juxta-anastomosis will be treated with the Merit WRAPSODY Stent Graft (AVG Anastomosis cohort).

Each cohort will be analyzed separately.

9.1 Analysis Population

Intent to Treat Population: The Intent to Treat (ITT) population will include all randomized subjects in the AVF Peripheral cohort, and all subjects enrolled in the AVG Anastomosis cohort.

Modified Intent to Treat Population: The Modified Intent to Treat (mITT) population will include all ITT subjects who receive treatment.

Per Protocol Population: The Per Protocol (PP) population will include all mITT subjects who additionally met all inclusion/exclusion criteria. This is a secondary analysis set for the primary safety and effectiveness endpoints, as well as secondary endpoints.

While mITT is intended as the primary analysis set for all safety and effectiveness endpoints, the primary safety and effectiveness endpoints will additionally be evaluated in the ITT and PP analysis sets as supportive information. All subjects excluded from mITT and PP analysis sets will be described in the final study report and the reasons detailed. If the ITT and mITT analysis sets contain the same subjects, then all mITT analyses will revert to the ITT analysis set and the mITT analysis set will be eliminated.

9.2 General Methodology

Subject data listings and tabular and graphical presentations of results will be provided. Descriptive statistics of continuous variables will be presented by treatment arm and include sample size, mean, median, standard deviation, minimum and maximum. For categorical variables, the number and percentage of subjects in each category will be presented by treatment arm. In general, number of subjects with missing data can be identified from the difference between number of mITT subjects and number of observations. Dichotomous variables will be evaluated using Fisher's exact tests. Categorical variables will be evaluated by Cochran-Mantel-Haenszel (CMH) Modified Ridit Scores, i.e., CMH of general association for nominal variables and CMH of row mean score for ordinal variables. Continuous variables will be evaluated by two-sample t-test. Time to event analysis will be carried out using the Kaplan-Meier method along with Greenwood standard error. If a subject does not have an event, the time point when a subject becomes un-evaluable will be considered as the censoring time for this subject. Unless otherwise specified, a two-sided 0.05 level of significance will be used to declare treatment arms significantly different.

9.3 Primary Endpoint Analysis

Endpoints will be analyzed using the modified intention-to-treat analysis set as described below. Each sub-study will be considered successful if both primary safety and effectiveness endpoints have been met. An additional supportive analysis may be conducted in the ITT analysis set for the primary safety and effectiveness endpoints.

9.3.1. Primary Safety Endpoint

The primary safety endpoint is the proportion of subjects without any localized or systemic safety event through 30 days post study procedure that affects the access or venous outflow circuit and resulted in reintervention, hospitalization, or death (not including stenosis or thrombosis). Endovascular procedures performed to treat safety events after the index study procedure will be considered surgeries.

9.3.2. Primary Effectiveness Endpoint

The primary effectiveness endpoint is the proportion of subjects with target lesion primary patency (TLPP) at 6 months (180 days). The key secondary effectiveness endpoint is the proportion of subjects with TLPP at 12 months (360 days) . Calculation of these endpoints will be based on the number of subjects with adequate follow-up. In addition, these endpoints will be estimated using Kaplan Meier estimates with standard error calculated using the Greenwood method. Time to loss of TLPP is defined as the interval of uninterrupted patency from initial study procedure to the next intervention performed on the target lesion.

9.5 Other Safety Data

All adverse events (AEs) collected will be coded. Events will be summarized cumulatively through the following time points: 30 days, 6 months, 12 months (all AEs) and 24 months (SAEs only). Frequency count of AEs and unique number of patients who had the AEs, for each coded term, will be presented. Also, the frequency and percentage of patients who had a Serious AE (SAE), or a related AE (by relationship to both implant procedure and device) will be tabulated separately by a coded term.

9.6 Site Poolability

Poolability of data across clinical study sites is justified on a clinical basis (i.e., all study sites use the same protocol) the sponsor monitors the site for protocol compliance, and the data gathering instruments are identical. The Food and Drug Administration also requires a statistical assessment of site poolability.

For the two randomized cohorts, poolability of subjects across clinical sites for the primary effectiveness and safety endpoint analysis will be tested using Cox proportional hazards regression. Included as independent variables in the Cox models will be treatment, site and the treatment-by-site interaction effect; if the interaction effect is not statistically significant (defined as $p>0.15$ on the interaction test) or the interaction effect is significant but not qualitative in nature, all data irrespective of site will be collected in a single analysis cohort. Sites with fewer than 9 subjects will be ranked by enrollment from

low to high, then starting from the lowest enrollment site, sites will be combined into a pseudo site until the combined size reaches the median enrollment among all sites. This process will be repeated until all resulting sites have enrollment equal to or greater than 9 subjects. This analysis will be performed on the primary analysis sets including all randomized subjects. Similar analyses will be conducted to assess treatment-by-geography (US vs. OUS) interaction.

For the non-randomized cohort, poolability analysis will be performed on the primary endpoints comparing across sites and geographies after adjusting for covariates difference. Logistic regression model will be utilized to include site as an independent variable, and the study outcome as dependent variable to assess outcome difference. If the p-value of site effect is less than 0.15, further analyses will be undertaken to investigate the imbalance of the study outcome. Sites with fewer than 6 subjects will be combined into a pseudo site as above.

These analyses will be performed on the primary analysis sets.

9.7 Sample Size

There are two hypotheses for each of the two cohorts in the study. One is for the primary effectiveness endpoint – target lesion primary patency at 6 months, and one is for the primary safety endpoint – localized or systemic safety event through 30 days post-procedure. The AVF Peripheral cohort will be a randomized controlled sub-study (1:1) of SG vs. PTA. The AVG Anastomosis cohort is a single arm Performance Goal (PG) sub-study.

<u>AVF Peripheral cohort</u>

For the primary effectiveness endpoint, the SG treatment (p_T) and PTA control (p_C) groups will be compared in a superiority format under the following hypothesis.

H_0: $p_T = p_C$

H_A: $p_T > p_C$

For the primary safety endpoint, the treatment (π_T) and control (π_C) groups will be compared in a non-inferiority format under the following hypothesis.

H_0: $\pi_T \geq \pi_C + 0.15$

H_A: $\pi_T < \pi_C + 0.15$

Sample size for the primary effectiveness endpoint was estimated using the two-group chi-square test. Assumptions included a two-sided 0.05 alpha and at least 80% desired power to show superiority of SG to PTA. A 78% primary patency rate was assumed in treatment and 60% in control. From these assumptions a sample size of 103 per arm was calculated and with an assumed compliance of 85% yielded 122 per arm or 244 in total.

For the one-sided 0.05 test of non-inferiority of SG to PTA on the primary safety endpoint, the event-free safety composite rate was assumed to be 95% in the treatment and control groups with a non-inferiority margin of 15% using the Ferrington-Manning test. Power for non-inferiority of the primary safety endpoint was 80% and the calculated sample size was 40 per arm. After assuming 5% lost to follow-up at 30 days the number per arm was 43 or 86 in total. Therefore, the overall sample size for this study cohort was determined by the effectiveness endpoint. With a total sample size of 244 the safety endpoint will have 99% power.

<u>AVG Anastomosis cohort</u>

The effectiveness performance goal of 60% was chosen as it represents the average value reported for stent graft 6-month TLPP for this indication.

For the primary effectiveness endpoint, the treatment (P_w) will be compared to the PG by the following hypothesis:

H_0: $P_W \leq 60\%$,

H_1: $P_W > 60\%$,

Rejection of the null hypothesis will signify that the 6-month TLPP of the WRAPSODY™ Endovascular Stent Graft is greater than the effectiveness PG of 60%.

The safety performance goal of 89% was established by subtracting a 10% margin from the average rate of 99% observed in the literature.

For the primary safety endpoint, the treatment (P_w) will be evaluated by the following hypothesis:

H_0: $P_W \leq 89\%$,

H_1: $P_W > 89\%$,

Rejection of the null hypothesis will signify that the 30-day safety of the WRAPSODY™ Endovascular Stent Graft is greater than the safety PG of 89%.

Sample size for the primary effectiveness endpoint was estimated using the one group exact binomial test. Assumptions included a one-sided 0.05 alpha and at least 90% desired power to show the SG meets the PG. A 74% primary patency rate was assumed in treatment and 60% PG. From these assumptions a sample size of 96 was calculated and with an assumed compliance of 85% yielded 113 subjects.

Sample size for the primary safety endpoint was estimated using the one group exact binomial test. Assumptions included a one-sided 0.05 alpha and at least 99% desired power to show the SG meets the PG. A 98% primary safety rate was assumed in treatment and 89% PG. From these assumptions a sample size of 88 was calculated and with an assumed compliance of 95% yielded 93 subjects.

A final sample size of 113 patients will be used based upon the effectiveness primary endpoint requirements. Study success for this cohort will be declared only if both primary endpoints (safety and effectiveness) meet their performance goals.

9.8 Handling of Missing Data

For all primary, secondary and exploratory analyses, no imputation of missing data is planned. In general, endpoint rates will be calculated as the number of subjects who had an endpoint prior to the milestone visit divided by the number of evaluable subjects who had sufficient follow up (e.g., at least 150 days for 6-month visit) plus any subjects who had an event prior to the milestone visit. In other words, the denominator will be adjusted for missing follow up data. A tipping point analysis will be done on the primary endpoints as a missing data sensitivity analysis. This analysis encompasses all possible imputation outcomes and thus is a rigorous set of sensitivity analyses.

9.9 Interim Analysis

There is no interim analysis planned with the purpose of altering the Protocol or planned statistical analyses.

9.10 Analysis

For the randomized AVF Peripheral cohort, the count and percentage of subjects with TLPP at 6 months will be presented by treatment arm. The percentages will be computed as

$\hat{p}_i = 1 - \frac{n_i}{m_i}, i = T(treatment), C(control)$. n_i is the number of subjects in each treatment arm who experienced non-patency event within 180 days post procedure, m_i is the number of subjects in each

treatment arm who experienced non-patency event within 180 days or had no non-patency event but followed up for at least 150 days. The hypothesis will be tested using the chi-square test, and the differences between treatments together with a two-sided 95% confidence interval will be calculated. For the primary safety endpoint, the count and percentage of subjects with a safety event at 30 days will be presented by treatment arm. The percentages will be computed as $\hat{\pi}_i = 1 - \frac{n_i}{m_i}, i = T, C.$ n_i is the number of subjects in each treatment arm who experienced an event within 30 days post procedure, m_i is the number of subjects in each treatment arm who experienced an event within 30 days or had no event but followed up for at least 23 days. Non-inferiority on the safety endpoint will be tested using the Farrington-Manning test. The differences between treatments together with the one-sided 95% upper confidence limit will be calculated.

For the nonrandomized AVG Anastomosis cohort, a one-sided p-value will be derived based on an exact binomial test. The study device will be considered to have achieved the primary effectiveness objective if the one-sided p-value is less than 0.05. Or equivalently, the lower limit of the one-sided 95% confidence limit based on exact method is greater than 60%. The same testing methodology will be used for the primary safety endpoint in comparison to the PG of 89%.

To control the overall Type I error (two-sided P=0.05 superiority and one-sided P=0.05 non-inferiority) in the randomized cohorts the following fixed sequence testing procedure will be taken:

Primary effectiveness superiority; if significant at two-sided alpha=0.05, proceed to

Primary safety non-inferiority; if significant at one-sided alpha=0.05 proceed to secondary endpoints.

The key secondary effectiveness endpoint with hypothesis testing is TLPP at 12 months (360 days). Other secondary effectiveness endpoints for hierarchical testing, in order, are:

- ACPP at 6 months (180 days)
- TLPP at 24 months (720 days)
- ACPP at 12 months (360 days)
- ACPP at 24 months (720 days)

Remaining secondary endpoints will be summarized with descriptive statistics, without formal statistical hypothesis testing.

The primary analysis will be completed when all subjects in a cohort complete the 6-month visit (or discontinue prior to the 6-month visit). As this analysis at 6 months (180 days) will be the primary effectiveness analysis and both effectiveness and safety primary endpoints must be met for study success, no alpha adjustment for multiplicity will be applied for this analysis. The final analysis will be completed when all subjects in the intended sample size for each cohort complete the study (24-month visit) and submitted as a post-submission report.

[redacted]

10.0 INVESTIGATOR RESPONSIBILITIES, RECORDS AND REPORTS

The Investigators are responsible for signing the Investigator Agreement prior to the commencement of the study and for ensuring that this trial is conducted according to this study protocol, GCPs, Declaration of Helsinki, 21 CFR Parts 50, 54, 56 and 812, ISO 14155:2020 (Section 10) and any other local, national or IRB / EC requirements that apply to clinical Investigations at their center.

It is also the Investigator's responsibility to ensure that all sub-investigators and staff assisting with this study have the appropriate qualifications and that they complete training on the protocol, investigational devices and study procedures, and that subject confidentiality is respected.

10.1 Informed Consent & Institutional Review Board / Ethics Committee

(21 CFR Parts 50 & 56; ISO 14155: 2020 Section 5)

Because this study is collecting medical data from subjects providing written informed consent, the Investigator at each site is responsible for securing (or ensuring) IRB / EC approval for this study Protocol and the Informed Consent documents. The local IRB / EC for each specific institution must review and approve this study protocol and the specific Informed Consent form to be used at that site **prior** to enrollment of their first subject. The Sponsor **must** also review and approve the final Informed Consent documents prior to their use. The Sponsor must receive a copy of any IRB / EC correspondence as well as the final approval letter and the final approved Informed Consent from each IRB / EC.

The Investigator is responsible for ensuring that all applicable local and national (21 CFR Part 50, ISO 14155:2020) requirements, and Declaration of Helsinki are met when completing the informed consent process. Written, informed consent is to be obtained for all subjects **prior** to enrollment and treatment in the study.

The Investigator or clinical site staff will not make amendments to this protocol or the Informed Consent form without **PRIOR** written approval from the Sponsor. All approved amendments must then be submitted to the local IRB / EC and national authorities, as appropriate for approval.

10.2 Withdrawal of Approval

If the Investigator's IRB or EC withdraws their approval to conduct this study for any reason, the Investigator **must** notify the Sponsor as soon as possible, but in no event later than **five working days** after the withdrawal of the approval.

10.3 Clinical Data Collection

Standardized electronic case report forms (eCRF) will be used to collect complete and accurate records of the clinical data from the WAVE trial according to the GCPs requirements. The Investigator and/or study staff under his/her direction is responsible for accurately recording the clinical data for this study and submitting it to the Sponsor in a timely manner.

[redacted]

10.5.1. Serious Adverse Events

The Investigator will report to the Sponsor by telephone, email, fax, or electronic CRF submission any SAE as soon as possible (within 24 hours of the Investigator becoming aware of the event or by the end of the next working day.) Additionally, SAEs should be reported to the IRB / EC, if required per the clinical site guidelines or as directed by the Sponsor. The Adverse Event eCRF is to be completed and submitted to the Sponsor within five (5) working days of the event.

10.5.2. Device Malfunctions or Failures

The Investigators will report any potential Device Malfunctions or Failures that occur, to the Sponsor within 24 hours of the Investigator becoming aware of the device malfunction or failure or by the end of the next working day. The report may be made via telephone, email or fax. The Investigator or study staff are to return the devices per the Instructions for Use for investigation if requested by the Sponsor. The Device Observation eCRF is to be completed and submitted to the Sponsor within five (5) working days of the event.

10.5.3. Deviations from the Investigational Plan

The Investigator must notify the Sponsor of any deviation from the Investigational Plan. The Investigator should also notify the IRB / EC as required per their local requirements or as directed by the Sponsor. This notice must occur as soon as possible, but in no case longer than five (5) working days after the Investigator becomes aware of a major deviation. Major deviations include, but is not limited to, those that involve the informed consent process, the inclusion/exclusion criteria of the study, **SAE reporting**, Randomization errors, device misuse or device accountability discrepancies, or any deviation that involves or leads to a serious adverse event in a study participant.

10.5.4. Investigator Final Report

The Investigator will report information and events according to the timelines in **Table 10**. Within three (3) months of study completion, the Investigator will provide a final study report that summarizes their enrollment and study participation. This report should include a summary of enrollment, AEs, SAEs, UADEs and Device Malfunctions and Failures. This report will be forwarded to the IRB / EC and the Sponsor after all of the enrolled subjects have completed their final follow-up visit or have exited the study and the study close-out visit has been completed, but no later than three (3) months following completion of the last follow-up visit.

Table 10 WAVE Investigator Reporting Timelines	
Form/Report	**Submission Timeframe**
Enrollment Notification CRF	Completion of Enrollment eCRF within 24 hours of enrollment.
Electronic CRFs	Completion within 72 hours of study visit.
Angiographic & X-ray Imaging	Submit to Core Lab within 3 working days of completion.
Adverse Events (non-serious)	Complete eCRF within 14 days of the Investigator becoming aware of the event.
Serious Adverse Events / UADEs	Submit notification to Sponsor within 24 hours of the site becoming aware of the event, or by the end of the next working day; submit to the local IRB / EC as required or as directed by the Sponsor.
Study Progress Reports	As required by the local IRB / EC (minimum annually).
Final Report to the IRB / EC	Within 3 months of Study completion.

10.6 Publication Policies

At the conclusion of the WAVE Study, a multi-center manuscript will be prepared for publication in a reputable scientific journal. The publication of the principal results from any single center experience within the trial is not allowed until the preparation and publication of the multi-center results. Exceptions to this rule require the prior approval of Merit Medical. The analysis of other pre-specified and non-pre-specified endpoints will be performed by Merit Medical and will require pre-approval by Merit Medical. For the purposes of timely abstract presentation and publication, such secondary publications will be delegated to the appropriate principal authors, and final analyses and manuscript review for all multi-center data and/or single-center experience reports will require approval from Merit Medical.

This study will be registered with www.clinicaltrials.gov.

11.0 SPONSOR RESPONSIBILITIES

As the Sponsor of this clinical study, Merit Medical has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the Food and Drug Administration (FDA) and ISO 14155:2020 (Section 9; OUS sites only). In this study, Merit Medical will have certain direct responsibilities and may delegate other responsibilities to Independent Contractors. Together, both Merit Medical and its Independent Contractors will ensure adherence to the sponsor's general duties (21 CFR 812.40; ISO 14155:2020 Section 9), selection of Investigators (21 CFR 812.43; ISO 14155:2020 Section 9.2.1), monitoring (21 CFR 812.46; ISO 14155:2020 Section 9.2.4), supplemental applications (21 CFR 812.35 (a) and (b)), record maintenance (21 CFR 812.140 (b)), and report submissions (21 CFR 812.150 (b)).

11.1 General Duties

(21 CFR 812.40; ISO 14155:2020 Section 9)

The Sponsor's general duties consist of submitting the IDE application to FDA, submitting the Investigational Plan to other applicable national regulatory agencies (as applicable), obtaining FDA, other national regulatory (as applicable) and IRB / EC approvals prior to shipping the devices, selecting qualified Investigators, and shipping devices only to those qualified Investigators. As the sponsor, Merit Medical is also required to obtain signed study agreements, including documentation of financial agreements between sponsor and site/investigator, to provide the Investigators with the information necessary to

conduct the study and adequate on-site training to conduct the trial, to ensure proper clinical site monitoring, and to provide the required reports to the Investigators, IRBs / ECs, other national regulatory agencies (as applicable), and FDA.

Merit Medical is responsible for obtaining and maintaining clinical study insurance in accordance with national and local requirements and providing a copy of the insurance policy to the Investigators, IRBs / ECs, other national regulatory agencies (as applicable).

Merit Medical will be responsible for providing quality data that satisfies federal regulations and informing about serious unanticipated adverse events and deviations from the protocol. Written progress reports and a final report will be prepared in coordination with the Angiographic Core Laboratory.

11.2 Selection of Clinical Sites & Investigators

(21 CFR 812.43; ISO 14155:2020 Section 9.2.1)

Merit Medical will select qualified clinical sites and Investigators who are experienced with percutaneous transluminal angioplasty and peripheral stenting in the access circuit vasculature. The Investigator must work with a qualified IRB / EC to oversee the rights, safety and welfare of the study participants. The clinical site must also have an adequate subject population and the appropriate staffing and equipment to meet the requirements of the study protocol and the expected enrollment time frames.

[redacted]

11.4 Investigational Site or Study Termination

The Sponsor reserves the right to terminate an investigational site from the Study for any of the following reasons:

- Failure to obtain Informed Consent
- Repeated failure to report Serious Adverse Events per protocol requirements
- Loss of or unaccountable device inventory
- Repeated protocol violations or safety concerns
- Repeated failure to complete Case Report Forms
- Failure to screen and enroll an adequate number of subjects

Sponsor reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRB/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination. Detailed information on how enrolled subjects will be managed after termination will also be provided. Possible reasons for premature study termination include, but are not limited to, the following.

- Occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Sponsor to suspend or discontinue development of the device.

11.5 Informed Consent & Institutional Review Board / Ethics Committee

(21 CFR Parts 50 & 56; ISO 14155:2020 Section 5)

All subjects must provide written informed consent in accordance with the local clinical site's IRB / EC. A copy of the consent form from each center must be forwarded to the Sponsor for review and approval prior to submitting it to the IRB / EC. Each site must provide the Sponsor with a copy of the clinical site's IRB / EC approval letter and the informed consent. Continuing review (e.g., institutional annual review) approvals for the continuation of the trial at each clinical site must also be forwarded to the Sponsor, as applicable.

All Protected Health Information (PHI) to be collected in the study will be described in the informed consent form, and all study data will be managed in accordance with the Privacy Law (HIPAA) or international privacy regulations [General Data Protection Regulation (GDPR)], as applicable.

11.6 Records & Record Retention

(21 CFR 812.140 (b) & (d))

The Sponsor and/or their designated independent contractors will maintain copies of correspondence, data, device shipments, clinical events (AEs, SAEs) and supporting documentation and other records and reports related to this clinical study.

The Sponsor, core laboratory and clinical sites will maintain the WAVE study records until at least two (2) years after the final study report is completed, or longer if required by local, national or international

regulatory agencies. The Sponsor will notify each site regarding the regulatory requirements for record retention during the study close-out visit.

11.7 Study Reports

(21 CFR 812.150 (b))

All information and data generated in association with the study will be held in strict confidence and remains the sole property of the Sponsor. The Investigator agrees to use this information for the sole purpose of completing the study and for no other purpose without prior approval of the Sponsor.

The Sponsor will submit the required FDA reports identified in this section of the regulation. This includes unanticipated serious adverse device effects, withdrawal of IRB / EC or FDA approval, current 6-month Investigators list, annual progress reports, recall information, final reports, investigators that use the device without obtaining informed consent, and significant risk device determinations.

Upon receipt of the final study data and the final reports from each center, the Sponsor will complete a final study report. Copies of the final report will be provided to each Investigator.

11.8 Supplemental Applications

(21 CFR 812.35)

As appropriate, the Sponsor will submit changes to the study protocol for national approval and subsequently to the Investigators to obtain IRB / EC approval prior to implementation.

12.0 QUALITY ASSURANCE AND ETHICAL STANDARDS

The study will be conducted according to the Declaration of Helsinki, GCPs, 21 CFR parts 50, 54, 56 and 812, ISO 14155:2020 (OUS sites only), and any additional IRB / EC, local (site and/or state requirements) and/or national requirements that apply to clinical studies of medical devices. As the study Sponsor, Merit Medical, has the overall responsibility for the conduct of the study, including the assurance that the study is in compliance with these guidelines, standards and requirements.

12.1 Institutional review Boards / Ethics Committees

A copy of the study protocol, proposed Informed Consent form, other written patient information and any proposed advertising material must be submitted to the IRB / EC for written approval. A copy of the written IRB / EC approval of the Protocol and Informed Consent form must be received by Merit Medical before recruitment of subjects into the study and shipment of investigational product.

The Investigator must submit and, where necessary, obtain approval from the IRB / EC as well as the FDA, for all subsequent significant protocol amendments and significant changes to the Informed Consent form. The Investigator should notify the IRB / EC of deviations from the protocol or SAEs / UADEs occurring at the site and other SAE / UADE reports received from Merit Medical in accordance with local procedures.

The Investigator will be responsible for obtaining annual IRB / EC approval and renewal throughout the duration of the study. Copies of the Investigator's reports and the IRB / EC continuance of approval must be sent to Merit Medical.

12.2 Informed Consent

A sample Informed Consent form template shall be provided to the Investigator to use to prepare for use at his/her site. The written Informed Consent documents should be prepared in the language(s) of the potential patient population.

The reviewing IRB / EC and the sponsor must first approve the Informed Consent forms that are used. The Informed Consent forms that are used should be in accordance with the current guidelines as outlined by the FDA Regulations, GCP guidelines, Declaration of Helsinki, and ISO Standards (OUS sites only).

Prior to participation in the clinical trial, each patient must give written Informed Consent after the context of the study has been fully explained to the patient in language that is easily understood by the patient. The patients must also be given the opportunity to read the consent, ask questions, and have those questions answered to their satisfaction.

Written Informed Consent must be recorded appropriately by means of the subject's, or their legal representative's dated signature, if applicable. The subject will receive a signed copy of the Informed Consent form.

12.3 Protocol Amendments

An Investigator may not make changes to this protocol without prior approval by the Sponsor. All significant changes to the protocol that may affect the following must be submitted and approved by the FDA before initiating the change:

- Validity of the data or information resulting from the completion of the approved protocol
- Relationship of the likely subject risk to benefit relied upon to approve the protocol
- Scientific soundness of the investigational plan
- Rights, safety, or welfare of the human subjects involved in the investigation

Any such change to the protocol must be approved by the FDA and submitted and subsequently approved by the site IRB / EC. Merit Medical will submit a copy of the protocol amendment to all Investigators for their IRBs / ECs to review and ensure the study continues to be conducted consistently across all sites. The investigative sites must send Merit Medical a copy of the IRB / EC approval letter for the protocol amendment.

Merit Medical may make certain administrative changes to the protocol without prior approval of the FDA or IRB / EC. Merit Medical will notify all investigative sites of such changes to ensure the study continues to be conducted consistently across all sites. The site IRBs / ECs will be notified of these changes.

12.4 Emergency Actions

Merit Medical accepts the right of the Investigator to deviate from the protocol in an emergency when necessary to safeguard the life or the physical well-being of a study subject. The Investigator must give notice of any emergency deviations and justification for the deviation to Merit Medical and the IRB / EC as quickly as possible after the episode, in any event no later than 24 hours after the emergency.

Emergency Use of the investigational device is not permitted in this study.

12.5 Protocol Compliance

A Protocol Deviation is defined as an event where the Clinical Investigator or site personnel did not conduct the study according to the protocol.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

Sponsor approval shall be documented in writing and maintained in clinical study management and Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control (e.g., subject was not available for scheduled follow-up office

visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation and will be reported via the appropriate eCRF.

Deviations must be reported to the Sponsor regardless of whether medically justifiable, pre-approved by the Sponsor or taken to protect the subject in an emergency. Subject specific deviations will be reported on the Protocol Deviation case report form. Non-subject specific deviations, (e.g., unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator agreement or not been trained in the use of the device, etc.), will be reported to the Sponsor reported via the applicable site monitoring visit report. Investigators will also adhere to procedures for reporting study deviations to their IRB / EC in accordance with their specific IRB / EC reporting policies and procedures.

Regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates of and reasons/root cause for each deviation from the Protocol. For reporting purposes, the Sponsor classifies study deviations as major and minor:

Major deviation: Any deviation from subject inclusion and exclusion criteria, subject informed consent procedures, SAE/MAE reporting, Randomization errors, device accountability discrepancies, or unauthorized device use.

Minor deviation: Deviation from a protocol requirement such as incomplete/inadequate subject testing procedures, follow-ups performed outside specified time windows, etc. Minor Deviations that continue to occur at an investigational site may be classified as Major Deviations if corrective action is not taken to secure future compliance to the Protocol.

12.6 Investigator and Staff Training

Training of the Investigators and clinical study staff is the responsibility of the Sponsor and their designee. Training may be conducted during an Investigator meeting, a site initiation visit, or appropriate training venues. Investigators and study staff will undergo training on the study devices and study protocol, eligibility criteria, device accountability, and proper storage of the equipment and supplies, prior to participating in the study. Training may encompass didactic information regarding the study devices and system, as well as hands-on practice with the device. Procedural technique and experience with the WRAPSODY Stent Graft System may be assessed by clinical/engineering personnel. Observations during the cases will also be discussed with the Investigator and study staff.

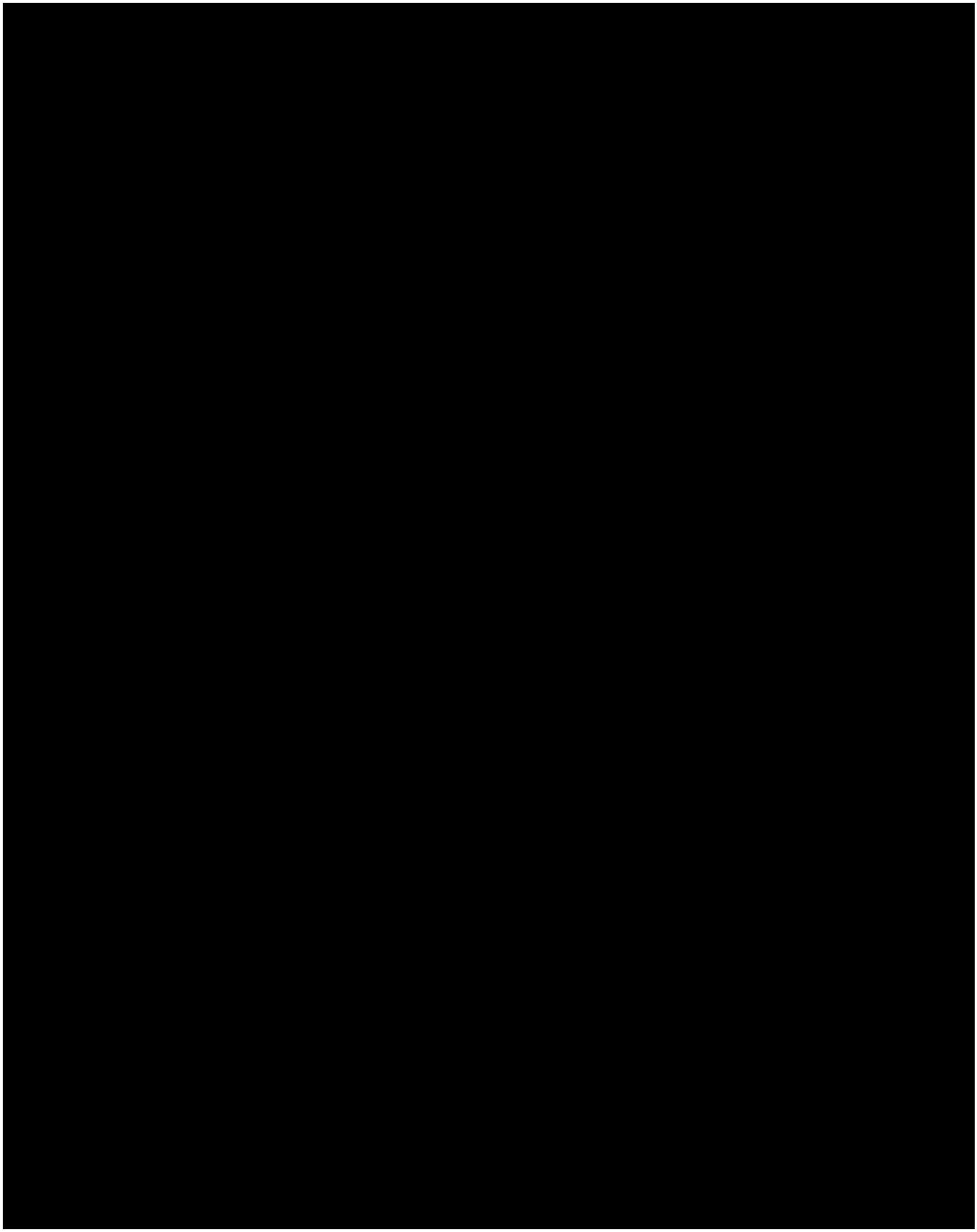
12.7 Audits and Inspections

The Principal Investigator for the site will also allow representatives of the governing IRB or EC, the United States Food and Drug Administration (FDA), and other applicable regulatory agencies to inspect all trial records, eCRFs, and corresponding portions of the subject's clinic and/or hospital medical records at regular intervals throughout the trial. These inspections are for the purpose of verifying adherence to the protocol, completeness and exactness of the data being transcribed into the eCRF, and compliance with FDA or other regulatory agency regulations.

The Principal Investigator for the site will inform the Sponsor or the Sponsor's designee in advance if they are to be audited or inspected by any regulatory agencies. The Sponsor or the Sponsor's designee will also inform the site if they are made aware of a pending audit or inspection by a regulatory agency.

The Investigator and/or designees must be available to respond to reasonable requests by authorized Sponsor and regulatory agency representatives during the monitoring and inspection process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current study (i.e., Inspection Observations and responses) or their qualification as an Investigator in

clinical studies conducted by the Sponsor. The Sponsor will provide any needed assistance to the clinical site for regulatory audits, if any.



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12.10 Clinical Events Committee

An independent Clinical Events Committee (CEC) will be responsible for systematic review and adjudication of specified events (e.g., pre-determined applicable device-related adverse events, all deaths, and interventions performed on the vascular access circuit) as outlined in the CEC Charter. At a minimum, all pre-specified protocol endpoints shall be reviewed, including all site-reported conduit interventions through end of study. In the case of an event with associated imaging, the CEC may review imaging adjudication as provided by the applicable core laboratory to assess the reported event. It should be noted that events requiring adjudication that have associated imaging shall have dual adjudication by the core laboratory for review and adjudication consistency. Core laboratory adjudication data shall be provided to the CEC for overall event adjudication. Processes shall be outlined in both the CEC Charter and Core Lab Manual.

At a minimum, the CEC shall consist of at least three (3) independent physicians, with experience in interventional peripheral endovascular procedures for dialysis access. In order to enhance objectivity and reduce the potential for bias, the CEC members shall be independent of the Sponsor as well as the investigational sites and investigators. The methodology for performing these responsibilities shall be developed and outlined in the CEC Charter. Operational provisions shall be established to minimize potential bias.

12.11 Data Management

Standardized eCRFs will be utilized by all participating sites. Investigators are responsible for the accurate completion and timely submission of the data collected during the trial. All data from the trial will be entered into eCRFs via a secure, web-based system with password protection. Incoming data will be automatically reviewed to identify inconsistent or missing data and any adverse events. Any data issues are to be promptly addressed with the investigator by the Sponsor designee and/or data manager. Quality assurance procedures will be established to ensure that complete, accurate and timely data are submitted, that protocol requirements are followed, and that complications, adverse events and adverse device effects are correctly reported and investigated, as appropriate. Investigators are to maintain all source documents as required by the protocol, including applicable laboratory results, applicable medications, supporting medical records, and signed Informed Consent forms. The source documents will be used during the regular monitoring visits to verify information from the database against data contained on the completed eCRFs.

The Investigator must maintain detailed records on all subjects who sign the Informed Consent and begin the pre-procedure evaluation. Only subjects who are enrolled, randomized (if applicable) and treatment is attempted or completed will have data entered into the eCRFs provided by the Sponsor. All data should be entered completely and promptly. For source documents, corrections should be made in a manner

that does not obscure or eliminate the original error, by striking through the original data with one line, and initialing and dating the change, along with the reason for the change (if not obvious).

Study Exit eCRFs are completed for all enrolled and treated subjects, regardless if they did or did not complete the trial (e.g., subject discontinuation, trial termination).

12.11.1. Data Handling

Each cohort will be analyzed separately. If any cohort reaches its target enrollment prior to the other cohort(s) completing enrollment, the fully enrolled cohort shall be monitored, locked and analyzed while the remaining cohorts continue to enroll subjects. The data for first cohort will be submitted for PMA review. Upon completion of the remaining cohorts, the individual cohorts shall be submitted as supplements when the 6-month follow-up data collection has been completed, monitored, locked and analyzed for the last subject in the intended number for that cohort.

12.13 Subject Compensation

The treated subjects will not be reimbursed or compensated for participating in the trial. Subjects may be reimbursed for study-specific out-of-pocket expenses (e.g., parking, lodging, etc.) if needed; this is subject to approval by Sponsor and/or IRB/EC.

12.14 Confidentiality

Confidentiality of subjects will be maintained throughout the WAVE Study. A unique identification code will be assigned to each subject participating in this trial. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity. The Sponsor and their representatives will make every reasonable effort to protect the confidentiality of the subjects participating in the WAVE Study.

13.0 STUDY DEFINITIONS

Access Circuit: Defined as the continuum from the heart and the arterial inflow through the AV access to the venous outflow back to the heart (KDOQI).

Access Circuit Primary Patency: Defined as time to loss of Primary Patency of the access circuit, which is the time post-procedure until any venous outflow circuit re-intervention, or access thrombosis or abandonment.

Access Site Hemorrhage: Bleeding from the access site which requires transfusion, hospitalization (either admission or extended stay), or further treatment for management. Hemorrhage needing ≥ 1 unit RBCs will be considered a serious adverse event.

Access Site Infection: Culture-proven wound infection or presumptive treatment with antibiotics for clinically diagnosed wound infection.

Access Thrombosis: A total occlusion within the AV access circuit due to thrombus formation which is rapidly evolving as confirmed by sudden onset of symptoms and documented by duplex ultrasound and/or angiography.

Allergic Reaction: An allergic reaction characterized by rash, upper respiratory congestion, urticaria, shortness-of-breath, or general collapse (anaphylaxis).

Anemia: Decrease from baseline in red blood cells, hemoglobin, or total blood volume that is associated with hemodynamic changes or requires transfusion, or a decrease in hematocrit to below 26%. Any documented anemic event requiring ≥2 units PRBCs will be considered an SAE.

Angina, Unstable: Angina that increases in frequency, intensity, or duration, which occurs at rest, or which is new in onset. Unstable angina is a syndrome that is intermediate between stable angina and myocardial infarction: it is characterized by an accelerating or "crescendo" pattern of chest pain that lasts longer than stable angina, occurs at rest or with less exertion than stable angina, or is less responsive to medication. Unstable angina and myocardial infarction are considered acute coronary syndromes.

Arteriovenous Fistula (AVF): An abnormal passage or communication between an artery and a vein which may be due to the percutaneous introduction of ancillary devices (e.g., needles, catheters, guide wires) confirmed by imaging studies.

Arteriovenous (AV) Access Abandonment: When a vascular access can no longer be used for prescribed 1 or 2 needle dialysis because it is unable to provide adequate flows and/or is deemed unsafe for the patient, and the associated problem cannot be corrected by any intervention, including medical, surgical, or radiologic interventions or rest (KDOQI)**.**

Assisted Target Lesion Primary Patency (aTLPP): Defined as time to loss of Assisted Primary Patency of the target lesion, which is the time from post-procedure until uncorrectable target lesion occlusion.

Bleeding Complication (Major): Bleeding resulting in ≥3 g/dl decrease in hemoglobin (if hemoglobin level not available, a decrease in hematocrit of ≥ 10%), or necessitating transfusion of >1 unit of PRBC's / whole blood or necessitates surgery/endoscopic intervention.

> **Access site:** Bleeding from the arteriotomy site which requires transfusion, hospitalization (either admission or extended stay), or further treatment for management.

Cardiac Arrhythmia: Electrical disruption of the heart rhythm requiring specific medication, DC shock, or pacemaker insertion to address condition.

Cardiogenic Shock: Subject presents with SBP < 80 mm Hg for more than 30 minutes unresponsive to fluids or requiring intravenous vasopressor agent or an intra-aortic balloon pump (IABP).

Catheter Dysfunction: The first occurrence of either (1) peak blood flow of 200 ml per minute or less for 30 minutes during a dialysis treatment, (2) mean blood flow of 250 ml per minute or less during two consecutive dialysis treatments, or (3) inability to initiate dialysis owing to inadequate blood flow, after attempts to restore patency have been attempted.

Cerebral Vascular Accident (CVA): See Stroke.

Closure, Abrupt: Occurrence of new (during the index procedure), persistent slow, reduced, or loss of flow within the target vessel that requires intervention other than the index or adjunct treatment. Abrupt closure may also be referred to as acute occlusion if there is a total loss of flow.

Closure, Late: Target lesion site occlusion that occurs greater than 30 days after the index procedure is completed (e.g., the subject has left the treatment area).

Closure, Subacute: Target lesion site occlusion that occurs after the index procedure is completed (e.g., the subject has left the treatment area) and within 30 days of procedure.

Contrast Media Reaction: An allergic reaction, immediate or delayed, associated with the intravascular administration of contrast media that results in symptoms (e.g. itching, hives) or physiologic changes requiring treatment (e.g. anaphylactic reaction) or death.

Death: Death is divided into 2 categories:

Cardiovascular death is defined as death due to any of the following:

1. Acute myocardial infarction.
2. Sudden cardiac death.
3. Death due to heart failure.
4. Death due to stroke.
5. Death due to other cardiovascular causes.
6. Death not attributable to any other cause (e.g., undetermined cause of death).

Non-cardiovascular death is defined as a death not due to cardiovascular causes (as listed above).

De Novo Lesion: An obstructive or occlusive lesion without previous endovascular or surgical intervention

Device Failure: A device that is used in accordance with the Instructions for Use, but the device does not perform according to the Instructions for Use and negatively impacts the treatment.

Device Malfunction: A malfunction of a device is an unexpected change to the device that is contradictory to the Instructions for Use and may or may not affect device performance.

Dissection: Disruption of an arterial wall resulting in separation of the intimal layer. May or may not be flow limiting.

Dissection Classifications (National Heart, Lung and Blood Institute – NHLBI)

Type A: Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.
Type B: Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles.
Type C: Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material.
Type D: Spiral shaped filling defect without delayed run-off of the contrast material in the antegrade flow.
Type E: Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen.

Type F: Filling defect accompanied by total coronary occlusion.

Embolization, Distal: Any distal emboli confirmed by imaging.

Embolization, Symptomatic: Clinical signs or symptoms of distal emboli detected in the treated limb to the treated lesion after the index procedure ***or*** noted angiographically and requiring mechanical or pharmacologic means to improve flow. This includes new abrupt occlusions or filling defects.

Enrollment: Subjects who are consented, meet all the study inclusion criteria and none of the study exclusion criteria, are randomized (if applicable) and treated or treatment is attempted with the assigned study device will be considered enrolled into the study. Subjects who do not meet all inclusion and exclusion criteria (e.g., target reference vessel diameter, target lesion length, etc.) will be considered an angiographic screen failure and will not be followed in the study (no data will be collected on these subjects). Angiographic screen failures will be tracked on the Screening & Enrollment Log.

Hematoma: Collection of blood (or its degradation products) which exceeds 5 cm in diameter, requires treatment, or prolongs hospitalization.

Hypertension: Systolic BP >140 mmHg, or diastolic >90 mmHg requiring specific medical therapy.

Hypotension: Any prolonged systolic blood pressure <80 mmHg associated with symptoms and requiring intravenous vasopressor medications.

Infection, access circuit: Infection involving the vascular access circuit, documented by lab culture or clinical evidence requiring medical treatment (irrigation, debridement, antibiotics, etc.) to resolve.

Infection, access site: Infection at the vascular access site, documented by lab culture or clinical evidence requiring medical treatment (irrigation, debridement, antibiotics, etc.) to resolve.

Infection, systemic: Systemic infection documented by positive lab culture or clinical evidence, requiring medical treatment to treat and resolve.

Intention to Treat (ITT): The principle of including outcomes of all subjects in the analysis who are enrolled, randomized (if applicable) and treated (attempted or completed) into the study, regardless of noncompliance, protocol deviations, or withdrawal.

Myocardial Infarction (MI): Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

Perforation: Puncture of a vessel wall.

Pseudoaneurysm: Disruption of the vessel wall characterized by an out-pouching or pocket with swirling, flowing blood outside of the confines of the lumen.

Reference Vessel Diameter, Proximal (RVD_{prox}): Diameter of normal vessel (healthy segment) immediately proximal to the treated segment.

Reference Vessel Diameter, Distal (RVD_{dist}): Diameter of normal vessel (healthy segment) immediately distal to the treated segment.

Respiratory Failure: New onset of respiratory insufficiency that requires placement of endotracheal tube and/or pneumothorax with or without chest tube.

Respiratory Insufficiency: Deterioration of subject's respiratory efforts that require supportive or medical treatment.

Restenosis: Reoccurrence of narrowing or blockage or target lesion. Recurrence stenosis within ± 10 mm proximal and/or distal to the target lesion as measured by angiography during repeat intervention.

Retroperitoneal Bleed: Bleeding into the back of the abdomen from a vascular access or puncture site.

Steal Syndrome: Ischemic signs and symptoms (pain, diminished radial pulse, coldness, cyanosis, necrosis) produced by an access device as a result of the diversion of arterial blood flow into the AV fistula.

Stent Fracture: Defined as clear interruption of stent strut observed in a minimum of two projections, determined by core lab examination of X-ray images.

Stent Strut Fracture Types:[29]

Type 0: No strut fractures.
Type I: Single strut fracture only.
Type II: Multiple single strut fractures that can occur at different sites.
Type III: Multiple strut fractures resulting in complete transection of the stent, without displacement of the stent segments.
Type IV: Multiple strut fractures resulting in displacement of segments of the stent.

Stroke: Any neurological deficit lasting 24 hours or longer, or lasting less than 24 hours with a brain imaging study showing infarction consistent with deficit. May be further categorized as:

- Ischemic Stroke: neurologic deficit meeting the study definition for Stroke that is attributed to thromboembolic event.
- Hemorrhagic Stroke: neurologic deficit meeting the study definition for Stroke that is attributed to bleeding into brain tissue, epidural, subdural, or subarachnoid space; or a combination of these sites.

Successful Dialysis: A successful dialysis session includes:

- Normal cannulation *and*
- Is not stopped prematurely

Target Lesion Primary Patency (TLPP): Defined as freedom from clinically-driven target lesion revascularization (CD-TLR) or access circuit thrombosis measured through 6 months post-procedure, which is the time interval of uninterrupted patency after study procedure to the next intervention performed on the target lesion or uncorrectable target lesion occlusion

Target Lesion Revascularization, Clinically-Driven (CD-TLR): Any re-intervention involving the target lesion in which the subject has clinical or physiologic abnormalities that indicate dialysis access dysfunction.

Target Lesion Revascularization, Non-Clinically-Driven: Any reintervention that does not meet the criteria for CD-TLR.

Thrombocytopenia: A persistent decrease in the number of blood platelets to subnormal levels.

Thrombus: Blood clot that obstructs a blood vessel.

Transient Ischemic Attack: A neurological event where symptoms last for less than 24 hours, with no evident permanent functional impairment.

Vessel Occlusion / Thrombosis at Groin/Access Puncture Site: Angiographic or ultrasonographic evidence of occlusion at the puncture site limiting antegrade flow to the distal limb.

Vessel Perforation / Rupture / Puncture of a Vessel Wall: Classified as follows:

Angiographic perforation: Perforation detected by the clinical site at any point during the procedure.

Clinical perforation: Perforation requiring additional treatment (including efforts to seal the perforation), or resulting in significant extravasation of blood from the site, abrupt closure, limb ischemia or death.

Vessel Pseudoaneurysm: Disruption of arterial wall confirmed by imaging study and requiring intervention.

14.0 ABBREVIATIONS

ACPP: Access Circuit Primary Patency
ADE: Adverse Device Effect
AE: Adverse Event
aTLPP: Assisted Target Lesion Primary Patency
AV: Arteriovenous
AVF: Arteriovenous Fistula
AVG: Arteriovenous Graft
CD-TLR: Clinically-Driver Target Lesion Revascularization
CEC: Clinical Events Committee
CRF: Case Report Form
CVC: Central Venous Catheter
DCB: Drug-Coated Balloon
DMC: Data Monitoring Committee
EC: Ethics Committee
eCRF: Electronic Case Report Form
ePTFE: Expanded Polytetrafluoroethylene
ESRD: End-Stage Renal Disease
FDA: Food and Drug Administration
GCP: Good Clinical Practice
GDPR: General Data Protection Regulation
HIPAA: Health Insurance Portability and Accountability Act
IFU: Instructions for Use
IRB: Institutional Review Board
ITT: Intent to Treat
KDOQI: The National Kidney Foundation Kidney Disease Outcomes Quality Initiatives
mITT: Modified Intent to Treat
OUS: Outside of the United States
PG: Performance Goal
PHI: Protected Health Information
PTA: Percutaneous Transluminal Angioplasty
RVD: Reference Vessel Diameter
SADE: Serious Adverse Device Effect
SAE: Serious Adverse Events
SG: Stent Graft
TAPP: Treatment Area Primary Patency
TCVO: Thoracic Central Vein Obstruction
TLPP: Target Lesion Primary Patency
UADE: Unanticipated Adverse Device Event

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