3D Holographic Guidance, Navigation, and Control (3D GN&C) for Endovascular Aortic Repair (EVAR)

Protocol Number: 1

National Clinical Trial (NCT) Identified Number: NCT06008613

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Funded by: NIH National Heart, Lung, and Blood Institute

Version Number: v.2

Date: 11/28/2023

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STATEMENT OF COMPLIANCE

Provide a statement that the trial will be conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable state, local and federal regulatory requirements. Each engaged institution must have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before implementation. Select one of the two statements below:

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: 3D Holographic Guidance, Navigation, and Control (3D GN&C) for Endovascular Aortic Repair (EVAR)

Study Description: This is an Early Feasibility Study to evaluate the usability, safety and functionality of 3D holographic guidance, navigation, and control (3D-GNC) as an adjunct to and confirmed by fluoroscopic imaging to be used with Cook Zenith Flex AAA Endovascular Graft.

Objectives: The goal of this clinical study is to evaluate the feasibility of using electromagnetic (EM) guidance and tracking to precisely place a Cook Zenith Flex AAA bifurcated stent graft during EVAR. EM guidance and tracking is enabled using a system consisting of:
(1) experimental 3D guidance, navigation, and control (3D-GNC) software developed by Centerline Biomedical, Inc., integrated with the company's FDA-cleared Intra-Operative Positioning System (IOPS),
(2) FDA-cleared compatible sensorized guidewires added to the Cook Zenith Flex delivery system, and
(3) 3D visualization on the IOPS mobile cart monitor and 3D holographic visualization overlaid on the patient during the procedure using a head mounted display (HMD), the Microsoft HoloLens 2.

EM guidance and tracking is hypothesized to improve the accuracy of stent graft placement in the target landing zone of the AAA, while also decreasing procedure times and limiting radiation dosage.

Endpoints: Primary Endpoints:

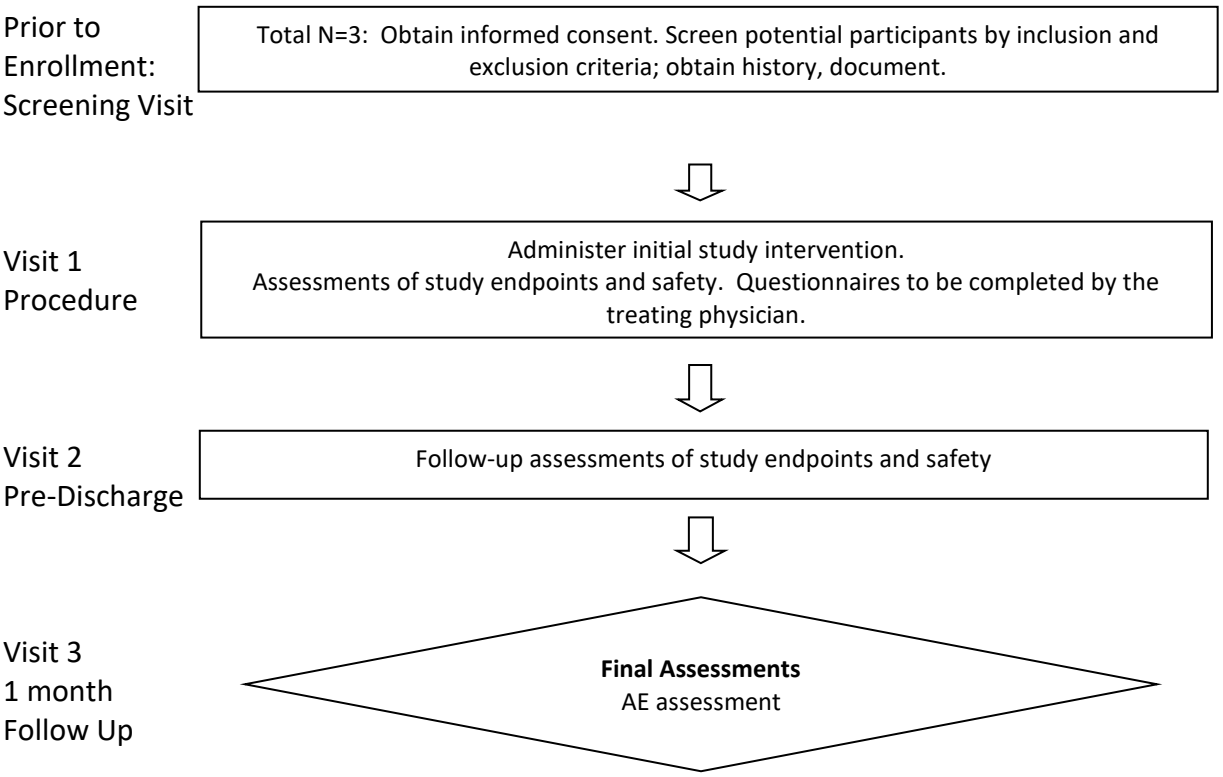
- Successful implantation of Cook Zenith AAA Endovascular Graft using the 3D-GNC device to pull the device down into position near the renal arteries along with conventional fluoroscopic imaging.
- Technical success is defined 3D-GNC placement in the intended location confirmed by fluoroscopy and digital subtraction angiography. Also followed by deployment of the graft at the intended target site, the absence of a type I or III endoleak, and graft patency without severe obstruction, confirmed by post-operative contrast-enhanced CT.
- Safety Endpoints:
  Incidence of SAE (serious adverse events) related to 3D-GNC device during the EVAR procedure or during immediate postoperative period until patient is discharged as well as incidence of non-SAE (non-Serious Adverse Events) related to 3D-GNC device during the

EVAR procedure or during immediate postoperative period until patient is discharged.

Study Population:	The population of subjects to be considered for enrollment for this study are those who determined by the treating surgeon to undergo an AAA repair by Cook Zenith AAA Endovascular Graft.
Phase:	Early Feasibility
Description of Sites/Facilities Enrolling Participants:	The study will be conducted at Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195
Description of Study Intervention:	The study procedure involves two FDA-cleared sensorized guidewires added to an FDA-approved, off-the-shelf Cook Zenith Flex AAA bifurcated stent graft delivery system, Microsoft HoloLens 2 for optional holographic visualization, and experimental software. One FDA-cleared IOPS sensorized guidewire is placed in the flush port at the hub and held in place using a Tuohy-Borst sidearm adapter and stop cock, while the second FDA-cleared IOPS sensorized guidewire is swapped for the stiff guidewire in the inner cannula once the delivery system has been advanced past the target deployment site using standard-of-care fluoroscopy for navigation. The Intervention is considered a standard EVAR procedure plus using IOPS as an adjunct to fluoroscopy for visualization & navigation.
Study Duration:	6 months
Participant Duration:	Up to 1 month Follow Up Visit or at 30 days if patient remain hospitalized

1.2 SCHEMA

Flow diagram



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Visit	Procedure / Enrollment, Study Visit 1	Discharge or at 14 days if remain hospitalized Visit 2, +/- 1 day	Follow-up visit, Study visit 3, 30 Days +/- 14 days
Informed consent	X			
Verify Inclusion / Exclusion Criteria	X			
Demographics	X			
Medical history	X			
Physical examination	X			
Vital signs	X			
Height	X			
Weight	X			
Aortic anatomy parameters (defined by CT)	X			
Hematology [a]	X			
Serum biochemistry [a]	X			
Pregnancy test [b]		X		
CT scan with contrast	X[c]		X[d]	X[d]
Administer study intervention		X		
Angiography		X		
Fluoroscopy		X		
Assessment of total contrast volume consumption		X		
Assessment of total air Kerma		X		
Adverse event review, evaluation and reporting		X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X

a. Laboratory assessment must be within 30 days prior to index procedure
b. Serum pregnancy test (women of childbearing potential) per standard of care.
c. CT-scan (with contrast) performed within 6 months before index procedure is accepted.
d. Post procedure follow up CT-scan is required either at discharge or at 30-day follow up visit.

2 INTRODUCTION

2.1 STUDY RATIONALE

Patient mortality rate for abdominal aortic aneurysms (AAAs) is approximately 80%, making them one of the leading causes of death in the U.S. It is estimated that more than 500,000 AAA patients worldwide are diagnosed annually in the developed world, with approximately 200,000 of these patients receiving treatment. If untreated, AAAs are dangerous and at risk of rupture.

AAAs can be treated with medical management, open surgical repair, and endovascular aneurysm repair (EVAR). Patients with small aneurysms below the recommended threshold for intervention, or those with perioperative risks precluding them from undergoing open surgical repair or EVAR, are typically treated with medical management. Historically, open surgical repair has been the gold standard for AAA treatment and is an acceptable treatment for younger patients. Open surgical repair of AAAs requires general anesthesia, a laparotomy or retroperitoneal exposure, and repair of the diseased aorta with a surgical graft. Elective surgical repair has a 3% to 5% 30-day mortality rate, and operative complication rates from 15-40%. The mortality rate is higher for patients with serious comorbidities such as heart, lung, or kidney disease, resulting in some of these patients being denied surgical intervention. Post-operative complications that may occur following surgical AAA repair include cardiac ischemia, arrhythmia, congestive heart failure, acute renal failure, acute pulmonary insufficiency, bleeding, distal thromboembolism and wound infection. Rare complications include ischemic colitis, stroke, and paraplegia. Impotence can occur in over 10% of male patients who have undergone aortic repair. Recovery from open repair can be prolonged and usually takes an estimated 6-12 weeks, requiring rehabilitation in a significant segment of patients. Serious late postoperative complications may occur 3-5 years after open repair, including intestinal obstruction, incisional hernia, aortoenteric fistula, graft infection, graft occlusion, and anastomotic aneurysms.

EVAR is a less invasive alternative to open surgical repair, and it carries lower rates of early mortality and morbidity. For patients who cannot undergo conventional surgical procedures due to a high operative risk, EVAR provides life-saving alternative treatment options. This method was pioneered in 1991 by Dr. Parodi, in which minimally invasive peripheral access was used to advance a delivery device to guide and deploy a stent-graft to the aneurysm site. The lower perioperative complication rates of EVAR have resulted in its dramatically increased utilization among vascular surgeons.

The standard of care for visualizing delivery devices and anatomical landmarks during EVAR is 2D x-ray fluoroscopy (“fluoro”). However, there are both quality and safety concerns related to the use of fluoro. The poor quality of the 2D x-ray projection images makes position and orientation tracking of endovascular devices challenging, especially when anatomy is unfavorable. As a result of the low-quality images, surgeons often increase fluoro time or dosage with magnification to compensate, which exposes the patient and operators to additional ionizing radiation. Furthermore, contrast dyes are required to visualize arteries under fluoro, and these dyes are potentially nephrotoxic and are contraindicated in patients with poor renal function to prevent renal failure. The poor visualization provided by fluoro limits the safety of these procedures, and can lead to increased procedure times, especially in patients with complex vascular anatomy. The 3D-GNC system integrated with IOPS could improve the safety and effectiveness of EVAR procedures by decreasing procedure time, limiting fluoro time and ionizing radiation, and improving device positioning accuracy.

IOPS is a 3D navigation system for endovascular surgery, intended for the evaluation of vascular anatomy as captured via 3D modeling from previously acquired scan data. It is intended for real time tip positioning and navigation using compatible catheters and guidewires used in endovascular interventions in the descending aorta. The system is indicated for use as an adjunct to fluoroscopy, the IOPS does not make a diagnosis. IOPS provides 3D vessel images that display the location of sensorized catheters and guidewires within patient anatomy in real-time with a dynamic model of the vessel anatomy. The IOPS uses electromagnetic field sensing equipment with sensorized guidewires and catheters and requires only a small amount of X-ray radiation and contrast dye for initial image registration and final stent graft fixation validation.

2.2 BACKGROUND

In this study, we will investigate the feasibility of combining Centerline Biomedical's IOPS with 3D holographic guidance, navigation, and control (3D-GNC) to improve stent-graft positioning prior to deployment during endovascular aortic repair (EVAR). This true 3D visualization system augments patient-specific 3D holograms of the aorta and a tracked stent graft device to the surgical field using an optical head-mounted display (HMD) to provide augmented (and "mixed") reality (AR/MR), rather than using 2D fluoro on a flat screen. The enhanced depth perception afforded by this 3D visualization system is most beneficial when navigating devices through challenging aortic anatomy, where 2D fluoro is most limited. We hypothesize that this system can prevent inaccurate device positioning, thereby decreasing the rate of post-op complications such as endoleaks or stent graft migration, costly re-intervention, and less favorable outcomes.

Previous work investigating the integration of AR [1-25]in and outside the OR has used cumbersome, custom-made, and/or costly technology. For example, Abi-Jaoudeh et al. explored the use of electromagnetic (EM) tracking to deploy thoracic EVAR stentgrafts[26] in a preclinical porcine model using a multi-detector row CT scanner. However, intraprocedural image guidance was limited to multiplanar reformatted CT images displayed on a 2D monitor instead of augmenting 3D models to the surgical field. The prototypes in this study also used only 5 DOF sensors, so orientation information was unavailable. Cochennec et al. used EM tracking with a 2D display to deploy fenestrated stentgrafts in a bench model[27] and quantified ostium-to-fenestration alignment, but this study was also done without true 3D holographic augmentation of the surgical field with digital content. In contrast, our 3D-GNC system is a new generation of surgical AR which leverages self-contained, affordable, highly interactive HMDs with IOPS. With 3D-GNC, 3D digital content is registered to the surgical field in alignment with the patient to increase 3D depth perception and facilitate effective device maneuvering, enhancing the operator's eye-hand coordination and intuitive positioning sense.

Results from our STTR Phase I grant demonstrated that 3D-GNC met the acceptance criteria for usability, procedure time reduction, stentgraft positioning and orientation accuracy, and significant radiation dose and contrast volume reduction with research prototypes integrated with the IOPS. In Phase I, a Zenith Spiral-Z AAA limb stentgraft was modified with a scallop, 6 degrees-of-freedom (DOF) sensor, and radiopaque (RO) markers for fluoro visualization. In the bench study, we used 3D-printed aortic models (n = 6) segmented from CT datasets with a wide range of aneurysmal morphology. Prototypes were built to track the stentgraft delivery device with IOPS. The IOPS-stentgraft1 wire incorporated a 5 DOF sensor near the stentgraft scallop for longitudinal advancement and a 6 DOF sensor near a nonmetal stent adjacent to the nose cone for orientation tracking. The delivery system was placed in a neutral position, the aortic phantom was draped, and the delivery device was repositioned using 3D-GNC. After deployment, photographs were taken of the landing zone and target ostium to measure accuracy

metrics. The 90th percentile of landing-zone error and orientation-error both met the acceptance criteria, having magnitudes of 1.0mm and 6.05°, respectively. After 60 trials (10 per phantom), 3D-GNC had a mean landing zone error of 0.5mm (SD = 0.36mm, 95% CI [0.43, 0.61]) and average scallop orientation error of 2.5° (SD = 2.7°, 95% CI [1.85°, 3.22°]). *In vivo*, using anesthetized swine, 10 interventionalists positioned and oriented the stentgraft delivery system to the ostia of renal or visceral branch vessels using open femoral artery access approach with 3D-GNC and standard fluoro. Procedure time, fluoro time, cumulative air kerma (CAK), and contrast material volume were tracked. Position and orientation (P&O) accuracy was determined by measuring target landing-zone distance error and scallop-ostium angular alignment error using contrast-enhanced cone beam CT (CBCT) imaging after each deployment. Technical success for 3D-GNC to position and orient the device at each renal-visceral branch ostium was 100%. In comparison with standard fluoro, 3D-GNC decreased procedure time by 56% ($p<0.001$). Positioning accuracy was comparable for both 3D-GNC and standard fluoro ($p=0.86$), while overall orientation accuracy was improved with 3D-GNC by 41.5% ($p=0.008$).

Having met the Phase I acceptance criteria, 3D-GNC was advanced to an NIH SBIR Phase II grant to further evaluate its effectiveness. The clinical study is an important next step in demonstrating the feasibility of 3D-GNC in humans. Cook Zenith Flex AAA bifurcated delivery systems are sensorized by adding two FDA-cleared IOPS sensorized guidewires without modification to the stent graft device.

2.2 Risk/Benefit Assessment

2.2.1 KNOWN POTENTIAL RISKS

Risks associated with using 3D-GNC/IOPS as an adjunct to fluoro during EVAR are predicted to be similar to those associated with the standard EVAR procedure:

a. Amputation 0.1%
b. Death 1%
c. Paralysis or paraparesis 0.1%
d. Anesthesia complications 3%
e. Edema Post-procedure syndrome 3%
f. Aneurysmal enlargement 6%
g. Embolism 6%
h. Occlusion/stenosis 3%
i. Aneurysm sac rupture 0.5%
j. Endoleak 10%
k. Pseudoaneurysm, 0.3%
l. Fistulas 1%
m. Aortic damage (perforation, dissection, bleeding, rupture) 1%
n. Fever 6%
o. Pulmonary complications 6%
p. Arterial or venous thrombosis 6%
q. Gastrointestinal complications 3%
r. Radiation complications 0.2%
s. Bleeding 6 %
t. Hematoma 9%
u. Coagulopathy 0.5%

v. Genitourinary complications (e.g., ischemia, erosion, fistula, incontinence, hematuria,) 9%
w. Renal failure/renal insufficiency 12%
x. Bowel complications (e.g., ileus, transient ischemia, infarction, necrosis) 3%
y. Hematoma (surgical) 3%
z. Stenosis of native vessel 3%
aa. Cardiac arrhythmia 9%
bb. Hepatic Failure 1%
cc. Surgical conversion to open surgery 1%
dd. Cardiac complications 6%
ee. Impotence 0.5%
ff. Vascular access site complications occlusion/stenosis 2%
gg. Cardiac failure or infarction 1%
hh. Infection 6%
ii. Vascular trauma 6%
jj. Claudication 6%
kk. Lymphatic complications 0.5%
ll. Wound complications 5%
mm. Contrast toxicity 3%
nn. Neurological complications (e.g., CVA, TIA) 3%
oo. Air embolism 1%

If the sensorized wires and/or systems malfunctions in any way, the operator can revert to the standard of care imaging system, fluoroscopy (fluoro), and complete the procedure. In the event of severe device malfunction, such as the inability to withdraw the delivery system, open conversion may be necessary.

Given that this is an investigational procedure, there may be unforeseeable risks. These risks are mitigated by the use of 3D-GNC + IOPS as an adjunct to fluoro with the option to revert to the standard of care (fluoro) in the event of any device malfunction.

2.2.2 KNOWN POTENTIAL BENEFITS

Potential benefits could be immediate expected potential benefits as well as long-term benefits to the subjects.

Immediate Potential Benefits to the subjects

- Reduced x-ray exposure According to an AAPM/RSNA Physics Tutorial for Residents (presented at the 1999 RSNA scientific assembly, published in RadioGraphics 2001;21:1033-1045), patients can receive 65 mGy/min for fluoroscopic and 1350 mGy/min for cine acquisitions. Saving even 1 minute in the course of an entire procedure is therefore a worthwhile endeavor.
- Reduced contrast dye exposure
- Reduced time of endovascular procedure / faster procedures
- IOPS uses proprietary algorithms to produce a patient specific personalized mathematically based anatomic model
- Algorithms provide interactive, precision visualization of the arteries and surgical instruments.

- IOPS gives surgeons means for real-time navigation and precise 3D visualization

Long-term potential benefits

- Lower risk of radiation induced complications, including cancer
- Lower risk of kidney damage due to nephrotoxic contrast dye
- Higher general quality of care
- Lower cost per procedure / higher OR utilization

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The additional risk to the subject for participation in this trial will be negligible. 3D-GNC + IOPS as an adjunct to fluoro provides risk mitigation by using the standard of care as a verification step for the investigational device. If the device malfunctions in any way, the attending surgeon can revert to the current standard of care, fluoroscopy, used solely on ionizing radiation for navigation of the endograft and complete the procedure.

A priori enumeration of expected adverse events for IOPS device, even those that are expected to occur at relatively low frequency minimizes the risk of occurrence of unanticipated adverse events and reduces to minimum potential risk to subjects. One of the most important risk management factors will be careful subject selection and the inclusion of experienced and trained investigators and investigative sites. Prior to enrollment, the investigative team must establish the suitability of the subject at the time of screening.

Based on the preclinical data for IOPS device, its characteristic, literature data for EVAR procedures and expected extent of probable risks and harms, but also listed benefits and their magnitude, as well as very detailed risk mitigations minimizing the probability of a harmful event, favorable risk/benefit profile for IOPS device is expected.

However, due to the investigational status of the 3D-GNC used in this manner, the benefit/risks are not yet fully known.

An independent medical monitor will adjudicate all SAEs for device or procedure-relatedness.

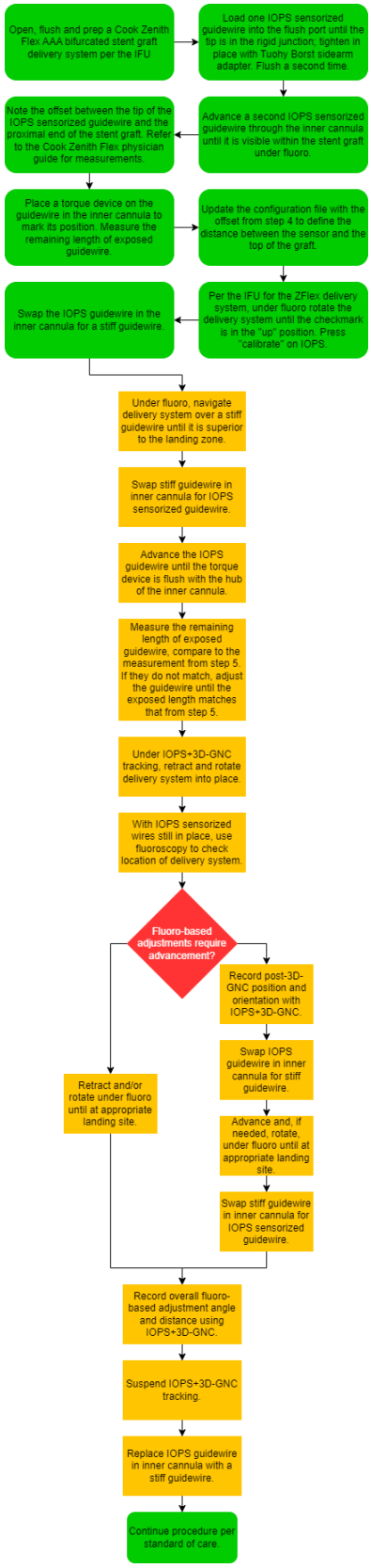
3 OBJECTIVES AND ENDPOINTS

The goal of this clinical study is to evaluate the feasibility of using electromagnetic (EM) guidance and tracking to precisely place a Cook Zenith Flex AAA bifurcated stent graft during EVAR. EM guidance and tracking is enabled using a system consisting of the following: (1) experimental 3D guidance, navigation, and control (3D-GNC) software developed by Centerline Biomedical, Inc., integrated with the company's FDA-cleared Intra-Operative Positioning System (IOPS) (2) FDA-cleared compatible sensorized guidewires added to the Cook Zenith Flex delivery system and (3) 3D visualization on the IOPS mobile cart monitor and 3D holographic visualization overlaid on the patient during the procedure using a head mounted display (HMD), the Microsoft HoloLens 2. Planning and execution of each case will be major steps in demonstrating feasibility of the technology beyond non-clinical and preclinical testing.

EM guidance and tracking is hypothesized to improve the accuracy of stent graft placement in the target landing zone of the AAA, while also decreasing procedure times and limiting radiation dosage. Using compatible sensorized guidewires within the delivery system and experimental software, 3D visualization of the tracked delivery system and patient vasculature during the procedure is enabled. This not only provides an improvement in image quality over standard 2D fluoro, but it also is hypothesized to reduce the dependence on ionizing radiation for guidance and navigation of devices. The Cook Zenith Flex delivery system is sensorized using two FDA-cleared IOPS sensorized guidewires so EM guidance and tracking of the delivery system is possible. Each FDA-cleared IOPS sensorized guidewire is equipped with a single 5 degrees-of-freedom (5DOF) sensor, two guidewires are needed to enable position and orientation tracking. A 3D model of patient vasculature is created in IOPS using the pre-op CT scan. During the procedure, this 3D model is registered to the patient's coordinate system in the room, and the location of the delivery system within the body is tracked using real-time position and orientation information from the sensors within an EM field created using a field generator mounted to the operating table. Refer to the IFU for IOPS for more details. To verify position and orientation tracking accuracy with the EM guidance and tracking system, the stent graft is first navigated using standard of care x-ray fluoroscopy above the target location. Per the IFU for the Cook Zenith Flex AAA delivery system, the delivery system shall only be advanced over a stiff wire. Once the IOPS guidewire is in the inner cannula, the delivery system will not be advanced to minimize the risk of vessel damage. Then, the stiff guidewire in the inner cannula is swapped for an IOPS sensorized guidewire. With one FDA-cleared IOPS sensorized guidewire in the inner cannula and a second FDA-cleared IOPS sensorized guidewire in the flush port, IOPS + 3D-GNC can be used to track the position and orientation of the stent graft. Under IOPS + 3D-GNC tracking, the delivery system will be retracted and rotated into place. Standard of care x-ray fluoroscopy is then used to check the position and orientation of the delivery system. If adjustments require advancing the delivery system, the post-3D-GNC position and orientation of the delivery system are recorded with IOPS+3D-GNC, then the IOPS guidewire in the inner cannula will be swapped for the stiff guidewire. After the advancement is made, the stiff guidewire is swapped back for the IOPS guidewire, and the overall adjustment angle and distance are recorded by IOPS+3D-GNC. If adjustments only require retracting and/or rotating the delivery system, these will be done with the IOPS guidewire still in place so IOPS+3D-GNC can record the adjustments in real time. Once the delivery system is confirmed at the deployment location, 3D-GNC tracking is suspended, a wire guide will be replaced within the device and the procedure then proceeds per standard of care. The flowchart on the following page further clarifies these procedural steps. 3D-GNC time, total procedure time, CAK, and fluoro time will be recorded as well.

Primary Endpoints:

- Successful implantation of Cook Zenith AAA Endovascular Graft using the 3D-GNC device confirmed by fluoroscopic imaging.
- Technical success is defined 3D-GNC placement in the intended location confirmed by fluoroscopy and digital subtraction angiography. Also followed by deployment of the graft at the intended target site, the absence of a type I or III endoleak, and graft patency without severe obstruction, confirmed by post-operative contrast-enhanced CT.
- Safety Endpoints:
  Incidence of SAE (serious adverse events) related to 3D-GNC device during the EVAR procedure or during immediate postoperative period until patient is discharged as well as incidence of non-SAE (non-Serious Adverse Events) related to 3D-GNC device during the EVAR procedure or during immediate postoperative period until patient is discharged.


Open, flush and prep a Cook Zenith Flex AAA bifurcated stent graft delivery system per the IFU
Load one IOPS sensorized guidewire into the flush port until the tip is in the rigid junction; tighten in place with Tuohy Borst sidearm adapter. Flush a second time.
Advance a second IOPS sensorized guidewire through the inner cannula until it is visible within the stent graft under fluoro.
Note the offset between the tip of the IOPS sensorized guidewire and the proximal end of the stent graft. Refer to the Cook Zenith Flex physician guide for measurements.
Place a torque device on the guidewire in the inner cannula to mark its position. Measure the remaining length of exposed guidewire.
Update the configuration file with the offset from step 4 to define the distance between the sensor and the top of the graft.
Per the IFU for the ZFlex delivery system, under fluoro rotate the delivery system until the checkmark is in the "up" position. Press "calibrate" on IOPS.
Swap the IOPS guidewire in the inner cannula for a stiff guidewire.
Under fluoro, navigate delivery system over a stiff guidewire until it is superior to the landing zone.
Swap stiff guidewire in inner cannula for IOPS sensorized guidewire.
Advance the IOPS guidewire until the torque device is flush with the hub of the inner cannula.
Measure the remaining length of exposed guidewire, compare to the measurement from step 5. If they do not match, adjust the guidewire until the exposed length matches that from step 5.
Under IOPS+3D-GNC tracking, retract and rotate delivery system into place.
With IOPS sensorized wires still in place, use fluoroscopy to check location of delivery system.
Fluoro-based adjustments require advancement?
Record post-3D-GNC position and orientation with IOPS+3D-GNC.
Swap IOPS guidewire in inner cannula for stiff guidewire.
Advance and, if needed, rotate, under fluoro until at appropriate landing site.
Swap stiff guidewire in inner cannula for IOPS sensorized guidewire.
Retract and/or rotate under fluoro until at appropriate landing site.
Record overall fluoro-based adjustment angle and distance using IOPS+3D-GNC.
Suspend IOPS+3D-GNC tracking.
Replace IOPS guidewire in inner cannula with a stiff guidewire.
Continue procedure per standard of care.

4 STUDY DESIGN

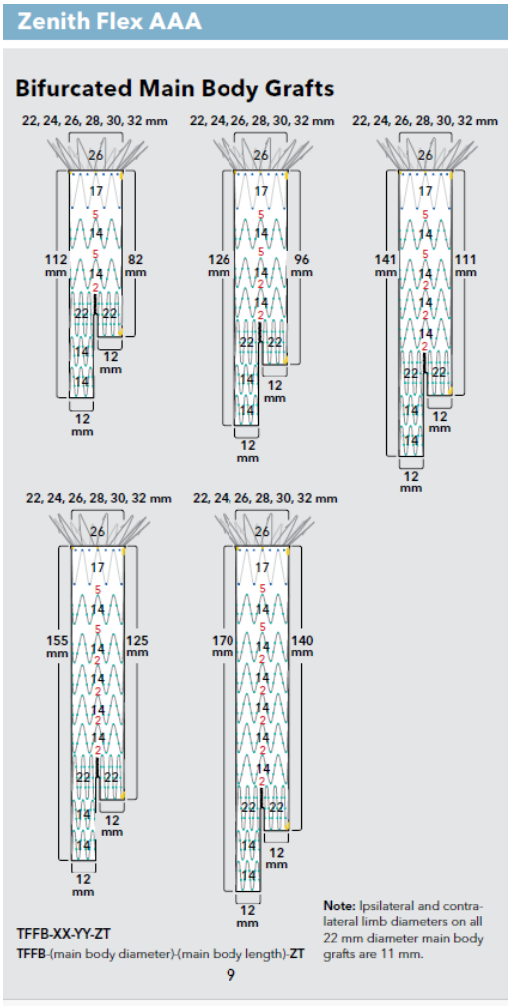
4.1 OVERALL DESIGN

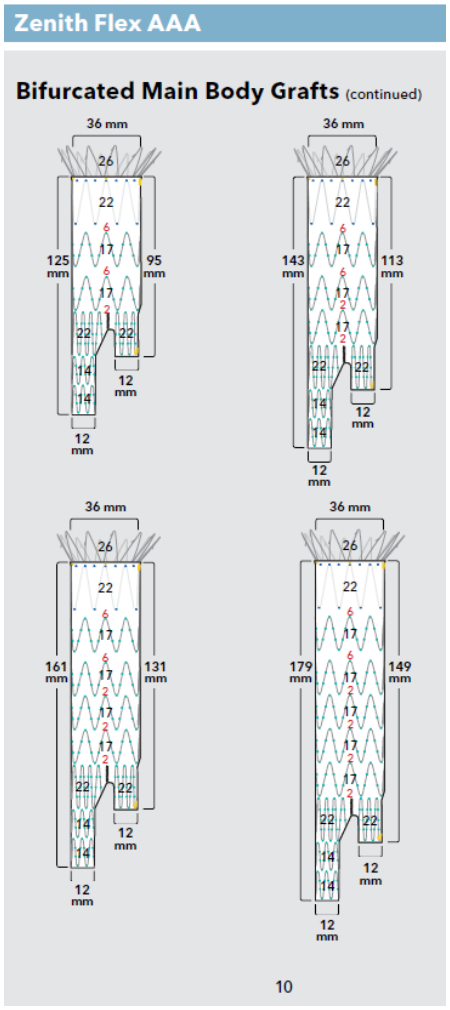
This study is a single-center, prospective, single arm, interventional study to evaluate the feasibility of using electromagnetic (EM) guidance and tracking to precisely place a Cook Zenith Flex AAA bifurcated stent graft during EVAR. The study will enroll 3 subjects at one site: Cleveland Clinic, Cleveland, Ohio.

EM guidance and tracking is enabled using a system consisting of the following: (1) experimental 3D guidance, navigation, and control (3D-GNC) software developed by Centerline Biomedical, Inc., integrated with the company's FDA-cleared Intra-Operative Positioning System (IOPS) (2) FDA-cleared compatible sensorized guidewires added to the Cook Zenith Flex delivery system and (3) 3D visualization on the IOPS mobile cart monitor and 3D holographic visualization overlaid on the patient during the procedure using a head mounted display (HMD), the Microsoft HoloLens 2.Planning and execution of each case will be major steps in demonstrating feasibility of the technology beyond non-clinical and preclinical testing.

EM guidance and tracking is hypothesized to improve the accuracy of stent graft placement in the target landing zone of the AAA, while also decreasing procedure times and limiting radiation dosage. Using compatible sensorized guidewires within the delivery system and experimental software, 3D visualization of the tracked delivery system and patient vasculature during the procedure is enabled. This not only provides an improvement in image quality over standard 2D fluoro, but it also is hypothesized to reduce the dependence on ionizing radiation for guidance and navigation of devices. The Cook Zenith Flex delivery system is sensorized by adding two FDA-cleared IOPS sensorized guidewires so EM guidance and tracking of the delivery system is possible. One FDA-cleared IOPS sensorized guidewire is placed in the flush port, the second guidewire is advanced through the inner cannula under fluoroscopy to a predetermined location between the top of the stent graft and the ipsilateral limb of the stent graft. The guidewire location will be determined during this step based on measurements from the Cook Zenith Physician's Pocket Reference Guide, visibility of the stents under fluoroscopy, the patient's anatomy and specific stent graft being used, and the 50cm circle dimension of the electromagnetic tracking field. A 3D model of patient vasculature is created in IOPS using the pre-op CT scan. During the procedure, this 3D model is registered to the patient's coordinate system in the room, and the location of the delivery system within the body is tracked using real-time position and orientation information from the sensors within an EM field created using a field generator mounted to the operating table. Refer to the IFU for IOPS for more details. The flush port is loaded with an IOPS sensorized guide wire loaded through a Tuohy-Borst with a stop cock. The device is flushed before and after the IOPS sensorized guide wire is placed. To verify position and orientation tracking accuracy with the EM guidance and tracking system, the stent graft is first navigated past the target location using standard of care x-ray fluoroscopy over a stiff guide wire. Then, the stiff wire in the inner cannula is removed and swapped for a sensorized FDA-cleared IOPS guidewire, which provides longitudinal position information for the stent graft. The IOPS guidewire in the inner cannula is advanced until its tip is located at a predetermined location between the top of the stent graft and the ipsilateral limb of the stent graft. The offset between the sensor at the tip of the IOPS guidewire and the top of the stent graft is updated in the configuration file. Stents are used as reference points under fluoroscopy to obtain the offset measurement, referring to the diagram in the Cook Zenith Physician's Pocket Reference

Guide, shown in the images below. A second sensorized FDA-cleared IOPS guidewire in the flush port that was already in position provides orientation information. 3D-GNC tracking is then used to navigate by withdrawing and rotating the stent graft precisely to the target site. Per the IFU for the Cook Zenith Flex, the delivery system shall only be advanced over a stiff wire. Therefore, when the IOPS guidewire is in the inner cannula, the delivery system will only be retracted and rotated into place since it was navigated past the target site under fluoro while the stiff wire was still in place. Finally, the position and orientation of the stent graft is confirmed using standard of care fluoroscopy prior to deployment. If fluoro-based adjustments requiring advancement of the delivery system are needed, the post-3D-GNC position and orientation of the delivery system are recorded with IOPS+3D-GNC, then the IOPS guidewire in the inner cannula will be swapped for a stiff guidewire during the adjustments. After the adjustments, the stiff guidewire is swapped back for the IOPS guidewire. If fluoro-based adjustments require only retraction and/or rotation, the IOPS guidewire in the inner cannula can remain in place. After adjustments are made and fluoro confirms the delivery system is at the target site, the overall adjustment angle and distance are recorded by IOPS+3D-GNC. Once the position and orientation are confirmed, IOPS+3D-GNC tracking is suspended, the IOPS guidewires are removed, and the stiff wire is placed in the inner cannula. Deployment of the stent graft then proceeds per standard of care. Post-op CT will also be used per the standard of care to verify the longitudinal position of the stent graft and the check-mark's true rotational position.





4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study is designed to show safety and feasibility of 3D-GNC used with Cook Zenith AAA endovascular graft. There are no controls being used in the analysis of the data. The data is meant to merely show that the system and its use is safe and meets the performance criteria already set.

4.3 END OF STUDY DEFINITION

End of study is defined as the date of discharge of the last patient enrolled in the study after the completion of the study intervention and collection of its patient data per protocol. A subject is considered to have completed the study if it has completed all phases of the study including the procedure and the discharge assessment and data collection.

After each scheduled review of the accumulating safety data, medical monitor will provide the PI with a written recommendation whether to continue the study as planned, suspend enrollment, or terminate enrollment in the clinical investigation early for safety reasons. Given the small size of the study, the medical monitor will serve the purpose typically performed by a clinical events committee (CEC) and DSMB. The medical monitor recommendations will be reviewed by the PI. The PI reserves the right to terminate the clinical investigation at any time and for any reason.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. The patient meets the instructions for use (IFU) for the 24-28 mm body Cook Zenith Flex AAA bifurcated stent graft.
    a. Adequate iliac/femoral access compatible with the required introduction system
    b. Non aneurysmal infrarenal aortic segment (neck) proximal to the aneurysm:
        i. With a length of at least 15mm
        ii. With a diameter measured outer wall to outer wall of no greater than 26mm and no less than 20mm
        iii. With an angle less than 60 degrees relative to the long access of the aneurysm and
        iv. With an angle less than 45 degrees relative to the axis of the suprarenal aorta
    c. Iliac artery distal fixation site greater than 10mm in length and 7.5-20mm in diameter (measured outerwall to outerwall).

2. Male/female, aged ≥ 18
3. Patient fulfilling criteria for needing endovascular repair of abdominal aortic aneurysm according to routine clinical practice criteria of the participating center
4. Women of childbearing potential must be non-pregnant, non-lactating, and not planning to become pregnant during the course of the trial; and have a negative urine or serum pregnancy test within 7 days prior to index procedure
5. Provide written informed consent as applicable and defined by site country regulation

6. Stated willingness to comply with all study procedures and availability for the duration of the study

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Contraindications for Cook Zenith Flex Aortic endograft:
    a. Patients with known sensitivities or allergies to stainless steel, polyester, solder (tin, silver), polypropylene, or gold
    b. Patients with a systemic infection who may be at increased risk of endovascular graft infection
2. Presence of electronic implants, e.g., cardiac pacemaker, AICD or nerve stimulator
3. Presence of metallic implants above the knee, e.g., artificial hip
4. Patients not willing or able to give informed consent
5. Pregnant women
6. Patients' inability to have a contrasted CT scan
7. Current or planned participation in any other investigational drug or medical device clinical study that has not completed primary endpoint(s) evaluation;
8. Other medical, social, or psychological issues that in the opinion of the investigator preclude the subjects from receiving this treatment, and the procedures and evaluations pre- and posttreatment
9. Anatomy outside of the IFU for a 24-28 mm Cook Zenith Flex AAA bifurcated stent graft

5.3 LIFESTYLE CONSIDERATIONS

Not Applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently undergo the study intervention or entered in the study. All informed consents, source documentation, rationale for screen failures and applicable documentation will be recorded.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Two FDA-cleared IOPS sensorized guidewires are used in this study to enable IOPS tracking of an off-the-shelf Cook Zenith Flex AAA bifurcated stent graft. Under sterile conditions in the operating room, while access is being established, an off-the-shelf Cook Zenith Flex AAA bifurcated stent graft delivery system will be sensorized using one FDA-cleared IOPS sensorized 0.035" guidewire in the flush port to allow orientation tracking. This IOPS sensorized guidewire is advanced through the flush port through a

Tuohy-Borst sidearm adapter (with a stop cock on the sidearm) to the rigid junction at the hub. This guidewire provides rotational information to track the orientation of the delivery system. The Cook Zenith device is advanced over a standard stiff wire into the aorta just above the intended deployment location. The stiff guide wire is removed and the second IOPS sensorized guidewire is advanced through the inner cannula to a predetermined location between the top of the stent graft and the ipsilateral limb of the stent graft. This guidewire provides longitudinal position information. Each IOPS wire contains one sensor, two wires are needed to enable electromagnetic tracking. The process for sensorizing the delivery system is as follows:

1. Open and flush a Cook Zenith Flex AAA bifurcated stent graft delivery system.
2. Prepare the delivery system per the IFU.
3. Pre-wet two IOPS sensorized guidewires to activate their hydrophilic coatings and improve lubricity.
4. Attach a Tuohy-Borst sidearm adapter to the luer fitting on the flush port side arm of the Zenith Stent graft. Attach a stop cock to the sidearm of the Tuohy-Borst sidearm adapter.
5. Load one IOPS sensorized guidewire into the flush port of the Cook Zenith Flex AAA delivery system, as shown in Figure 1. Advance the guidewire to the rigid junction at the hub, as shown in detail in Figure 2. The exact depth of the guidewire tip in the rigid junction of the flush port is arbitrary and is taken into account during calibration.

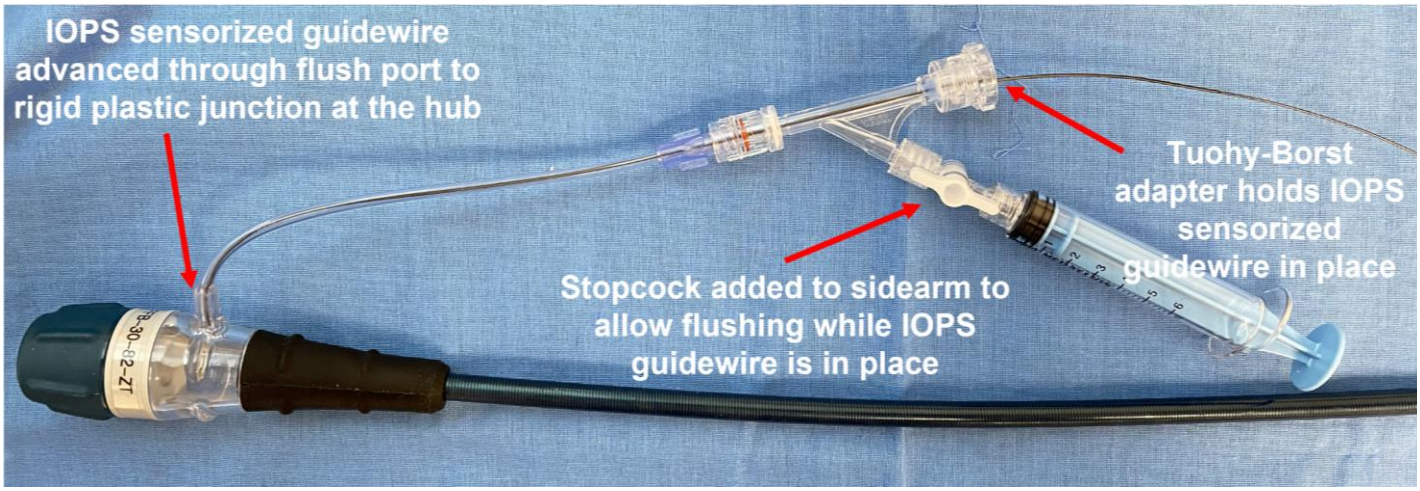


Figure 1: Cook Zenith Flex AAA delivery system with IOPS sensorized guidewire in the flush port.

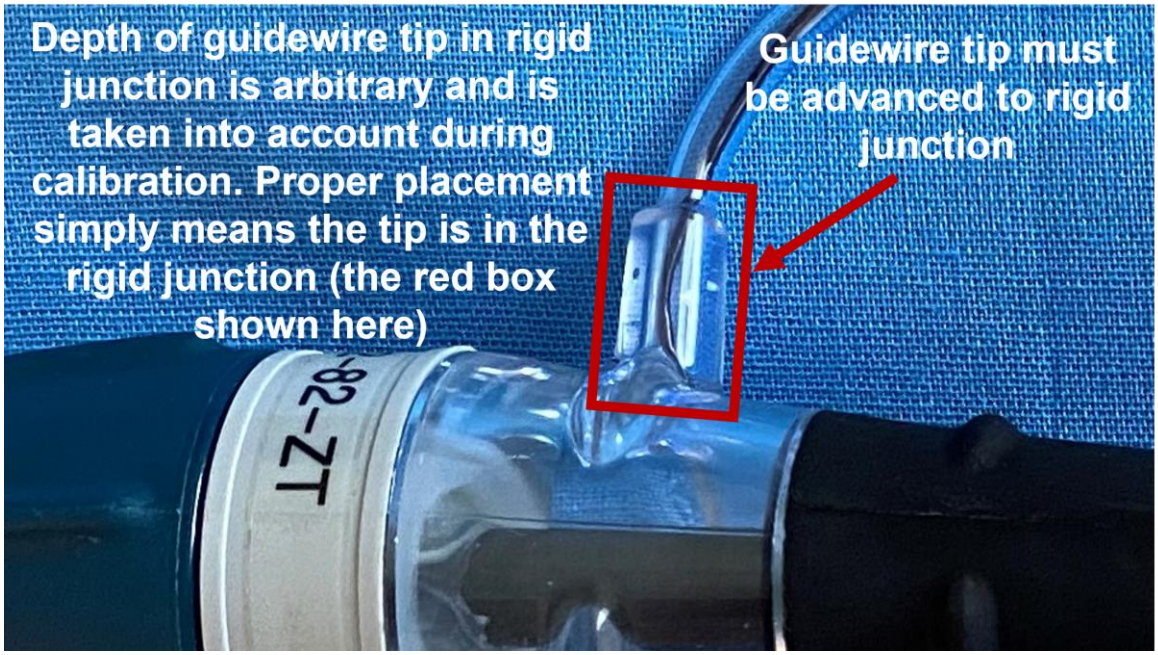


Figure 2: Guidewire for rotational information must be advanced to the rigid junction at the hub.

6. Reflush the stent graft via the stop cock on the sidearm and tighten the Tuohy-Borst down on the sensorized wire to achieve hemostasis and maintain position.
7. Advance the second IOPS sensorized guidewire through the inner cannula until it is visible within the stent graft under fluoroscopy. Choose the calibrated location for the IOPS guidewire between the top of the stent graft and the ipsilateral limb of the stent graft based on measurements from the Cook Zenith Physician's Pocket Reference Guide, visibility of the stents under fluoroscopy, the patient's anatomy and the specific dimensions of the stent graft being used, and the 50cm circle dimension of the electromagnetic field. Note the offset between the

sensor in the tip of the IOPS guidewire and the proximal end of the stent graft, using the measurements in the Cook Zenith Physician's Pocket Reference Guide and the visible stents under fluoroscopy as references.

8. Mark the position of the IOPS guidewire in the inner cannula using a torque device. Measure the length of remaining exposed IOPS guidewire. Update the configuration file with the offset between the IOPS guidewire and proximal end of the stent graft from step 7.
9. Under fluoroscopy outside the patient, rotate the delivery system until the checkmark on the contralateral limb is observed to be in the proper "up" position. For the Cook Zenith Flex, this occurs when the checkmark is observed as a straight line on the patient's contralateral side. A user then presses "calibrate" on IOPS to lock in the angular calibration.
10. The IOPS sensorized guidewire in the inner cannula can now be removed.
11. The Zenith stent graft is introduced into the patient over a standard stiff guide wire and navigated using standard of care fluoroscopy into the aorta until located just above the renal arteries superior to its intended deployment target landing zone.
12. The stiff guide wire is removed from the inner cannula.
13. The stiff wire in the inner cannula is swapped for the IOPS sensorized guidewire, which is placed in its calibrated position within the stent graft by advancing it until the torquer meets the hub. The remaining exposed guidewire can be measured and compared to that from step 8 to further confirm its position.
14. IOPS + 3D-GNC is used to retract and rotate the delivery system precisely to the target landing zone.
15. Fluoroscopy is used to verify the position and orientation of the delivery system. Fluoro-based adjustments are recorded using IOPS+3D-GNC.
    a. If fluoro-based adjustments require advancement of the delivery system, the post-3D-GNC position and orientation of the delivery system are recorded with IOPS+3D-GNC, then the IOPS guidewire in the inner cannula is swapped for a stiff guidewire during advancement. After the adjustment, the wires are switched back so IOPS+3D-GNC can record the overall adjustment angle and distance.
    b. If fluoro-based adjustments require only retraction and/or rotation of the delivery system, the IOPS guidewire in the inner cannula can remain in place. Overall adjustment angle and distance are recorded by IOPS+3D-GNC.
16. IOPS+3D-GNC tracking is suspended. The IOPS sensorized guidewire in the inner cannula of the delivery system is replaced by the stiff wire for deployment of the Zenith stent graft.
17. Procedure continues per the standard of care.

Additional detail on the sensorization and calibration procedures can be found in the attached "3D-GNC-SoftwareDesignSpec." Before insertion, the main body delivery system is placed on the patient's abdomen under fluoroscopy to determine the orientation of the contralateral limb radiopaque marker, per the IFU for the Cook Zenith Flex delivery system. The sidearm of the hemostatic valve is used as an external reference to the contralateral limb radiopaque marker. Simultaneously, a calibration step is added to define the "up" position of the sensorized delivery system relative to the orientation of the radiopaque marker. The calibration is performed when the radiopaque check-mark is observed under fluoro to be in the "up" position, which occurs when the check-mark is observed as a straight line on the patient's contralateral side.

Per the IFU for IOPS, the registration CBCT scan is acquired. This registration scan allows the IOPS to spatially orient the aorta model in the coordinate space of the patient during the procedure. The sensors at the tips of the two sensorized IOPS wires, as well as the proximal end of the stent graft, are captured

within the registration scan. The IOPS guidewire in the inner cannula is located in a predetermined location between the top of the stent graft and the ipsilateral limb of the stent graft. Since the depth offset between the IOPS guidewire in the inner cannula and the stent graft is fixed, only angular calibration based on the IOPS guidewire in the flush port is needed. With the sensorized delivery system in the tracking field and visible under fluoro the delivery system is rotated so that the checkmark indicates that the contralateral limb is in the proper orientation relative to the "up" vector of the tracking field. For the Cook Zenith Flex the proper orientation of the checkmark occurs when it appears as a straight line on the patient's contralateral side. At this point a user clicks the "Calibrate" button in the IOPS software. This records calibration information based on the current tracking data for the sensors.

Intra-Op
After modification and calibration, the standard EVAR procedure is followed, using an experimental version of IOPS software as an adjunct to fluoroscopy to assist with placement of the stent graft. The delivery system is first navigated over a stiff wire past the target landing zone using standard of care x-ray fluoroscopy. Then, the stiff wire is swapped for the IOPS guidewire, and IOPS+3D-GNC is used to precisely retract and rotate the delivery system to the target landing zone. The position and orientation of the stent graft is confirmed using x-ray fluoroscopy prior to deploying the stent graft. During the procedure, the physician has the option to view the 3D aorta model and EM tracked devices on a 2D monitor on the IOPS mobile cart (with option to display on OR monitor) or use the Microsoft HoloLens 2. The HoloLens 2 is a head-mounted display (HMD) which uses augmented reality (AR) to project a hologram of the patient's aorta model and EM tracked devices onto the patient's abdomen, enabling true 3D visualization.

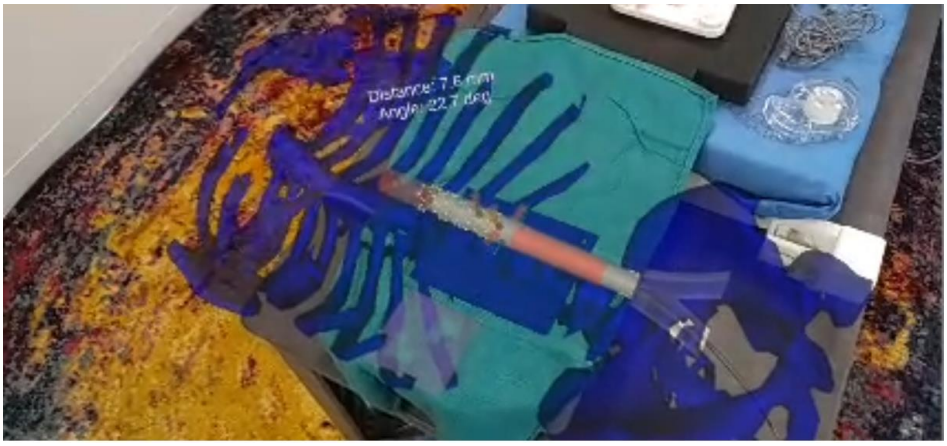


Figure 2: The HoloLens 2 projects a hologram of the EM tracked devices within the patient's aorta model onto the patient's abdomen.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The investigational device is kept in a secure location with restricted access, stored according to the conditions outlined in the Instructions for Use (IFU). The investigational product is intended solely for use by investigators and can only be used in clinical study subjects. Study documentation that must be maintained includes:

- Packing slips provided with each investigational product shipment (signed and dated)
- Accountability records of each subject operated with the investigational device (this may include source documents and/or package labels of investigational devices used)
- An up-to-date and accurate investigational device accountability log
- Copies of Investigational product Return Forms (sterile and opened/malfunctions)

The Investigator and/or authorized designee will maintain adequate records of the receipt, use, and disposition of the investigational devices as required by protocol and applicable local regulations.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Device Name	PMA/510k #	Indications
Zenith AAA Endovascular Graft And H&L-B One-Shot Introduction System	P020018/S001-059	The device is indicated for the endovascular treatment of patients with abdominal aortic or aorto-iliac aneurysms having morphology suitable for endovascular repair.
Intra-Operative Positioning System; Simple Curve Catheter, Reverse Curve Catheter ; Angled Tip Guidewire ; Tracking Pad ; Guidewire Handle	K190106	The IOPS (Intra-Operative Positioning System) is intended for the evaluation of vascular anatomy as captured via 3D modeling from previously acquired scan data. It is intended for real time tip positioning and navigation using sensor equipped compatible catheters and guidewires used in endovascular interventions in the descending aorta. The system is indicated for use as an adjunct to fluoroscopy. The IOPS does not make a diagnosis.

6.2.3 PRODUCT STORAGE AND STABILITY

The IOPS Mobile Cart will be stored at the Cleveland Clinic in the locked storage area with restricted access between cases. Prior to each case, the IOPS Mobile Cart will be disinfected and placed in the operating room.

Between cases, the HoloLens2 headset will be stored in a locked storage cabinet with restricted access. Prior to each case, the HoloLens2 will be cleaned and disinfected using the following procedure:

- A dry, lint-free microfiber cloth will be used to remove dust from the visor.
- A cloth lightly moistened with medical 70% isopropyl alcohol will be used to gently wipe the visor and all other hard surfaces of the headset.
- The HoloLens2 will be dried completely.

After cleaning/disinfecting the HoloLens2, it will be staged in the non-sterile zone of the operating room. An assistant will place the headset on the surgeon's head and adjust it to their specifications, such that the surgeon remains sterile by not touching the headset after scrubbing in. Any adjustments to the headset will be made by an assistant.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

In the event the 3D-GNC use was stopped for any reason, or a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator may choose to revert to standard fluoroscopy to complete the patient's procedure. This discontinuation will be reported as an adverse event (AE). If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason for discontinuation of the study device use
- Alternate procedure
- AE/SAE
- Physician Usability Questionnaire

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

In addition to the patient's right to withdraw from the trial at any time, an investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- Withdrawal of consent – Subject decides to withdraw from the study. This decision must be an "independent decision" that is documented in the source documentation and in the CRF.
- Investigator discretion – The Investigator may choose to withdraw a subject from the study if there are safety concerns
- Death
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to schedule their procedure for more than 26 weeks.

Subjects who sign the informed consent form but do not receive the study intervention may be replaced. Subjects who sign the informed consent form and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

Per standard of care for EVAR procedures, a follow-up 30-day post-op CT scan should be acquired.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Enrollment/Screening Visit

The subject will be considered enrolled into the study after all of the following criteria have been met:

- Signed and dated ICF, this may occur up to 30 days prior to index procedure
- Verification that subject meets all study entrance criteria
- Completion of all baseline procedures

The following baseline assessments must be performed, and the subject must meet all inclusion criteria and none of the exclusion criteria prior to the initiation of the study intervention with the 3D-GNC + IOPS device:

1. **Demographic Data:** including but not limited to age, sex, race, and ethnicity.
2. **Medical/Surgical History:** including but not limited to a vascular and non-vascular clinical history, risk classification assessment (by ASA grade, NYHA CHF class, and SVS/ISCVC categorization), documented history of COPD, medical and surgical cardiovascular background (i.e., history of cardiac, kidney or peripheral vascular disease, diabetes, hypertension, bleeding history, hypercholesterolemia, TIA, stroke, renal insufficiency, allergies, tobacco use), small bowel ischemia, erectile dysfunction, infertility status (for all female subjects), and other relevant medical history that can influence a patient's quality of life (both positively and negatively).
3. **Physical Examination:** Body Mass Index (BMI) as determined from height and weight measurements, blood pressure (BP), heart rate (HR), and oxygen saturation must be completed prior to index procedure.
4. **Laboratory Evaluations:** The following tests must be completed within 6 weeks prior to index procedure: a) Hematology tests: complete blood count (CBC) – WBC, HgB, HCT, Platelets b) Chemistry tests: complete biochemistry test per routine practice.
5. **CT scan (with contrast):** CT scan (with contrast) is required for the screening assessment. CT scan can be performed during screening period or preexisting CT scan with contrast not older than 6 months can be used for screening purposes.
6. **Aortic anatomy with morphology** (aneurysm size, neck length, iliac morphology, neck and iliac angulations)

7. **Pregnancy test** for women with childbearing potential per standard of care.

All screening assessments must be completed prior to the subject's index procedure. All pre-index procedure assessments will be carried out as specified in the schedule of events.

Index Procedure

The Instructions for Use (IFU) for the IOPS device provide details on the product, safety, storage, design, deliverability, and sizing specifications. The IFU for the Cook Zenith Flex AAA bifurcated stent graft delivery system provide details on the product, safety, storage, design, deliverability, and sizing specifications. The information within each of these respective documents should be referenced prior to each procedure and implantation of the investigation device. All subjects will undergo a pre-procedure evaluation. Each procedure will be performed in an operating room, or an interventional suite equipped for angiography and open surgical procedures. The method of anesthesia for each procedure will be chosen on a case-by-case basis in consultation with the anesthesiologist and implanting physician. The subject will be placed in a supine position, prepped, and draped in a sterile manner. Bilateral access will be gained per local practice. The ipsilateral side will be determined by the implanting physician and based upon pre-operative imaging of the iliac arteries.

Index procedure represents standard EVAR procedure with adjunct usage of investigated device, IOPS + 3D GN&C, while EVAR part of the procedure will be performed by local clinical, site-specific practice. Procedure starts with initial arterial access on either the contralateral or ipsilateral limb and concludes when the access sites are closed in a standard manner according to local practice (e.g., no wound oozing or bleeding). The index procedure is divided in the series of the steps as follows:

Fluoroscopy section 1
Step 1. Insert introducer sheath via artery access over stiff guide wire
Step 2. Remove introducer sheath and place Cook Zenith Flex AAA delivery system into infrarenal aorta over stiff guide wire
Step 3. Navigation/adjustment of delivery system using standard of care fluoroscopy until located above the target site

IOPS + 3D-GNC (device positioning) section
Step 4. Swap stiff guidewire in inner cannula for IOPS sensorized guidewire. Delivery system now has one sensorized guidewire in the inner cannula and one sensorized guidewire in the flush port
Step 5. Retract and rotate Cook Zenith Flex AAA delivery system to target site using IOPS + 3D-GNC

Simultaneous IOPS + 3D-GNC and fluoroscopy section
Step 6. Angiography to mark renal arteries
Step 7. Confirmation using fluoro that Cook Zenith Flex AAA delivery system is located at target site
Step 7a. If fluoro reveals adjustments require advancement of the delivery system, record the post-3D-GNC position and orientation of the delivery system with IOPS+3D-GNC, then swap the IOPS guidewire in the inner cannula for a stiff guidewire during the adjustment. Switch the wires back after the adjustments are made
Step 7b. If fluoro-based adjustments require only retraction and/or rotation of the delivery system, the IOPS guidewire in the inner cannula remains in place

Step 8. IOPS+3D-GNC records the overall fluoro-based adjustment angle and distance to assess system accuracy

Fluoroscopy section 2

Step 9. Suspend IOPS+3D-GNC tracking
Step 10. Remove IOPS sensorized guidewires from Cook Zenith Flex AAA delivery system
Step 11. Re-insert the stiff wire into the inner cannula of the Cook Zenith Flex AAA delivery system
Step 12. Deployment of first component (body) of the stent graft
Step 13. Additional angiographies to visualize lowest renal artery
Step 14. Catheterization of contralateral limb
Step 15. Implantation of contralateral limb
Step 16. Implantation of additional components
Step 17. Ballooning
Step 18. Final angiography
Step 19. Additional corrections if necessary

During the procedure, the following metrics will be tracked:

- Total procedure time
- 3D-GNC time
- Total fluoro time
- Cumulative Air Kerma (CAK)
- Assessment of volume of contrast used
- Post-3D-GNC adjustments in tracked delivery device position & orientation under fluoro
    - Acceptance criteria: 80^{th} percentile of the distribution of adjustment in tracked delivery device position & orientation will be ≤ 6mm and ≤ 21^{o}, respectively
    - The stent graft will be retracted and rotated into place using the 3D-GNC system. Then, fluoro will be used to check the accuracy of the reported position and orientation from 3D-GNC. The magnitude and direction of all adjustments made using fluoro will be recorded. If fluoro-based adjustments require only retraction and rotation of the delivery system, the IOPS guidewire in the inner cannula remains in place and adjustments are tracked live. If fluoro-based adjustments require advancement of the delivery system, the position and orientation of the delivery system post-3D-GNC is recorded, then the IOPS guidewire in the inner cannula is swapped for the stiff guidewire. The adjustments are made with the stiff guidewire in place, then the stiff guidewire is swapped back for the IOPS guidewire so IOPS+3D-GNC can record the overall adjustment angle and distance.
- Operator-suggested improvements to 3D-GNC
    - Feedback will be collected using a standard system usability scale (SUS) and a usability-related end-user requirements survey
- Adverse event monitoring
    - Monitoring will begin once the subject is enrolled into the study
    - Refer to section 8.2 Safety and other assessments

If a device malfunction occurs, detailed data on complications and their management will be collected, reported, and recorded in CRF within 72 hours of the index procedure date. In the event of a device failure/malfunction, Cleveland Clinic will follow their standard of care procedures and investigator is allowed to switch to standard EVAR protocol to ensure the safety of the subject. In case that conversion

to open surgery occurs, it will be recorded on the eCRF. Cleveland Clinic will follow their standard of care procedures and/or use commercially-available products to ensure the safety of the subject.

Post-Procedure Care
The procedure is considered complete when the access sites are closed in a standard manner according to local practice (i.e. no oozing or bleeding). If the subject leaves the OR/interventional suite with the catheter sheath introducer in place, the moment the subject leaves the OR/interventional suite is considered the end of the procedure.

Peri-procedure/Visit 1

1. **Adverse event monitoring**: monitoring will begin once the subject is enrolled into the study. Refer to section 8.2 Safety and other assessments.

Discharge/Visit 2

All subjects will undergo a discharge assessment as defined by the Schedule of Events in addition to the standard of care procedures at the site which should include the following:

1. **Adverse event monitoring:** monitoring will begin once the subject is enrolled into the study. Refer to section 8.2 Safety and other assessments.
2. **If the site's standard of care requires additional imaging assessments prior to discharge, these will be performed.**

Follow-up/Visit 3

All subjects will undergo a follow-up assessment, which may be in-person, a phone call, or a virtual visit, as defined by the Schedule of Events in addition to the standard of care procedures at the site, which should include the following:

1. **Adverse event monitoring**: monitoring will begin once the subject is enrolled into the study. Refer to section 8.2 Safety and other assessments.
2. **30-day Post-Op CT scan**: per standard of care for EVAR procedures, a post-op CT scan should be acquired if not done prior to initial hospital discharge.

8.2 SAFETY AND OTHER ASSESSMENTS

The subject will be considered enrolled into the study after all of the following criteria have been met:

- Signed and dated ICF, this may occur up to 30 days prior to index procedure
- Verification that subject meets all study entrance criteria
- Completion of all baseline procedures

The following baseline assessments must be performed, and the subject must meet all inclusion criteria and none of the exclusion criteria prior to the initiation of the study intervention with the 3D-GNC + IOPS device:

1. **Demographic Data:** including but not limited to age, sex, race, and ethnicity.
2. **Medical/Surgical History:** including but not limited to a vascular and non-vascular clinical history, risk classification assessment (by ASA grade, NYHA CHF class, and SVS/ISCVC categorization), documented history of COPD, medical and surgical cardiovascular background (i.e., history of cardiac, kidney or peripheral vascular disease, diabetes, hypertension, bleeding history, hypercholesterolemia, TIA, stroke, renal insufficiency, allergies, tobacco use), small

bowel ischemia, erectile dysfunction, infertility status (for all female subjects), and other relevant medical history that can influence a patient's quality of life (both positively and negatively).

3. **Physical Examination:** Body Mass Index (BMI) as determined from height and weight measurements, blood pressure (BP), heart rate (HR), and oxygen saturation must be completed prior to index procedure.
4. **Laboratory Evaluations:** The following tests must be completed within 6 weeks prior to index procedure: a) Hematology tests: complete blood count (CBC) – WBC, HgB, HCT, Platelets b) Chemistry tests: complete biochemistry test per routine practice.
5. **CT scan (with contrast):** CT scan (with contrast) is required for the screening assessment. CT scan can be performed during screening period or preexisting CT scan with contrast not older than 6 months can be used for screening purposes.
6. **Aortic anatomy with morphology** (aneurysm size, neck length, iliac morphology, neck and iliac angulations)
7. **Pregnancy test** for women with childbearing potential per standard of care.

All screening assessments must be completed prior to the subject's index procedure. All pre-index procedure assessments will be carried out as specified in the schedule of events.

During the study period no specific safety assessments or procedures will be performed apart from the observation of occurrence of adverse events, major adverse events and unanticipated adverse device effects as described in section 8.3 and respective data collection in CRF.

Assessment of the occurrence of an Adverse Event "AE" will be based on changes in the subject's signs and symptoms. AEs will be monitored until a subject completes the study unless the Investigator determines the event is related to the investigational device, in which case they will be monitored until resolution if possible. Medical care will be provided, as defined in the informed consent, for any AE related to study participation. Adverse Events will be collected on an AE CRF and applicable source documentation.

The following should not be considered an AE:

- A condition requiring a preplanned procedure unless the condition worsened since screening
- A preexisting condition found as a result of screening, unless the condition has worsened since enrollment.

The Investigator will record at a minimum, the nature, serious/non-serious, treatment and outcome of the AE, and will determine their association to the investigational products or procedures involved in the clinical study.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event (AE) means any untoward medical occurrence associated with the use of the device in humans, whether or not considered device related. Abnormal laboratory findings are considered AE only when deemed clinically significant.

Pre-existing conditions at admission are not considered adverse events for the purpose of the study analysis. Additionally, common standard of care practices are excluded as adverse events.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – A reaction that follows a reasonable temporal (i.e. time) sequence from study procedure, followed a known pattern of response to the study treatment and could not be explained by the subject's clinical or concurrent disease state (including concurrent treatments or drug use)
- **Possibly Related** – A reaction that follows a reasonable temporal (i.e. time) sequence from study procedure, followed a known pattern of response to the procedure but may have been produced by the subject's clinical or concurrent disease state (including concurrent treatments or drug use)
- **Not Related** – Any event that is clearly and definitely due to extraneous cause (e.g. disease, environment, etc.).

8.3.3.2 EXPECTEDNESS

PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 ADVERSE EVENT REPORTING

In this study, all adverse events (AEs) will be collected from point of implant until end of subject participation (study completion or consent withdrawn). Subjects should be actively queried for the occurrence of adverse events at all study time-points. AE information will be recorded in the subject's

source documentation and entered into the CRF. All AEs, regardless of relatedness or outcome, must be reported via the Adverse Event From of the CRF.

The investigator is responsible for maintaining adequate source documentation relating to AE diagnosis, investigation and treatment. Procedures for investigation and treatment of adverse events should be according to site standard of care and investigator judgement.

8.3.5 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.3.6 REPORTING OF PREGNANCY

Subjects who become pregnant during the study will be withdrawn from all protocol-specific assessments which require CT. All other assessments will be performed at scheduled visits.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.4.2 UNANTICIPATED PROBLEM REPORTING

An investigator shall submit to the Centerline Biomedical and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the Centerline Biomedical first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This is not a hypothesis driven study. Categorical data will be summarized as frequency (number) and percent of total and continuous data will be summarized as mean, standard deviation, median, interquartile range and minimum/maximum values.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be

informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and Centerline Biomedical. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the PI.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Centerline Biomedical, representatives of the Institutional Review Board (IRB), regulatory agencies or device company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, or Institutional policies.

Certificate of Confidentiality

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 SAFETY OVERSIGHT

An independent Medical Monitor will be appointed to monitor the study by reviewing the case report forms, SAE and AE forms at specified intervals throughout the study and will be responsible for the oversight of safety.

10.1.5 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Study monitoring will be performed by experienced and appropriately trained personnel appointed by the investigator to ensure that the investigation is conducted accordance with the FDA IDE regulations.

Monitoring will be conducted by the independent monitor in CCF HVI Research Department.
HVI (Heart and Vascular Institute) Research Department, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195.

On-site and/or remote monitoring will occur at regular intervals throughout the duration of the trial, and monitor visit with summary of findings will be outlined in monitoring report.
Monitoring activities may include:

- Study Initiation visit
- Review of training and delegation of authority log
- Review of FDA/IRB approval letters and correspondences
- Review of informed consent to ensure:
    - That the subject signed and dated the informed consent form for him/herself
    - A valid and effective version (reviewed and approved by the IRB) of the consent form was used
    - That the informed consent process was appropriately documented
- Confirmation that the study staff is conducting the study in compliance with the protocol approved by the IRB.
- Source Document Verification (i.e., review all subjects' charts for: study eligibility, primary and secondary endpoints data, and that the protocol specific source documents are on file)
- Ensuring the data reported on the CRF is consistent with the source documentation

- Review of outstanding queries on the CRF
- Review of all subject research records to ensure the following:
    - All AEs and SAEs have been reported including any abnormal exam findings determined to be clinically significant.
    - AEs have been reviewed, attribution has been assigned and signed by investigator in a timely manner.
    - AEs and SAEs have been submitted to the IRB and FDA if needed per IRB/FDA reporting criteria; and
    - All deaths have been reported appropriately
- Ensuring any protocol deviation that meets reporting requirements has been reported to the IRB
- Ensuring investigational products have been properly handled
- Verification of device used
- Study termination/closure visit

10.1.6 INSTITUTIONAL REVIEW BOARD

The protocol shall be evaluated and approved by the Institutional Review Board at the Cleveland Clinic prior to proceeding with the study.

Institutional Review Board
Alan Lichtin, MD – IRB Chairman
Cleveland Clinic
9500 Euclid Ave, OS-1
Cleveland , OH 44195
(216) 444-2924

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Centerline Biomedical, and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in the electronic case report form (CRF) derived from source documents should be consistent with the data recorded on the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol and International Conference on Harmonisation Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within the10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to sponsor. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary endpoint by contacting the study sponsor.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the medical device industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIH National Heart, Lung, and Blood Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

10.2.1 INVESTIGATOR AGREEMENT

Dr. Francis Caputo, as a study P.I. will certify all participating investigators will sign the investigator agreement and no investigator will be added until the investigator agreement is signed in accordance with 21 CFR 812.43.

- Investigator responsibilities include, but not limited to:
- Conducting the study in accordance with the investigational plan, signed agreement and applicable regulations protecting the rights and safety of study subjects
- Informing all subjects that the device being utilized is for investigational purposes, and ensuring that the requirements relating to obtaining informed consent and IRB approval are met
- Ensuring that IRB approval is secured prior to staring the study and ensuring continuing review and approval as required throughout the investigation
- Ensuring and supervise all associates, colleagues, and employees assisting the conduct of the study are informed about their obligations, are adequately qualified and trained, and meet their commitments
- Maintaining adequate and accurate records and ensuring those records are available for inspection at any time
- Ensuring that conducting the study does not give rise to conflict of interest
- Controlling of all investigational devices

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee

SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
2	27 Nov 2023	Updated sensorization and calibration steps to allow the specific location of the IOPS guidewire in the inner cannula to be selected during the case, as opposed to always being placed at the proximal end of the stent graft.	This update allows the physician to select the optimal calibrated position of the IOPS guidewire in the inner cannula based on the patient's anatomy and the stent graft dimensions.

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