STUDY TITLE:

"**Intravascular Ultrasound Imaging Guidance for Optimal Revascularization of Limb Arteries**"

STUDY NICKNAME: INVIGOR

Protocol IRB #: 025-412

National Clinical Trial #: NCT07353905

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Principal Investigator:	**Subhash Banerjee, MD**
Co-Principal Investigator:	**Anand Gupta, MBBS, MPH;** **Zachary Rosol, MD;** **Sameh Sayfo, MD** **John Eidt, MD**
Statistician:	**Anand Gupta, MBBS, MPH**
Data Management:	**TBD**

PROTOCOL SIGNATURE PAGE

Study Title: Intravascular Ultrasound Imaging Guidance for Optimal Revascularization of Limb Arteries

Protocol Number: V1.6

IRB Number: 025-412

I have read this protocol and agree to adhere to the requirements outlined within. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will review and discuss this material with them and ensure they are fully informed regarding the requirements of this protocol. I will also ensure that this study is conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory agencies and their requirements.

_____

Principal Investigator (Printed Name)

_____ _____

Principal Investigator (Signature) Date

ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
CLIA	Clinical Laboratory Improvement Amendments
CLTI	Chronic limb threatening ischemia
CNS	Central Nervous System
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
LE	Lower Extremity
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IVUS	Intravascular ultrasound
PAD	Peripheral arterial disease
PI	Principal Investigator
RCT	Randomized controlled trial
SAE	Serious Adverse Event
TLR	Target lesion revascularization

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SYNOPSIS

Title	Intravascular Ultrasound Imaging Guidance for Optimal Revascularization of Limb Arteries
Short Title	INVIGOR
Study Objectives	Primary Objective: To compare the primary patency rates at 6 months between IVUS-guided and non-IVUS-guided LE endovascular interventions. Secondary Objective: 1. To evaluate differences in procedural and technical successes rates. 2. To assess the impact of IVUS on clinical outcomes, including target lesion revascularization (TLR), amputation-free survival, and functional improvement. 3. To analyze cost-effectiveness by comparing procedural costs, complications, and reintervention rates between the two groups.
Study Outcomes and Endpoints	**Primary Endpoint**: Primary patency at 6 months (defined as freedom from restenosis ≥50%, or an increase in peak systolic velocity ≥2.5 times reference proximal segment or TLR) **Secondary Endpoints**: Procedural success, clinically driven-TLR (CD-TLR), amputation-free survival, functional status improvement Rutherford class improvement), and cost-effectiveness, all evaluated at 12 months.
Study Design	Prospective multicenter randomized controlled trial
Accrual Objective	Enrollment goal N=350

Study Duration	3 years (36 months)
Recipient Inclusion Criteria	○ Age ≥18 years ○ Symptomatic LE PAD - Rutherford Class 2-5 ○ Angiographic evidence of >50% stenosis ○ Undergoing LE peripheral artery intervention ○ Target lesion is iliac, femoropopliteal, profunda or supramalleolar below-the-knee arteries (target lesions extending into the abdominal aorta and inframalleolar BTK may be included).
Recipient Exclusion Criteria	○ Prior intervention at the target lesion within 6 months ○ Target lesion is abdominal aorta or inframalleolar BTK arteries.
Sponsor:	Baylor Scott and White Research Institute
Principal Investigator:	Subhash Banerjee, MD
Co-Investigators:	Anand Gupta, MBBS, MPH; Zachary Rosol, MD; Sameh Sayfo, MD John Eidt, MD
Study Sites:	**Baylor Scott & White Health (BSWH) system/ Baylor University Medical Center (BUMC):** • Patients will be recruited from up to **10** Baylor Scott & White Health System (BSW) sites in Texas • Potential Non-BUMC/BSWH sites to be added such as Ballad Health (Wellmont), Cleveland Clinic, Oklahoma Heart, and Ascension Seton
Study Site Locations:	Coordinating Center: The Heart Hospital Dallas
Funding	• Baylor Scott & White Research Institute: Cardiovascular Research Review Committee (CVRRC) funding will be used as seed money for study start up, training of sites, and initial patient enrollment. • Grant funding by Philips Inc.

Principal investigator	• Subhash Banerjee, MD & Baylor Scott & White Research Institute.
Medication and Doses:	NA
Devices:	NA
Procedures:	**Per standard of care, non-investigational procedure.** 1:1 Randomization to either of the below 2 groups: • **IVUS group**: Pre-and post-procedural IVUS to guide atherectomy, balloon angioplasty-based treatments and/or stent placement • **Control group**: Standard angiography-guided intervention without IVUS
Data collection source	• EPIC chart reviews • Catheterization laboratory cloud-based imaging archival system • XL PAD registry (BSWRI IRB # 017-114) • Subject questionnaires • Data from external sites- TBD
Efficacy Assessments:	Based on primary and secondary endpoints.
Safety Assessments:	Procedural safety and device related safety parameters.

STUDY TEAM CONTACT INFORMATION

Name	Contact Information	Role on Study
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Sarah Weideman		Clinical Study Coordinator

1. STUDY OBJECTIVES

1.1 OBJECTIVES

1.1.1 Primary Objective

To compare the primary patency rates at 6 months between IVUS-guided and non-IVUS-guided LE endovascular interventions.

1.1.2 Secondary Objective

1. To evaluate differences in procedural and technical successes rates.
2. To assess the impact of IVUS on clinical outcomes, including target lesion revascularization (TLR), amputation-free survival, and functional improvement.
3. To analyze cost-effectiveness by comparing procedural costs, complications, and reintervention rates between the two groups.

1.2 ENDPOINTS

1.2.1 Primary Endpoint

Primary patency at 6 months (defined as freedom from restenosis ≥50% or an increase in peak systolic velocity ≥2.5 times reference proximal segment or TLR)

1.2.2 Secondary and Exploratory Endpoints

The secondary outcomes evaluated at 12 months include:

1. Procedural success
2. Clinically driven-TLR (CD-TLR)
3. Amputation-free survival
4. Functional status improvement (Vascular Quality of Life Questionnaire (VascuQoL-6), Rutherford class improvement)
5. Cost-effectiveness

2. HYPOTHESIS

The use of IVUS during LE PAD endovascular intervention improves procedural outcomes, reduces restenosis rates, and enhances major adverse limb event free survival compared to standard angiography-guided intervention without IVUS.

3. BACKGROUND

Lower extremity (LE) peripheral arterial disease (PAD) is a major cause of morbidity, secondary to lifestyle limiting claudication, chronic limb threatening ischemia (CLTI), and increased risk of cardiovascular events. Endovascular intervention is the preferred treatment for symptomatic LE PAD, yet restenosis and suboptimal deployment of non-stent and stent-based treatments remain significant challenges. Intravascular ultrasound (IVUS) has emerged as a promising tool for optimizing endovascular therapy by providing real-time, high-resolution imaging of vessel morphology, plaque burden, and atherectomy, balloon and stent optimization.[1, 2]

Our group as the coordinating center for the XLPAD registry (BSWRI IRB 017-114), a multicenter U.S. CMS approved quality registry has established the core laboratory reproducibility of IVUS imaging in lower extremity arteries.[3]

However, its routine use remains debated due to procedural costs and lack of definitive randomized controlled trial (RCT) evidence supporting improved long-term outcomes.[4-6] Currently, IVUS is used in <5% of cases in the U.S.[7, 8]

4. STUDY DESIGN

4.1. DESCRIPTION OF STUDY DESIGN

This is a prospective multicenter randomized controlled trial to evaluate the safety and clinical outcomes of Intravascular ultrasound (IVUS) guided lower extremity (LE) arterial endovascular intervention involving the iliac, femoropopliteal, profunda and supramalleolar below-the-knee arteries in patients with symptomatic peripheral artery disease (PAD) (Rutherford class 2-5). (Figure 1)

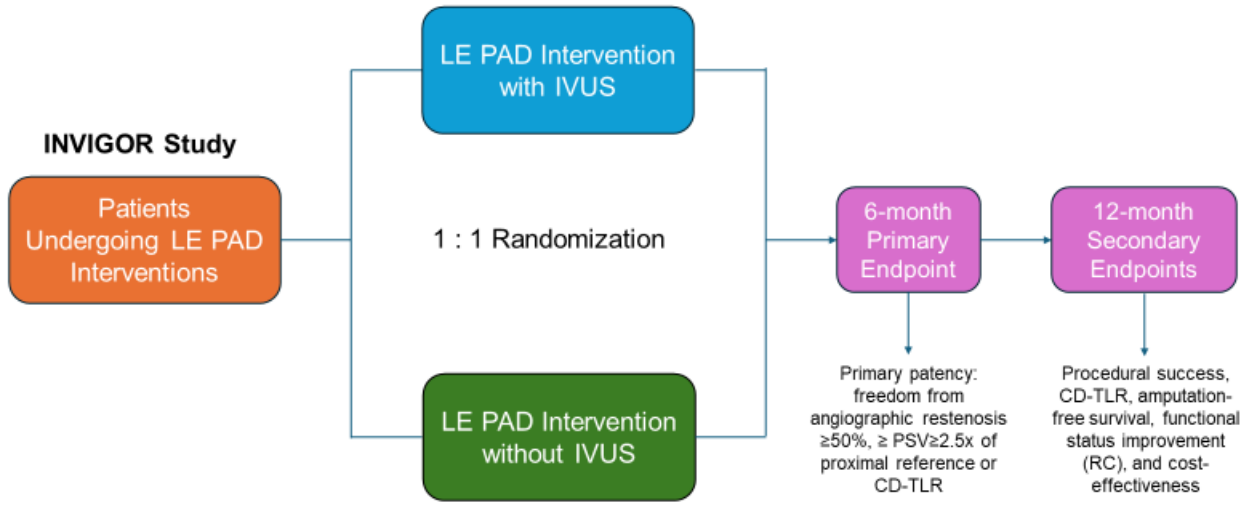

Figure 1: LE: lower extremity, PAD: peripheral artery disease; IVUS: intravascular ultrasound; PSV: peak systolic velocity on Duplex ultrasound; CD-TLR: clinically-driven target lesion revascularization; RC: change in Rutherford class

Figure 1

- **Randomization:** 1:1 allocation to IVUS-guided versus standard angiography-guided intervention
- **Intervention:**
  - IVUS group: pre-and post-procedural IVUS to guide atherectomy, balloon angioplasty-based treatments and/or stent placement
  - Control group: Standard angiography-guided intervention without IVUS

- **Endpoints:**
    - **Primary Endpoint:** Primary patency at 6 months (defined as freedom from restenosis ≥50% or an increase in peak systolic velocity ≥2.5 times reference proximal segment or TLR)
    - **Secondary Endpoints:** Procedural success, clinically driven-TLR (CD-TLR), amputation-free survival, functional status improvement (Vascular Quality of Life Questionnaire (VascuQoL-6), Rutherford class improvement), and cost-effectiveness, all evaluated at 12 months.
    - **Exploratory Endpoints:** Walking Impairment Questionnaire (WIQ) at 12 months
- **Recruitment: 24 months (Up to 10 BSW and 1-4 external sites).**
- **Follow-up:** Clinical and duplex ultrasound follow-up at 6 months post-intervention (duplex ultrasound would not be necessary in the event that a CT Scan or repeat revascularization at the target lesion is performed within ±30 days of the 6-month follow-up date).
- **Study duration:** 36 months
- **Data Collection tool:** BSWH REDCap
- **Procedure insurance coverage:** the Angiography guided LE revascularization procedure will be per SoC, covered by the subject's insurance.
- *The IVUS guided LE revascularization procedure will also be billed to subject insurance*.

5. SELECTION OF PARTICIPANTS AND ENROLLMENT GOALS

Patients will be recruited from up to 10 Baylor Scott & White Health System (BSW) sites in Texas, integrated using

- a unified EMR
- catheterization laboratory cloud-based imaging archival system
- centralized data collection on ongoing basis through the XLPAD registry participation

Enrollment goals:

Study wide enrollment goal: 350

BSWH Sites (first phase of initiation): Dallas, Plano, McKinney, Waxahachie, Ft Worth, Temple.

No one site should enroll more than 60% of subjects.

External site enrollment goal: TBD

Enrollment period: 24 months

5.1. INCLUSION/EXCLUSION CRITERIA

5.1.1. INCLUSION CRITERIA

1. Age ≥18 years
2. Symptomatic LE PAD - Rutherford Class 2-5
3. Angiographic evidence of >50% stenosis
4. Undergoing LE peripheral artery intervention

5. Target lesion is iliac, femoropopliteal, profunda or supramalleolar below-the-knee arteries (target lesions extending into the abdominal aorta and inframalleolar BTK may be included).

5.1.2. EXCLUSION CRITERIA

Individuals who meet the below criteria are not eligible for enrollment as study participants:

1. Prior intervention at the target lesion within 6 months
2. Target lesion is abdominal aorta or inframalleolar BTKStudy Procedures

5.2. SCREENING/BASELINE VISIT

Centers will identify potential study participants with symptomatic PAD (Rutherford class 2-5) undergoing LE endovascular intervention being evaluated for atherectomy, balloon angioplasty-based treatments and/or stent placement.

The research study will be explained in lay terms to each potential research participant, and the potential participant will sign an informed consent form before undergoing any study procedures.

The study personnel will review the participant's medical records for medical history, record the participant's demographic information, and have the patient complete the VASCUQOL-6 and WIQ (optional) questionnaire.

The following procedures, assessments, and laboratory measures will be reviewed via the medical record for the baseline screening visit (after consent has been obtained):

1. Medical chart review for medical and surgical history
2. Lab reports, scans and other testing reports from medical chart
3. Other information available from subject medical chart for the study data collection

5.3. ENROLLMENT

5.3.1. RANDOMIZATION

Once a participant has consented, all inclusion criteria are met as determined by the treating physician, and the treating physician has confirmed intervention in the target lesion will take place during the procedure, they will be assigned a unique participant number and randomized to IVUS vs non-IVUS control group. Once randomized, the participant is considered enrolled in the study.

1:1 Randomization will be done via an automated REDCap randomization module integrated into the data capture system. If the patient does not meet inclusion criteria intra-procedurally and is not randomized, the patient is considered a screen failure.

5.3.2. PROCEDURE

LOWER EXTREMITY ENDOVASCULAR INTERVENTION PER STANDARD OF CARE

These interventions will be done per standard of care and include:

- Balloon angioplasty
- Stenting
- Atherectomy
- Intravascular lithotripsy
- Drug-coated balloon angioplasty
- Adjunctive use of embolic protection devices
- Other FDA approved treatments

INTRAVASCULAR ULTRASOUND (IVUS) GUIDED ENDOVASCULAR INTERVENTION PER CLINICAL TRIAL

Subjects will be randomized 1:1 to have IVUS guided endovascular intervention versus the usual angiography guided endovascular intervention. Intravascular ultrasound (IVUS) is a medical imaging technique that uses ultrasound to visualize the inside of blood vessels, typically for heart coronary arteries.

A special catheter with an ultrasound transducer is inserted into a blood vessel, typically through a puncture in the groin. The ultrasound probe emits high-frequency sound waves that bounce off the vessel wall, creating echoes. A computer converts these echoes into real-time images of the vessel's interior.

Uses of IVUS:

- Diagnosing heart conditions: Identifying plaque buildup, assessing the severity of atherosclerosis, and evaluating the structure of artery walls.
- Guiding angioplasty and stenting: Helping doctors determine the optimal location and size of stents.
- Evaluating stent placement: Assessing if the stent is properly expanded and if there are any complications like in-stent restenosis.
- Assessing the effectiveness of interventions: Determining if angioplasty or atherectomy has been successful.

ANGIOGRAPHY GUIDED ENDOVASCULAR INTERVENTION PER STANDARD OF CARE

Angiography is the standard method of care to guide endovascular interventions. Angiography is a medical imaging technique used to visualize blood vessels. It involves injecting a contrast agent into the blood vessels and using X-rays or other imaging methods to take pictures of the vessels.

5.3.3. PRE/POST-PROCEDURE AND DATA COLLECTION

Data collection for all participants will occur at enrollment through hospital discharge, at 6 months and 12 months post procedure.

Phone calls/text messages will be made to study participants by the research team to remind them of their clinical follow-up appointments. Patient reported VASCUQOL or other study information will be collected via direct patient contact, by phone, text, and emails up to 30 days after the follow-up date. This will be included in the patient ICF.

At each study time point, the study coordinator will collect and enter data into the web-based data system (Redcap), including medications of interest, labs, and events of interest, such as deaths and adverse events. Data will also be collected from the XL PAD registry (BSWRI IRB 017-114).

If the index procedure is considered a technical failure (>30% residual stenosis in the target lesion), the 6-month follow-up data on the duplex ultrasound will not be collected as the vessel is known to not be patent.

6.2.4 CORE LABORATORY IMAGING

Our group has established the core laboratory reproducibility of IVUS imaging in lower extremity arteries.[3]

All pre- and post-procedural imaging (IVUS and angiography) will be uploaded to the central cloud-based imaging archival system and analyzed by the XLPAD Core Laboratory at Baylor Scott & White Research Institute. The core lab will not be blinded to treatment group allocation and will assess vessel dimensions, plaque burden, stent expansion, and post-procedure luminal gain.

6. UNKNOWN AND POTENTIAL RISKS AND BENEFITS TO PARTICIPANTS

6.1. RISKS ASSOCIATED WITH LOWER EXTREMITY ENDOVASCULAR INTERVENTION PROCEDURES

6.1.1. VASCULAR ACCESS RISK

Vascular access during the procedure may cause slight discomfort, pain, bleeding, or bruising at the vessel access site. Rarely, fainting, or infection may occur.

7.1.2. Contrast-Induced Nephropathy Risk

Contrast agents used during angiography may affect kidney function, particularly in participants with preexisting renal insufficiency.

7.1.3. Radiation Exposure Risk

Participants may be exposed to ionizing radiation during angiographic procedures. The amount of radiation exposure is generally considered at low risk but may be cumulative over multiple procedures.

7.1.4 Risks of IVUS

- Vessel injury catheter manipulation
- Vessel spasm or thrombosis
- Distal embolization
- Rare allergic reaction to catheter materials or medications used during the procedure

6.1.2. INTERNET-BASED DATA COLLECTION

Data from this study will be entered into a computerized database, Redcap. All information will be saved and transmitted in the encoded form. Only authorized personnel requiring a password will be permitted to enter data. There is a risk, although minimal, of unauthorized persons obtaining confidential information. Even though identifying information will be removed, the people who get this information may be able to figure out who the subjects are. The kinds of health information that might be given to these people include results from lab tests, pathology, or other tests like x-rays. This information might also include notes and other information in the participants' medical records.

6.2. POTENTIAL BENEFITS

For participants in this study, the use of IVUS could improve long-term patency of the lower extremity revascularization procedures, reduce the need for reinterventions, and have a better patient quality of life.

7.4 OVERALL RISK BENEFIT RATIO

The potential risks identified are justified by the anticipated benefits that may be afforded to subjects undergoing LE endovascular interventions.

7. CRITERIA FOR PARTICIPANT AND STUDY COMPLETION AND PREMATURE STUDY TERMINATION

7.1. PARTICIPANT COMPLETION

Participants will have completed the study at the year 1 data collection time point, or once the study has been closed. All participants will be actively followed for at least 1 year post procedure.

7.2. PARTICIPANT WITHDRAWAL CRITERIA

Participants may be prematurely terminated from the study for the following reasons:

1. The participant elects to withdraw consent from future study activities, including follow-up.
2. The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
3. The participant dies.
4. The investigator no longer believes participation is in the best interest of the participants.

8. SAFETY MONITORING AND REPORTING

8.1. OVERVIEW

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Appropriate notifications will be made to site principal investigators, Institutional Review Boards (IRBs), and health authorities, if applicable.

Information in this section complies with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, 21CFR Parts 312 and 320, and applies the standards set forth in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0: http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx.

Further details regarding what events will be captured are summarized below.

8.2. DEFINITIONS

8.2.1. ADVERSE EVENT (AE)

Any untoward or unfavorable medical occurrence associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2.)

Adverse events collected for the purpose of this study will be limited to the below:

1. Myocardial Infarction (MI)
2. Stroke
3. Amputation
4. Bleeding

8.2.2. SERIOUS ADVERSE EVENT (SAE)

Due to the minimal risk nature of this study and the routine nature of the procedures, serious adverse events reported for this study are limited in scope. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor it is an adverse event listed in section 9.2.1 (myocardial infarction, stroke, amputation, or bleeding) and results in any of the following outcomes (21 CFR 312.32(a)).

1. Death.
2. A life-threatening event: An AE or SAE is considered "life-threatening" if, in the view of the investigator its occurrence places the subject at immediate risk of death. It does not include an AE or SAE that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. 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 above.

The exception is that a death will always be reported as an SAE.

8.3. GRADING AND ATTRIBUTION OF ADVERSE EVENTS

8.3.1. GRADING CRITERIA

The study site will grade the severity of adverse events experienced by the study participants according to the criteria set forth in the NIAID/Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. This document (referred to herein as the DAIDS Grading Table) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events.

For additional information and a printable version of the DAIDS Grading Table, consult the DAIDS web site: http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the DAIDS Grading Table:

Grade 1 = Mild adverse event

Grade 2 = Moderate adverse event

Grade 3 = Severe and undesirable adverse event

Grade 4 = Potentially life-threatening

Grade 5 = Death

Adverse events Grade 3 or higher according to the DAIDS Grading Table that are definitely or possibly related to a study procedure or study intervention will be reported.

8.3.2. ATTRIBUTION DEFINITIONS

The relationship, or attribution, of an adverse event to the study intervention/procedure will be determined by the treating physician (who is a PI or SUB-I on the study) and recorded on the appropriate AE case report form. The relationship of an adverse event to the study procedure or intervention will be determined using the descriptors and definitions provided in Table 9.3.2.

Table 9.3.2 Attribution of Adverse Events

Code	Descriptor	**Relationship** (to primary intervention and/or other concurrent mandated study therapy or study procedure)
UNRELATED CATEGORY		
1	Unrelated	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Definite	The adverse event is clearly related.

8.4. COLLECTION AND RECORDING OF ADVERSE EVENTS

8.4.1. COLLECTION PERIOD

Adverse events will be collected from the time of procedure until a participant completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

8.4.2. COLLECTING ADVERSE EVENTS

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the participants.
- Interviewing the participant [e.g., using a checklist, structured questioning, diary, etc.].
- Receiving an unsolicited complaint from the participants.

- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 9.3, *Grading and Attribution of Adverse Events.*

8.4.3. RECORDING ADVERSE EVENTS

Throughout the study, the investigator will record adverse events and serious adverse events as described above on the appropriate case report form. The investigator must record pertinent information including, but not limited to, dates that each adverse event occurred, what treatment was prescribed, the outcomes, any follow-up information, and the investigator's opinion of the attribution of the event. All reports should include:

- Participant ID
- Site PI
- Date of the event
- Last study intervention
- Description of the event-including intervention(s)
- Outcome-state if resolved or not; with or without residual sequela; if not completely resolved, a follow-up report will be submitted to the coordinating center.
- Grade of each toxicity
- Attribution for each toxicity and for each agent

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the participant prematurely withdraws (without withdrawing consent) or is withdrawn from the study, whichever occurs first.

8.5. REPORTING OF SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS

8.5.1. REPORTING OF SERIOUS ADVERSE EVENTS TO SPONSOR

This section describes the responsibilities of the investigator to report serious adverse events to the sponsor. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

SAE Reporting Guidelines:

1) All SAEs will be reported to the study PI
2) Any unanticipated study problem that does not fit the definition of an adverse event, but which may, in the opinion of the affiliate site Principal Investigator, involve risk to the participant, affect others in the research study, or significantly impact the integrity of research data will also be reported
3) Reporting to the local affiliate site IRB will follow local regulations and guidelines.

8.5.2. REPORTING OF ADVERSE EVENTS TO IRB

All investigators shall report adverse events in a timely fashion to their local IRBs in accordance with applicable regulations and guidelines.

8.6. SAFETY MONITORING REVIEW

9.6.1 DSMB

The independent data safety monitoring board (DSMB) that is already established for the IRB-approved XLPAD Registry (#017-114) will serve as the DSMB for this study. The Committee will meet once every 6 months, and their recommendations will be disseminated to all participating sites. The database will have audits and control checks quarterly throughout the course of the study by the Data Safety Committee. The DMSB report will be sent to the IRB within 10 days of the quarterly audit.9.6.2 Data coordinating center

The central coordinating site for the XLPAD registry comprises a core laboratory, REDCap secure data collection system, trained personnel, coordinators, biostatistician, study managers and an independent data safety monitoring board. The REDCap database for the IRB approved study, XLPAD Registry (#017-114) will be used in addition to an INVIGOR REDCap database with a randomization module and study specific provisions like the questionnaires.

9.6.3 Executive Committee (EC)

The EC that is already established for the IRB-approved XLPAD Registry (#017-114) will serve as the EC for this study.

9. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

- **Sample Size Calculation:**
- Based on prior studies, we estimated a 12-month primary patency rate of 75% in the IVUS group versus 60% in the control group. Also, the study by Ko et al. (2025)[6] exhibited a primary patency rate of 83.2% in the IVUS - guided group, compared to 69.5% in the angiography-guided group, indicating a relative improvement of approximately 13.7%.
- Using a two-sided, two-sample Z-Test with unpooled variance, with a Type I error rate (α) of 0.05. The control group proportion (P2) is assumed to be 0.695. To detect a proportion difference (P1 - P2) of 0.137 (or P1 of 0.832) with 80% power, the number of subjects needed will be 148 in Group 1 (treatment) and 148 in Group 2 (control). Anticipating a 15% dropout rate, 175 subjects should be enrolled in Group 1, and 175 in Group 2 for a total of 350 patients, to obtain final group sample sizes of 148 and 148, respectively, and a total sample size of 296 patients. The sample size was computed using PASS 2025, version 25.0.2.[9]
- **Analysis:**
    - Kaplan-Meier survival analysis for time-to-event outcomes
    - Cox proportional hazards model for predictors of restenosis and TLR

- Cost-effectiveness analysis using quality-adjusted life years (QALYs) and incremental cost-effectiveness ratio (ICER)
- Subgroup analyses based on lesion complexity (TASC classification), stent use, and CLTI presentation.

- **Study Feasibility analysis:** Patients will be recruited from up to 10 Baylor Scott & White Health System (BSW) sites in Texas, integrated using a unified EMR and catheterization laboratory cloud-based imaging archival system and centralized data collection on an ongoing basis through the XLPAD registry participation (BSWRI IRB 017-114). The central coordinating site for the registry comprises a core laboratory, REDCap secure data collection system, trained personnel, coordinators, biostatistician, study managers, and an independent data safety monitoring board.
- **Participation of non-BSW sites** currently involved in the XLPAD registry (BSWRI IRB 017-114)
- **BSW sites collectively perform approximately 900 peripheral artery interventions per year.** A site feasibility survey with respect to IVUS (Philips) system availability and willingness to participate has been confirmed.
- **Core Laboratory:** Our group has established the core laboratory reproducibility of IVUS imaging in lower extremity arteries.[3]
- At 60% enrollment, the protocol allows for the provision of an interim analysis to determine either termination of the study, or additional patient enrollments beyond the pre specified sample with an appropriate statistical penalty if needed. This decision will be made by the study executive committee.

10. ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE.

10.1. STATEMENT OF COMPLIANCE

This clinical study will be conducted using good clinical practice (GCP), as delineated in Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance, and according to the criteria specified in this study protocol.

10.2. INFORMED CONSENT PROCESS

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or designee listed on the Investigator of Record form (or FDA 1572 if applicable) will review the consent and answer questions. The prospective participant will be told that being in the study is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representatives) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing. The consent form will be revised when important new safety information is available; the protocol is amended, and/or new information becomes available that may affect participation in the study. Study participants will be re-consented if new information affecting participant safety is made available.

The consent process will also be done via a phone call by the study team and the consent form emailed via DocuSign Module 11 for signatures. Subject phone number and email will be collected for this purpose.

10.3. PRIVACY AND CONFIDENTIALITY

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number, and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

11.4.1 Crossover Policy

Crossovers from the angiography-guided (control) arm to IVUS-guided intervention will be allowed only in cases of:

- Unanticipated complications during the procedure (e.g., angiographic ambiguity, vessel perforation, or dissection requiring further imaging),
- Operator judgment that proceeding without IVUS poses undue patient risk.

All crossovers must be documented with rationale, timestamped, and reviewed by the coordinating center within 48 hours.

A limit of <10% crossover is anticipated. Exceeding this threshold will prompt review by the DSMB.

11.4 2 Statistical Handling of Crossover

Use a combination of analytic strategies:

a. Intention-to-Treat (ITT) Analysis (Primary)

All patients are analyzed according to their original randomization group, regardless of crossover. This maintains randomization and reflects real-world treatment effects.

b. Per-Protocol (PP) Analysis (Secondary)

Exclude crossover patients or analyze them in the arms they actually received. This gives insight into treatment efficacy when protocol is strictly followed.

c. As-Treated Analysis (Exploratory)

Analyze based on actual treatment received. This may be biased due to loss of randomization but helpful for hypothesis generation.

d. Sensitivity Analyses

Perform sensitivity analysis using:

- **Inverse Probability of Censoring Weighting (IPCW)**
- **Complier Average Causal Effect (CACE) models**
- **Instrumental variable methods** (using randomization as an instrument)

The **CACE model** or **Complier Average Causal Effect** is a statistical method used in RCTs to estimate the **true treatment effect among participants who actually comply with their assigned treatment**—in this case, for those who *would have stayed in their assigned group* (e.g., no IVUS vs IVUS), had there been no crossover. In the **INVIGOR trial**, if some participants cross over from **control (no IVUS)** to the **IVUS** arm, standard intention-to-treat (ITT) analysis might **underestimate** the actual effect of IVUS. That's because ITT keeps them in their original group regardless of the treatment they actually received. CACE analysis will help **isolate the effect of IVUS** in those who complied with their assignment—without throwing out the randomization benefits.

To address potential treatment crossovers, we may also conduct **Instrumental Variable (IV) analyses** using randomization as the instrument. A two-stage least squares (2SLS) approach will estimate the causal effect of IVUS use on primary and secondary outcomes, including primary patency and target lesion revascularization. This IV approach corrects potential noncompliance while preserving the randomized design's internal validity.

The exact methodology would be decided after completion of recruitment.

11.4.3 Justify Crossover in DSMB and IRB Reporting

The DSMB will monitor crossover frequency. If crossover exceeds 10% of control arm subjects, the trial steering committee may implement protocol reinforcement, investigator retraining, or protocol amendment to preserve randomization fidelity.

12 REFERENCES

1. Jang JS, Jin HY, Park YA, Yang TH, Seo JS, Kim DK, Wi JH. Meta-Analysis of Intravascular Ultrasound-Guided Versus Angiography-Guided Endovascular Treatment in Lower Extremity Artery Disease. Am J Cardiol. 2025 Mar 15;239:8-17.
2. Meng W, Guo J, Pan D, Guo L, Gu Y. Intravascular Ultrasound-Guided Versus Angiography-Guided Endovascular Therapy for Femoropopliteal Artery Disease: A Scoping Review. J Endovasc Ther. 2025 Jun;32(3):627-634.
3. Soney H, Kakkilaya A, Vazquez DF, Banerjee R, Rosol Z, Tsai S, Banerjee S. Reproducibility of Femoropopliteal Artery Intravascular Ultrasound Imaging in Patients With Peripheral Artery Disease. Am J Cardiol. 2023 Jul 15;199:1-6.
4. Allan RB, Puckridge PJ, Spark JI, Delaney CL. The Impact of Intravascular Ultrasound on Femoropopliteal Artery Endovascular Interventions: A Randomized Controlled Trial. JACC Cardiovasc Interv. 2022 Mar 14;15(5):536-546.
5. Shin J, Ahn CM, Lee SJ, Lee SH, Lee YJ, Kim BK, Hong MK, Jang Y, Kim TH, Park HW, Jang JY, Lee JH, Park JH, Kim SH, Im E, Park SH, Choi D, Ko YG; IVUS-DCB investigators. Twenty-Four-Month Outcomes of Intravascular Ultrasound-Guided Drug-Coated Balloon Angioplasty for Femoropopliteal Artery Disease. J Am Heart Assoc. 2025 Aug 19;14(16):e041564.
6. Lee J, Jang JY, Ahn CM, Lee SJ, Lee SH, Lee YJ, Hong SJ, Kim JS, Kim BK, Hong MK, Jang Y, Kim TH, Park HW, Lee JH, Park JH, Kim SH, Im E, Park SH, Choi D, Ko YG; IVUS-DCB Investigators. Intravascular Ultrasound Predictors of 12-Month Patency Loss Following Drug-Coated Balloon Angioplasty for the Femoropopliteal Artery. Am J Cardiol. 2025 Jul 1;246:58-64.
7. Rymer JA, Secemsky EA. Use of Intravascular Ultrasound to Optimize Peripheral Vascular Interventions: How Do We Optimize Outcomes and Improve Uptake? Circ Cardiovasc Interv. 2023 Apr;16(4):e013016.
8. Divakaran S, Parikh SA, Hawkins BM, Chen S, Song Y, Banerjee S, Rosenfield K, Secemsky EA. Temporal Trends, Practice Variation, and Associated Outcomes With IVUS Use During Peripheral Arterial Intervention. JACC Cardiovasc Interv. 2022 Oct 24;15(20):2080-2090
9. PASS 2025 Power Analysis and Sample Size Software (2025). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

13 APPENDIX A. SCHEDULE OF EVENTS

Study Schedule of events

Weeks	Screen	Randomization/ Index Procedure	6 month (±30 days)	12 month (±30 days)
CLINICAL				
Eligibility Review*	**X**			
Medical History*	**X**			
Surgical history*	**X**			
Lab / scan reports*	**X**			
Informed Consent (remote)**	**X**			
VascuQoL- 6 & WIQ (WIQ is optional)	**X**			**X**
Randomization via REDCap		**x**		
SoC LE intervention procedure*		**x**		
Core Lab analysis		**x**	→	→
Phone call/email/text reminders by research team			**X**	**X**
Clinic visit*			**x**	**x**
Duplex ultrasound *			**x**	

Weeks	Screen	Randomization/ Index Procedure	6 month (±30 days)	12 month (±30 days)
Adverse Event Assessment*		**x**	→	→
XL PAD Registry data (IRB # 017-114)	**x**	**x**	**x**	**x**

*Data collection only
** Remote consenting via phone call with signatures via DocuSign Module 11.