JET ISR XLPAD Angiography and Ultrasound Core Laboratory Protocol

The XLPAD core laboratory protocol (CLP) is designed to adjudicate study angiograms and Duplex ultrasound studies (DUS) performed as per study defined criteria on eligible patients, as per JET ISR specified criteria outlined in the study protocol. This document is a companion to the main study protocol and the JET ISR study protocol supersedes all criteria and conditions listed in this CLP.

Angiography: Peripheral artery angiography of the lower extremities submitted to the core laboratory (core lab) should meet the following minimum criteria:

1. Cineangiography and/or digital subtraction angiography (DSA) images/run of the target femoropopliteal artery (FP) in-stent restenotic (ISR) segment of pre-existing metallic stents (not covered PTFE stents) with minimal or no overlap with the underlying bones and minimal or no motion artifacts in at least an anterior-posterior (AP) projection (similar angulation for all angiographic images; orthogonal or near orthogonal projections at the discretion of the operator) and with optimal contrast density.
2. Presence of a radio-opaque ruler beside the target lesion with no overlap with the target lesion preferably adhered to the inner aspect of the thigh. Visualization of the sheath on imaging runs whenever possible is highly recommended.
3. Contrast type and dilution will be at the discretion of the operator, however target vessel should be fully and optimally opacified without streaming artifacts.
4. Selective angiography of the FP artery with image of the sheath or catheter used for contrast injection is preferred.
5. The FP ISR target segment should be preferably captured in one image frame whenever possible, along with 10 mm segments proximal and distal to the target lesion. In the event the entire lesion length is not captured on a single frame image, overlapping images of the target lesion ISR segment with the radio-opaque ruler in view should be captured. The dimensions of all prior stents implanted in the target vessel and lesion should be provided whenever possible.
6. Angiographic/DSA of the entire FP artery should be provided.
7. Height of the table and image intensifier should be kept constant with capture of the radio-opaque ruler and or a catheter for image calibration. This is required to determine reference vessel segment.
8. Static, image frame(s) (preferably non-DSA) of the target lesion ISR prior to any intervention without any underlying bony artifacts is needed to determine the type of baseline stent fracture if any.
9. Static, image frame(s) (preferably non-DSA) of the target lesion ISR at the end of the index procedure without any underlying bony artifacts is needed to determine the type of stent fracture post-treatment (if any).
10. Angiographic or DSA image/run of the below-the knee run-of vessels to the level of the ankle captured before and after target lesion intervention is required.
    i. Dedicated angiographic/DSA images of the target lesion at the following procedure stages are required:
    ii. Baseline: prior to any guide wire or device intervention of the target FP ISR segment.
    iii. Post-Jet Stream (JS) atherectomy: angiographic image to determine residual stenosis following all treatments with the JS atherectomy device. This image will be compared to the baseline image to determine device and/or procedural success.
11. Index procedure angiographic images will also be utilized to determine reference vessel diameter, lesion length, severity of stenosis, type of stent fracture (if any) pre and post-procedure and type of restenosis **(CPL Form 1)** and presence or absence of distal embolization.
12. Size of pre-existing metallic stents in the target FP artery segment should be provided to the core lab if available. The measured stent diameter will be used as the reference FP vessel diameter. In the presence of overlapping stents with different diameters an average of the measured stent diameters will be used. Stent diameter measurements will be obtained by making multiple (≥2 measurements) within the target lesion and the reference diameter determined as an average of these measurements).
13. If the ISR segment in diffusely diseased and an angiographic reference vessel (near normal) segment is not present, the reference vessel diameter will be based on stent dimension(s) provided and in the absence of such information, measurement of the stent diameter will be made as described above.

14. Site training: All participating site investigators will have to complete an on-line or web-based tutorial on optimal angiographic/fluoroscopic and Duplex imaging protocol for the study, potential errors, strategies to avoid imaging errors and the process of ongoing quality monitoring and continued core lab training. Participating operators and other study personnel will be required to complete this training and confirmation of the completion of this training will be provided to the study sponsor/PI.
15. Minimum qualifying images/angiographic runs an quality audit:

Pre-intervention	Post-intervention	Comments
Plain film	Plain film	Assessment of fracture
Angiogram of lesion	Angiogram of lesion	Assessment of lesion treatment
Foot angiogram	Foot angiogram	Assessment of distal embolization

In the absence of any of the above qualifying images/angiographic runs, the core laboratory will assess adequacy of the provided images and make an expert decision on available information to provide efficacy and safety information. This decision will be made by the core laboratory director (medical/technical) and/or by XLPAD chair. In an event, all required study information is not obtainable from the site provided images, a comment regarding 'sub-optimal imaging' will be entered into core lab data collection form and both site and sponsor/PI will be informed. A cumulative report will be provided to the sponsor/PI and to sites regarding overall study or site-specific image quality and adherence to protocol, respectively. This image quality audit will be performed at 20%, 50% and 80% of patient image analysis by the core lab. Quality audit information will also be used to plan study and imaging protocol training and/or re-training.

16. Response time: A response time of 5 business days will be needed to provide an initial quality check whenever necessary/indicate and all analysis of a source data will be completed within 90 business days.
17. Core laboratory contact: The core lab personnel will be available for the sites to contact directly regarding any question about image acquisition/troubleshooting. Core lab technical director will be the point of contact between 9 am and 5 pm CST Monday-Friday at:214-857-3048. Emergency after hours and weekend contact number is 972-890-5375.
18. Site contact information: Core lab will maintain site PI, coordinator and other staff business and emergency afterhours phone/cell and email/fax contact information. This contact information will be used for transmitting quality audit, training and other relevant information.
19. Reported angiographic variables:
    a. Number of run-off BTK vessels in the target limb: N; mean±standard deviation (SD)
    b. Lesion length (mm): N; mean±SD
    c. Treated length (mm): N; mean±SD
    d. Lesion diameter (mm): N; mean±SD
    e. Stenosis severity (%):
        i. Baseline
        ii. Post-JS atherectomy
        iii. Post-procedure
    f. TASC class:
        i. A: N; %
        ii. B: N; %
        iii. C: N; %
        iv. D: N; %
    g. Total occlusion: N; %
    h. Vessels treated:
        i. SFA: N; %
        ii. Popliteal: N; %

iii. SFA+popliteal: N; %

20. All images to be transferred in DICOM format on a CD/DVD labeled with patient ID in pen (no adhered tape) and mailed to the core lab address (provided in the CLP form using sponsor provided mail-in option with tracking number).
21. Only index procedure angiograms will be required for submission to the core lab with accompanying information outlined in the **CLP Form 1**.
22. Technical aspects of angiographic analysis:

Technical condition	Detail	Comment
Core lab analysis software	Angio: CAAS Version 7.3 Pie Medical Imaging, Inc. (Maastricht, Netherlands) DUS: Phillips Imaging Version 3.3.1.1070 (5684 PC Best, The Netherlands)	
Computer terminals	Core Lab Folder. \imcfscl02\IMCHome\IMCHomeA-M (Z)	Password protected UTSW computers.
Room location	Room 375 and 377 in Building 1 Clinical Research Unit CRU 4500 S Lancaster Road, Mail Code 151/3S, Dallas TX 75216	
Security protocol	1. Privacy training of all analysts and core lab personnel 2. Locked access to core lab analysis room per Dallas VA security protocol 3. Secure password to analysis computer terminals 4. Access log to analysis computer terminals 5. Secure time stamp of all analysis terminal operations 6. Periodic audit of core lab activity, procedures including security and analysis reliability	
Angiographic analysts	1.Hao Xu	
Data server/back-up	UT Southwestern server	Data back-up will be done per UTSW IT policy
Source data receipt, tracking	Source data and tracking worksheets will be kept in locked office-room 377. Deidentified reports and image CDs will be kept in locked office –room 375. Both offices are within the CRU at VANTHCS. Data from analysis will kept as paper form in room 375 and on iMedNet portal.	iMedNet EDC has an audit trail.
Source data archiving	Source will be archived in long term storage per VANTHCS policy and on iMedNet in electronic format.	
Image quality reporting	Quality of image and completeness of data worksheet will be achieved within 5 business days of receipt of images by core lab	Core lab will provide reports related to data and image quality to sites and coordinating center within 5 business days of receipt.

Analysis quality checks	Analysis quality checks will be done by Core Lab Director-Dr. Shirling Tsai or Houman Khalili,MD on biweekly basis.	
Vendor validation protocol	Vendor validation protocol will be provided to sponsor.	
Cumulative data analysis	Cumulative data analysis will be done on SAS 9.4 version (SAS Institute, Cary, NC).Reports will be generated from iMednet	Biostatistician will conduct data analysis.
Third party data storage	iMedNet data storage and tracking	Established contract with Dallas VA Research Corporation
Site training	On-line core lab protocol training and submission of angiographic/Duplex ultrasound test CD/DVD studies (de-identified)	

Duplex ultrasound (DUS): Peripheral artery DUS of the lower extremities submitted to the core laboratory (core lab) should meet the following minimum criteria:

1. Three DUS studies will be submitted for core lab analysis: post-index procedure to up to 45 days post-post procedure (labeled index DUS); 6-month DUS and 1-year DUS.
2. A contemporary model of DUS machine should be used to acquire DUS images for core laboratory interpretation. The transducer should operate at the highest clinically appropriate frequency, recognizing that there is a trade-off between resolution and penetration. This should usually be at a frequency of 3.5 MHz or greater, with the occasional need for a lower-frequency transducer.
3. Recording device of appropriate DICOM format.
4. Equipment gain and display settings should be optimized while imaging vessels with respect to depth, dynamic range and focal zones.
5. Color-flow Doppler should be added to supplement B-mode images with proper color scale to demonstrate areas of high flow and color aliasing.
6. Power Doppler could be used to validate low flow states or occlusions.
7. Cursor sample size should be small and positioned parallel to the vessel wall and/or direction of blood flow.
8. A spectral Doppler angle of 60 degrees or less will be used to measure velocities.
9. Spectral Doppler gains will be set to allow a spectral window and optimized to reduce artifact.
10. Areas of suspected stenosis or obstruction should include spectral Doppler waveforms and velocity measurements recorded at and distal to the stenosis or obstruction.
11. Sites of intervention (i.e., stents) will include spectral Doppler waveforms and velocity measurements from the proximal, mid and distal sites.
12. Plaque should be assessed and characterized.
13. Identify and use color Doppler for proper assessment of vessels.
14. Measure PSV (Peak Systolic Velocity) and EDV (end diastolic velocity) every 30 mm of distal common femoral artery, proximal, mid and distal FP artery.
15. Label all vessels according to anatomy and intervention status pre and post intervention.
16. In patients with a significant FP artery stenosis or occlusion, flow into the popliteal artery should be examined with color Doppler interrogation (CDI) to determine degree and integrity of flow reconstitution.
17. Long axis B-mode images must be obtained from:
    a. Common Femoral Artery (CFA)
    b. Superficial Femoral Artery (SFA)
    c. Popliteal Artery
18. For spectral analysis:
    a. Only angles of 60 or less will be acceptable and document PSV nearest proximal vessel for increase of PSV at any point
    b. Calculate the PSV ratio
    c. Cross-sectional or longitudinal residual diameter measurements with or without the use of CDI are notoriously inaccurate and do not correlate well with contrast angiographic findings
    d. Spectral Doppler waveforms and velocity measurements must be documented from:
        i. CFA
        ii. SFA
        iii. Popliteal Artery
19. For good quality DUS examination:
    a. Apply heal toe technique for 60 angle measurement
    b. Doppler sample volume should be thru entire course of vessel
    c. Obtain measurements every 30 mm of distal common femoral artery, proximal, mid and distal FP artery
    d. For transverse B mode use 90 degrees between vessel and beam
20. Reasons for paucities in DUS exam:
    a. Incorrect angles
    b. Label mismatch for blood vessel

c. Low quality images
d. Incomplete worksheet
e. No gray scale images

21. Reported DUS variables indicated in **CPL Form 2.**
22. All images to be transferred in DICOM format on a CD/DVD labeled with patient ID in pen (no adhered tape) and mailed to the core lab address (provided in the CLP form using sponsor provided mail-in option with tracking number).
23. All study specified (three) DUS study CD/DVDs will be required for submission to the core lab with accompanying information outlined in the **CLP Form 2**.

JET ISR XLPAD Angiography and Ultrasound Core Laboratory Protocol Form 1 (CLP Form 1)

Patient ID:

Procedure date:

Site number:

Contact phone: Contact email:

Mail tracking number:

Index procedure:

1. **Vascular access:**
   - Access site: right common femoral artery, left common femoral artery, left radial artery, right radial artery, left popliteal artery, right popliteal artery, other: _____
   - Diagnostic angiography sheath diameter size: 4F, 5F, 6F, 7F, 8F, other: _____
   - Diagnostic angiography catheter (other than sheath): 3F, 4F, 5F, other: _____
2. **Baseline target lesion description:** *provided based on operator visual estimates*
   - Target Lesion Location:
   - Radio-opaque ruler present: yes or no
   - FP artery ISR: left or right
   - Baseline target lesion angiogram: yes or no
     - Length & diameter of preexisting metallic stents in target vessel (if available)
     - AP angulation:
     - Target lesion length (single or cumulative lesion lengths separated by intervening ≤5 cm)
     - Treated length (mm)
       - Communicate target lesion location to DUS sonographer by indicating proximal and distal edge lesion distance from mid patella a per study protocol instruction
     - Target lesion diameter (mm)
     - Maximal percent (%) severity of stenosis:
     - Calcification:circle one
       - Grade 0: no visible calcification
       - Grade 1: unilateral calcification <5 cm in length
       - Grade 2: unilateral calcification ≥5 cm in length
       - Grade 3: bilateral calcification <5 cm in length
       - Grade 4: bilateral calcification ≥5 cm in length
     - Type of stent fracture:
       - 0: no stent fracture
       - I: single strut fracture

- II: multiple stent fractures
- III: complete transverse fracture without displacement
- IV: complete transverse fracture with displacement

- Type of restenosis: NIH-neointimal hyperplasia

Restenosis type	Distribution of NIH	Pattern of NIH	Intervening no/minimal NIH	Stent fracture
0	No ISR			Use stent fracture classification
I	Focal (<10 mm)	Concentric & eccentric	Yes	Sub-class Ia for presence of stent fracture
II	Diffuse (≥10 mm)	Concentric	No	Sub-class IIa for presence of stent fracture
III	Diffuse	Concentric	Yes	Sub-class IIIa for presence of stent fracture
IV	Diffuse	Concentric & eccentric	Yes	Sub-class IVa for presence of stent fracture
V	Diffuse	Concentric & eccentric	No	Sub-class Va for presence of stent fracture

- Baseline below-the knee (BTK) run-off vessel: yes or no

- Include number of run-off vessels: 1, 2 or 3 (circle one)

- Baseline BTK flow: no flow; faint flow defined as penetration of contrast without perfusion, partial flow and complete flow, represented as 0, I, II and III flow grades, respectively (circle one)

- Presence of distal embolization: yes or no (Distal embolization defined as an intravascular filling defect completely or partially occluding the vessel lumen and associated with brisk or reduced contrast flow) (circle one)

3. **Post-JS atherectomy and procedure target lesion description:** *provided based on operator visual estimates*
    - Radio-opaque ruler present: yes or no
    - FP artery ISR: left or right
    - AP angulation:
    - **Post-JS atherectomy target lesion angiogram**: yes or no
    - AP angulation:
    - Maximal residual percent (%) severity of stenosis:
    - Dissection:
        - Type of stent fracture:
            - 0: no stent fracture
            - I: single strut fracture
            - II: multiple stent fractures
            - III: complete transverse fracture without displacement
            - IV: complete transverse fracture with displacement
    - BTK run-off vessel: yes or no
    - Number of run-off vessels: 1, 2 or 3
    - Presence of distal embolization: yes or no
    - BTK flow: no flow; faint flow defined as penetration of contrast without perfusion, partial flow and complete flow, represented as 0, I, II and III flow grades, respectively
    - Bail-out treatment planned: yes or no
    - Type of bail-out treatment: balloon angioplasty, stent or other: _____(list)
    - **Post-procedure target lesion angiogram**: yes or no
    - Maximal residual percent (%) severity of stenosis:
    - Dissection: yes or no; if yes select one of the following: circle one
        - Type A: small radioluscent area with lumen of the vessel disappearing with the passage of contrast
        - Type B: Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles
        - Type C: Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material
        - Type D: Spiral shaped filling defect with delayed runoff of the contrast material in the distal vessel
        - Type E: Persistent luminal filling defect with delayed runoff of the contrast material in the distal vessel
        - Type F: Filling defect accompanied by total coronary occlusion

- Type of stent fracture:
  - 0: no stent fracture
  - I: single strut fracture
  - II: multiple stent fractures
  - III: complete transverse fracture without displacement
  - IV: complete transverse fracture with displacement

- BTK run-off vessel: yes or no

- Number of run-off vessels: 1, 2 or 3

- Presence of distal embolization: yes or no

- BTK flow: no flow; faint flow defined as penetration of contrast without perfusion, partial flow and complete flow, represented as 0, I, II and III flow grades, respectively

4. **Operator name:**

5. **Operator signature:**

6. **Study CD/DVD labeling procedure:** Label study CD/DVDs with non-erasable marker to include study participant ID, procedure date and indicate one of the following: angiogram; index DUS, 6-month DUS, 1 year DUS.
7. **Core lab mailing address and contact information:**

   Preeti Kamath

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   Dallas, Tx-75216

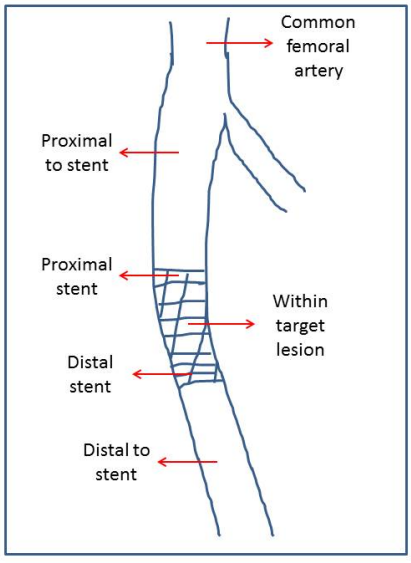
   Preeti.Kamath@va.gov

   Phone: 214-857-3048

JET ISR XLPAD Angiography and Ultrasound Core Laboratory Protocol Form 2 (CLP Form 2)

1. Patient ID:
2. Exam date:
3. Site number:
4. Contact phone: Contact email:
5. Mail tracking number:
6. **Visit: (circle one)**
   - Index DUS
   - 6m DUS
   - 1y DUS
7. **Limb:**
   - Right
   - Left
8. Target lesion location (lesion treated with study device e.g mid SFA)
9. **Complete PSV/EDV data capture for FP ISR:**

Location*	PSV (cm/sec)	EDV (cm/sec) only if abnormal
Common femoral artery		
Proximal to stent		
Proximal stent		
Within target lesion (at least one with highest PSV)		
Distal stent		
Distal to stent		



*Use above locations to designate DUS images

10. The entire femoropopliteal segment should be scanned to document the lesion as well as restenosis at follow-up. For a single lesion case, the peak systolic velocity (PSV) at the nearest normal segment preceding the target lesion will be used as the reference. If there are sequential lesions and a normal segment between them then the normal reading will be used as a reference for the distal lesion. If

there are sequential lesions but no segment between them with normal flow then the normal segment for the most proximal lesion will be used.

11. Comments (if any)

12. Name of technician performing study

13. Technician signature
14. **Study CD/DVD labeling procedure:** Label study CD/DVDs with non-erasable marker to include study participant ID, procedure date and indicate one of the following: angiogram; index DUS, 6-month DUS, 1 year DUS.
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