



CSP#578
Prevention of Serious Adverse Events Following Angiography
The PRESERVE Trial



OPERATIONS MANUAL

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Introduction

This Operations Manual is meant to guide study staff in conducting CSP #578, “Prevention of Serious Adverse Events Following Angiography,” in a consistent and ethical manner. It is intended as a supplement to the study protocol. This Operations Manual is the reference guide for the day-to-day activities of the study. Since the success of a cooperative study depends to a large extent on the cooperation of all personnel and close adherence to standardized procedures by each participating medical center, it is important that everyone involved in the study become familiar with the protocol and the operational details prior to the beginning of patient screening.

The Operations Manual contains details for implementing the study protocol, including site management procedures, procedures for recruitment and randomization, obtaining informed consent, collecting and reporting study data, and safety monitoring.

It is important that all study personnel, especially the Local Site Investigator (LSI) and Study Coordinator (SC), carefully read, understand, and follow the procedures outlined in the Operations Manual to ensure uniformity in the conduct of the study among participating centers.

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I. Site Management Procedures

A. Site Initiation Requirements

The following site specific tasks must be completed before sites can begin enrolling patients in CSP #578:

1. Identify a Local Site Investigator, Study Coordinator, and Program Support Staff

Each study site has a Local Site Investigator (LSI) and a Study Coordinator (SC). In addition, each site will be staffed with a half-time research assistant (RA). In most cases, the SC will be an RN. After the LSI, SC and RA have been identified, sites need to contact the Project Manager at the MAVERIC CSPCC and provide the name, office phone number, cell phone/pager number, fax number, and address (including email address) of the LSI, SC, and RA. This information will be made available in the study personnel directly on the CSP578 internet-based SharePoint site.

Sites should use their Site Personnel Signatures & Delegated Responsibilities Log (DRL) to document personnel performing significant study-related activities and the date they started/stopped. The DRL will be provided to coordinators as part of the SMART packet at the time of kick-off. Site staff should complete the DRL after training. The start date is the date that the staff personnel have been trained on VA guidelines and study specific procedures. Documentation in the DRL should include information for the LSI, SC and RA along with any identified Site Co-Investigators or Sub-Investigators. All local pharmacy staff do NOT need to be listed on the DRL. However, the designated study pharmacist or research pharmacist should be listed with the delegated responsibilities of dispensing study drug and maintaining study product accountability records. Once all study personnel have been noted, the DRL must be scanned and uploaded to the appropriate site documentation folder in SharePoint (See Section X.B.). From that point on, whenever any change in site personnel is made, the DRL must be updated, filed, and scanned and uploaded to SharePoint.

a. Sharepoint study website

CSP#578 will use a common study SharePoint, which is an internet-based site that contains study related materials, documents, communications, and study directory. This site is private and can only be accessed with permission assigned by the server administrator.

How to access the CSP #578 Sharepoint Website:

Access can be obtained via this web address:

<https://vaww.ord.research.va.gov/CSP/Boston/csp578/default.aspx>.

Only use this site for the purpose intended. Do not attempt to modify the site or folders from the site. The Boston MAVERIC SharePoint administrator is Paul Truland. He can be contacted at Paul.Truland@va.gov.

2. Identify pharmacy and other relevant site personnel

The LSI should identify one pharmacist at his/her local pharmacy to serve as the site study pharmacist and take responsibility for working with him/her on this trial. Many VA Medical Centers have a designated research pharmacist who is responsible for providing local pharmacy support for research studies. If no such person exists, the LSI may need to talk to the Chief of the Pharmacy to help identify a designated pharmacist or individual to

serve in this capacity. We strongly believe that the site study pharmacist should have some clinical trial experience, but this is not mandatory. After the designated local pharmacist has been identified, contact the MAVERIC CSPCC to provide his/her name and contact information, including office number, cell phone number, (and pager number if available). This is important as there may be instances in which the local pharmacist will need to be contacted immediately and/or emergently.

Because the good will and cooperation of staff within the cardiac catheterization laboratory and the interventional radiology suite are vital to the recruitment of study patients and ongoing data collection, it is important that you establish excellent working relationships with hospital personnel working in these venues. The LSI and the SC should meet with the staff in the cardiac catheterization laboratory and the interventional radiology suite, including interventional radiologists performing non-coronary angiograms, as well as the local pharmacy service well in advance of the study start date. At these meetings, the team should give an overview of the study along with its anticipated start-up date. Requests made for personnel to assist in identifying patients and in procedure-related and study-related data collection should be explained and the potential benefits to patients at high risk of developing acute kidney injury following contrast dye exposure discussed. The site team should try to make the demands of the study as unobtrusive as possible and make every effort not to interfere with the work of personnel in these hospital venues. The LSI should initiate these contacts with other services and should accompany the SC to these meetings to assist in answering any questions or concerns. It is also possible that non-coronary angiograms are performed at certain sites by vascular surgeons or other non-radiology providers. In such instances, we encourage the study team to contact such providers to establish collaboration in order to include their patients in the study and involve them, as appropriate, in study activities. This can include having them serve as site sub-investigators.

Finally, because blood will be collected, processed, and stored for up to 1 week prior to shipping to the central study laboratory, sites should ensure that they have access to a centrifuge for sample processing and a refrigerator with continuous temperature monitoring. If these are not already available we recommend speaking with personnel from the local clinical laboratory or a colleague with a research laboratory regarding use of a centrifuge and access to a refrigerator with space for the short-term storage of blood specimens. Otherwise, this equipment will need to be purchased. It will be necessary to maintain a record of temperature monitoring of the refrigerator that is used for specimen storage which will need to be available during your annual site visit.

3. Obtain VA Central Institutional Review Board (VA Central IRB) approval of Local Site Investigator Application (VA Central IRB Form 104)

This study is being conducted under the auspices of the VA Central IRB. Therefore, the VA Central IRB is considered the IRB of record. Each participating site has signed a Memorandum of Understanding (MOU) with the Veterans Health Administration (VHA) Central Office. This MOU sets forth the agreed upon respective authorities, roles, and responsibilities of the VA Central IRB for the initial and continuing review, as well as review of amendments, monitoring, reporting, and other relevant requirements. By agreeing to participate in the study, VA medical centers delegate responsibility for global

monitoring of the ongoing study to the VA Central IRB and MAVERIC CSP coordinating center.

All VA Central IRB forms are available through their website at: www.research.va.gov/vacentralirb/default.cfm.

Site study personnel will work with the National Coordinator at the Study Chair's Office at the VA Pittsburgh Healthcare System to complete VA Central IRB Form 104, "Local Site Investigator Application." The LSI will complete Form 104 using the approved template version of study documents contained in VA Central IRB Form 108, originally submitted by the Study Chair's office and approved by the VA Central IRB, as the basis for his/her application. VA Central IRB form 108 can be located at: 12-17 CSP 578 12-17 Final Approval Documents. Once Form 104 and other required documents have been completed for the LSI application, the site study coordinator will submit the forms on the CSP#578 SharePoint in the site appropriate LSI folder. The Project Manager or National Coordinator will review the LSI application, and then submit the application package to the VA Central IRB using a site specific submission folder. All submissions of study documents to the VA Central IRB will be done by the Study National Coordinator and/or personnel at MAVERIC.

The study site will be notified when the VA Central IRB grants approval for the local application and the approval notification will be available at the VA Central IRB website (Folder 2, LSI Project Documents). This documentation of local site application approval, along with any correspondence, must be saved and filed by the local SC in the appropriate 'Site Documents' folder in the CSP 578 Study SharePoint (See Section X.B.). Please keep in mind that while site staff are expected to communicate directly with the VA Central IRB for certain activities, such as responding to specific requests made by the VA Central IRB, copies of all communications should be sent to the Project Manager at MAVERIC CSPCC and the National Coordinator at the Chair's Office and filed in the Essential Documents Binder (EDB). Note: only use the VA Central IRB SharePoint Website for the purpose intended. Do not attempt to modify the SharePoint site or folders contained within.

4. Obtain a letter from the ACOS for R&D stating that the site can initiate research
The Research and Development (R&D) Committee at the local VA Medical Center retains ultimate responsibility for oversight of the conduct of the protocol within its own institution. After Form 104 has been approved by the VA Central IRB, you will need to obtain a memorandum/letter from the Associate Chief of Staff (ACOS) for R&D at your facility stating that you may initiate study procedures. This documentation must be filed in the appropriate 'Site Documents' folder in CSP#578 SharePoint (See Section X.B.).
5. Enter necessary information into "PROMISE" database
Once your ACOS for R&D has said that you may initiate research, you may request funds. Before your site can receive funding, information regarding the LSI must be entered into the "PROMISE" database by designated personnel in the local site R&D Office. The following information should be provided to the local site research office for data entry into the "PROMISE" system: Project Number CSP # 578, Local Site Investigator (LSI) name, degree, Social Security Number, and Medical Center number.

6. **Upload all required site documentation to the study SharePoint website, including a CSP Investigator Agreement, Conflict of Interest form, Medical License and CV for the LSI and any co-Investigators or sub-Investigators.**

These documents *must be signed and dated* by the LSI as well as any Co-Investigators or sub-Investigators, scanned and uploaded to the appropriate 'Site Documents' folder in SharePoint (See Section X.B.). Upon medical license expiration the LSI must re-load a current license.

Sites may not be funded until all required documentation is received.

7. **Upload certification and accreditation of site's clinical laboratory as well as a listing of laboratory normal values that will be obtained as part of the study protocol (i.e., serum creatinine, urine creatinine, urine albumin, urine protein).** This information must be scanned and uploaded to the appropriate 'Site Documents' folder in SharePoint (See Section X.B.). Please note the laboratory certification expiration date and upon expiration, re-upload the new certification.

8. **Establish a patient travel reimbursement system**

Participants will have the choice to either come back to the VA at which the angiogram was performed **or go to a participating CBOC or another VA closer to the participant's home** to have the 4-day and 90 day (and confirmatory sample if needed) collected. The study mobile specimen collection agency can also obtain this blood at the patient's home. Participants who choose to return to the VA will receive reimbursement to cover the costs of travel to and from their place of residence to the VA at which the angiogram was performed as well as parking . Mileage calculations will be made using standard geomapping. Participants who travel a total of 50 miles or more will receive \$40. Participants who travel less than 50 miles total will receive \$20. The Travel Funds Accountability log is an Excel spread sheet which each site will utilize to track disbursement of funds. The log will be maintained in the site's Share Point for CSP 578. Entries to the site's spread sheet should be kept up to date to ensure available monies. (See Appendix 18 for a Travel Reimbursement Log sample). The SC will need to contact the local site business office and research office to determine the method of reimbursement that is applicable to their site. Patients should be informed that there may be a delay in payment for up to several months depending on the method of reimbursement utilized at their site.

9. **Secure office space, study equipment, and office supplies**

CSP #578 involves interviewing patients in person as well as on the telephone. We expect most patient interviews to occur in the catheterization lab, radiology suite, or the hospital floor. Efforts should be made to protect the confidentiality of patient information during study personnel-patient interactions.

Your office area will need to be large enough to accommodate a locked file cabinet(s) for your records and forms. Access will be limited to study personnel only.

Site staff must have access to a computer connected to the VA network. Any protected health information (PHI) that must be shared via email must be encrypted; therefore, any

study personnel who may need to share PHI study data via email must have a current VA Public Key Infrastructure (PKI) certificate giving them the ability to accept and send encrypted emails. Information on obtaining this certificate is available from your facility's Privacy Officer or Information Security Officer. Procurement of PKI should be done well in advance of study start up.

Access to a secure fax machine is necessary since some forms (i.e., the patient Contact Information Form, the Informed Consent Form and HIPAA Authorization will need to be faxed directly to the MAVERIC CSPCC. Access to a scanner is necessary since most administrative and regulatory forms, such as the Delegated Responsibilities Log and Investigator Agreement, must be signed, scanned and then uploaded to the appropriate 'Site Documents' folder in SharePoint. Other office supplies (e.g., file cabinet) must be purchased using the funds allocated for supplies at each hospital.

The MAVERIC CSPCC will provide sites with digital pH analyzers for post-angiography urine testing. Sites will be responsible for maintaining this equipment throughout the duration of the study (See Appendix 15). Study personnel should familiarize themselves with the analyzer before study kick-off. Site staff must have access to a scale for taking a participant's weight if necessary.

10. Establish local procedures for processing blood and urine samples

The study includes the collection of blood samples at baseline, 4 days and 90 days that will need to be processed by study personnel, stored in a temperature-monitored refrigerator until shipped to the central laboratory and then shipped to the central laboratory. Necessary space and equipment (including centrifuge for sample processing and refrigerator for storage) need to be obtained or identified and local procedures developed for:

- Phlebotomy for blood samples obtained at the local site
- Receipt of samples obtained by the mobile blood drawing service (Hooper Holmes)
- Centrifugation of blood samples
- Transfer of serum into shipping vials
- Storage of samples until shipping
- Shipping of vials to the central laboratory

11. Ensure access to and review of all necessary study documents

Study personnel must be familiar with all study procedures as documented in the protocol and this Operations Manual prior to screening patients for eligibility. Please contact the Project Manager at the MAVERIC CSPCC if you do not have access to any of the following study materials:

- Operations Manual with all appendices including the study protocol
- Copies of the VA Central IRB approved Informed Consent Form (VA Form 10-1086) with current VA Central IRB approval stamp and date
- Copies of the HIPAA Authorization template
- Copies of the study's source document worksheets (paper source document worksheets developed by MAVERIC CSPCC)
- Essential Documents Binder from the CSP Site Monitoring, Auditing and Resource Team (SMART)
- Participant Study Binders from SMART

- Participant Consent Forms Master File from SMART
- VA Central IRB Approved New Project Application submitted by the Study Chair
- VA Central IRB Approved Local Site Application

The SC or RA should make copies of the complete Operations Manual as necessary to ensure all study personnel have access to these study reference documents. All source document worksheets, approved consent form template and other study related materials are available on the CSP#578 Main SharePoint site (See Section X.A.).

12. Ensure receipt and access to study pharmaceutical supplies

Your pharmacy will receive blinded study IV fluids (sodium bicarbonate and saline) along with N-acetylcysteine capsules and a matching placebo from the Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) in Albuquerque. These items will be shipped directly to each hospital prior to start-up, as described in the Drug Treatment and Handling Procedures (DTHP) which can be found in Appendix 12

Other miscellaneous pharmaceutical supplies (e.g., Latex-free non-powdered gloves sizes medium and large) must be purchased using the funds allocated for supplies at each hospital. It is your responsibility to maintain the equipment, manuals, and test materials in good order.

13. Ensure access to and review of online study resources

Ensure authorized users have access to and are familiar with using SharePoint for document management; the IWRS system for patient screening, randomization and kit assignment; and DataLabs for entering case report forms. Each of these systems is described in detail in this Study Operations Manual.

14. Ensure required trainings are completed by all study personnel

In-person, study-related trainings will take place during the study kick-off meeting. Additional training after the start of the study will be provided as needed. In addition to attending these trainings, site personnel must complete all VA required online trainings for the conduct of clinical research. Contact your site's research office to determine the necessary VA online trainings. Training on shipping hazardous materials is required. Contact your VA research office for information on access to these trainings. Certificates of completion for all online trainings must be uploaded to the appropriate 'Site Documents' folder in SharePoint (See Section X.B.). Trainings must be kept current and all re-certifications should be uploaded to the appropriate 'Site Documents' folder in SharePoint. A table summarizing required trainings for clinical trial personnel can be found in Appendix 3.

15. Establish a Recruitment Plan/Strategies and Patient Screening Routine

Each site must develop its own specific recruitment plans/strategies before the trial begins. This plan should include contingencies should recruitment goals fail to be met. Specifics of such strategies may be generated with the help of the LSI and personnel in the cardiac catheterization laboratory and interventional radiology suite.

Sites should set up a routine to establish a pattern of referrals and seek out potential candidates for enrollment who are scheduled for an angiography procedure. A HIPAA Waiver of Informed Consent for screening purposes has been granted by the VA Central IRB. This Waiver allows each site to access and use patient medical record information to identify prospectively any patients who may meet study eligibility criteria and to focus recruitment efforts on those patients.

16. **Review the Required Content and Organization of the Investigator Study File**

Detailed information on these requirements and how to create a subject filing system can be found in Section I.E and Section IX. A. respectively.

17. **Complete an Investigational Drug Information Record (VA Form 10-9012) for the study IV saline, study IV sodium bicarbonate and N-acetylcysteine capsules and provide to your local pharmacy, if required by your site.**

Copies should also be maintained in the appropriate 'Site Documents' folder in SharePoint (See Section X.B.). Individual authorized to prescribe study interventions (IV fluids, NAC/placebo) must be a member of the study team and be included on VA Form 10-9012.

18. **Complete a Statement of Investigator (FDA Form 1572) and file in the appropriate 'Site Documents' folder in SharePoint (See Section X.B.)**

This form is a basic contract between a clinical investigator and the Food and Drug Administration (FDA). It is required in all clinical trials conducted under an Investigational New Drug (IND) Application. CSP#578 is being conducted under an IND. Study coordinators should be listed in Section#6 of the 1572.

Revised CSP#578 Site Start-Up Checklist

ACTION	Completed or Verified by Site	Completed or Verified by MAVERIC
To be completed prior to Central IRB approval:		
Site Personnel- Identify and provide contact information to MAVERIC.		
Credentialing- Ensure all site personnel have VA research credentialing		
CIRB Application- Prepare local site investigator application for VA Central IRB approval		
Training:		
SharePoint- Ensure all site personnel utilizing SharePoint have completed training		
IWRS- Ensure all site personnel who will be utilizing IWRS have completed training		
DataLabs- Ensure all site personnel who will be utilizing DataLabs have completed training		
Blood shipment- Ensure all site personnel responsible for the shipment of blood have completed training		
Training- Ensure all site personnel have completed all other required trainings (see appendix 3 of the operations manual) prior to working on the study		
Study Interest- Work with local cath lab staff and physicians to establish interest in the study		
Lab Storage- Establish process for temporary blood specimen storage (refrigeration at 4 degrees)		
Office space- Secure for site personnel and ensure access to a working computer with internet access and a printer, scanner, copier, and fax machine.		
PKI Certificates- Ensure staff responsible for emailing PHI have PKI certificates allowing them to send and receive encrypted emails.		
Patient Screening- Establish a routine that utilizes the prescreening log		
Recruitment- Establish plan and strategies		
pH Analyzer- Review instructions (appendix 15 of the operations manual) and order the cleaning solution as specified		
Binders- Purchase to use as participant study binders (tabs are provided by SMART)		
To be completed after Central IRB approval:		
R&D Application- Prepare required documents for Local R&D committee approval of the study		
CIRB Site Access- Contact Project Management at MAVERIC to request access for the SC and RA		

IWRS Access- Ensure that personnel needing access have obtained an account NOTE - Requirements for IWRS access: (1) site has been Central IRB approved, (2) individual has completed IWRS training, (3) individual is VA research credentialed, and (4) individual submits an IWRS access request		
DataLabs Access- Ensure that personnel needing access have obtained an account NOTE - Requirements for DataLabs access: (1) site has been Central IRB approved, (2) individual has completed DataLabs training, (3) individual is VA research credentialed, and (4) individual provides VA username and domain name to Project Management at MAVERIC		
SharePoint Access- Ensure necessary personnel obtain access to the SharePoint site NOTE - Requirements for SharePoint access: (1) site has been Central IRB approved, (2) individual has completed SharePoint training, (3) individual is VA research credentialed, and (4) individual provides VA username and domain name to Project Management at MAVERIC		
Upload:		
CIRB Approval- Upload Central IRB approval documentation to SharePoint		
CVs- Upload signed & dated CVs for all site personnel to SharePoint		
COI Statements- Upload conflict of interest statements for all investigators (LSI and co/sub-investigators) to SharePoint		
Investigator Agreements- Upload CSP Investigator Agreement, signed & dated by the LSI, to SharePoint		
Medical Licenses- Upload copies of all current medical licenses held by all investigators (LSI and co/sub-investigators) to SharePoint		
DRL- Complete and upload the Designated Responsibilities Log to SharePoint		
1572 Form- Complete 1572 Form and ensure it is uploaded to SharePoint		
Lab Documentation- Upload documentation of certification and accreditation of site's clinical laboratory as well as a listing of laboratory normal values to SharePoint		
Training Log- Complete the site personnel training log and upload to SharePoint		
Fillable Consent Forms- Obtain approved ICF and HIPAA forms in a fillable PDF format from MAVERIC		
Participant Reimbursement- Work with your local VA to establish participant compensation system and become familiar with the participant reimbursement tracking log available on SharePoint		
To be completed following Local R&D Committee approval:		
R&D Approval- Ensure Local R&D committee approval documentation is uploaded to SharePoint		
SMART- Obtain study materials from SMART <ul style="list-style-type: none"> • Essential Documents Binder • Tabs for participant study binders 		

<ul style="list-style-type: none"> Participant Consent Forms Master File 		
<p>Funding Request- Ensure ACOS for R&D completes the initial funding request for your site and submits to MAVERIC</p> <p>NOTE – Requirements for VACO to release funding to sites: (1) site has been Central IRB approved, (2) site has received local R&D approval, (3) site ACOS for R&D has submitted formal funding request using template prepared by MAVERIC</p>		
<p>UPS Account- Obtain UPS account information from Project Management at MAVERIC</p>		
<p>Request Shipping Supplies- Project Management will notify MAVERIC Lab to send the initial supply shipment at least 2-3 days in advance of a site needing supplies</p>		
<p>Request Study Drugs- Project Management will notify Pharmacy that all site documents required by pharmacy (CIRB approval, Local R&D approval, & Form 1572) are ready on SharePoint and study drug can be shipped</p>		
<p>ABML Notification- Project Management will notify ABML that site is almost ready to begin recruitment</p>		
<p>Tracking Consent Forms- Project Management will create site ICF/HIPAA tracking sheet & ICF/HIPAA folder on MAVERIC server</p>		
<p>HH Notification- Project Management will notify Hooper Holmes that the site is almost ready to begin recruitment</p>		
<p>Tumbleweed Account- Ensure each person needing Tumbleweed account information from Hooper Holmes has received it and become comfortable with the system and placing blood draw orders</p>		
<p>Receive Shipping Supplies- Receive initial supplies from MAVERIC Lab</p> <p>NOTE – this shipment will include the pH analyzer & operations manuals for any primary LSI or primary SC who did not receive one at the kickoff meeting</p>		
<p>Receive Study Drugs- Ensure the local pharmacy has received blinded study IV fluids and drug capsules and is prepared to disseminate and track study drugs</p> <p>NOTE – Items that must be on SharePoint before Pharmacy can ship study drugs: (1) Form 1572, (2) CVs for everyone on Form 1572, (3) Central IRB approval letter, and (4) local R&D approval letter</p>		
<p>PROMISE System- Ensure designated personnel at the local R&D office enter investigator information into the “PROMISE” system</p>		
<p>Tracking Training- Project Management will create spreadsheet for tracking site personnel credentialing and training</p>		

B. Responsibilities of Staff at the Participating Medical Centers

1. Local Site Investigator (LSI)

The LSI is responsible for the scientific and administrative conduct of the study at his/her medical center. He/she must be familiar with the FDA guidance for Site Investigators (See Appendix 9), VHA Handbook 1200.05 LSI section. Specific duties of the LSI or his/her designee (e.g., study staff) are to:

- a. Complete submissions for initial and continuing VA Central IRB review, as well as local site R&D Committee review as required.
- b. Obtain approval from the VA Central IRB for all proposed recruitment advertising and report all protocol deviations.
- c. Hire, ensure adequate training of, and supervise the study staff at his/her medical center.
- d. Ensure that all training has been documented as required
- e. Establish a system for identifying potential study participants.
- f. Ensure that participants are appropriately consented.
- g. Ensure that his/her medical center is maintaining adequate performance standards, requirements such as participant accrual goals, data quality and timeliness and adherence to the protocol.
- h. Determine whether patients meet eligibility criteria and qualify for the study.
- i. Monitor participants during the study for the development of Adverse Events (AEs) and Serious Adverse Events (SAEs).
- j. Evaluate any AEs and SAEs for relation to the study interventions (N-acetylcysteine or placebo; IV sodium chloride or IV sodium bicarbonate) and make appropriate changes to the participants treatment regimen per protocol.
- k. Report all AEs and SAEs as per protocol.
- l. Monitor the work of the SC and RA to ensure that all data collected on the study source document worksheets are accurate and entered into DataLabs in a timely and accurate fashion.
- m. Electronically sign case report forms as required.
- n. Notify the MAVERIC CSPCC, Chair's Office, and CSPCRPCC of any personnel changes.
- o. Provide visible support within the medical center to the Study Coordinator in an effort to identify study participants and to obtain data in a timely manner.
- p. Ensure that approved protocol changes are instituted at his/her medical center in a timely manner.
- q. Prepare documentation and assist study monitors in their performance of site reviews.
- r. Report to MAVERIC CSPCC and the VA Central IRB all problems involving risks to subjects or others that occur during the study per VHA Handbook 1058.01.
- s. Evaluate all protocol deviations and make all necessary notifications.
- t. Attend annual study meetings, site investigator conference calls, etc as required.

2. Study Coordinator (SC)

The SC will screen, consent, and enroll participants via IWRS, collect data on source document worksheets, enter data into the electronic case report forms in DataLabs, coordinate with the mobile specimen collection agency to schedule participant's follow-up blood collections post angiography if he/she cannot return to the site, contact participants by phone during the follow-up period per protocol, obtain participant permission prior to requesting medical records from non-VA facilities as needed, and provide clerical support to the LSI. The specific study duties and responsibilities of the SC are to:

- a. Serve as liaison between the LSI and the VA Central IRB and local R&D Committee.
- b. Ensure open and regular communication is maintained between the local site and the Study Chair's office and the MAVERIC CSPCC.
- c. Update the Delegated Responsibilities Log to reflect any personnel changes and upload to the appropriate site documentation folder on SharePoint.
- d. Serve as the primary point of contact for all participants in the study.
- e. Identify and screen potential participants to ensure they meet eligibility requirements.
- f. Thoroughly and clearly explain the study to the patient (under the direction of the LSI) and, if necessary, the patient's primary care provider, family, significant other, or legal representative.
- g. Conduct the informed consent procedures and ensure all aspects of the process are met, including documentation of consent as delegated by the LSI.
- h. Enter screening information into the Interactive Web Response System (IWRS) to randomize the participant.
- i. Obtain study drug assignment(s) using the IWRS.
- j. Explain study policies and procedures to the participant, and encourage participant compliance with the protocol.
- k. Ensure the collection of blood and urine as per the study protocol at the time of angiography
- l. Coordinate timing and completion of study procedures for the participant during the pre-, intra- and post-angiography periods.
- m. Schedule and conduct follow up telephone interviews.
- n. Provide participants with a schedule of follow-up contacts during study.
- o. Coordinate with the mobile specimen collection agency to schedule participant's follow-up blood draws if he/she cannot return to the VA site.
- p. Collect clinical and other data required per the schedule outlined in the protocol.
- q. Receive blood specimen from mobile collection agency and arrange for proper temporary specimen storage prior to shipping to the Central Study Laboratory .
- r. Ship stored blood specimens to the Central Laboratory on a weekly basis.
- s. Ensure all forms are accurately completed and entered into DataLabs in a timely fashion (within 5 working days of completing the source document worksheet).
- t. Submit copies of the completed Informed Consent (VA Form 10-1086) and HIPAA Authorization forms via secure fax to the MAVERIC CSPCC.

- u. Ensure that study related records for each participant are complete and up-to-date, including the Participant Study Binder, consent forms, CRFs, Progress Notes in CPRS, and source documentation worksheets.
 - v. Ensure that the flagging mechanism has been created in the participant's medical record in CPRS in accordance with local site policy and outlined in the Local Site Investigator application.
 - w. Obtain data on hospitalizations (VA and non-VA) as needed.
 - x. Maintain site-specific study documents in SharePoint (e.g., site signature log, training certificates, etc.).
 - y. Notify the Pharmaceutical Project Manager at the CSPCRPCC in Albuquerque when additional study medications are needed if enrollments and randomizations are occurring more rapidly than expected and a shortage of drugs becomes a concern. Individual sites are responsible for ordering extra study drugs to meet unexpectedly high enrollment and randomization rates.
 - z. Ensure all protocol deviations and safety reports are submitted to the VA Central IRB and local R&D Committee as required.
3. Program Support Staff: Research Assistant (RA) (0.5 FTEE research assistant)
 The RA will provide general administrative support to the SC and assist as needed in conducting the trial at the site. Specific duties may include, but are not limited to, participant recruitment; conducting the informed consent and ensuring all aspects of the process are met, including documentation of consent as delegated by the LSI; data entry; scheduling participant specimen collection; and contacting participants during follow-up and obtaining medical records from non-VA facilities.

C. Site Continuation Requirements

Medical centers will only continue participation if adequate recruitment and proper study and regulatory procedures are maintained.

1. VA Central IRB continuing review, and R&D Committee reviews
 Annual reviews are to be done prior to the anniversary of the initial approval of the study by the VA Central IRB and not necessarily by the anniversary of the start of patient recruitment or IRB approval of the local site. Reviews may be conducted more frequently than yearly at the discretion of the various study monitoring committees. It is the responsibility of the Local Site Investigator and the VA Central IRB to ensure that these yearly reviews occur in a timely fashion.

The VA Central IRB will notify the LSI, with a copy to the ACOS for R&D, of an impending review two to three months in advance to facilitate scheduling with the appropriate committee. The SC will work with the National Coordinator at the Study Chair's Office to submit reports on the status of the study at the medical center to the VA Central IRB using VA Central IRB form 115a, "Application for Continuing Review — Local Site Investigator." The MAVERIC CSPCC will provide the SC with any materials requested for this yearly review, except for blinded outcome data.

Once Form 115a has been completed, the National Coordinator will submit the application to the VA Central IRB. The site will be notified when documentation of VA Central IRB approval of the submission (consisting of either a VA Central IRB approval memo signed by VA Central IRB Board Chair or the portion of the VA Central IRB meeting minutes pertaining to the Board's approval of the study) is available to download from the VA Central IRB website. This documentation, along with the submission and any correspondence, must be saved and filed in the appropriate 'Site Documents' folder in SharePoint (See Section X.B.). Please keep in mind that while site staff are expected to communicate directly with the VA Central IRB for certain activities, such as responding to specific requests from the VA Central IRB, copies of all communications should be sent to the Project Manager at MAVERIC CSPCC and the National Coordinator at the Chair's Office.

Annual local R&D Committee review is not required at all sites depending on local policy. If annual review is required at your site, follow local procedures.

2. Maintaining Adequate Performance Standards Requirements

1. *Patient Accrual*

Each participating site is expected to enroll 233 participants over a recruitment period of 30 months. This corresponds to approximately 8 participants per month or 2 participants per week per site.

Recruitment rate (calculated by dividing the number of randomized participants by the number of expected participants) will be continuously monitored and sites recruiting less than 75% or between 75% and 90% of expected participants will be subject to remediation such as action plans or monitoring. Problems with accrual will first be dealt with at the Chair's Office, and if need be, will be addressed at the level of the Executive Committee. Sites under 75% cumulative recruitment after a three month ramp up period may be placed on probation.

Once a site is placed on probation, failure to meet the requirements specified by the end of the probation period may result in a recommendation for termination. In the event that the site is terminated, support will be provided for the follow-up of any participants already enrolled at that site.

2. *Adherence to Protocol*

The study will be managed by the Executive Committee which provides general oversight of the trial conduct, accrual, retention, quality, data systems, and management in accordance with the protocol.

Strict adherence to the protocol is expected of every participating site and will be monitored at the national and local levels and by the study's Data Monitoring Committee (DMC). Documentation of all protocol deviations is required and any site with repeated major violations may be terminated. By agreeing to participate in this study, the clinical site delegates responsibility for global monitoring of the study to the Executive Committee, the DMC, the VA Central IRB and the

MAVERIC CSPCC and its Human Rights Committee. Local R&D Committees involved in research at the participating sites may require that the LSI submit reports concerning the status of the trial as well.

3. *Data Timeliness/Quality*

All source document worksheets for this study should be completed and entered into DataLabs within five working days of completion. Please review each form for completeness prior to the participant leaving the study site.

All queries will be handled electronically through DataLabs. It is expected that all data queries will be answered within five working days of receipt.

3. Participating in All Required Data Audits

Each site can expect to be visited during the trial by a GCP auditor from the SMART team in Albuquerque. See Section XII for more details. Other visitors from CSP may include personnel from the Chair's Office, the MAVERIC CSPCC, or the Human Rights Committee.

4. Requesting Annual Site Personnel Salary Funding

Each site must request funding for site personnel for the upcoming fiscal year via their local R&D office. The MAVERIC CSPCC Budget Analyst will email the budget request form to the site ACOS for R&D, Local Site Investigator, and Study Coordinator. It is important to include all anticipated site personnel salary costs on this request form (i.e., anticipated salary increases for the Study Coordinator, Research Assistant). Any requests for additional funding must be approved by VA Central Office.

D. Replacing Site Staff during the Study

Site staff must update the Designated Responsibilities Log (DRL) noting a termination date for the individual leaving and adding the new staff person. The original must be filed in the Investigator Study File, and a copy uploaded and filed in the appropriate 'Site Documents' folder in SharePoint (See Section X.B.).

1. Replacement of a Local Site Investigator

- The current LSI will suggest an appropriate replacement to the Study Chair, who will inform the MAVERIC CSPCC and CSPCRPCC of the proposed change.
- A letter must be sent, with the signature of the ACOS for R&D, nominating the replacement LSI to the Study Chair in Pittsburgh.
- The Study Chair will poll the members of the Executive Committee for their approval of the replacement.
- When approved by the Executive Committee, a letter will be sent from the Study Chair in Pittsburgh to the MAVERIC CSPCC Director requesting approval of the new LSI.
- If the MAVERIC CSPCC Director concurs with the Study Chair's letter, he will forward the letter to CSP VACO for final approval.

- Site staff will complete a “Change in Local Site Investigator Form” (VA Central IRB Form 134) and send to the Study Chair in Pittsburgh for submission to the VA Central IRB for approval.
 - If the informed consent form needs to be updated with the new Local Site Investigator’s information, it must be re-submitted to the VA Central IRB for review and approval.
 - Site staff must ensure all appropriate documentation including the DRL, contact information, a signed and dated CV, completed conflict of interest form and investigator agreement, and all required training certificates are uploaded and filed in the appropriate ‘Site Documents’ folder in SharePoint (See Section X.B.). The LSI’s medical license must be forwarded to the CSPCRPCC.
 - The new LSI must complete GCP Training provided by SMART as soon as it can be arranged.
2. Replacement of a Study Coordinator
- The LSI will contact the National Coordinator at the Chair’s Office or the Project Manager at the MAVERIC CSPCC and inform them when the person will be leaving, who the replacement will be, and when the new person will start.
 - If the informed consent form needs to be updated with the new Study Coordinator’s information, it must be re-submitted to the VA Central IRB for review and approval.
 - Site staff must ensure all appropriate documentation is updated including the DRL, contact information and all required training certificates are uploaded and filed in the appropriate ‘Site Documents’ folder in SharePoint (See Section X.B.). The new SC must complete GCP Training provided by SMART as soon as it can be arranged.
3. Replacement of Program Support Staff (Research Assistant)
- The SC will contact the National Coordinator at the Chair’s Office or the Project Manager at the MAVERIC CSPCC and inform them when the person will be leaving, who the replacement will be, and when the new person will start.
 - Site staff must ensure all appropriate documentation including the DRL, contact information and all required training certificates are uploaded and filed in the appropriate ‘Site Documents’ folder in SharePoint (See Section X.B.).
 - If the informed consent form needs to be updated with the new Program Support Staff information, it must be re-submitted to the VA Central IRB for review and approval.
 - The new RA must complete GCP Training provided by SMART as soon as it can be arranged.

E. Organization of the Investigator Study File

The Investigator Study File consists of all records and materials at the participating site pertaining to the study. This includes participant files (both case report forms and the corresponding source documents, e.g., medical records, laboratory reports, source document worksheets, etc.), regulatory files, and other study-related correspondence and documents.

The Investigator Study File must be complete, well organized, readily identifiable, and accessible. To help sites develop and maintain study files meeting these requirements,

SMART will provide an Essential Documents Binder (EDB), Participant Study Files Organizers, and a Participant Consent Forms Master File (binder).

1. Essential Documents Binder (EDB)

Each participating site will receive an Essential Documents Binder (EDB) to aid in organizing the Investigator Study File; i.e., all records and documents related to the trial. Due to space limitations, it is not possible to place the entire Investigator Study File in the EDB. This binder is to serve as a directory to all of the study documents and records at the site and secondarily as a repository for those items that can be accommodated by the binder. The binder is divided into the following sections:

- Protocol & Amendments
- Operations Manuals
- Consent Forms / Information Provided to Participants
- Participant Log / Clinic Lists in CPRS
- IRB submissions / notifications / approvals
- Unanticipated Problems and Safety Reporting (Includes Serious Adverse Events & Safety Reports & DMC Summaries)
- Notes-to-File
- Investigator Responsibilities / Agreements (with Sponsor, Institution, VA Central IRB, FDA, etc)
- Study Site Personnel (Signatures & Delegated Responsibilities; Qualifications and Training)
- Site-Sponsor Correspondence
- Conference call minutes (section tab provided)
- Investigator Brochure (DIR / VA Form 10-9012)
- Investigational Products Accountability Records
- Laboratory (Accreditation, Normal Ranges of Test Values)
- Participant Files
- Visitor Log

Certain sections of the EDB contain logs that are to be completed as items are added:

- Participant Log
- Record of Approved Consent Form Versions
- Participant Consent/Re-Consent Tracking Log
- Site Personnel Signatures & Delegated Responsibilities Log
- Documentation of Qualifications and Training of Study Site Personnel
- VA Central IRB Submission Tracking Logs
 - Tracking Log of Local Site Investigator's CIRB Submissions
 - Tracking Log of Principal Investigator's/Study Chairman's CIRB Submissions (on behalf of the study)
- Unanticipated Problems Involving Risks to Participants or Others (UPIRPOs) / Serious Adverse Events (SAEs) Log
- Log of Safety Reports / Data Monitoring Committee (DMC) Summaries from Sponsor

These logs are to be printed and must be maintained in the EDB during the trial and will be collected a minimum of once per year by SMART. These logs also must remain available after the study is over. An electronic format of each of these logs is provided to help facilitate this task. Current copies of these logs can be found on the SMART website under “GCP Tools”: <https://vawww.csp.research.va.gov/smart.cfm>

The SC will be responsible for maintaining the EDB and should make it readily accessible to all study personnel. The binder should be continually updated and kept current throughout the course of the trial. As essential documents accumulate, additional binders will be needed and can be organized as breakout binders. Also certain documents, e.g., study protocols and operations manuals, may be more conveniently kept separate from the EDB with a note of explanation placed in the appropriate section of the EDB to note the location.

The EDB must contain a COMPLETE record of all the essential documents, even documents available elsewhere in the facility. The Sponsor and LSI will rely on the EDB to provide a complete and ready source for required study documents both during and after the study is completed, and only by maintaining a complete “free-standing” file can this be assured.

The EDB must contain all correspondence with the VA Central IRB and Sponsor. Electronic VA Central IRB submissions and subsequent approvals and acknowledgements must be printed and retained even though certain of these items may be retrievable from the VA Central IRB website. Email communications of substance with the Sponsor or VA Central IRB are also to be printed and filed.

2. Participant Study Binder

GCP requires that LSIs keep adequate and accurate case histories for study participants. A Participant Study Binder, provided by SMART for each participant, will be established and will contain the supporting source documentation from the participant’s medical record, the source document worksheets, and/or various other records and documents pertaining to the participant. Other than Form 01: Eligibility and Randomization, Form 02a: Initial Study Drug Assignment and Form 02b: Additional or Replacement Study Drug Assignment, it is not necessary to print out and retain in the Participant Study Binder completed electronic case report forms (CRFs) from Datalabs. Each binder contains pre-printed divider pages for each study event (for example, baseline, 5 days post-procedure, 35 days post-procedure, 90 days post-procedure), listing on the divider which CRFs must be completed at that event. A list of other CRFs that may be completed is also included. The SC will be responsible for establishing and maintaining these binders and must assure that study-related records generated by the LSI or other study team members are incorporated into them as appropriate.

a. *Source Documentation*

Source documentation must be maintained to ensure integrity of the study data. Source documentation is defined as the original recording of study data. The Participant’s Study Binder must either contain the source document (SD) for the electronic CRF data or must provide a clear indication of where the SD can be found. Every data point recorded in the eDC will have a supporting “original” entry

recorded first in the medical record or other notes, source document worksheet, logs, etc., unless otherwise specified by the Sponsor. This practice helps ensure compliance with the requirement that supporting documents be readily identifiable and accessible.

In addition to supporting and allowing verification of specific CRF data, source documentation should document the progress of the participant throughout the trial. At a minimum, a progress note should be entered into CPRS for each scheduled event (i.e., day 5, 35, 90 telephone call/patient interview), as well as for those instances where the SC is unable to contact the study participant for a scheduled study event.

Once the progress note is entered into CPRS, the note should be printed and placed into the clinical research file (CRF) of the study participant. The medical record must also be flagged per institutional policy/procedures to indicate that the participant is enrolled in an interventional research study. Included in the progress notes should be information on adverse events, participant compliance with instructions, telephone contacts, and any study data not recorded elsewhere in the medical record. Ideally, these notes will be written or co-signed by the Local Site Investigator.

The following outline provides the minimum standards for study visit progress notes. The degree of detail illustrated below is sufficient in studies employing detailed SD worksheets or other primary source documents. Greater detail is required if the progress note is the only support/documentation for the data recorded at the visit. Compose a note in CPRS that documents:

- Study title and/or number and visit number.
- Confirmation that visit procedures were performed or specifies those not performed and why. (If all procedures were performed, a statement to that effect will suffice)
- Any changes in medication or state no change in medication.
- New or continuing adverse events with details or the absence of adverse events.
- Assessment of participant compliance and any re-training provided during the visit.
- Team members seeing the participant during the visit in addition to the author of the progress note.
- Sign/date the note and forward to the local LSI for acknowledgement if authored by study staff.

3. Participant Informed Consent Forms Master File

The LSI is responsible for ensuring that participant informed consent, HIPAA authorization and other releases, as necessary, are obtained and documented as described in the study protocol and this Operations Manual. Participants will be provided with signed copies of the informed consent forms and HIPAA authorization forms. The participant's original signed and dated informed consent form(s), HIPAA Authorization forms, and other authorizations/releases must be filed in the Participant Consent Forms Master File (partitioned for each participant). A copy of the signed informed consent form and HIPAA authorization form must also be filed in the participant's medical record. This is typically accomplished by sending copies of the documents to medical

records for scanning into the participant's electronic medical record, as per local Medical Center policy.

The informed consent process is not simply having the patient sign the informed consent document. Informed consent is the process during which the study is completely explained to the participant, they have an opportunity to ask questions about the study, and after fully understanding the details of the study, including the risks and potential benefits, they agree, without coercion, to participation in the study. The participant's signature on the informed consent form provides one necessary form of documentation of the informed consent process. Documentation of the informed consent process also requires the entry of a detailed progress note into the medical record (CPRS). This progress note shall contain, at minimum, the elements specified in VHA Handbook 1200.05 and CSP policy. Ideally the note will include:

1. Name of the study and the date informed consent obtained.
2. The names of individuals present during the informed consent discussion including the person obtaining consent and any other individuals present.
3. Documentation that the Informed Consent Form was reviewed and explained and that the participant had the opportunity to ask questions and that all questions were answered to their satisfaction.
4. Documentation that the participant appeared capable of understanding the risks and benefits of the study and the informed consent process
5. Documentation that the informed consent form was signed prior to the initiation of any study procedures
6. Documentation that the participant received a signed copy of the signed informed consent form and HIPAA Authorization for their records.

F. Study Closeout Procedures and Record Retention Requirements

Near the close of the trial, sites will be instructed in the requirements for final data submission/cleaning and completion of any required documentation.

At the close of the trial, Local Site Investigators will be instructed in the requirements for record retention and archiving study documents at their site. Original source documents that are a part of the participant's VA medical record stay in that record, but copies of these documents or identification of the documents' location are to be retained in the investigator's file along with copies of the source document worksheets. The MAVERIC CSPCC should be contacted concerning record disposal or alternative provisions for record storage.

All research records relating to this CSP study shall be retained indefinitely after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner. **YOU MUST NEVER DESTROY ANY STUDY RECORDS WITHOUT WRITTEN AUTHORIZATION FROM MAVERIC CSPCC.**

G. Maintaining Patient Confidentiality

It is CSP policy to protect the confidentiality of participant study data to the extent permitted by law. In order to protect confidentiality, participant identifiers, such as names or social security

numbers will not be routinely placed on study data forms with the exception of Form 03: Participant Contact Information. Instead, a unique study generated participant identification number will be assigned to each participant. This unique number will be placed on each study form to allow each form for a particular participant to be identified as belonging to him/her. The local site will be responsible for maintaining a cross-walk of the participant ID number and the participant's name and contact information in a screening log book which will be kept in a locked filing cabinet in their designated research office. The information will only be accessible to authorized study personnel. The participant ID number will be placed on all source document worksheets and will be used to enter data into the IWRS and DataLabs for a particular participant.

Form 03: Participant Contact Information is the only source document worksheet which has patient identifying information on it. Once completed, it should be stored separately from other completed forms in a locked filing cabinet at each site. This data will be entered on a paper TeleForm and faxed to MAVERIC CSPCC at 857-364-4009. Patient identifying information such as address and social security number will allow the MAVERIC CSPCC to access central VA data and other national databases as described in the study protocol. It will be stored electronically in a separate file from other study data with access restricted to authorized personnel at the MAVERIC CSPCC. Access to the cross-walk file linking this information will be restricted to the clinical site and to authorized personnel at the MAVERIC CSPCC where the link will be maintained.

Any paper documents with patients' personal identifiers and all study site records should be kept in a secure location (i.e., locked filing cabinet) and away from public scrutiny. Only authorized study personnel may access any identifying study data. Use locked file cabinets and keep office doors locked when no one is using the office where the personally identifiable data are stored.

H. Research Misconduct

The success of a VA cooperative study depends on the timely, accurate, and honest collection of all research data. The LSI is responsible for ensuring the validity of reported data. The LSI is also responsible for the proper supervision of research that pertains to this study performed by other study staff at his/her medical center. Unfortunately, isolated instances of fraudulent data have been reported in cooperative clinical trials. Research misconduct is defined as:

- Fabrication; falsification; or plagiarism in proposing, performing, or reviewing research; or in reporting research results.
- Research misconduct does not include honest error or differences in opinion.

To constitute research misconduct, behavior must:

- Represent a significant departure from accepted practices of the relevant research community.
- Be committed intentionally, knowingly, or with reckless disregard for the integrity of the research.

In order to establish a finding of research misconduct, the allegation must be proven by a preponderance of the evidence; i.e. “the allegation is more likely than not to be true.”

VHA Handbook 1058.2 provides extensive details concerning how accusations of fraud in research will be investigated. The availability of the original experimental records is the appropriate response to a complaint of fraudulent presentation of data. Written, detailed, and explicit procedures for data gathering, storage, retrieval, and analysis are required. It is the responsibility of all investigators to maintain records of all experimental protocols and data sufficient to allow subsequent verification. This data must be retained unless written authorization from the MAVERIC CSPCC has been obtained.

Compared to single-center studies, cooperative studies are somewhat protected from fraudulent data. Numerous people inspect the data and comparisons can be made between participating centers, all of which follow the same protocol. Site visits to ensure that Good Clinical Practice (GCP) is being followed are made on a routine basis by the GCP Monitoring Group of the Site Monitoring, Auditing and Resource Team (SMART). However, all participants in this cooperative study should be alert to the possibility of research fraud, and should report any suspected instances to the Study Chair’s Office and the MAVERIC CSPCC.

I. Termination of a Study Site

Medical centers will only continue participation if adequate recruitment occurs and proper procedures are maintained. Sites are expected to enroll and randomize an average of 2 patients each week. Failure to achieve this target may lead to termination of the site. Any medical center with repeated protocol deviations in the absence of valid justification, and after remedial protocol training, will be recommended for termination. Termination of a center will occur after approval by the Executive Committee with the concurrence of the Data Monitoring Committee and the Director of the Cooperative Studies Program.

The VA Central IRB is authorized to modify, suspend or terminate approval of research that has been associated with unexpected serious harm to subjects, or is not being conducted in accordance with 45 CFR 46 or the VA Central IRB's decisions, conditions and requirements. Local Site Investigators must have a plan for continuity of patient care should site suspension or termination occur. Any suspension or termination of approval shall include a statement of the reasons for the VA Central IRB's action and shall be reported promptly to the Study Chair, appropriate institutional officials, and the department or agency head.

J. Study Subject Transfer Procedures from One Site to Another

Prior to initiating a subject transfer, contact the MAVERIC CSPCC to ensure a receiving study site is eligible to receive the subject. In general, a study site cannot refuse to transfer or receive the transfer of a study subject. However, there may be some circumstances in which a study site may not be able to receive a subject transfer. These include:

- The study site has an expired VA Central IRB review
- The study site is closed or in the process of closing
- The study site is under suspension due to an audit issue
- Poor institutional performance

- The study Local Site Investigator believes that his/her site is not currently able to handle additional subjects due to limited staffing or study site capacity issues.

1. Transferring Site Procedures

To initiate the subject transfer, the transferring study site must:

- a) Provide the subject with a current list of eligible study sites and discuss which would be the most convenient site for them.
- b) Contact the receiving study site by phone regarding plans for subject transfer once the subject has agreed to be transferred to a specific study site.
- c) With the subject's permission, the transferring study site can initiate contact with the receiving study site while the subject is in the office and the subject can speak directly to the receiving study site. If that is not possible, contact the subject by phone and notify them that the receiving study site has been contacted regarding the transfer and advise them to call the receiving study site to initiate contact.
- d) Complete and submit all outstanding forms. Review and answer all DCF's in DataLabs. Review the reports from the MAVERIC CSPCC to make certain that all forms are up-to-date, all queries are resolved, and the completed forms are signed electronically by the Local Site Investigator (if applicable).
- e) Send a copy of the subject's complete chart, including a copy of the current signed Informed Consent, and other information in the chart such as source documentation, nurse, physician or study site staff notes, subject history, etc., to the receiving study site according to VA regulations for transfer of Protected Health Information. If subject information cannot be released without subject authorization (as possibly mandated by the Local Site Investigator or local site procedures), ask the subject to sign a medical release (if they have not already done so) so that there is authorization to send a copy of the chart to the receiving study site. Send COPIES via a trackable mail system such as UPS. **DO NOT SEND THE ORIGINALS.** When sending the UPS package, ensure that a signature is required.
- f) Flag the original chart appropriately to indicate the subject has been transferred.

2. Receiving Site Procedures

To complete the subject transfer, the receiving study site must:

- a) Contact the original Study Site to discuss the study history of the subject.
- b) Confirm with the original Study Site that all required forms have been submitted and any outstanding queries or DCF's have been resolved. The receiving Study Site may contact the MAVERIC CSPCC to confirm that follow-up activities are up-to-date.
- c) Confirm the receipt of the subject's complete chart. Contact the transferring Study Site if the chart is not received per discussion with the Study Site.
- d) Contact the subject, preferably by phone, to initiate contact and review upcoming study procedures.
- e) Obtain the subject's signature on the Study Site's Informed Consent (this is required) and fax a completed copy to MAVERIC CSPCC at **857-364-4009** for adjudication.

- f) Contact MAVERIC CSPCC to obtain the appropriate permissions to access and enter case report form data for the individual subject. Note in the comments field that the subject was transferred from another site.

The subject is the responsibility of the transferring Study Site until the transfer has been completed by the receiving Study Site. The transfer is complete only after the receiving Study Site obtains a copy of the subject's chart from the transferring Study Site, contacts the subject to confirm the transfer, and an Informed Consent Form is signed by the subject at the receiving Study Site.

MAVERIC CSPCC will ensure the Pharmacy Coordinating Center in Albuquerque is contacted to determine a procedure for drug assignment transfer, the MAVERIC CSPCC Data Management staff is contacted to update standard study reports to reflect the transfer, and any other study group(s) who have access to or involvement in the collection, entry, monitoring, cleaning or analysis of study data is notified of the subject transfer (e.g., SMART, HERC, etc.).

II. Study Protocol Procedures

A. Recruitment

Recruitment is scheduled to occur over the first 30 months of the study. **Enrollment of at least 2 patients per week at each of the participating centers is expected.**

Patients undergoing coronary or non-coronary angiography will be recruited from the cardiac catheterization laboratory, interventional radiology suite/clinic, or other hospital venues that perform angiographic procedures (e.g., operating room) at each participating medical center. LSIs should periodically review the study and its goals with other physicians and house staff who work with this patient population in order to capture as many potential study patients as possible.

B. Pre-Screening

Through the approval of the HIPAA waiver by the VA Central IRB, sites are able to access and use patient medical record information and procedure logs to prospectively screen and identify patients who are scheduled to undergo an elective or urgent coronary or non-coronary angiography with iodinated contrast media. From this pool of patients, study coordinators will use the Pre-Screening Log (Form 00) on the CSP578 SharePoint as a tool to help identify potential study patients who may be eligible to participate in the trial. **Please refer to Appendix 20.**

A patient is eligible if:

- They are undergoing coronary or non-coronary angiography with iodinated contrast
- The screening eGFR is 45-59.9 ml/min with diabetes or if the screening eGFR is 15-44.9 with or without diabetes
- And the answers to all of the GREEN questions are “No”.

DIRECTIONS: Save the log to your secure research drive and include your site ID number at the top of the form. Fill out a row for each patient undergoing an angiogram.

IMPORTANT: If a patient is potentially eligible, but does not enroll, it is necessary to provide the reason the person did not enroll.

EVERY FRIDAY: Remove the first column (column A) that contains patient initials and the last 4 digits of their SSN), and send the log to Lee.Mandich@va.gov. **It is necessary to encrypt the email if you leave PHI contents in the log**

Note:

- Non cardiac angiography includes angiograms in which iodinated contrast is injected into an artery other than the coronary arteries. Examples include: pulmonary angiogram, cerebral angiograms, peripheral extremity angiogram (arm/leg), and aortoangiogram. Computed Tomography (CT) scans and CT angiography do NOT meet eligibility criteria.
- Dialysis includes intermittent hemodialysis, peritoneal dialysis, continuous renal replacement therapy or sustained log efficiency dialysis.

Once a potentially eligible patient is identified (all of the answers on the Pre-Screening Log are completed and potential eligibility is established), a member of the study team should notify a member of the team performing the angiography procedure or the patient's primary provider that the patient may be eligible to participate in our study. The precise mechanism for this notification will vary site to site depending on local circumstances. Probable mechanisms will include but are not limited to face-to-face or telephone discussion, or secure/encrypted email. The study team member will need to ask the person from the treatment team to introduce the study to the patient and let a study team member know (via one of the probable mechanisms described above) if the patient is interested and can be approached by a study team member. Alternatively, if a member of the angiography team identifies a potential participant, they will ask the patient whether they would be willing to speak with the study team about this study and if the patient agrees, the study team will be contacted by one of the mechanisms described above informing them that the patient has agreed to be contacted about the study.

A study team member will contact potentially eligible patients either by telephone or in person to describe the study. An IRB-approved telephone script is provided to sites for this purpose. For anyone contacted by telephone, if there is time, the informed consent form (ICF) will be mailed to them if they so desire **for reading ahead of time (but signatures may only be obtained in-person)**. If time doesn't allow for this, the informed consent process will begin in-person when the patient arrives on site for their angiography procedure. The Informed Consent document will be administered by trained study staff members (LSI, Co-I, SC, or RA). The patient needs to be given sufficient time to review the document and the opportunity to raise any questions. As much time as is required for the patient to understand the information in the informed consent form will be allowed. Once the entire informed consent process has been completed and the ICF has been signed, a study team member will complete Form 01. Eligibility and Randomization.

C. Obtaining Informed Consent

Informed consent will be documented in this trial by the use of an Informed Consent Form (VA form 10-1086) that has been approved by the Central IRB. The Informed Consent Form template provided in the LSI application package must be used by the study team and adapted as needed to meet local needs. Any changes made to this template locally must be justified and the form must be submitted for approval by the VA Central IRB before being used. The Informed Consent Form template contains all of the basic required elements of informed consent. The Informed Consent Form template, as revised by the local site and approved by the VA Central IRB, must be filed in the appropriate site documentation folder on SharePoint (See Section IX.B.).

The LSI is responsible for ensuring that patient consent is obtained and documented as described in the study protocol and in full compliance with VA requirements. CSP policy allows any study team member thoroughly familiar with the protocol to present the consent form and discuss the general features of the trial, but requires that the LSI, or clinically equivalent sub-investigator, be available as needed to answer questions.

A study team member, usually the SC or the RA, will provide and review with the patient the Informed Consent Form along with a copy of the Research & Development pamphlet, "Volunteering in Research" (See Appendix 11). Each patient must be allowed to read the

Informed Consent Form in order to have some understanding of the study before discussing it with the SC (or other qualified study personnel). The SC (or other qualified study personnel) will review and discuss the study with the patient and answer any questions he/she may have. In discussing the study with the patient, the SC (or other qualified study personnel) may provide additional details beyond those contained in the consent form, but no substantive addition, deletion, or modification to these statements is allowed.

During the informed consent process, the general purpose of the study will be explained to the patient. The treatment comparisons will be clearly described. The randomization process, the concept of placebos, the study timeline and patient expectations, along with the risks associated with the treatments and procedures will be reviewed. The importance of patient confidentiality will be stressed and a description of the process for maintaining this confidentiality will be given. It must be clear that the patient fully understands each aspect of his/her participation.

Always ensure that the most current VA Central IRB approved version of the ICF is used. The header must be completely filled out on every page including the patient's name. The date listed in the header should be the date the information was reviewed by the patient. Ensure that the patient's name, signature and date along with the same information for the person who obtained consent are present. If there are any mistakes made on the form and something is crossed out and corrected, it must be initialed and dated by the person who made the correction. Immediately after completing the informed consent process and having the participant sign the ICF and HIPAA Authorization, use the ICF Checklist (**APPENDIX 4**) to verify all items are completed, checking off each item when verified and entering the needed dates and other information as specified. If mistakes or problems on the ICF or HIPAA Authorization are found, resolve the issue right away while the participant is still in the clinic. The MAVERIC CSPCC will review all ICFs and HIPAA Authorization forms and contact the sites if any deficiencies are noted.

The U.S. Department of Health & Human Services, Office of Civil Rights enacted the Health Information Privacy and Accountability Act (HIPAA) in 1996 to provide requirements for protecting the privacy of health information and providing individuals with certain rights with respect to their health information. In conjunction with the informed consent procedure, patients will review and be asked to sign the Authorization for Release of Protected Health Information Form as required by HIPAA. As with the ICF, always ensure use of the most current version of the HIPAA Authorization form and that the header and footer information is completed on every page. The patient must sign and date in the "Participant Authorization" section. A form to revoke HIPAA authorization will be provided to the subject for use in the event he/she wishes to revoke his/her authorization in the future.

If the patient does not consent to participate in the study, he/she will not be screened further or enrolled, and will be referred back to the appropriate clinical team for treatment.

For all patients who consent to participate in the study including patients who fail to meet eligibility criteria based on Form 01. Eligibility and Randomization, the consent must be scanned and uploaded into CPRS, and a consent progress note entered into the patient's electronic medical record to document that the patient consented to participate in the study prior to any study related procedures taking place. Essential elements of this consent note or progress note include (See Appendix 14 for template consent note):

1. Name of the study and the date informed consent obtained.
2. The names of individuals present during the informed consent discussion including the person obtaining consent and any other individuals present.
3. Documentation that the Informed Consent Form was reviewed and explained and that the participant had the opportunity to ask questions and that all questions were answered to their satisfaction.
4. Documentation that the participant appeared capable of understanding the the risks and benefits of the study and the informed consent process
5. Documentation that the informed consent form was signed prior to the initiation of any study procedures
6. Documentation that the participant received a signed copy of the signed informed consent form and HIPAA Authorization for their records.

The medical record should be flagged for all randomized patients to indicate that the patient is participating in a research clinical trial. Screen failed patients should not have their medical records flagged. Procedures for flagging medical records vary by site, so a study team member should speak with their local R&D office for information on local procedures and requirements. After obtaining the patient's informed consent, the original signed and dated Informed Consent Form and HIPAA Authorization form should be kept in the Investigator File; in this case, in the Participant Consent Forms Master File. Copies of each document should be distributed as described below:

1. Copy to the patient (*including a blank HIPAA Revocation Form for his or her use in the future if they wish*)
2. Copy or written assurance, by the LSI, that the signed consent is available for viewing and printing in the electronic medical record to the local research pharmacy, per local policy
3. Copy for inclusion in the patient's medical record
4. Copy of the signature pages as well as Form 3 faxed to the MAVERIC CSPCC via the secure fax line at 857-364-4009. A CSP#578 ICF/HIPAA Fax Cover Sheet should be used.*

*In the event that the fax line is down, sites will ship ICF packets to MAVERIC via UPS overnight shipping. Each site coordinator has received a unique UPS username and password from MAVERIC for shipping to the central laboratory (ABML). The same username and password will be used for shipping documents to MAVERIC. If you need to request this information again, please contact Project Management at MAVERIC.

We would highly suggest you ship your consents and related documents on either Thursday or Monday of the week. Please do not ship on Fridays.

Make sure you are shipping **photocopies** of the following for **each participant** who enrolled during that week:

1. Signature page of ICF
2. Signature page of HIPAA
3. Completed Form 3 (the typed PDF version, not the worksheet)
4. Completed fax cover sheet

Step 1: Once on the UPS website, click on the Create a Shipment tab. To ship to MAVERIC – select “MAVERIC CC” from the drop down Address Book list . Once MAVERIC is selected, it will automatically populate with the address details.

Step 2: Where is this Shipment Coming From? Confirm the address listed is the same as your site and that the contact information is correct (should list the site coordinator).

Step 3: What Are You Shipping? Select the number of packages to ship and what type of package. It should be only 1 package and the packaging type must be UPS Letter. Enter the weight of the shipment. Anticipated weight with the documents will be dependent on the number of documents shipped, but it should not exceed ½ lb. You do not need to include package dimensions.

Step 4: How would you like to ship? Make sure UPS Next Day Air is selected. Note within this section, there is a check box for **Send e-mail notification**. Click on the box and a check mark will appear. Once this page is complete you will be automatically prompted to enter the e-mail address for confirmation of delivery.

Step 5: Enter “0” for the number of patient samples. Make sure the site location is your VA Hospital city name.

Step 6: How would you like to pay? Confirm the ‘Central Biorepository’ is selected. Confirm that ‘Review shipping details before completing the shipment’ is checked, and then click on **Next**.

Step 7: Enter your email address for shipment notification. The MAVERIC email is already in the system. This ensures that both you and MAVERIC are aware when the documents have been delivered and/or if any problems have occurred with the shipment. A suggested email blurb is outlined in the example. You can include a personal email message such as “Participants consent for week of ____ thru ____” for your reference. Once this is complete, click on **Next**.

Step 8: You will then be brought to the review page (**Review Your Shipment Details**). After reviewing the information for accuracy, click **Ship Now**.

Step 9: A prompt will appear to select the printer your computer is connected to. Select Print to print out the label. You can also print out the label from the Shipment Confirmation page.

Step 10: Shipment Confirmation. You will then be brought to a page displaying a summary of the shipping services you selected. Because email notifications have been generated, this information has been sent to MAVERIC as well.

Step 11: Retain a copy of the UPS notification emails. We suggest setting up a **UPS Notification** folder within Outlook.

Step 12: This printed shipping label will then be placed in a clear plastic envelope and attached to the outside of the UPS letter package (shipping materials provided by your research department).

If you have questions about the process to attach the packing slip or any of the above items, please contact the Project Manager at MAVERIC.

The LSI is responsible for ensuring that patient consent is obtained and documented as described in the study protocol and in compliance with VA requirements. **Failure to properly obtain informed consent will result in disciplinary action by the Chief Research and Development Officer and could result in the dismissal of the participating LSI.**

Required Forms for obtaining informed consent

- a. Informed Consent Form (VA form 10-1086) – signed by patient
- b. HIPAA Authorization – signed by patient
- c. HIPAA Revocation of Authorization (*not to be signed, but provided to the patient for his/her future use, if desired*)
- d. “Volunteering in Research” pamphlet - given to patient
- e. CSP#578 ICF/HIPAA Fax Cover Sheet
- f. ICF Checklist

Surrogate Consent

PLEASE NOTE: Surrogate consent of participants is **NOT** permissible in this trial. Any participant that is not capable of providing a valid informed consent without a LAR (legally authorized representative) is not eligible to be enrolled into this trial.

Special Considerations:

1. Blind Participants

Consenting of a blind participant will require that 2 witnesses be present for the entire consent process. Both witnesses will need to sign and date the ICF documenting their presence during the process and the concurrence of the participant to enroll in the trial.

2. Participant with disabilities that are physically unable to document concurrence

Consenting of a participant who possess the ability to provide a valid informed consent but, due to some level of physical incapacitation (loss of limb(s), etc.), are not able to properly document their concurrence will need to have a witnesses present that will sign and date the ICF documenting the concurrence of the participant to enroll in the trial.

Participant Consent Tracking Log

Once a participant is consented, Study Coordinators will fill out the Participant Tracking Log (Form 00 in the Source Document Worksheets library on the CSP578 Study Sharepoint site) in order to keep track of all follow-up dates for each participant. Please refer to Appendix 20 for detailed instructions.

D. Determining Patient Eligibility

1. Inclusion Criteria

Patients 18 years of age or over undergoing elective or urgent coronary or non-coronary angiography involving iodinated contrast dye who have either:

- eGFR 45-60 ml/min/1.73m² **AND** diabetes;
- **OR**
- eGFR <45 ml/min/1.73m² regardless of diabetic status

The SCr measurement used to calculate eGFR in order to determine eligibility must have been measured within 30 days prior to angiography. If more than one SCr has been measured in the prior 30 days, the **most recent value** should be used to assess eligibility. Patients in whom a SCr has not been measured within 30 days, will be administered the informed consent and after signing the ICF, will be asked to provide a blood sample that will be delivered to the local VA laboratory to have SCr measured as a stat order to determine if the patient meets the eligibility criteria for kidney function defined above.

a. *Defining eGFR*

Most VA laboratories automatically generate an eGFR value from the SCr measurement. This eGFR value should be used to determine subject eligibility. In the event in which the laboratory does not automatically generate an eGFR value from the SCr, the study coordinator should calculate the eGFR using the 4-variable Modification of Diet in Renal Disease (MDRD) formula. The specific 4-variable MDRD formula used will depend on whether the screening SCr value was measured using an isotope dilution mass spectroscopy (IDMS) -traceable or non-IDMS traceable laboratory methodology. Information on whether an individual laboratory uses an IDMS or non-IDMS traceable method should be obtained from the VA laboratory personnel.

Screening SCr using non-IDMS traceable lab method

For creatinine in mg/dL:

$$eGFR = 186 \times \text{Serum Creatinine}^{-1.154} \times \text{Age}^{-0.203} \times [1.212 \text{ if Black}] \times [0.742 \text{ if Female}]$$

For creatinine in $\mu\text{mol/L}$:

$$eGFR = 32788 \times \text{Serum Creatinine}^{-1.154} \times \text{Age}^{-0.203} \times [1.212 \text{ if Black}] \times [0.742 \text{ if Female}]$$

Screening Scr using IDMS traceable lab method

Use the equations above multiplied by 0.94086.

In the event in which it is not known whether the laboratory uses an IDMS traceable method, the calculation should use the formula for a non-IDMS traceable method. A calculator for these formulas will be available on the CSP 578 Study SharePoint for your use.

b. *Defining diabetes*

Diabetes is defined as at least one of the following:

- the current use of oral hypoglycemic medications or insulin; or
- Hgb A1C value of $\geq 6.5\%$ within the previous 12 months; or
- Medical record documentation of end-organ diabetic disease (e.g., diabetic retinopathy, diabetic nephropathy and/or diabetic neuropathy).

2. Exclusion Criteria

- a. Stage 5 chronic kidney disease (CKD) (eGFR < 15 mL/min/1.73m²) based on the screening SCr measured as part of routine clinical care within 30 days prior to angiography.
- b. Current need for hemodialysis, peritoneal dialysis, continuous renal replacement therapy, or slow low efficiency dialysis (SLED) as documented in the patient's medical record
- c. Known unstable baseline serum creatinine (Scr) at the time of angiography defined by a change (increase or decrease) in Scr of $\geq 25\%$ over the 3 days prior to the angiography. To determine this, the SC will review all of the patient's Scr measurements taken over the three days prior to the angiography and look for an increase or decrease of 25% or more between the most recent measure and any other measurement taken within the past three days. If the subject had no Scr measurement taken, or only one, then they would not meet this exclusion criterion because we are looking for "known" Scr instability only.
- d. Emergent angiography procedures defined as an anticipated duration of < 3 hours between the identification of the indication for angiography and the time of the planned procedure. Study personnel may need to consult with the clinical team to make this determination.
- e. Decompensated heart failure requiring any of the following at the time of angiography:
 - IV inotropic medications: inamrinone, milrinone (Primacor), dobutamine
 - IV vasodilator medication: nesiritide (Natreacor)
 - Isolated ultrafiltration therapy
 - Intra-aortic balloon pump
- f. Known allergy to N-acetylcysteine (NAC) based on patient interview or medical record review
- g. Prior **anaphylactic allergy** to iodinated contrast based on patient interview or medical record review
- h. Receipt of intravascular iodinated contrast within the **5 days** preceding angiography based on medical record review

- i. Receipt of oral or IV N-acetylcysteine (NAC) within the 48 hours preceding angiography based on patient interview and/or medical record review
 - j. Prisoner
 - k. Pregnancy:
If a woman who is sexually active and able to have children (meaning she is not post-menopausal [she has had a menstrual period within the previous 12 months], has not had tubal ligation or has not had her uterus or both ovaries removed), she must have a negative urine pregnancy test to be considered eligible for the study. After completing the informed consent process and a signing the ICF, she should be asked to provide a urine sample so a pregnancy test can be performed at the VA laboratory. If the test indicates that she is not pregnant, then you may continue to determine eligibility. If the test is positive, she should be excluded.
 - l. Ongoing participation in **an unapproved concurrent interventional study. Dual participation in other interventional trials must be approved by the respective Study Chairs and the Chief Research and Development Officer.** Ongoing participation in an observational study that does not involve an intervention is permitted.
2. Required forms for determining patient eligibility
 - a. Form 01: Eligibility and Randomization

E. Randomization

A patient will be randomized only after it has been determined that all eligibility criteria have been met. The local site will electronically submit Form 01: Eligibility and Randomization via IWRS (please see the IWRS User Manual for complete instructions). If the subject meets all eligibility criteria, once all of the questions on the electronic form have been answered, a randomization button will automatically appear at the bottom of the form. Once the “Submit Eligibility Form and Randomize Participant” button has been pressed, a table will automatically be generated and shown on the form which includes a randomization number (which is associated with a particular study treatment), randomization Date and Time, and the username of the individual who performed the action. The information in this generated table must then be recorded on the source document worksheet for Form 01. There is also an option to print off a copy of the submitted eligibility and randomization form to attach to your source document worksheet.

If the subject does not meet all eligibility criteria (for example, the answer to the question “Does the subject have stage 5 chronic kidney disease” is entered as “Yes”), then no randomization button will appear. This patient would be considered a “screen failure.”

Note: Form 01 Eligibility and Randomization data must be entered into the IWRS system for all patients who have signed informed consent forms, including screen failures (See IWRS User Manual for details). In the event the electronic randomization system is not functioning properly, sites are expected to follow procedures for manual randomization. For details of manual randomization please see Section X.D.

Note 2: Until Form 01 Eligibility and Randomization has been updated to reflect new eligibility criteria, please follow steps outlined in Operations Memorandum #2 clarification of CSP578 Form 01-Eligibility and Randomization completion with protocol v1.3.

F. Study drug assignment

Following randomization, the SC or other study team member will complete Form 02a: Initial Study Drug Assignment by entering their Site Number, Participant ID number, Randomization Number (as determined on Form 01), and what type of drug assignments are required (IV fluids and/or NAC, initial vs. replacement). In most circumstances, the study drug assignment will be assigned electronically after choosing the option “Automatically request study drug assignment from Albuquerque (CSPCRPCC).” Once this option is chosen, the table at the bottom of the form will automatically be populated with the unique Study IV Fluid Bag number and/or NAC-578 bottle number to dispense. This information should be printed on a local printer, recorded on the source document worksheet, a copy should be provided to the site’s local pharmacist so the drugs can be dispensed and a copy should be filed in the participant’s binder.

In the event that the electronic data capture (eDC) system is not working properly, site staff would still be able to obtain a study drug assignment via a manual process which involves contacting the CSPCRPCC directly by phone and is described in Section X.D.

1. IV fluids

Study IV fluids will be provided to sites by the CSPCRPCC. The CSPCRPCC will monitor inventory levels centrally and automatically generate orders for additional study IV fluid as needed. However, if higher than expected numbers of patients are scheduled for angiography and anticipated to enroll in this trial, individual sites should contact the CSPCRPCC to order additional study IV fluid as needed. Further instructions regarding the disposition and storage of the study medication can be found in the document, “Drug Treatment and Handling Procedures” (DTHP) (Appendix 12).

The number of study IV fluid bags that will be needed for an individual patient will depend on the fluid regimen used and the patient’s weight in kg. This table depicts the estimated number of bags based on two different IV fluid regimens that may be used. While these are recommended study IV fluid protocols that may be used, other regimens that do not deviate from the study protocol may be chosen by the treating provider. The Study IV Fluid Table (Appendix 25) lists minimum, maximum, and recommended infusion rates for administration prior to, during, and after angiography. During off-hours, the site personnel must coordinate with the local pharmacy and nursing staff to ensure additional study IV fluid bags are available and administered properly.

Fluid regimen	Weight	Anticipated number of bags
3 ml/kg/hr x 1 hr pre procedure; 1.5 ml/kg/hr intra-procedure; and 1.5-3 ml/kg/hr x 2-4 hours post procedure	≤100 kg	1-2
	>100 kg	2
1 ml/kg/hr x 12 hrs pre procedure; 1.5 ml/kg/hr intra-	<40 kg	1-2
	40-80 kg	2-3

procedure; and 1 ml/kg/hr x 12 hours post procedure	>80 kg	3
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2. NAC and placebo

NAC/placebo capsules will be provided to sites by the CSPCRPCC. The CSPCRPCC will monitor inventory levels centrally and automatically generate orders for additional study drug as needed. However, if higher than expected numbers of patients are scheduled for angiography and anticipated to enroll in this trial, individual sites should contact the CSPCRPCC to order additional NAC/placebo as needed. Further instructions regarding the disposition and storage of the study medication can be found in the document, “Drug Treatment and Handling Procedures” (DTHP) (Appendix 12)

3. Required forms for study drug assignment

- a. Form 02a: Initial Study Drug Assignment
- b. Form 02b: Subsequent Study Drug Assignment, if applicable.

G. Pre-angiography procedures

1. Collect baseline blood sample

Blood will be drawn to assess pre-procedure renal function. Complete Form 24: Study Blood Specimens and mark “Baseline” for the “Type of Blood Specimen.” This blood sample will be sent to the study’s Central Laboratory for Scr testing. The timing of this pre-angiography blood draw is critical since the administration of IV fluids may lead to hemodilution and artifactual lowering of Scr. **The participant’s baseline blood sample must be drawn following enrollment and randomization and PRIOR TO the initiation of study IV fluids and PRIOR TO the administration of NAC/placebo.**

2. Obtain weight measurement, if needed

If the participant has not had a weight measurement taken within 72 hours of their angiography, obtain the participant’s weight.

3. Collect urine sample to be tested at the local site laboratory to measure the subject’s albumin/creatinine ratio (ACR)

This urine sample should be ordered by a member of the study team and the order signed by the LSI or Co-I. It should be delivered to the local VA laboratory for measurement. **If urine albumin is not run at the laboratory, a total urine protein and urine creatinine should be collected. If this urine specimen is not collected prior to angiography, it should be collected following angiography. Please refer to Appendix 7 for further clarification.**

4. Initiate study IV fluids

The process by which orders for study IV fluids are entered into CPRS may vary by site. Order sets for various study IV fluid regimens, can be incorporated into CPRS. Please contact your local Clinical Informatics staff for details of how to add such order sets into CPRS at your site.

After collecting the baseline blood sample, pre-procedure study IV fluid (3-12 mL/kg) should be administered over at least one hour at an infusion rate of not less than 1 mL/kg per hour and not more than 3 mL/kg per hour prior to the angiography procedure. The recommended infusion prior to angiography for outpatients is 3 mL/kg/hr for one hour. The treating provider retains discretion to administer larger volumes of the randomly allocated study IV fluid (up to a maximum of 12 mL/kg) over a duration of up to 12 hours pre-procedure. The delivery of smaller volumes of study IV fluid over shorter durations than the pre-specified minimums described above and the delivery of larger volumes of study IV fluid over longer durations than the pre-specified maximums described above is not permitted by the study protocol and would constitute a protocol deviation. For inpatients (i.e., considered hospitalized), the recommended (default) pre-angiography study IV fluid administration protocol is 1 mL/kg/hr for 6-12 hours. **Please reference the Study IV Fluid Table (Appendix 25) for infusion rates.**

It is recommended that study IV fluids be administered through a dedicated IV line, however, under certain circumstances this may not be feasible and the site personnel should consult with the local site pharmacist to determine the compatibility of the additional IV fluid with normal saline **and** sodium bicarbonate.

Rescheduled Angiography procedures:

- If the patient's angiography procedure is **cancelled on short notice after randomization, and scheduled for > 12 hours after they have commenced their pre-procedure study IV fluids**, the pre-procedure study IV fluids should be stopped. The provider caring for the patient will need to decide if and which non-study IV fluids s/he wants to use **until study fluids are restarted as per protocol prior to rescheduled angiography.**
- If the procedure is **rescheduled to be performed within 12 hours of the start of study fluids**, study fluid can be continued, but the total volume of study IV fluid to be administered would need to comply with the protocol-specified volume of pre-procedure fluid (i.e., 3-12 mL/kg).
- If the procedure is to be **delayed by more than 12 hours**, study fluids need to be stopped and can be started anew within the 12 hours prior to the scheduled procedure time using a fluid administration regimen that complies with the study protocol. If there is an interruption in the administration of study fluids, a protocol deviation form should be completed.
- If the patient has **started pre-procedure study IVF, and the angiography is bumped to a later time on the same day**, capture data on all pre-procedure study IVF. In such a case, the pre-procedure study IVF volume and rate of administration would be left at the discretion of the provider but would need to comply with the specified minimum and maximum allowed volumes/durations.

Study personnel should speak directly with the nurse caring for the patient prior to their angiography to inform them of the need to track study IV fluid administration. Study **Form 12** (Study IV Fluid Workflow) should be given to the nurse with instructions to use this form to record the volume and duration of pre-angiography study IV fluid administration. In addition, the nurse should be alerted that all study fluid bags will need to be saved and collected by a member of the study team.

Administration of study fluids must comply with the guidelines specified in the study protocol. **For the purpose of defining protocol deviations**, administration of pre-procedure study fluid **over less than 45 minutes or more than 12 hours and 30 minutes** will constitute as protocol deviation. Administration of a total volume of pre-procedure study fluid of **less than 2.5 mL/kg or more than 13 mL/kg** will be defined as a protocol deviation.

5. Administer study drug capsules

The process by which orders for study NAC/placebo are entered into CPRS may vary by site. An order set for the first 2 doses of NAC can be generated and placed in CPRS. Similarly, an order set for continuation of NAC for patients who remain hospitalized can also be generated and entered into CPRS. Please contact your local Clinical Informatics staff for details of how to add such order sets into CPRS at your site.

The subject should be administered their first 1200 mg oral dose of study capsules (NAC or placebo) approximately 1 hour prior to angiography.

If study NAC/placebo is administered before the procedure and the procedure is delayed until later that day, no protocol violation form is required. The patient should not receive another dose of NAC/placebo until after the procedure.

If the procedure is delayed for >12 hours and the patient received the pre-procedure NAC/placebo before the delay in procedure, a protocol deviation form is required and another dose of pre-procedure NAC/placebo should be administered approximately 1 hour before the rescheduled procedure and an additional 9 doses should be given after the procedure.

6. Angiography procedures cancelled after randomization and before or after study drug administration

If the angiography procedure is **cancelled after randomization (and will not be rescheduled) but before the patient has started pre-procedure study IVF or study NAC/placebo**, then the subject is terminated from the study and Form 22: Early Subject Withdrawal Form should be completed.

If the patient has started pre-procedure study IVF or study NAC/placebo and the angiography procedure is cancelled and will not be rescheduled, the pre-procedure IV fluids should be stopped. Intra-procedure and post-procedure study drug will not be administered, and post-procedure urine specimen and 4-day blood sample will not be

collected. Report data on any pre-procedure study drug administered and complete a protocol deviation form. If the procedure was cancelled because of an adverse reaction to the study drug, it is very important that this event be reported using the appropriate form (Form 19 or 20). Proceed to schedule interviews to complete required study forms for all follow up time points and for 90 day blood draw.

If the angiogram was canceled (with or without study IVF or NAC/placebo being administered **and is being rescheduled**, the patient can continue with the study at the time of the rescheduled angiogram. The patient will not be re-randomized in this situation. If the rescheduled angiogram is within 30 days of the patient signing the Informed Consent Form, there is no need to readminister this form. However, if the procedure is schedule for > 30 days from the time the original ICF form was signed by the participant, a new ICF will need to be completed by the patient and a repeat screening creatinine obtained to confirm continued eligibility*. Study IVF and NAC/placebo should be administered as outlined in the protocol for the rescheduled angiogram. If the rescheduled angiogram is to occur the next day, study IV fluids and NAC/placebo can be restarted as outlined in the study protocol before the angiogram.

***NOTE: Under no circumstances will a participant be re-randomized. Please contact Pharmacy, MAVERIC, or the Chair's Office for guidance.**

7. Recommend discontinuation of non-steroidal anti-inflammatory medications
Formally recommend to the treating provider that selective and non-selective non-steroidal anti-inflammatory medications other than once daily aspirin be stopped prior to the procedure and held for 4 days following angiography, as the use of these medications increases the risk for CIAKI. This recommendation should be discussed with the relevant providers when the study team meets with them to discuss the study at start-up.
8. Complete required forms after study IVF and study medication has been ordered:
 - a. **Form 03:** Participant Contact Information
 - b. **Form 04:** Military History
 - c. **Form 05:** Blood Pressure and Weight
 - d. **Form 06:** Pre-Procedure Laboratory Values
 - e. **Form 07:** Demographics
 - f. **Form 08:** Pre-Procedure Non-Study Medication
 - g. **Form 09:** Medical History
 - h. **Form 10:** Pre-Procedure Non-Study IV Fluid

If there is a time constraint between enrollment and the start of the angiography procedure, the site staff should prioritize the completion of Form 03 – Form 07 as these require subject interview. If necessary, Forms 08 – Form 10, which are completed primarily via electronic medical record review, can be completed following the angiography procedure.

H. Intra-angiography procedures

1. Continue administration of study IV fluids at an infusion rate of 1-1.5ml/kg per hour during angiography

The study specified rate of intra-procedural fluid administration is 1-1.5 ml/kg/hr. Exceeding the recommended maximum hourly infusion rate of intra-procedural fluid administration would result in a protocol deviation.

If a patient requires bolus administration of IV fluid in excess of 250 ml during the angiography procedure, non-study isotonic saline should be administered rather than study IV fluid since the bolus administration of large volumes of bicarbonate poses potential safety concerns due to abrupt systemic alkalemia. This will need to be communicated to providers performing angiography and personnel in the cardiac catheterization laboratory or venue at which angiography is taking place. However, if bolus of IV fluid <250 ml is required, study IV fluid can be used. Adding a bolus of <250 ml of study fluid to the intra-procedure specified rate would not result in a protocol violation.

If the reason that extra intra-procedure IV fluids are needed is due to a lengthy study procedure and there is concern on the part of the patient's treating provider(s) that the patient should not receive high volumes of post-procedure IV fluids, there is sufficient flexibility in the post procedure study IV fluid regimen such that fluids can be administered in relatively small rates over longer periods of time while complying with the study protocol (i.e., 6-12 ml/kg over 4-12 hours).

The volume and duration of intra-angiography study IV fluid administration needs to be tracked using Form 12 (Study IV Fluid Workflow). Study personnel should work with clinical care personnel (i.e., nursing staff, catheterization laboratory staff) to ensure the accurate collection of these data. In addition, the angiography team should be alerted that all study fluid bags will need to be saved and collected by a member of the study team.

Administration of study fluids must comply with the guidelines specified in the study protocol. For the purpose of **defining protocol deviations**, administration of intra-procedure study fluid at a rate of **<0.5 mL/kg/hour** for the duration of the angiography procedure or at a rate of **>2 mL/kg/hour plus 250 mL** for the duration of the angiography procedure will constitute a protocol deviation. **Please reference the Study IV Fluid Table (Appendix 25) for infusion rates.**

2. Contrast dye used

All subjects should receive either iso-osmolal contrast media (i.e., iodixanol) or non-ionic, low-osmolal contrast media. The selection of the specific contrast agent and the volume of contrast administered will be at the discretion of the treating provider. The protocol recommends avoiding ioxaglate (Hexabrix) and iohexol (Omnipaque) due to their association with higher risks of contrast nephropathy. This information should be communicated to the providers performing the angiographic procedures at each institution and clinical personnel in the catheterization lab or site of angiographic

procedure. If ioxaglate (Hexabrix) or iohexol (Omnipaque) are administered, the SC will ascertain from the treatment team the reason that particular agent was used.

I. 0-12 hours post-angiography

1. Continue administration of study IV fluids

Study IV fluids (≥ 6 ml/kg) should be administered over ≥ 2 hours following the procedure at an infusion rate of **not less than 1 mL/kg per hour** and not more than **3 mL/kg per hour**. The study specified (**recommended**) rate of IV fluid administration post-procedure for outpatients is **1.5 ml/kg/hr for 4 hours**; for hospitalized patients the recommended (default) rate of 1 ml/kg/hour for 6 to 12 hours may be used.

Providers retain discretion to administer larger volumes of the randomly allocated study IV fluid **up to a maximum of 12 mL/kg infused over 12 hours post-procedure**. The delivery of smaller volumes of study IV fluid over shorter durations than the pre-specified minimums described above or the delivery of larger volumes of study IV fluids over longer durations than the pre-specified maximums described above is not permitted under the study protocol and would constitute a protocol deviation. **Please reference the Study IV Fluid Table (Appendix 25) for infusion rates.**

The volume and duration of post-angiography study IV fluid administration needs to be tracked using Study form 12 (Study IV Fluid Workflow). Study personnel should work with clinical care personnel (i.e., nursing staff) to ensure the accurate collection of these data. In addition, the nurse should be alerted that all study fluid bags will need to be saved and collected by a member of the study team.

Administration of study fluids must comply with the guidelines specified in the study protocol. For the purpose of **defining protocol deviations**, administration of post-procedure study fluid **over less than 2 hours or more than 12 hours and 30 minutes** will constitute as protocol deviation. Administration of a total volume of post-procedure study fluid of **less than 5.5 mL/kg or more than 13 mL/kg** will be defined as a protocol deviation

If a patient develops volume overload during the angiography and a clinical decision results in the patient not receiving post-procedural fluids, a protocol deviation would be required.

3. Administer study drug capsules

The subject should be administered their second 1200 mg oral dose of study capsules (NAC or placebo) approximately 1 hour following the angiography procedure.

4. Collect urine specimen for pH testing

Obtain a urine specimen from the subject approximately **2 - 4 hours** following the angiography procedure and measure pH using the pH meter provided by MAVERIC CSPCC (See appendix 15 for instructions in using the pH meter).

1. Complete required forms 0-12 hours post-angiography
 - a. **Form 11:** Procedure Related Data
 - b. **Form 12:** Study IV Fluid Administration
 - c. **Form 13:** Post Procedure Urine pH Results
 - d. **Form 14:** 12 Hours Post Procedure

J. 12 hours-4 days post-angiography

These post-angiography procedures will differ depending on whether the subject is discharged from the hospital within 4 days following their angiography.

1. Procedures for **subjects discharged within 4 days** following their angiography
 - a. *Schedule follow-up visit for patient to provide 4-day blood sample or schedule mobile specimen collection visit to obtain a blood sample 4 days following the subject's angiography procedure*

Work with the subject to determine an appointment time for them to return to the VA site at which they underwent angiography, **go to a community based outpatient clinic (CBOC) or another VA facility near the participant's home to have the blood drawn,** or to have mobile specimen collection agency staff visit them at their residence to obtain a blood sample. The 4 days post-angiography blood sample should be collected within 1 calendar day of the 4-day post-angiography time point (**4 ± 1 day**). In the event that a blood sample was collected outside of the aforementioned time period, a protocol deviation will need to be documented. If the blood sample is collected by the **mobile collection agency or CBOC or another VA facility near the participant's home,** the blood specimens will be mailed by the mobile specimen collection agency or CBOC to the SC at the local VA.

The SC/RA will send one aliquot of all 4-day blood samples to the study's Central Laboratory for Scr testing. A second aliquot will be delivered to the VA hospital laboratory by the study team for Scr testing.

Complete Form 24 Study Blood Specimens and mark "4 days following angiography" for the "Type of Blood Specimen." One 4-day study barcode label should be placed on the tube going to the Central Laboratory, and the second 4-day study barcode label should be placed on Form 24.

- b. *Contact mobile specimen collection agency with the subject's location and agreed upon visit date and time for their 4-day blood collection.*
- c. *Notify provider of laboratory test ordered*

Notify the provider who performed the angiography via encrypted email or secure messaging that a 4-day SCr will be processed in the VA hospital laboratory as part of the study and let them know that an encrypted email will be sent to them with the results of this test within two days of the test result being reported by the laboratory. In the event that the angiographic procedure was performed by a radiologist who is not involved in following and/or caring for the patient subsequent to the procedure, notification of the SCr testing will be directed at the provider who ordered the angiogram and/or the patient's primary provider. The same procedure should be utilized to notify this provider of the SCr results.

- d. *Dispense bottle of study drug capsules for subject to take home and instruct them on how to properly take and record the study medication taken on the study medication diary*

Subjects should be instructed to take **4 capsules twice a day** (recommended dosing is morning and evening, approximately 12 hours apart) **for a total of four days** beginning on the day after their angiography. They should record all of the study capsules they take on their study medication diary.

NOTE: The medication diary will not be collected by study staff, but should be used as a guide for the participant to answer questions about medication compliance during the 5 day post-angiography phone interview. The patient should be instructed that if they are hospitalized at another hospital during the 4 days following the angiogram, they should bring their study NAC/placebo pills with them and obtain permission from the provider caring for them at the hospital to continue to take the study medication.

- e. *Provide the return envelope for their study medication with instructions on use.*

Study subjects should be instructed to use the pre-addressed envelope **with prepaid postage** to return their empty medication bottle, or any remaining study medication they have after taking all of their required doses, to the Study Coordinator or Research Assistant **using the United State Postal Service (USPS)**. The SC or RA will document receipt in the medication tracking log (See Appendix 22), and return any remaining study medication to the study pharmacist. Patients should be asked about the return of pills during the follow up telephone calls on day 5, day 35, and day 90. If the patient is unable to complete the mailing process, please instruct them to return the medication to the Study Coordinator or Research Assistant for proper medication handling.

- f. *Provide contact information*

Sites will provide a wallet sized pocket card containing numbers for the patient to contact the SC if they have any questions regarding their study medication; if they

was collected outside of the aforementioned time period (3-5 day window), a protocol deviation will need to be documented.

b. *Notify provider of laboratory test ordered*

Notify the provider who performed the angiography via encrypted email that a 4-day SCr will be processed in the VA hospital laboratory as part of the study and let them know that an encrypted email will be sent to them with the results of this test within two days of the test result being reported by the laboratory. In the event the angiographic procedure was performed by a radiologist who is not involved in following the patient subsequent to the procedure, notification of the SCr testing will be directed at provider who ordered the test and/or the patient's primary provider. The same procedure should be utilized to notify this provider of the SCr results.

c. *Administer study drug capsules*

Subjects will be administered their study medication capsules (NAC or placebo) twice daily for the remaining four days following their angiography. The study coordinator or investigator will enter the orders for NAC/placebo to be continued twice daily for four additional days. This procedure will vary site to site. The specific process whereby orders are entered and completed may vary by site.

d. *Return any of the subject's unused study capsules to the site pharmacy*

Unused study capsules should be returned to the site pharmacy. The site pharmacy will store the returned unused study capsules and return them to the CSPCRPCC when instructed by the CSPCRPCC.. In the event the patient is admitted to a hospital and does not continue/complete their study medication, a protocol deviation will need to be documented.

3. Complete required forms 12 hours-4 days post-angiography

a. Form 15: Hospitalizations within 4 days Post-Procedure

K. 5-8 days post angiography

1. Complete phone interview with subject

If the subject remains in the hospital, the interview should be performed in-person. Otherwise, the interview should be conducted over the phone using provided Telephone Scripts (Appendix 24). Information to be collected includes compliance with study medication, occurrence of adverse events, what treatment the patient believes he/she received and verification that the 4-day blood sample was collected as scheduled. If any hospitalization occurs, then adverse event reporting procedures should be followed (See Section III.)

If the participant hasn't sent the empty study medication bottle and/or unused study capsules, then instruct them to return the bottle and any remaining study capsules using the pre-addressed envelope **with prepaid postage using the USPS**. If the participant is unable to complete the mailing process, please instruct them to return the medication to the site Study Coordinator or Research Assistant for proper medication handling.

2. Review EMR

The EMR should be reviewed for the occurrence of any hospitalization since the subject was discharged following their angiography procedure. If a hospitalization is identified, then adverse event reporting procedures should be followed (See Section III.) Upon enrollment, if your site permits, an alert system in CPRS should be set up to automatically notify study staff if a study subject is admitted to a VA hospital

3. Complete required forms 5-8 days post angiography

- a. Form 16: 5 Days Post Procedure

L. 35-49 days post angiography

1. Complete phone interview with subject

Information to be collected includes the occurrence of adverse events since the last telephone contact 5-8 days post angiography. If an adverse event is reported, then adverse event reporting procedures should be followed (See Section V.)

If the participant hasn't sent the empty study medication bottle and/or unused study capsules, then instruct them to return the bottle and any remaining study capsules using the pre-addressed envelope **with prepaid postage using USPS**. If the participant is unable to complete the mailing process, please instruct them to return the medication to the Study Coordinator or Research Assistant for proper medication handling.

2. Review EMR

The EMR will be reviewed for the occurrence of any hospitalization since the subject was discharged following their angiography procedure. If a hospitalization is identified, then adverse event reporting procedures should be followed (See Section V.)

3. Complete required forms 35-49 days post angiography

- a. Form 17: 35 Days Post Procedure

M. 75 days post angiography

1. Schedule the subject's 90 day blood draw

Approximately two weeks prior to the subject's 90 day assessment, contact the subject to determine if they will be able to return to the VA hospital at which the angiography was performed to have their blood drawn at 90 days post-angiography. If they are able, schedule a date and time for them to return and instructions on where to meet the study staff for this blood draw. If the subject is unable to return to the VA hospital, determine a

convenient time for the patient to go to a CBOC or another VA facility near the participant's home to have the blood drawn, or for the mobile specimen collection agency staff to come to the subject's place of residence to obtain a blood sample 90 days post-angiography.

2. If needed, contact mobile specimen collection agency with the subject's location and agreed upon visit date and time for their 90 day blood collection.

N. 90-104 days post angiography

1. Obtain subject's blood sample as determined previously (See Section II.M above). This sample will be sent to the study's Central Laboratory for Scr testing. If a 90-day blood sample cannot be collected within the allowable window, please file a protocol deviation and notify the Chair's office and MAVERIC CSPCC so that ABML can be properly notified of a missing sample. Sites should check 90-day blood draw reports at least once a week to stay on track for follow-up. Study reports are available on each site's Sharepoint subsite.

Since the 90-day blood sample measures the primary study endpoint, it is extremely important that the study coordinator does all that he/she can to obtain the sample regardless of delays in collection. Every effort must be made to collect this specimen. If attempts to schedule within the 90-104 day time frame have failed, **attempts should continue up to 180 days post-procedure** (3 months post the 90-day mark). In addition to phone calls and letters, reviewing CPRS or VistaWeb for upcoming clinic appointments and using that provider to contact the patient may be useful. If the participant can be contacted, but the blood specimen can only be scheduled outside the 180-day mark, it should still be scheduled and collected. **If the coordinator cannot establish contact with the patient within the 180-day timeframe post-procedure, the participant will be considered lost to follow-up.** Notify MAVERIC either when 90-day blood sample is collected or unable to be collected.

Any SAE occurring after 90 days does not need to be reported. Ongoing SAEs that began before 90-day mark can be followed to resolution as long as the participant is still active in the study, i.e hasn't completed all blood collections.

2. If necessary, obtain a confirmatory blood sample
The Central Laboratory will report the results of the participant's Scr test obtained 90 days post-angiography to the MAVERIC CSPCC. If it is determined that the subject had a **≥50% increase in the 90-day SCr value compared to their baseline study value**, the MAVERIC CSPCC will contact the site to notify them that they need to obtain another blood sample from the patient to confirm these results.

This sample should be obtained **within two weeks** of site notification of the 90 day SCr result. In this situation, the same procedures to obtain the confirmatory blood sample outlined in Section II.M. should be followed. If the 50% increase is confirmed, site staff

will notify the patient's primary care provider of this result using an institutionally approved notification method (e.g., encrypted e-mail). This information is available on the site study reports located on each site's Sharepoint subsite. Sites should check confirmatory blood draw reports at least once a week to stay on track for follow-up. If a confirmatory blood sample cannot be collected within the allowable window, please file a protocol deviation and notify the Chair's office and MAVERIC CSPCC.

3. Complete phone interview with subject

Information to be collected includes the occurrence of adverse events since the last telephone contact. If an adverse event is reported, then adverse event reporting procedures should be followed (See Section III.) The interview will also be used to verify that the 90 day blood sample was collected as scheduled.

If the participant hasn't sent the empty study medication bottle and/or unused study capsules, then instruct them to return the bottle and any remaining study capsules using the pre-addressed envelope with prepaid postage using USPS. If the participant is unable to complete the mailing process, please instruct them to return the medication to the Study Coordinator or Research Assistant for proper medication handling.

4. Review EMR

The EMR will be reviewed for the occurrence of any hospitalization since the subject was discharged following their angiography procedure. If a hospitalization is identified, then adverse event reporting procedures should be followed (See Section V.) If a hospitalization is identified, appropriate hospitalization records/discharge notations will need to be reviewed to identify select events/outcomes that constitute secondary study outcomes as defined in the protocol.

5. Complete required forms 90 days post angiography

- a. **Form 18:** 90 Days Post Procedure
- b. **Form 24:** Study Blood Specimens

6. Remove CPRS flag from participant file

- a. Approximately two weeks after shipping the 90-day blood sample to Central lab, check the Scr Confirmatory Testing report. Remove the CPRS flag for any participant that does not need a confirmatory blood draw (and has completed SAE follow-up). Those patients requiring confirmatory blood draws will need to have a confirmatory blood draw completed before removing the CPRS flag. Those patients with ongoing SAEs will need to be followed for 30 days post 90-day blood draw and can then be closed.

O. 1 year post angiography

Data collection occurring at 1 year post angiography will be managed by the MAVERIC CSPCC (i.e., not by participating study sites). Specifically, the following information related to tertiary (exploratory) endpoints will be retrieved from several national databases:

- Development of end-stage renal disease within one year following angiography defined by the requirement for chronic dialysis for ≥ 3 months based on documentation in the *United States Renal Data System*.
- Death within one year following angiography based on documentation in the *VA Beneficiary Identification and Records Locator System*, the *National Center for Health Statistics National Death Index database*, or the *Social Security Administrations' Death Master File*.

P. Termination of Study Participant

Please refer to APPENDIX 26 for common scenarios regarding patient withdrawal. Should a patient decide to withdraw from study treatment, every effort should be made to contact the patient (or a knowledgeable informant) by phone according to the protocol schedule to determine whether any of the endpoint events have occurred unless the patient explicitly withdraws consent for follow-up and refuses to provide further information.

1. When a patient indicates that they would like to stop their involvement with CSP 578, please do the following:
 - a. Indicate you are sorry to hear that they want to stop their involvement with the study
 - b. Ask the patient if they are willing to be followed for the remainder of the study. They may be contacted at certain points for questions over the telephone but they would not need to participate in any further study procedures.
 - i. If they are ok with being contacted, please indicate missed visits in Datalabs for any future in-person visits.
 - 1) To indicate this, mark the CRF **as not collected**. This is used to identify forms that were purposefully left blank.
 - ii. If the patient **does not** wish to be contacted further,

Indicate that it is fine that they wish to not be contacted, but **would it be possible for the study to passively follow them through the remaining duration of the study by reviewing their medical records?**
 - iii. If they are willing to be passively followed,

In Datalabs, indicate all visits to be missed visits (see 1.c.i.1-4) and monitor only for AE/SAEs.
 - iv. If the patient **does not** wish to be passively followed through the remaining duration of the study,
 - 1) Ask patient to sign and date the HIPAA revocation form.
 - 2) Fax the signed&dated HIPAA revocation form with cover sheet to MAVERIC at 857-364-4009.

Should a patient decide to withdraw from the study, participating sites will be required to complete Form 22 Early Participant Withdrawal which includes details regarding the reasons for patient withdrawal. In addition, patients who withdraw from the study will be asked for permission to analyze their existing study data and link their data with long-term outcomes. End

of study participation is achieved after the 90 day study procedures are completed as outlined in Section II.N.

1. Early participant termination

The patient may discontinue participation in this trial at any time without penalty or loss of benefits to which the subject is otherwise entitled. If any of the participant's clinical providers, the LSI, or member of the DMC or the monitoring bodies for CSP 578 feel that adherence to the protocol will be detrimental to a participant's health or well-being, the interest of the participant will take precedence and s/he will be withdrawn after consultation with the Executive Committee. In the event that a participant's participation is discontinued prior to the completion of the 90 day study procedures, Form 22 Early Participant Withdrawal should be completed and the CSPCC Project Manager should be contacted.

2. Participants considered lost to follow-up

A participant will be considered lost to follow-up after a minimum of four telephone contacts and one mailed contact have been attempted over a period of two months. In the event a participant is considered lost to follow-up, Form 22 Early Participant Withdrawal should be completed.

Participant's death

In the event of a participant's death during the trial, Form 22 Early Participant Withdrawal should be completed and procedures for adverse event reporting should be followed (See Section V on Serious Adverse Event Reporting). Note: even though a participant's death will be captured on Form 20 Endpoint_SAE Form, it is also necessary to complete Form 22 Early Participant Withdrawal to signal to the DataLabs eDC system that further data collection will not occur for this patient.

1. If a patient dies prior to DAY 90, then the following should be completed:

A. Source Document Work Sheets

• Form 20

- Under Question 3, event description, please include the cause of death. **Do not** just record 'death'. If the cause of death is unknown, then record 'death-unknown cause'. Every attempt should be made to obtain the death certificate to have documentation of the official cause of death. Once obtained, please complete a follow-up SAE form to record the official cause of death.
- If a previously reported SAE that was still ongoing was the cause of the death, then report the death as a follow up to the initial SAE.

• Form 22

B. Enter into DataLabs

C. Follow up by emailing Todd Conner that an SAE occurred.

2. VA Central IRB:

A. Notify Todd for assistance in determining SAE determination (if you wish)

B. VA Central IRB Form 119 (located on CSP 578 SharePoint under Central IRB forms library);

NOTE: SAE's, UAP's, and Protocol Deviations MUST be uploaded to the VA Central IRB SharePoint site using the link below. The person uploading will need permission to access the site. The permissions are not limited and are separate from the other VA Central IRB SharePoint site that has your project documents. You can contact Lindsey Martin Lindsey.Martin2@va.gov if you do not yet have permission to upload. The instructions on how to upload are also below.

<http://vaww.vha.vaco.portal.va.gov/sites/pride/vacirb/Shared%20Documents/Forms/Standard1.aspx>

To upload a report, follow the steps below.

- Double click into 12-17 CSP 578 folder
- Click the "Upload" button
- Click "Browse" to find your document
- Click "OK"

The VA Central IRB is automatically notified by e-mail when the report has been submitted. You will receive a confirmation e-mail once the report has been processed.

Participant Termination and Reinclusion into the Study

If a participant:

- Has a cancelled procedure
- Did not initiate study IV fluid and/or NAC
- Was withdrawn from the study (by completing 'Form 22. Early Participant Withdrawal' and/or 'Discontinued' eCRFs)

and is **subsequently rescheduled for the procedure**, email the Project Management team at the MAVERIC Coordinating Center requesting that the early withdrawal forms be reset.

The MAVERIC CSPCC will reset the form using the JIRA request system. Once the request is completed, Project Management will contact the site to indicate the request is completed and the electronic CRFs are now available for use for the given participant.

III. Blood Collection Procedures

A. General overview of blood collection process

Blood samples will be collected from participants at **baseline, 4 days** post-angiography, and **90 days** post-angiography for serum creatinine analysis. Patients who are unable to return to their local VA for the required blood draw have the option of having a mobile phlebotomist from Hooper Holmes come to their home and collect the blood locally, **or the participant can go to a CBOC or another VA facility closer to the participant's home.**

As soon as the participant informs the Study Coordinator that he or she prefers a local blood draw, the Study Coordinator will contact Hooper Holmes to request a mobile phlebotomy appointment for the participant. Once the Study Coordinator has entered the request via email Hooper Holmes staff will contact the participant to set up an appointment for the blood draw. The assigned phlebotomist will confirm the appointment with the participant 24 hours in advance of the scheduled time.

When a Hooper Holmes phlebotomist draw blood samples, the phlebotomist will centrifuge the blood as soon as possible and ship the separated blood to the Study Coordinator at the local VA via overnight courier. If the blood is drawn on a Friday, Saturday, Sunday, federal holiday, or the day before a VA or federal holiday, the phlebotomist will store the spun blood in a dedicated specimen refrigerator maintained between 2-8 ° C until the first day it can be shipped back to the site.

NOTE: If the blood is drawn at a CBOC or other VA facility, Study Coordinators will have to notify the phlebotomist to follow 578 blood collection procedures (including separating, packaging, and shipping the sample back to the study site). Please refer to the Training and Reference Materials folder on Sharepoint for tips when contacting outside facilities.

When participants are able to return to the VA for their blood draws, sites will follow their local procedures for drawing blood samples. Once drawn, the blood will be spun in a centrifuge to separate the serum. Sites will pipette 1- 3 mL of serum into a storage vial and store in a dedicated laboratory refrigerator maintained between 2-8 ° C until shipment to the Central Lab.

On a weekly basis, sites will batch ship serum specimens to the Advanced BioMedical Laboratories (ABML, the Central Lab) in refrigerated shippers. Every two weeks, ABML will return the shippers to the sites for re-use. ABML will store the serum samples in a -80 ° C freezer until receipt of all samples from a participant. All three samples will be analyzed together. (See Appendix 17 for a flow chart depicting the complete blood collection process.)

B. Mobile specimen collection procedures

1. If participants are unable to return to the VA for the 4-day or 90 day blood **draw and they live within 100 miles of the VA location**, site personnel will work with the participant to determine a suitable time for a Hooper Holmes phlebotomist to complete the blood draw at the participant's home.
2. Once the participant has communicated their preferred time(s) the Study Coordinator will place an order for phlebotomy service using the secure email service "Tumbleweed". **The**

Study Coordinator will fill out and email via Tumbleweed the Hooper Holmes Blood Draw Order Sheet located in the Source Document Worksheets library on Sharepoint.

- a. A representative from Hooper Holmes will send an encrypted email to study personnel with instructions on how to register with Tumbleweed in advance of patient enrollment. Registration will require an email address and the creation of a password.
 - b. Once registered with Tumbleweed, study personnel may send Hooper Holmes secure encrypted email messages (i.e. Blood Draw Orders). To send a Blood Draw Order,
 - i. Open a browser window and navigate to <https://hhesecure.com/messenger>
 - ii. Login using email address and password created during registration
 - iii. Once logged in, select “Compose”
 - iv. Compose new email to Hooper Holmes and insert the completed Blood Draw Order Form located in the Source Document Worksheets library on Sharepoint. Click Send.
3. The email message will contain the VA Blood Draw Order and should be sent to veteransaffairs@hooperholmes.com. The SC will include the following information in the order as described in the Blood Draw Order Form available on the study SharePoint site:
- a. Order request date
 - b. Participant name, address, phone number, and date of birth
 - c. Required window of blood draw and any information they may have obtained from the participant regarding desired appointment (for example, 2:00pm on Thursday)
 - d. Number of tubes required (one or two)
 - e. SC/RA name and contact information
 - f. The VA Medical Center address where the specimen should be sent
 - g. Any additional comments, if applicable

Orders will be received by Hooper Holmes between Monday-Friday 8:00am-6:00pm Eastern Time.

If it is not feasible for the order to be placed via Tumbleweed, the study personnel may call 888-373-9288 to place an order for a phlebotomist. (*Note: If leaving a voicemail, do NOT leave details of the order in a message. State the need for an order and leave a callback number.*)

4. A representative from Hooper Holmes will contact the participant directly and determine the best time and location for the phlebotomy appointment. The representative will then work with their mobile phlebotomists to identify one who will fill the appointment.
5. The Hooper Holmes identified phlebotomist will contact the participant the day before the scheduled blood draw appointment to confirm . the time, location, and answer any questions the participant may have at that time.
6. The phlebotomist will travel to the participant’s location for the appointment and follow the procedures below:
 - a. Verify the participant’s full name and date of birth by requesting to see their driver license, government or VA issued ID, or passport
 - b. Draw the required blood specimen
 - c. Label the tube(s) with the participant’s name, date of birth, date and time drawn
 - d. Centrifuge and package the tubes

- e. Clean up all biohazardous and other waste before leaving the participant's home
 - f. Ship tubes back to the SC at the VA Medical Center originally making the request. Specimens collected Monday through Thursday should be shipped to arrive next day. The phlebotomist will store specimens collected Friday, Saturday, or Sunday in a refrigerator (2-8 °C) until they can be shipped on Monday.
7. If the phlebotomist has difficulty collecting blood, they will make up to 3 attempts to collect the blood assuming the patient agrees. The following procedures will be followed:
 - If the 4-day draw is unsuccessful, no further attempts will be made but it will be reported to the SC as unsuccessful.
 - If the 90 day draw is unsuccessful, the SC will be notified. The SC will attempt to get the participant to return to the VA facility for another draw attempt. If the participant refuses to return to the VA, HH should be requested to make another attempt at the 90 Day draw. Having the participant increase fluid intake within 8 hours of the scheduled blood draw may improve success of the collection.. If at all possible, a different phlebotomist will be used.
 8. A Hooper Holmes representative will email the study staff who placed the order to let them know the collection has been completed and give them the tracking number for the shipment.
 9. Once the phlebotomist has shipped the package and confirmed delivery, he/she will destroy any participant contact information.

C. Site specimen collection procedures

For study blood specimens collected at the VA site, the following procedures should be followed:

1. Pre-label BD vacutainer 10 mL serum separator tubes with participant's name, date of birth, date and time of blood draw. If it is a baseline or 90 day serum creatinine, use one tube. For 4 day post angiography serum creatinine, label two tubes since one tube will go to local laboratory for serum creatinine determination. You will need a signed order for this local creatinine determination and an appropriate label for your laboratory. Complete blood draw according to local procedures
2. Gently invert the tube no more than 5 times
3. Allow the blood to clot, preferably in upright tube for at least 30 minutes, but not longer than 4 hours. Do NOT remove stopper during clotting or centrifugation
4. Blood should be centrifuged at 1200 X g for 15 minutes. If a centrifuge is not readily available to study personnel, please work with the local VA laboratory to arrange for specimen centrifugation

D. Serum Labeling, Transfer, and Storage

Once blood has been drawn and centrifuged, the serum will be transferred to a grenier-one cryovial for short term storage before shipment to Central Lab. The cryovial will be labelled with a specimen-specific bar code that will tell the Central Lab the participant ID and the type of specimen collected. Because all of the information is contained in the barcode, do NOT write any personal information about the participant on the label or elsewhere on the tube.

Once the sample has been spun, pipette 1 – 3 mL into a 4 mL Greiner Bio-One cryovial for short-term storage following the procedures below:

1. Identify the correct label for the specimen. Labels should be kept in the participant's study binder for safekeeping and easy access.
 - a. Labels are coded with a unique 9 digit identifier such as: 101-1001-00. The first three digits identify the study site number. The next four digits are the subject's assigned study ID. The final two digits indicate which specimen was collected. They are coded: '00' for baseline, '04' for 4-day blood draw, '90' for 90 day blood draw, and '99' for confirmatory draw
2. Select the appropriate label and place it on the tube. The label should be placed vertically so that the barcode runs straight down the tube. DO NOT wrap the label around the tube.
3. Using a graduated sterile transfer pipette and following aseptic techniques, remove the serum. Transfer at least 1 mL of serum to the pre-labeled cryo-tube, but no more than 3 mL. Screw cap on tightly.
4. Store tube in a dedicated laboratory refrigerator maintained between 2-8° C until shipment to the Central Lab.

A 4-day sample should be sent to the local site laboratory for determination of serum creatinine and this sample can be drawn in a separate blood collection tube. This sample will require a locally generated order and label. The order should be signed by the LSI or designee.

E. Missing or Lost Samples

Under rare circumstances, a sample may be lost after shipment from the mobile collection agency or on shipment to the Central Laboratory. Baseline samples cannot be redrawn. For 4-day samples, if there is sample remaining in the local laboratory it may be retrieved and sent to the Central Laboratory. Otherwise, they cannot be redrawn unless the loss is discovered less than 120 hours after angiography. If 90 day samples are lost, the participant should be contacted to have the sample redrawn as soon as possible. The MAVERIC CSPCC should be notified immediately, if the site learns that a sample has been lost. The sample can be redrawn beyond the specified 104 day window, but a protocol deviation will need to be reported.

IV. Central Laboratory

A. Shipment of Serum Specimens

1. Sites will store serum in a dedicated laboratory refrigerator with a temperature log until shipment to Advanced BioMedical Laboratories (ABML, the Central Lab). Shipment will occur weekly on a Tuesday or Wednesday. Note that anyone shipping serum must be properly trained at the Kickoff meeting, or have evidence of other IATA approved training for shipping of hazardous goods. On the day of shipment, sites must notify ABML of their intent to ship. Study Coordinators should digitally send the shipping manifest to ABML by email: shipping@abiolab.com, or by FAX: (856) 829-9471. A fillable PDF of the ABML shipping manifest is located in the Source Document Worksheets library on Sharepoint.
2. Package specimens in the Biological Substance, Category B Shipper (the EXAKT-PAK) with frozen cold packs.
 - a. Transport tube: All specimens should be stored in Greiner Bio-One transport tubes. This tube is the Primary Container.
 - b. Ensure the gray foam insert is in the proper BioHazard plastic bag.
 - c. Ensure the absorbent pad is placed in the bottom of the screw-top canister. This is the IATA certified absorbent.
 - d. Place the bagged gray foam insert into the screw-top canister. This is the Secondary Container.
 - e. Insert the serum tubes into the holes in the gray foam insert.
 - f. Bleed as much air as possible out of the biohazard bag, then seal.
 - g. Replace the gray foam disk on top of the sealed bag.
 - h. Screw on the lid of the canister. When properly closed, the o-ring gasket should not show.
 - i. Place the canister in the cut-out in the bottom of the box.
 - j. Place 2 frozen gel-packs on top of the canister.
 - k. Replace the white foam top.
 - l. Fold the plastic liner flat. Do not tape.
 - m. Place the shipping manifest on top of the plastic liner. This serves as the required packing list.
 - n. Close the inner and outer box flaps. Tape the top and side seams of the box with excess tape.
3. Email or fax the completed shipping manifest to ABML as directed above.

B. Receipt by Central Lab

Upon receipt of the shipments, Central Lab will send an email confirming the receipt of the shipment to the shipping site. Central Lab will also note any issues found with the shipment, if applicable, and will cc MAVERIC on any emails that state an issue with a shipment. After a site has made two shipments to Central Lab, the shippers and the shipping materials will be returned to the sites in a large shipper for re-use.

C. Ordering Supplies

When sites run out of cold shippers, barcode labels, or cryovials, SC/RAs can fax a lab supply request sheet to the MAVERIC biorepository to request more supplies (See appendix 16). When received, MAVERIC biorepository will confirm receipt of the request and will give sites an estimated time for shipment of materials.

V. Adverse Event (AE)/Serious Adverse Event (SAE) Reporting

A. Definitions

Adverse events (AEs) are defined as “any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable and unintended event, including an abnormal laboratory finding, symptom, or disease associated with the research or the use of a medical investigational test article. An AE does not necessarily have to have a causal relationship with the research.” [VHA Handbook 1058.01] **A reportable AE is an event that emerges after the participant has signed the consent having been absent prior to consenting, or worsens relative to the pre-consenting state.**

Serious adverse events (SAEs) are a subset of AEs which meet any of the following criteria:

- a. Results in death
- b. Is life threatening AE
- c. Requires inpatient hospitalization or prolongation of existing hospitalization
- d. Results in persistent or significant disability or incapacity
- e. Is a congenital anomaly/birth defect
- f. Is an important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the participant and may require medical, surgical, behavioral, social or other intervention to prevent one of the outcomes above.

Relatedness. An AE or SAE is considered study-related if it is clearly or possibly caused by research procedures or participation. An AE or SAE is not study related if it is solely caused by underlying disease, condition, treatment, or if it is solely caused by circumstances other than the research or underlying disease. All AEs or SAEs with a reasonable causal relationship to the study interventions should be considered “related.” A definitive relationship does not need to be established. Relatedness must be determined by a Local Site Investigator.

Study Interventions in this trial are intravenous isotonic fluids (IV isotonic sodium chloride or isotonic sodium bicarbonate) and oral NAC/placebo capsules.

Unexpected or unanticipated refer to an event or problem that is new or greater than previously known in terms of nature, severity, or frequency given the procedures described in protocol-related documents and the characteristics of the study population. For human research, protocol-related documents may include the protocol, informed consent document, clinical investigators’ brochure (i.e. Drug Information Report), product labeling, etc.

Pre-existing medical conditions are medical conditions present prior to the participant signing the consent form. These should not be reported as an AE or SAE unless a change in the frequency or severity has occurred.

Index Procedure: The angiographic procedure for which study fluids and NAC/Placebo were given. This procedure itself is not an AE or SAE for CSP #578. If an AE or SAE occurs during the index procedure, then it must be reported on the appropriate Case Report Form.

Planned Procedures: Diagnostic or elective procedures for pre-existing conditions scheduled prior to the participant signing the consent form for CSP#578 that occur while the participant is being followed for the study. These procedures will not be considered AEs or SAEs. However, if an event occurs during the planned procedure that meets the definition of an AE or SAE, then it must be reported.

B. Adverse Events and Serious Adverse Events Data Collection

Adverse Events

Only data regarding non-serious AEs that are **related** or **possibly related** to one of the study interventions must be reported to the Sponsor on Form 19; however, all AEs must be collected and recorded on the CSP #578 AE Tracking Log (provided by SMART as part of the study conduct tools distributed to sites) in order to document the LSI's assessment of relatedness to the study intervention and determination of whether the AE is serious. Summaries of all AEs will be reported to the Central IRB at the time of site's continuing review

Collection Period:

- Begins at the time a participant is **consented**.
- Ends at **35 days** post-angiography or termination of study participant if earlier. Collection timeframe includes the 35th day post-angiography. See Section II.P. for termination definitions.
- Follow-up reports must be submitted on any initially reported AE if it becomes an SAE.

Collection of multiple simultaneous related AEs:

If a participant reports multiple simultaneous related AEs, each of these events needs to be reported as a **separate** related AE unless the Local Site Investigator feels that they are part of a related syndrome. For example, a participant reports experiencing nausea, vomiting and diarrhea. If the Local Site Investigator feels these symptoms are all part of a gastrointestinal syndrome, then one AE for gastrointestinal syndrome would be reported. If he/she feels they are not related to a single syndrome, then three separate AE reports should be completed.

Serious Adverse Events

All SAEs must be collected regardless of their relatedness to one of the study interventions. In addition, all SAEs must be collected and recorded on the CSP# 578 AE Tracking Log. Summaries of all AEs will be reported to the Central IRB at the time of site's continuing review.

Collection Period:

- Begins at the time a participant is **consented**.
- Ends after **90 days** post-angiography or termination of study participant if earlier. Collection timeframe includes the 90th day post-angiography. See Section II.P. for termination definitions.
- Follow-up reports on all unresolved SAEs should be submitted at least every **30 days** until resolution.

Collection of multiple simultaneous SAEs:

If a participant reports multiple simultaneous SAEs, each of these events needs to be reported as a **separate** SAE unless the Local Site Investigator feels that they are part of a related syndrome. For example, an SAE is reported for a hospitalization for one diagnosis and during that hospitalization the participant experiences five more events, then these six events needs to be reported as **separate** SAEs.

C. Responsibilities of Site Staff

Study Investigator Responsibilities

Overseeing the accurate collection and reporting of data regarding related AEs and all SAEs is ultimately the responsibility of the Local Site Investigator. The LSI is responsible for monitoring participants for related AEs and all SAEs, reviewing the accuracy and completeness of related AE and all SAEs reported, providing an assessment of relatedness and ensuring compliance with all reporting requirements.

Study Coordinator Responsibilities

The Study Coordinator is responsible for actively eliciting information on AEs during the baseline angiography visit and the follow-up phone calls on Day 5 and Day 35. The Study Coordinator will actively monitor for SAEs through reviewing the participant's electronic medical record (setting up alerts in CPRS for hospitalizations if possible) and interviewing the participant during follow-up phone calls on Day 5, Day 35, and Day 90. Participants will also be provided with a number to contact if they are hospitalized or experience an AE between follow-up phone calls.

When an AE occurs, the Study Coordinator must ask appropriate follow-up questions to determine the exact nature of the event and obtain appropriate medical records. The LSI in consultation with the Study Coordinator, will determine if an AE is considered serious and assess relatedness. The Study Coordinator, in consultation with the LSI, is responsible for completing the CSP #578 AE Tracking Log and if appropriate, the source document worksheet for Form 19 (AE) or Form 20 (Endpoint_SAE), and documenting the event in the patient medical record (CPRS).

If a participant receives care at a non-VA facility for a related AE or any SAE, the Study Coordinator will be responsible for obtaining the required release of information form signed by the participant and acquiring the pertinent medical records (i.e., discharge summary) from the facility as needed (See Appendix 13 for copy of VA Release of Information form). Upon receipt of the discharge summary from a non-VA hospitalization, the Study Coordinator should file a copy along with the SAE form in the Participant's Study Binder. A copy of the hospital discharge summary should also be uploaded to CPRS to allow source data verification (SDV).

All AEs (in first 35 days post-angiography) and SAEs (for 90 days post angiography) must be documented in the source record (e.g., the electronic VA medical record and/or the Participant's Study Binder). In this way, a permanent record is created that provides information on the participant's clinical course while in the study.

D. Reporting Procedures

Once the Study Coordinator has completed Form 19 (AE) or Form 20 (Endpoint_SAE) and the Local Site Investigator has reviewed the form for accuracy and completeness, it should be entered into the DataLabs eDC system. The DataLabs system will automatically generate notices to both the MAVERIC CSPCC and the CSPCRPCC for SAEs. The CSPCRPCC will be responsible for evaluating all SAEs for participant safety concerns. The CSP#578 Data Monitoring Committee (DMC) will be notified in a format as requested by the DMC Chair. If DataLabs system is down for an extended period of time, the site must FAX or email a hard copy of Form 20 to the MAVERIC CSPCC (857-364-4009) and the CSPCRPCC (505-248-3205).

SAEs must be reported via DataLabs within 72 hours of the site becoming aware of the event. Not to do so is a violation of the protocol.

Certain AEs and SAEs are reportable to the VA Central IRB (see Section E., last column of table below). If a Local Site Investigator and/or Study Coordinator believe that an AE or SAE needs to be reported to the VA Central IRB or are unsure of the need to report a specific AE or SAE, the Local Site Investigator must contact the Study Pharmacist. If the Study Pharmacist, in consultation with other Study Leadership, determines the AE or SAE must be reported to the VA Central IRB, the Study Coordinator must complete VA Central IRB Form 119, Report of Serious Adverse Events and Unanticipated or Unexpected Problems or Adverse Events. This form is available on the VA Central IRB website: <http://www.research.va.gov/vacentralirb/forms/investigator-forms.cfm>. Once completed, this form should be directly uploaded to the VA Central IRB SharePoint site: <https://vaww.ord.portal.va.gov/sites/pride/SiteDirectory/AEUAP/default.aspx> within 5 business days of becoming aware of the event. The VA Central IRB will inform the submitted site if they require follow-up information to be submitted. Please keep in mind that while site staff are expected to communicate directly with the VA Central IRB for certain activities, such as responding to specific requests from the VA Central IRB, copies of all communications should be sent to the Project Manager at MAVERIC CSPCC and the National Study Coordinator at the Chair's Office.

All other AEs and SAEs that are not immediately reported to the VA Central IRB will be reported by the Study Coordinator in the annual VA Central IRB continuing review submission.

E. Summary

	Type Reported to Sponsor	Begin Collection	End Collection	Follow-up required on unresolved events?	Report to MAVERIC CSPCC and CSPCRPCC?	Report to VA Central IRB within 5 business days?	Report to VA Central IRB at time of continuing review?
Adverse Events (AE)	Only those considered related or possibly related	Once participant is consented	35 days post angiography Or Termination of Study Participant	Only if the AE becomes an SAE	Yes, by entering Form 19 into DataLabs in a timely fashion	ONLY if Study Leadership determines AE is related, unexpected and increases risk of harm	All AEs not reported within 5 business days
Serious Adverse Event (SAE)	All, regardless of relatedness	Once participant is consented	90 days post angiography Or Termination of Study Participant	Yes, complete follow-up form at least every 30 days until event is considered resolved.	Yes, by entering Form 20 via DataLabs within 72 hours of becoming aware of event	ONLY if Study Leadership determines SAE is unanticipated or unexpected	All SAEs not reported within 5 business days

VI. Unblinding Procedures

A. 24-hour Emergency Call Service

The CSPCRPCC in Albuquerque will not provide Emergency Code Envelopes to the sites' Pharmacy Service. Emergency unblindings will be managed through the 24-hour emergency call service (505-248-3203). This number is also listed on the patient ID cards given to each patient participating in CSP #578. The system managed by the PCC will electronically capture up-to-date study drug assignment information gathered from the IWRS. . .

B. Authorization to Break the Blind

Under unusual circumstances, chiefly related to participant safety, unblinding may be necessary. This is usually done after consultation with the Study Chair, Steven Weisbord MD, MSc or Study Co-Chair, Paul Palevsky MD. If Dr. Weisbord and Dr. Palevsky are unavailable, the PCC Clinical Research Pharmacist (Todd Conner PharmD) or the Study Director (James Kaufman, MD) should be contacted. Current telephone numbers are listed in the study personnel directory on the CSP578 Main SharePoint Site.

If unblinding is required in an emergency, the Local Site Investigator or Study Coordinator must contact the CSPCRPCC through the 24-hour emergency call service to obtain study drug assignment information. The CSPCRPCC will notify the Study Chair's Office and the MAVERIC CSPCC by telephone as soon as possible after an unblinding has occurred. . If the CSPCRPCC receives a request for unblinding information from anyone other than the LSI or SC, the CSPCRPCC will refer the requester to the LSI or SC or, in his or her absence, the CSPCRPCC will confer with the parties above.

VII. Protocol Deviations

A one-time departure from the current VA Central IRB approved protocol after a subject has been enrolled is considered a protocol deviation. For example, not administering the blinded study drug capsule prior to the subject’s angiography would be a protocol deviation. Each protocol deviation will be evaluated by the MAVERIC CSPCC and Study Chair’s Office and a determination made regarding the validity of any justification for the violation.

3. Notify the National Coordinator at the Chairs’ Office in Pittsburgh and the Study Pharmacist of the deviation as soon as possible
4. Report deviations to the VA Central IRB as required, using IRB Form 129, “Report of Protocol Deviations or Violations,” and upload to the VA Central IRB website. While site staff are expected to communicate directly with the VA Central IRB, copies of all communications must be sent to the Project Manager at MAVERIC CSPCC and the National Coordinator at the Chairs’ Office. Note that certain protocol deviations must be reported to the VA Central IRB within 5 business days of becoming aware of the deviation, if it is likely to substantially adversely affect any of the following:
 - the rights, safety, or welfare of the research participant;
 - the participant’s willingness to continue participation; or
 - the integrity of the research data, including VA information security requirements.
5. Complete Form 23: Protocol Deviations and submit via DataLabs.
6. Keep detailed records of the deviation in the Participant’s Study Binder and **only enter a progress note into CPRS if the protocol deviation adversely affects the safety of the participant or others.**
7. In addition to the actions noted above, depending on the deviation reported, other specific actions may need to be taken as shown in the table below:

Protocol Deviation	Additional action
Informed Consent Form or HIPAA Authorization signed after study procedures started	Notify VA Central IRB within 5 business days and document patient’s consent and/or HIPAA Authorization when feasible.
Inclusion/exclusion criteria violated	Discuss with the Study Chair’s office whether or not the subject should remain in the study. If not, notify the subject immediately and complete Form 22: Early Subject Withdrawal.
Required blood or urine specimen not obtained	If a subject is considered lost to follow-up, complete Form 22: Early Subject Withdrawal
Subject follow-up contact did not occur	If a subject is considered lost to follow-up, complete Form 22: Early Subject Withdrawal
Inappropriate intervention unblinding	In addition to the Study Chair’s Office and MAVERIC CSPCC, the Study Pharmacist at the CSPCRPCC must be contacted immediately.
Serious adverse event not reported appropriately to MAVERIC CSPCC/CSPCRPCC	Contact the MAVERIC CSPCC by phone and submit the Form 20: Endpoint_SAE Report immediately and complete a Protocol Deviation Form 23.
Drug accountability issue	Contact the Study Pharmacist at the CSPCRPCC to discuss how to proceed.
Angiography procedure cancelled after	Stop pre-procedure study drugs. Intra-procedure

initiation of pre-procedure study drug	and post-procedure study drugs will not be administered, and post-procedure urine specimen and 4-day blood sample will not be collected. Complete Form 23. Protocol Deviation form.
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Any medical center with repeated protocol deviations in the absence of valid justification, and after remedial protocol training, may face termination.

Delayed Reporting:

If an SAE or Protocol Deviation are reported late to the Central IRB, sites do **not** need to file a separate Protocol Deviation Form 129 explaining the delay to the CIRB. Instead, include an explanation for the delayed submission in the SAE or Protocol Deviation for the original event.

Protocol deviation reporting for events related to the administration of study IV fluids outside of the protocol mandated rates/volumes can be submitted at the time of continuing review, unless they substantially adversely affect any of the following:

- the rights, safety or welfare of the research participant
- the participants willingness to continue participation or
- the integrity of the research data including VA information security requirements

In the event that a protocol deviation related to study IV fluid administration affects one or more of these domains, it should be reported **within 5 business days of becoming aware** of it. The study Chairman's office should be contacted in the event there is a question about whether the deviation met any of these criteria.

VIII. General Data Collection Procedures

A. Creating a Subject Filing System

SMART will provide sites with comprehensive study conduct tools including the Essential Documents Binder, Participant Study Binder Tabs (Sites will supply their own binders), and Participant Consent Forms Master File to aid in organizing and maintaining records in compliance with the protocol and GCP.

Sites will receive source document worksheets and other study-related forms from the MAVERIC CSPCC. These documents will be available on the CSP 578 SharePoint site and accessible by all study team members.

Each subject enrolled in this study will have at least one three-ring Participant Study Binder. The binder contains only information for this study with all forms placed in the appropriate section as indicated on the binder tabs. Binders should contain information on only one participant.

In this study, Study Coordinators will utilize paper source document worksheets to facilitate the collection of study specific information. Before a patient is seen for the study, the source document worksheets for that time period should be assembled and reviewed. After the forms are completed, original copies must be filed in the binder under the appropriate visit number along with the supporting source documents from the subject's medical record or other starting place. This system provides the Local Site Investigator with all study related information about the subject.

The Participant Study Binder should be easily accessible so that anybody on the study team who needs it can locate and access it. The Subject Study Binders should be stored in a locked cabinet and be marked as Confidential Data for CSP #578.

A tracking list of study participants needs to be kept separately from the Participant Study Binders. The list should also be stored in a locked cabinet and be marked as Confidential Data for CSP #578. SMART will provide this tracking list, and other study conduct tools, to participating Study Coordinators at the study kickoff meeting.

B. Site ID Number and Participant ID Number

Site IDs run consecutively beginning with 101, 102, 103, etc. They are NOT based on VA Station Numbers. Please refer to the site directory (Appendix 2) for the site identification numbers.

Every patient signing an informed consent for study participation will be assigned a unique Participant ID Number which will be a seven-digit numeric code. The first three numbers of the participant number represent the Site ID Number. The last four numbers are sequential and should start with 1001.

C. Source Document Worksheets

Electronic copies of all required source document worksheets can be accessed by sites from the SharePoint main study site. Each source document worksheet should be printed off and placed in the appropriate sections of the Participant's Study Binder. Information gathered on source document worksheets must be entered into their corresponding electronic case report form via the eDC.

IX. SharePoint Document Management System

MAVERIC CSPCC uses SharePoint to create a unique web page from which all trial related activities are managed. Study staff will be provided with formal training on how to use this system and should be familiar with how to access and navigate the main CSP#578 SharePoint site as well as their own subsite. CSP578 SharePoint access will be granted to the research credentialed study staff who completes this formal training. Contact Project Management for any questions.

A. Main Study SharePoint Site

The main web page includes items such as the central study file, postings of study wide announcements, meeting agendas and minutes, a study personnel directory, answers to frequently asked questions, access to local site pages (described in Section B. below) and the central study file which houses common study wide documents including the Operations Manual, study protocol, source document worksheets, and the ICF template.

B. Site specific SharePoint sub-sites

Each site will have their own SharePoint subsite to which only they will have access. Links to each site's subsite will be found on the main study SharePoint page. Sites will use their subsite page to post local announcements or contact information, upload and maintain site specific documentation and access the eDC system to enter trial related data.

Each study subsite has a homepage on which the left margin has links to important documents and libraries.

The screenshot shows a SharePoint subsite homepage. On the left, a navigation menu is visible, with a red box highlighting the 'Documents' section. The main content area includes a 'Welcome to your CSP578 SharePoint subsite!' message, a 'Local Site Calendar' for August 2014, and a 'Site Users' section listing various groups and users.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
27	28	29	30	31	1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31	1	2	3	4	5	6

Each of the links is described further below:

Source Document Worksheets—This library contains all forms, logs, and scripts that study staff will need to complete patient enrollment and follow-up.

IWRS—This link will take you to CSP578's Interactive Web Response System for eligibility, randomization, and initial/subsequent study drug assignment.

DataLabs—This link will take you to CSP578's electronic data capture system.

Site Documents—This document library will be maintained on each site's subsite for site specific announcements and documentation. Access to this subsite is limited only to the site staff at that location and CSP personnel as appropriate (including MAVERIC CSPCC, CSPCRPCC and SMART). Site staff are responsible for uploading all required documentation which includes:

1. **10-9012 Forms**, if required by local policy (completed *Investigational Drug Information Record VA Form 10-9012*)
2. **1572 Forms** (completed *Statement of Investigator FDA Form 1572*)
3. **Consents**
 - Approved stamped ICF and HIPAA Templates
4. **CVs** (including a current, signed and dated CV for the Local Site Investigator and all other study personnel listed on the Site Personnel Signatures & Delegated Responsibilities Log (DRL))
5. **Funding Requests**
6. **Investigator Agreements** (required for the Local Site Investigator and any physician listed as a co-investigator on the DRL)
7. **Lab Info** (including lab certifications, QC and validation documents (if available) and documentation of lab normal values)
8. **Local R&D Committee Submissions, Correspondence and Approvals** (as required)
9. **Site Correspondence** (with the MAVERIC CSPCC or Study Chair's Office, including any memos)
10. **Site Personnel Signatures & Delegated Responsibilities Log (DRL)** (current and older versions)
11. **Site Visits** (e.g., SMART, HRC)
12. **Conflict of Interest forms** (Conflict of Interest forms are required for the Local Site Investigator, Study Coordinator and any physician listed as a co-investigator on the DRL)
13. **Training Certificates** (to include site training logs and updates)
14. **LSI CIRB Submissions, Correspondence and Approvals** (to include protocol deviations and serious adverse events submitted by the site to the CIRB)
15. **Notes to file**
16. Other folders may be created as needed.

Travel Reimbursement Log—This link will take you to the folder containing the log used to record information on participants requiring reimbursement for travel to study site

Reports—This library contains site-specific reports regarding site performance.

Central IRB Forms—This link will take you to the Central IRB website, which contains investigator-initiated forms for CIRB submission

X. Electronic Data Capture (eDC) and Data Management

As per 21 CFR 11 and VA Handbook 6500, system users must not share their username and password with other users, access the system with another user's login, nor allow anyone to access the system under their own system login. System users will be held accountable for actions taken and data entered under their system login.

A. Data Flow

CSP#578 trial data is collected and managed using electronic data capture (eDC), on which all study staff will receive formal training during the Kickoff meeting. Electronic versions of the paper source document worksheets were created using the IWRS and DataLabs systems. The electronic versions of the paper source document worksheets are called case report forms. Data entered by the site into IWRS and DataLabs electronic case report forms are submitted to MAVERIC CSPCC via secure, web-based interfaces. The three electronic systems that will be used for data collection in CSP#578 are briefly described below:

1. Interactive Web Response System (IWRS):
IWRS will be used to screen, randomize, and assign study drug to participants.
2. DataLabs:
DataLabs will be used to collect baseline and follow-up data, report adverse events, and document protocol deviations.
3. SharePoint:
SharePoint will be used for document management. The URL for the study SharePoint site will be emailed to your VA email address.

B. Case Report Forms

The case report forms are summarized below by study event.

- Eligibility and Randomization
 - Form 01(IWRS)
- Study Drug Assignment and Resupply
 - Forms 02a and 02b (IWRS)
- Baseline
 - Form 03: Participant Contact Information (TeleForm – fax to MAVERIC)
Note: Participant Contact Information will be completed on a Teleform and faxed to MAVERIC at **857-364-4009**. See Section G. “Maintaining Patient Confidentiality” for more information.
 - Form 04: Military History (DataLabs)
 - Form 05: Blood Pressure and Weight (DataLabs)
 - Form 06: Pre-Procedure Laboratory Values (DataLabs)
 - Form 07: Demographics (DataLabs)
 - Form 08: Pre-Procedure Non-Study Medications (DataLabs)
 - Form 9: Medical History (DataLabs)
 - Form 10: Pre-Procedure Non-Study IV Fluid (DataLabs)

- Form 11: Procedure Related Data (DataLabs)
- Form 12: Study IV Fluid Administration (DataLabs)
- Form 13: Post-Procedure Urine pH (DataLabs)
- Form 14: 12 Hours Post-Procedure (DataLabs)
- Form 24: Study Blood Specimens
- 4 days Post-Procedure
 - Form 15: Hospitalizations within 4 days Post-Procedure (DataLabs)
 - Form 24: Study Blood Specimens (DataLabs)
- Day 5 Post-Procedure
 - Form 16: 5 Days Post Procedure (DataLabs)
- Day 35 Post-Procedure
 - Form 17: 35 Days Post Procedure (DataLabs)
- Day 90 Post-Procedure
 - Form 18: 90 Days Post Procedure (DataLabs)
 - Form 24: Study Blood Specimens (DataLabs)
- Safety Events
 - Form 19: Adverse Event (AE) (DataLabs)
 - Form 20/21: Endpoint_SAE Form/Endpoint_SAE Follow-up (DataLabs)
- Confirmatory Blood Draw
 - Form 24: Study Blood Specimens (DataLabs)
- Common Forms
 - Form 22: Early Participant Withdrawal (DataLabs)
 - Form 23: Protocol Deviation (DataLabs)

C. Form Completion Instructions

Instructions for completing study related forms can be found in the Facts for Form Completion guidelines (Appendix 7). In addition, detailed instructions including screenshots showing how to complete all study-related forms in IWRS and DataLabs can be found in Appendices 5 and 6, respectively.

Information is saved in the system as well as a redundant site. Any entity governing research programs may audit the information at any time. Submitted participant and study information may be viewed by the sites for follow-up, tracking, and auditing.

Any study data that is changed in the system after submission will require the user to note a reason code and comment regarding why the change was needed. This complies with quality assurance requirements.

D. **Manual back-up procedures** (in the event eDC is not functioning properly)

1. Randomization and initial study drug assignment

If the IWRS System is not accessible to the Study Coordinator, the Study Coordinator will call and fax the completed Form 01 (Eligibility and Randomization) to the MAVERIC CSPCC Project Manager at **857-364-4009**. The MAVERIC CSPCC Project Manager will confirm eligibility. Once confirmed, the Study Coordinator will fax or email a copy of the completed Form 01 (Eligibility and Randomization) to the Albuquerque CSPCRPCC Study Pharmacist or Project Manager. The Albuquerque CSPCRPCC Study Pharmacist will fax or email the randomization number and the initial

study drug numbers to the Study Coordinator. The Study Coordinator must enter this data on Form 01 (Eligibility and Randomization) and Form 02a (Initial Assignment) in the IWRS system once the system resumes functionality. See IWRS Manual for directions on entering randomization and study drug numbers into IWRS during a system outage.

2. Subsequent study drug assignment

If the IWRS system is down, site staff must contact the Albuquerque CSPCRPCC Study Pharmacist to obtain the study drug number(s). The Albuquerque CSPCRPCC Study Pharmacist or Project Manager will instruct the Study Coordinator to enter the study drug number(s) on Form 02b (Subsequent Assignment) in the IWRS system once the system resumes functionality. See IWRS Manual for directions on entering study drug numbers into IWRS during a system outage.

3. Serious adverse event reporting

If the DataLabs system is down and a site needs to report a serious adverse event, site staff must FAX or email a hard copy of Form 20 (Endpoint_SAE) to the MAVERIC CSPCC (857-364-4009) and the CSPCRPCC (505-248-3205). As soon as the system is up and running, Form 20: Endpoint_SAE paper source document worksheet data should be entered into DataLabs.

4. All other data collection activities

Other than the data collection activities noted above which require immediate action, all other study data can be entered once the electronic system is back up and running.

E. Data Queries

Data queries are generated when there is a question regarding a data value entered into an electronic case report. Specific instructions on how to answer data queries will be a part of the formal training all study staff receive on the eDC system.

F. Missing Data

After completing a paper source document worksheet and prior to submitting entered data in the eDC system, check to be sure all data fields are complete and accurate. Required data fields which are submitted as "Blank" will not be validated and a Data Correction Form (DCF) may be issued.

G. Missing Case Report Forms

Case report forms that are not completed due to a missed contact should be "Marked Not Answered" in DataLabs.

XI. Data Monitoring Procedures

A. Good Clinical Practices

This trial will be conducted in compliance with Good Clinical Practices (GCP), a term referring collectively to regulations and guidelines governing the conduct of clinical research. The intent of these regulations is to safeguard subjects' welfare and assure the validity of data resulting from the clinical research. The VA Cooperative Studies Program will assist Local Site Investigators (LSIs) in complying with GCP requirements through its Site Monitoring, Auditing and Resource Team (SMART) based in Albuquerque, NM. SMART serves as the Quality Assurance arm of CSP for GCP compliance. SMART will provide manuals and materials to assist clinics in organizing essential study documents and records and will be available throughout the trial to advise and assist investigators regarding GCP issues.

B. Source of GCP Materials and Guidance

Site Monitoring, Auditing and Resource Team (SMART)
VA Cooperative Studies Program
Clinical Research Pharmacy Coordinating Center
2401 Centre Avenue SE
Albuquerque, NM 87106-4180
Telephone: (505) 248-3203
FAX: (505) 248-3205

Materials provided by SMART include:

- Essential Documents Binder for site (1 per site)
- Essential Documents Binder for pharmacy (1 per site - sent directly to the local research pharmacist)
- Participant Consent Forms Master File (1 per site)
- Participant Study Binder (1 per participant)
- Source Documentation Guidance
- Rubber stamps (as needed)

C. Site Visits and Audits

Routine monitoring site visits will be conducted annually at each site by clinical research monitors from the SMART team. Additional monitoring visits may be conducted as deemed necessary by study leadership or SMART. The LSI and SC will be contacted before the visit to arrange a mutually agreeable time for the visit. Prior to the visit, SMART will email a confirmation letter to the LSI and SC with copies to the appropriate study and site personnel. This letter will confirm the date(s) of the visit and provide a "Checklist for SMART Site Visit" (i.e., a list of all regulatory documents required to be faxed to SMART prior to the visit and documents that need to be up-to-date and available during the visit). The focus of these 2-3 day visits will be to monitor investigator regulatory compliance, protocol adherence, and overall research practices.

At each monitoring visit the monitor will perform the following activities:

- Sign in per local policy
- Conduct Opening Meeting /Agenda review with study staff
- Review Essential Documents Binder (study regulatory documents)
- Review signed informed consent forms (ICFs) & HIPAA Authorization Forms

- Review participant records for unreported SAEs/Unanticipated problems
- Review sample of participant records:
 - Ensure participant meets study entry criteria (inclusion/exclusion criteria)
 - Verify source documentation supports the selected study specific data points entered on paper case report forms (CRFs), SD worksheets or in the electronic database.
- Conduct Pharmacy review, if appropriate ~ study product and records
- Maintain ongoing summary of issues and recommendations – ensure any issues identified and not resolved at previous visit have been adequately addressed
- Conduct an Exit Interview with LSI/SC

Independent of the SMART monitoring program, the SMART Auditing & Resource Group will conduct routine audits. In addition, “for-cause” audits of participating sites may also be conducted if requested by the MAVERIC CSPCC or other members of study management. Routine or “for-cause” audits may be announced or unannounced.

Routine site visits by the National Study Coordinator and the MAVERIC CSPCC Project Manager are planned for this study. Other visitors from CSP may include personnel from the Human Rights Committee.

Visits by the FDA are unlikely to occur while the trial is ongoing but the agency may schedule a visit at any time. The site will be notified in advance by either the FDA or the MAVERIC CSPCC. If notification is received directly from the FDA, the LSI should contact the MAVERIC CSPCC and SMART in Albuquerque as soon as possible. SMART will send personnel to assist the site in preparing for the site visit.

D. Central Monitoring

Based on the August 2013 FDA guidance for Industry “Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring” is intended to assist sponsors of clinical investigations in developing risk-based monitoring strategies for investigational studies. Sponsors of clinical investigations are required to provide oversight to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity.

In contrast with Industry, academic coordinating centers, cooperative groups, and government organizations, such as Cooperative Studies Program Coordinating Center (CSPCC), use on-site monitoring less extensively. To meet the guidance from the FDA, it is our plan to augment or combine with on-site monitoring activities, by implementing a central monitoring approach and focus on risk-based critical study parameters to oversee the study effectively.

The Electronic Data Capture (EDC) enables centralized access to trial data and the ability of statistical analysis to identify data trends not easily detected by on-site monitoring at clinical sites; this assessment will also identify which sites may require additional training and/or monitoring.

The critical data elements that CSPCC will focus on for centralized monitoring are:

- Verification that initial informed consent was obtained appropriately, prior to any study-specific procedures.
- Monitor data quality through routine review of submitted data in real-time to identify missing data, inconsistent data, data outliers, and potential protocol deviations.
- Conduct analysis of site characteristics, performance metrics (e.g., high screen failure rates, high frequency of eligibility violations, and delays in reporting data), and clinical

data to identify trial sites with characteristics correlated with poor performance or noncompliance.

- Complete administrative and regulatory tasks (e.g., collecting and archiving regulatory documents).

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf>

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf>

XII. Appendices

APPENDIX 1:

Important Study Leadership Contact Information

Types of Questions	Name/Title	Location	Email Address	Phone Number
clinical & medical issues; protocol questions; study design; subject eligibility; Central IRB submissions	Steven Weisbord, MD, MSc Study Chair Paul Palevsky, MD Study Co-Chair Lee Anne Mandich, MSN, RN Jill Schaefer, MS, CCRP National Study Coordinators	Pittsburgh, PA	Steven.Weisbord@va.gov Paul.Palevsky@va.gov Lee.Mandich@va.gov Jill.Schaefer@va.gov	412-360-3911 412-360-3932 412-360-3605 412-360-2131
clinical & medical issues; study design	Jim Kaufman, MD Chester Conrad, MD, PhD Study Directors	Boston, MA	James.Kaufman@va.gov Chester.Conrad@va.gov	212-686-7500 x7473 857-364-4201
EDB questions; site monitoring & auditing; GCP issues;	Carol Fye, MS, RPh, CCRP Chief of Monitoring	Albuquerque, NM	Carol.Fye@va.gov	505-248-3203
data quality; data integrity	Soe Soe Thwin, PhD Biostatistician	Boston, MA	Soesoe.Thwin@va.gov	857-364-5589
AE/SAE & PD reporting; IWRS support; study drug	Todd Conner, PharmD Clinical Research Pharmacist Brandi Dillard Pharmacy Project Manager	Albuquerque, NM	Todd.Conner@va.gov Brandi.Dillard@va.gov	505-248-3203 Fax: 505-248-3205 505-248-3203
regulatory issues; meeting arrangements; operational issues; site training; SharePoint & DataLabs support; general questions	Kan Mehta, MS Project Manager Yara Tayeh, MPH Project Coordinator	Boston, MA	Kandarp.Mehta2@va.gov Yara.Tayeh@va.gov	857-364-4837 857-364-6026
study reports; DataLabs support	Chris Donnelly, MPH Data Manager	Boston, MA	Christopher.Donnelly2@va.gov	857-364-2332
personnel & travel questions; funding & budget issues	Mercedes Andino Chief of Administration Sabrina Russell Budget Analyst	Boston, MA	Mercedes.Andino@va.gov Sabrina.Russell@va.gov	857-364-4064 857-364-6270

APPENDIX 2:
Site Directory

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Research Assistant:

TBD

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APPENDIX 3: Training Requirements

Training	How often is training required?	Who is required to take the training?	How is the training accomplished?	Alternate training
Electronic Systems (DataLabs , IWRS, SharePoint, 21CFR11)	Once per version	Anyone accessing study-related electronic systems	In-person training at the study kick-off meeting	Documentation of material review or Completion of exercises
Protocol	Once per version	Anyone listed on the DRL ^a	Initial version: In-person attendance at the study kick-off meeting Version updates: study conference call or meeting	Documentation of material review
Operations Manual	Once per version	Anyone listed on the DRL ^a	Initial version: In-person attendance at the study kick-off meeting Version updates: study conference call or meeting	Documentation of material review
Quality Assurance	One time	Primary Site Investigator(s) and Primary Site Coordinator(s)	In-person attendance at the study kick-off	Documentation of material review
Administrative & Financial Issues	One time	Primary Site Investigator(s) and Primary Site Coordinator(s)	In-person attendance at the study kick-off	Documentation of material review
Blood Shipment	Every two years	Anyone responsible for the shipment of blood	At the study kick-off meeting or completion of online course	Documentation of other IATA approved training
Good Clinical Practice (SMART's Training)	One time	Primary Site Investigator(s), Primary Site Coordinator(s), and Research Assistant(s)	Online Training	No alternative training available
Good Clinical Practice/Human Subjects Protection (CITI Training)	Every two years	Anyone listed on the DRL	Online Training	No alternative training available
VA Information Security and Rules of Behavior	Annually, or as required by VA	Anyone listed on the DRL ^a	Online Training	No alternative training available
Privacy and HIPAA Training	Annually, or as required by VA	Anyone who accesses PHI	Online Training	No alternative training available

a. except the research pharmacist

APPENDIX 4: Site Checklist for Informed Consent Form and HIPAA Authorization

Site Checklist for Informed Consent Form and HIPAA Authorization

This checklist is intended to help you verify that the Informed Consent Form (ICF) and HIPAA Authorization forms have been completed appropriately.

Immediately after completing the informed consent process and having the participant sign the ICF and HIPAA Authorization, verify all items listed on the checklist are completed, checking off each item when verified and entering the needed dates and other information as specified.

If mistakes or problems on the ICF or HIPAA Authorization are found, resolve the issue right away while the participant is still in the clinic. To make a correction on these documents:

1. Draw one line through the incorrect entry,
2. Write in the correct information, and
3. Initial and date the corrected information.

Once you have verified that the ICF and HIPAA Authorization are completed without errors and have completed the Checklist, send the Checklist to MAVERIC along with the fax cover sheet; photocopies of fillable Form 03 and the two signature pages.

For the Checklist ICF Question 4 on the following page, the box numbers are described below:

I agree to participate in this research study as has been explained in this document.		
BOX 1 _____ Participant's Name	BOX 2 _____ Participant's Signature	BOX 3 _____ Date
BOX 4 _____ Name of person obtaining consent	BOX 5 _____ Signature of person obtaining consent	BOX 6 _____ Date

Site Checklist for Completion of Informed Consent Form and HIPAA Authorization

INFORMED CONSENT FORM (ICF)	
1. The participant was consented prior to any study procedure being completed.	<input type="checkbox"/>
2. All the header information is present and correct (Participant Name, Date, Title of Study, Name of Local Site Investigator and name of VA Facility).	<input type="checkbox"/>
3. The person who explained the study to the participant has written their name in the first paragraph on the last page and circled their appropriate title.	<input type="checkbox"/>
4. The signature box is completed correctly.	<input type="checkbox"/>
a. The typed or written name of the participant is present in box 1.	<input type="checkbox"/>
b. The participant signed their name in box 2.	<input type="checkbox"/>
c. The participant dated their signature in box 3. Record date signed: _____	<input type="checkbox"/>
d. The name of the person obtaining consent is written in box 4.	<input type="checkbox"/>
e. The person obtaining consent signed the consent form in box 5.	<input type="checkbox"/>
f. The person obtaining consent dated their signature in box 6. Record date signed: _____	<input type="checkbox"/>
5. The dates for each of the signatures (participant and person obtaining consent) are consistent.	<input type="checkbox"/>
6. The future research question has been completed on the last page.	<input type="checkbox"/>
a. The participant circled yes or no.	<input type="checkbox"/>
b. The participant entered their initials in the space provided.	<input type="checkbox"/>
7. The current Central IRB approved version of the ICF was used to consent the participant.	
○ The most recent approved ICF for my site is: _____	<input type="checkbox"/>
○ Record the LSI Approval or Verification Date (bottom right corner of ICF): _____	<input type="checkbox"/>
HIPAA AUTHORIZATION	
1. The participant's name is included in the footer at the bottom of every page.	<input type="checkbox"/>
2. The participant signed the last page of the authorization form.	<input type="checkbox"/>
3. The participant dated their signature. Record date signed: _____	<input type="checkbox"/>
4. The current version of the HIPAA Authorization was used to consent the participant.	
○ The most recent version of the HIPAA Authorization form at our site is: Record the version (located on of bottom of form): _____	<input type="checkbox"/>
HIPAA REVOCATION	
1. The participant did NOT sign the HIPAA revocation page. (unless they truly intended to revoke HIPAA authorization)	<input type="checkbox"/>
2. Blank HIPAA revocation was given to the participant along with photocopies of the two consent documents.	<input type="checkbox"/>

Staff Name _____

Date _____

PRESERVE (CSP 578) IWRS User Manual

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1. Overview

The PRESERVE (CSP 578) IWRS is a web-based system created by the Albuquerque Pharmacy Coordinating Center (PCC) to facilitate the randomization of and study medication assignment for research subjects participating in the PRESERVE clinical research study. The IWRS provides authorized users with the following primary functions:

- Submission of eligibility and randomization forms, including
 - Saving draft forms
 - Allowing manual randomization
- Study medication assignments for randomized participants, including
 - Initial assignment
 - Subsequent assignment

2. User Registration

Before you can perform any of the above functions you must register with the IWRS and be granted access by a site administrator (you will receive automatic email notification once your registration request is approved by the administrator). To register with the IWRS, navigate to the following website and complete the registration form (see Figure 1):

https://www.csp.research.va.gov/ctsc/application/webs/578/views/users/registration_form.cfm

Figure 1: New User Registration Form

New User Registration Form

Before you can access the PRESERVE (CSP 578) drug assignment site, you must submit a registration form. Once you have successfully submitted the registration form, the manager of this site will be notified. You will receive an email notification after your information has been reviewed and you have been granted access.

Username*
Your username will be how you will be identified within the system

Password*
Must be at least eight characters and include: a lower-case character, an upper-case character, a number and a special character (=|@#%&*~!~!~!)

Password Confirmation*
Please re-type your password

Who You Are

Before you can register you must enter some personal information and record your role in the study. This information will be reviewed by the site manager prior to authorization.

First Name*

Last Name*

Site Number*
Your three-digit study site number

Position*
Your position (e.g. Site Coordinator, Investigator)

Email Address*

Email Verification*
Please re-enter your email address

Human User Verification

To prohibit malicious software from attempting to register at this site, please enter the study's acronym below.

Study Acronym*
Please enter the study's acronym (not case sensitive).

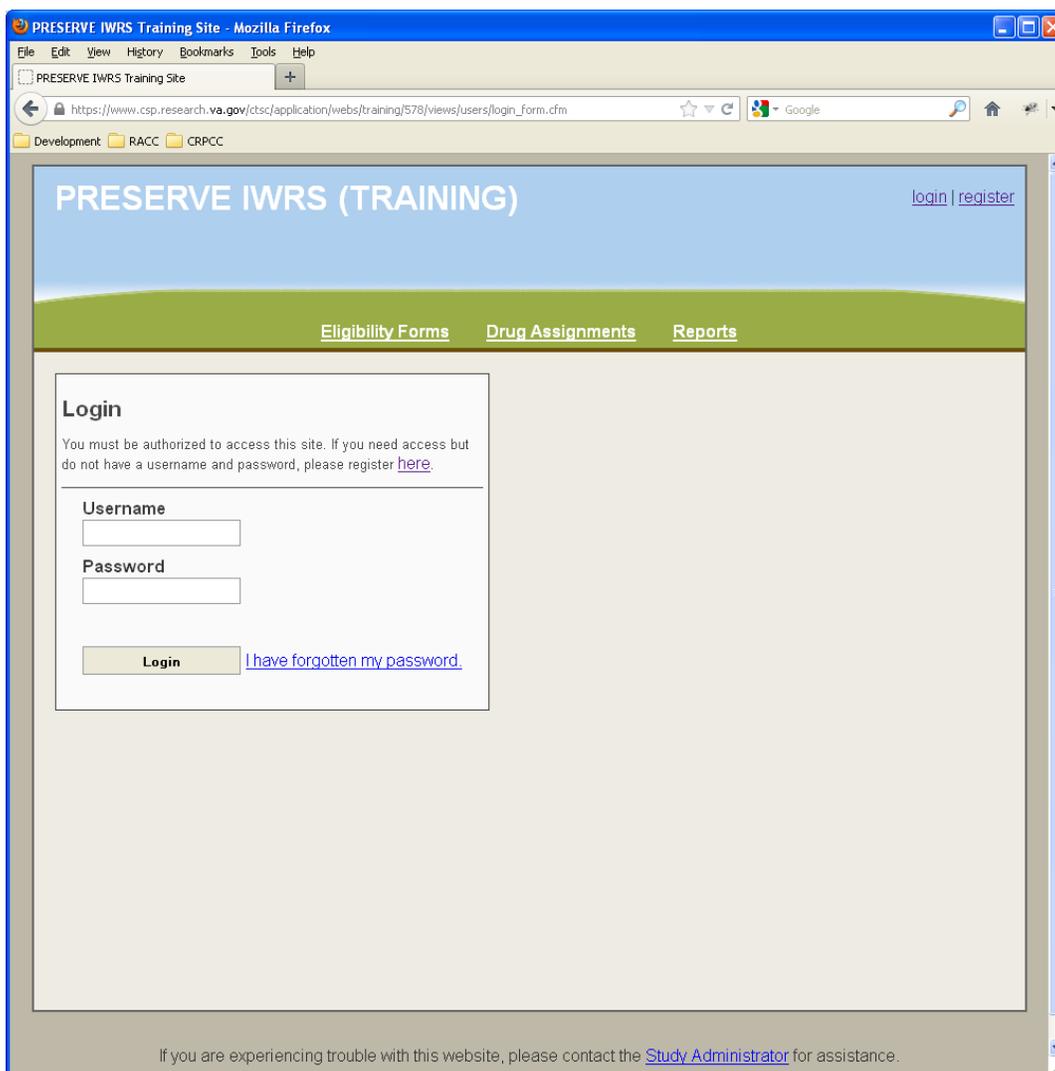
Notes:

- a) Remember that Username must not exceed 20 characters
- b) Enter “preserve” for Study Acronym (not case sensitive)

After you have registered with the IWRS and a site administrator has granted you access to the system, you will receive an email notifying you that you have been given access to the system and can now login at the login page (see Figure 2):

https://www.csp.research.va.gov/ctsc/application/webs/578/views/users/login_form.cfm

Figure 2: IWRS Login Page



3. Submission of Eligibility and Randomization Forms

One of the primary functions you will perform in the IWRS is participant randomization to obtain the STUDY treatment assignment the patient will be randomly assigned to. Before you can randomize a participant, you must fill out a 'Form 01: Eligibility and Randomization' for the prospective participant. The IWRS will use the answers you provided on the eligibility form to determine whether or not the participant is eligible for randomization. To create a new eligibility and randomization form for a participant, perform the following (see Figure 3):

1. Click the 'Eligibility Forms' link at the top of the IWRS.
2. Click the 'New F01: Eligibility and Randomization Form' button in the top-right corner of the Recorded Eligibility and Randomization Forms table.

Figure 3: Eligibility Forms

The screenshot shows the 'PRESERVE IWRS (TRAINING)' interface. At the top, it says 'Site Number: 999' and 'Logged in as: lexijones' with a 'logout' link. Below the navigation bar, there are tabs for 'Eligibility Forms', 'Drug Assignments', 'Reports', and 'Confirm Shipment Arrival & Inventory Management'. The main content area is titled 'Recorded Eligibility and Randomization Forms' and contains a table with columns for 'Participant ID', 'Randomization Number', 'Form Is Submitted and Locked', 'Saved On', and 'Saved By'. A red circle highlights a button labeled 'New F01: Eligibility and Randomization Form' located above the table.

	Participant ID	Randomization Number	Form Is Submitted and Locked	Saved On	Saved By
view	999-1357	R9991024	Yes	November, 29 2012 09:54:08	TMaher
view	999-1234	R9991023	Yes	November, 28 2012 08:10:04	ztaylor
view	999-1081	R9991022	Yes	November, 28 2012 08:20:03	browld
view	999-1080	R9991021	Yes	November, 27 2012 13:45:20	browld
view	999-1648	R9991019	Yes	November, 26 2012 11:44:44	michodon
view	999-1010	R9991018	Yes	November, 26 2012 07:37:10	mplotz
view	999-1040	R9991017	Yes	November, 23 2012 13:32:06	Clare
view	999-1956	R9991016	Yes	November, 23 2012 15:31:13	kobrien
view	999-1111	R9991015	Yes	November, 23 2012 15:27:22	mplotz
view	999-1071	R9991014	Yes	November, 23 2012 13:13:20	acroucher
view	999-1565	R9991013	Yes	November, 22 2012 15:59:23	eleanorallison
view	999-1225	R9991012	Yes	November, 22 2012 10:03:12	bconway

3. Complete the eligibility form (see Figure 4)
 - a. If you are not ready to submit the form, but would like to save your progress (you may complete/submit the form later by editing the form), click the 'Save Eligibility Form' button.
 - b. If you are ready to submit and lock the form, select 'Yes' to "Do you want to randomize the participant and lock the form?".
 - c. You will be asked whether you wish to record a manual randomization performed by Albuquerque Pharmacy Coordinating Center (see figure below) which would only occur during a system outage (i.e., the IWRS system is down when you attempt to login). This answer should always be 'No' unless the system was down and the manual randomization process was implemented. If so, you will be prompted to enter the randomization number that was provided to you by a study member of the Albuquerque Pharmacy Coordinating Center. Refer to the manual randomization process described in the Operations Manual.
 - d. When all the relevant questions have been answered and you are ready to randomize, click the "Submit Eligibility Form and Randomize Participant" button.

Figure 4: Do you want to randomize the participant and lock the form?

The screenshot shows a web form with three sections. The first section asks, "Do you want to randomize the participant and lock this form?" with radio buttons for "No" and "Yes" (selected). The second section asks, "Is this to record a randomization performed by the Albuquerque Pharmacy Center during a system outage?" with radio buttons for "Blank", "No", and "Yes" (selected). The third section is titled "Randomization Number (RSSNNNNN)" and includes a text box for the number, with a note: "R='R'; SSS=three-digit site number, NNNN=four-digit randomization number." At the bottom of the form is a dark blue button labeled "Submit Eligibility Form and Randomize Participant".

Randomization tips:

If all the eligibility questions on the electronic form have been answered correctly (ie. the participant is fully eligible), a randomization button will automatically appear at the bottom of the form. Once the "Submit Eligibility Form and Randomize Participant" button has been pressed, a table will automatically be generated and shown on the form, which includes a randomization number (which is associated with a particular study treatment), randomization Date and Time, and the username of the individual who performed the action. The information in this generated table must then be recorded on the source document worksheet for Form 01. There is also an option to print off a copy of the submitted eligibility and randomization form to attach to your source document worksheet.

If the eligibility criteria is not answered correctly (for example, the answer to the question "Does the participant have stage 5 chronic kidney disease" is entered as "Yes"), then no randomization button will appear. You will need to go back to the original form to review the participant's eligibility to verify the participant.

A. Handling of Screen Failures at US Sites

- Form 01: Eligibility and Randomization data must be entered in the IWRS for all consented individuals at US VA sites, even screen failures (i.e., those who do not meet full eligibility criteria and therefore will not be randomized).
 - Note: this should only apply to the rare patient who does not have a serum creatinine for measurement of the eGFR in the 30 days prior to enrollment. Thus, the patient was consented in order to obtain a serum creatinine, but subsequently did not meet the inclusion criteria for eGFR.
- To enter Form 01 data for screen failures, complete all of the eligibility criteria and click the 'Save Eligibility Form' button. Be sure to select 'No' to the question "Do you want to randomize the participant and lock the form?".

Figure 5: Form 01: Eligibility and Randomization Form

PRESERVE IWRS (TRAINING)

Site Number: 999

Logged in as: [liza.ivanova](#)
[logout](#)

Eligibility Forms
Drug Assignments
Reports
Confirm Shipment Arrival & Inventory Management
Manage Users

FORM 01: Eligibility and Randomization Form

Please enter the participant's eligibility information as recorded on Form01: Eligibility and Randomization. The randomization number generated by submitting this form must be recorded on the source document worksheet. You may print off this form after it is submitted to include with your source documents.

Participant ID (SSS-NNNN) SSS=three-digit site number, NNNN=four-digit enrollment number.

Re-Type Participant ID (Must Match Participant ID)

1.) Is the participant located at a VA site or an Australian site?
 Blank AUS VA

2.) Is the participant at least 18 years of age?
 Blank No Yes

3.) Is the participant willing to comply with four day and ninety day follow-up assessments?
 Blank No Yes

4.) Has the participant signed the informed consent form? (surrogate consent not allowed)
 Blank No Yes

5.) Has the participant (with or without diabetes) had an eGFR measurement less than 45ml/min/1.73m² in the past 30 days?
 Blank No Yes

6.) Has the participant had an eGFR measurement between 45 and 60ml/min /1.73m² in the past 30 days and is he/she diabetic (defined as current use of oral hypoglycemic medications and/or insulin)?
 Blank No Yes

7.) Does the participant have Stage 5 chronic kidney disease (eGFR less than 15 mL/min/1.73m²)?
 Blank No Yes

8.) Is the participant currently receiving hemodialysis, peritoneal dialysis, continuous renal replacement therapy, or sustained low efficiency dialysis (SLED)?
 Blank No Yes

9.) If the participant has had at least two serum creatinine measurements over the three days prior to the angiography, has there been a change of 25% or more between the most recent measure and any other measurement taken within the three days prior to the angiography?
 Blank No Yes

10.) Is the participant's planned angiography emergent (i.e., the time between the determination of need for angiography and the time of the planned procedure is less than 3 hours)?
 Blank No Yes

11.) Does the participant currently have decompensated heart failure requiring any of the following: IV inotropic medications (inamrinone (Inocor), milrinone (Primacor), dobutamine), IV vasodilator medications: nesiritide (Natrecor), isolated ultrafiltration therapy, an intra-aortic balloon pump
 Blank No Yes

12.) Does the participant have a known allergy to N-acetylcysteine?
 Blank No Yes

13.) Has the participant had a prior allergic reaction to iodinated contrast defined as hives and/or trouble breathing?
 Blank No Yes

14.) Has the participant received intravascular iodinated contrast within the 7 days preceding the planned time of angiography?
 Blank No Yes

15.) Has the participant received oral or IV N-acetylcysteine within the 48 hours preceding the planned time of angiography?
 Blank No Yes

16.) Is the participant currently pregnant?
 Blank No Yes

Do you want to randomize the participant and lock this form?
 No Yes

[Save Eligibility Form](#)

If you are experiencing trouble with this website, please contact the [Study Administrator](#) for assistance.

4. Study Medication Assignments for Randomized Participants

The PRESERVE IWRS allows two types of study medication assignments: Initial Assignments and Subsequent Assignments (see

Figure 6).

Figure 6: Drug Assignments

PRESERVE IWRS (TRAINING) Logged in as: [lexijones](#)
[logout](#)

Site Number: 999

[Eligibility Forms](#) [Drug Assignments](#) [Reports](#) [Confirm Shipment Arrival & Inventory Management](#)

Recorded Assignments [New F02a: Initial Assignment](#) [New F02b: Subsequent Assignment](#)

Details	Participant ID	Randomization Number	Type of Assignment	Assigned At	Assigned By
	999-1234	R9991023	Subsequent IV Assignment	November, 28 2012 16:20:19	ztaylor
	999-1357	R9991024	Subsequent IV Assignment	November, 29 2012 10:00:43	TMaher
	999-1357	R9991024	Initial Assignment	November, 29 2012 09:58:43	TMaher
	999-1234	R9991023	Subsequent IV Assignment	November, 28 2012 14:54:47	ztaylor
	999-1234	R9991023	Subsequent NAC Assign..	November, 28 2012 14:54:34	ztaylor
	999-1234	R9991023	Subsequent NAC/Placebo...	November, 28 2012 13:17:13	ztaylor
	999-1234	R9991023	Initial Assignment	November, 28 2012 13:12:33	ztaylor
	999-1234	R9991023	Subsequent IV Assignment	November, 28 2012 08:24:33	ztaylor
	999-1234	R9991023	Subsequent IV Assignment	November, 28 2012 08:11:41	ztaylor
	999-1081	R9991022	Subsequent IV Assignment	November, 28 2012 08:33:42	browld
	999-1081	R9991022	Initial Assignment	November, 28 2012 08:28:37	browld
	999-1080	R9991021	Subsequent IV Assignment	November, 27 2012 13:51:11	browld

A. Initial Assignment

An initial assignment assigns a single bag of IV bicarbonate or normal saline and one bottle of NAC or matching placebo to a participant. To create an initial assignment, perform the following steps (see Figure 7):

1. Click the 'Drug Assignments' link at the top of the IWRS.
2. Click the 'New F02a: Initial Assignment' button at the top-middle of the Recorded Assignments table.
3. Fill out the initial assignment form and click the 'Request Study Medication' button.

Figure 7: Form 02a: Initial Assignment

PRESERVE IWRS (TRAINING) Logged in as: [lexijones](#)
[logout](#)

Site Number: 999

[Eligibility Forms](#) [Drug Assignments](#) [Reports](#) [Confirm Shipment Arrival & Inventory Management](#)

Form 02a: Initial Assignment Form

Fill out this form, after you randomize a participant, to assign an IV fluid bag and a bottle of NAC or matching placebo to the participant.

NOTE: If you are recording an initial assignment that was made, in coordination with the Albuquerque Pharmacy Center, during a system outage, click [here](#).

Participant ID (SSS-NNNN)
SSS=three-digit site number,
NNNN=four-digit enrollment number.

Randomization Number
'R' followed by seven-digits (e.g.
R1234567).

[Request Study Medication](#)

4. If the drug assignment was performed by study personnel at the Albuquerque Pharmacy Coordinating Center during a system outage, click the link in the **NOTE:** section of the form (Red circled area in Figure 7). You will be redirected to a page where you can enter the study drug numbers that were provided to you (see Figure 8). Refer to the manual drug assignment process described in the Operations Manual for further details.

Figure 8: Form 02a: Initial Assignment Form (Manual)

PRESERVE IWRS (TRAINING) Logged in as: [liza.ivanova](#)
[logout](#)

Site Number: 999

[Eligibility Forms](#) [Drug Assignments](#) [Reports](#) [Confirm Shipment Arrival & Inventory Management](#)
[Manage Users](#)

Form 02a: Initial Assignment Form (Manual)

Only fill out this form if you are recording an assignment that was performed by the Albuquerque Pharmacy Coordinating Center during a system outage.

NOTE: If you have reached this form in error and need to perform a standard initial assignment click [here](#).

Participant ID (SSS-NNNN)
SSS=three-digit site number,
NNNN=four-digit enrollment number.

Randomization Number
'R' followed by seven-digits (e.g.
R1234567).

IV Bag Number
Enter the bag number provided by
the CSP pharmacy center.

**NAC or matching placebo
Bottle Number**
Enter the NAC or matching placebo
bottle number provided by the CSP
pharmacy center.

Record Assignment

If you are experiencing trouble with this website, please contact the [Study Administrator](#) for assistance.

B. Subsequent Assignments

Subsequent assignments are performed if the participant needs an additional bag of bicarbonate/normal saline, or if a bottle of NAC/matching placebo must be replaced. To make a subsequent assignment, perform the following steps (see Figure 9):

1. Click the 'Drug Assignments' link at the top of the IWRS.
2. Click the 'New F02b: Subsequent Assignment' button in the top-right corner of the Recorded Assignments table.
3. Fill out the subsequent assignment form including the reasons for re-supply and click the 'Request Study Medication' button. If the reason for re-supply is because the study product was inadvertently given to another study or non-study patient (mishandled), please complete a Form 23 Protocol Deviation in DATALABS and notify MAVERIC CSPCC. In this instance, you will need to provide information regarding what bag/kit number was wrongly allocated to which patient. If the patient is in the study, specify the subject ID.

Figure 9: Form 02b: Subsequent Assignment Form

PRESERVE IWRS (TRAINING) Logged in as: [lexijones](#)
[logout](#)

Site Number: 999

[Eligibility Forms](#) [Drug Assignments](#) [Reports](#) [Confirm Shipment Arrival & Inventory Management](#)

Form 02b: Subsequent Assignment Form

Fill out this form to assign an additional IV fluid bag or bottle of NAC or matching placebo.

NOTE: If you are recording a subsequent assignment that was made, in coordination with the Albuquerque Pharmacy Center, during a system outage, click [here](#).

Request Type
Specify type of medication needed:
NAC/Placebo or Bicarbonate/Saline

Participant ID (SSS-NNNN)
SSS=three-digit site number,
NNNN=four-digit enrollment number.

Randomization Number
'R' followed by seven-digits (e.g.
R1234567).

Reason
Record the reason for requesting this
assignment.

Request Study Medication

4. If the drug assignment was performed by study personnel at the Albuquerque Pharmacy Coordinating Center during a system outage, click the link in the NOTE: section of the form (Red circled area in Figure 9). You will be redirected to a page where you can enter the study drug numbers that were provided to you. Refer to the manual drug assignment process described in the Operations Manual for further details.

Figure 10: Form 02b: Subsequent Assignment Form (Manual)

PRESERVE IWRS (TRAINING) Logged in as: [liza.ivanova](#)
[logout](#)

Site Number: 999

[Eligibility Forms](#) [Drug Assignments](#) [Reports](#) [Confirm Shipment Arrival & Inventory Management](#)
[Manage Users](#)

Form 02b: Subsequent Assignment Form (Manual)

Only fill out this form if you are recording an assignment that was performed by the Albuquerque Pharmacy Center during a system outage.

NOTE: If you have reached this form in error and need to perform a standard subsequent assignment click [here](#).

Request Type

Specify type of medication needed:
NAC/Placebo or Bicarbonate/Saline

Participant ID (SSS-NNNN)

SSS=three-digit site number,
NNNN=four-digit enrollment
number.

Randomization Number

R' followed by seven-digits (e.g.
R1234567).

Reason

Record the reason for requesting
this assignment.

IV Fluid Bag or NAC or Matching Placebo Bottle Number

Enter the IV fluid bag number or NAC
or matching placebo bottle number
provided by the Albuquerque
Pharmacy Center.

If you are experiencing trouble with this website, please contact the [Study Administrator](#) for assistance.

Figure 11: Register New Study Medication

PRESERVE IWRS (TRAINING)

Site Number: 999

Logged in as: [lexijones](#)
[logout](#)

[Eligibility Forms](#) [Drug Assignments](#) [Reports](#) [Confirm Shipment Arrival & Inventory Management](#)

Register New Study Medication Form

Before study medication can be made available for assignment, you must register the box with the system.

Medication Type*
NAC or matching placebo or IV solution?

Box Number*
four-digits

Re-type Box Number*
four-digits

Medication Status*
Should contents be made available for assignment?

[Register New Box](#)

CSP#578 PRESERVE DataLabs Instruction Manual

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How do I get DataLabs Access?

Study staff will receive an email asking to complete DataLabs training activities. Follow the directions in the email to complete all the training activities. A research credentialed study staff who completed the training will be granted CSP578 DataLabs access. Contact Project Management for any questions.

How do I screen and randomize a study participant?

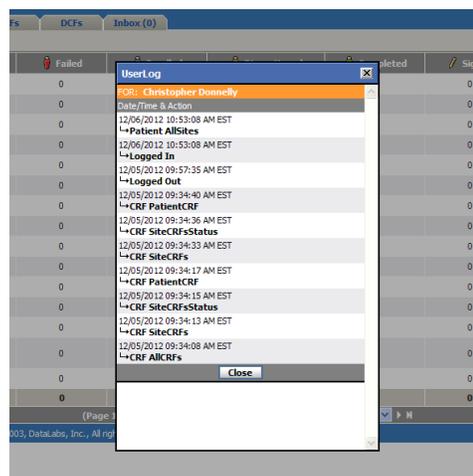
Participants will be screened and randomized using the Interactive Web Response System (IWRS), not DataLabs. Please refer to the IWRS User Manual for instructions.

When do I log into DataLabs?

Log into DataLabs after you have consented, screened, and randomized a participant, and you have baseline or follow-up form data to enter.

How do I log into DataLabs?

1. Open Internet Explorer (version 5.0 or higher)
2. In the address field, enter ["https://www.csp.maveric.va.gov/csp578"](https://www.csp.maveric.va.gov/csp578) and press Enter
3. Enter your username into the Log-in dialog box (first initial of first name, plus last name)
4. Enter your password into the Log-in dialog box (must be at least 8 characters; at least one uppercase letter, one lowercase letter, and one number)
5. Click on OK



If you have typed everything into the system correctly, the system will allow you to enter the DataLabs System and will open the activity log security feature.

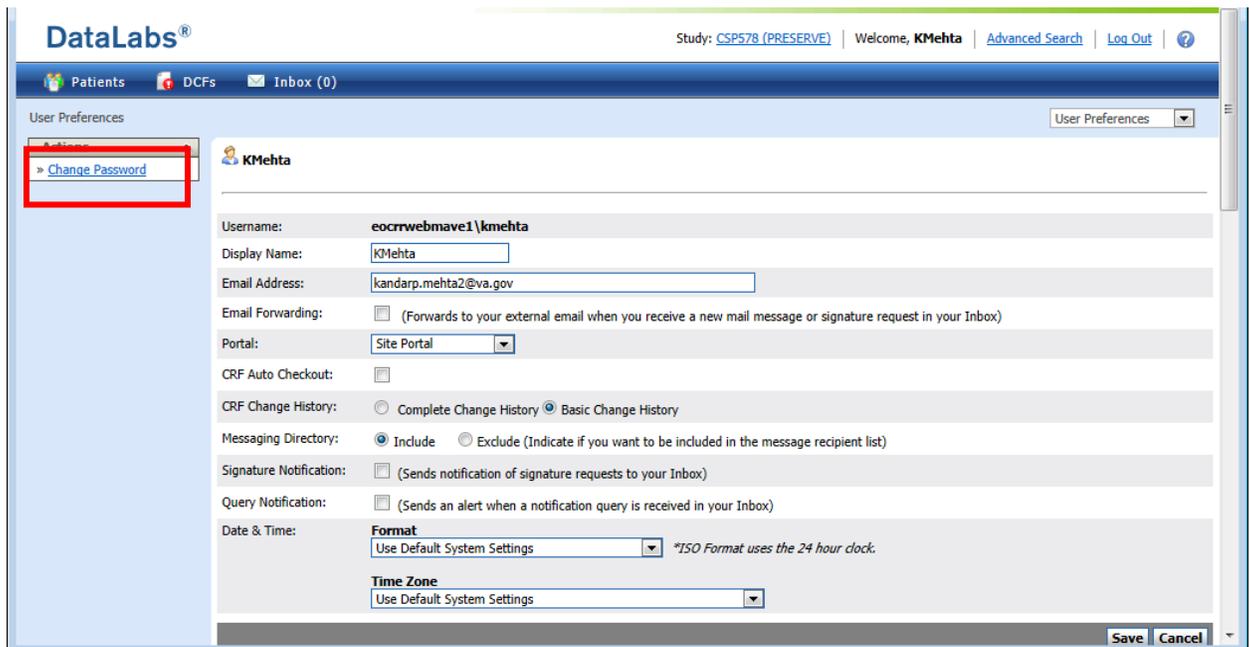
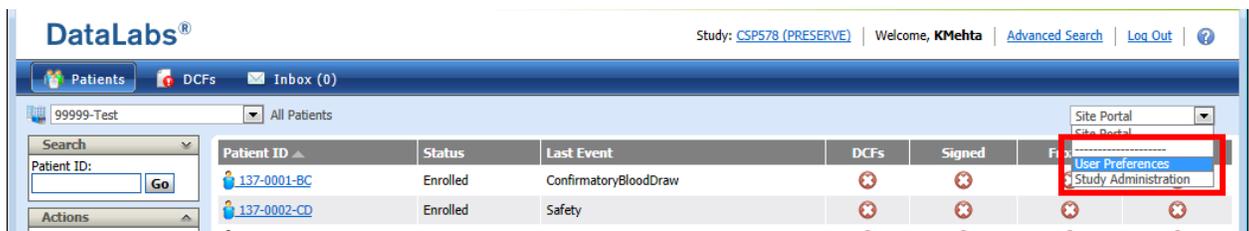
If you have incorrectly entered your username or password into the dialog box, the system will not grant you access. You will need to select the "try logging in again" link to reenter your username and password. Please note that you only have 3 log-in attempts before the system locks you out for 15 minutes.

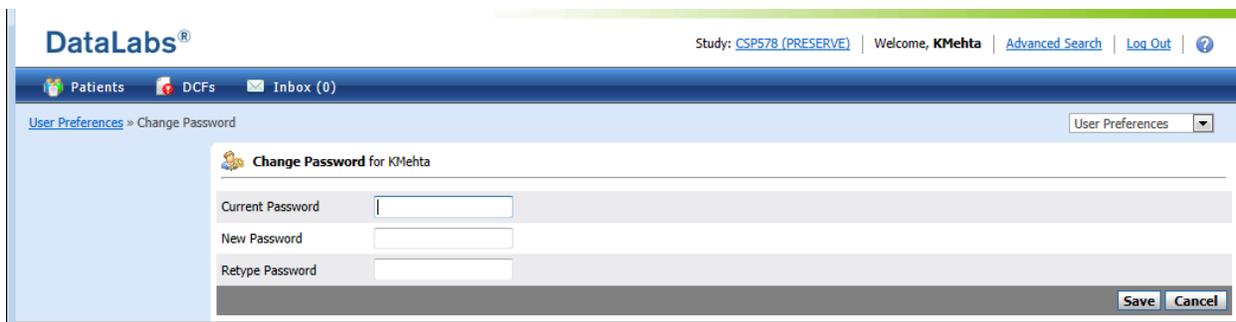
6. Click on Close, to exit out of the Activity Log Box

How do I reset/change my password?

1. Enter your username and a fake password.
2. When the system rejects your log-in attempt, click the “forgot your password?” link. An email will be sent to you with a link to re-set your password.
3. Click the link in the email; this will bring you to a re-set password screen.
4. Enter a new password and re-type password (for verification purposes) then click the “submit” button
 - a. Log into DataLabs again with the new password you created.

Additionally, users can reset passwords using “User Preferences” and following the steps outlined below.

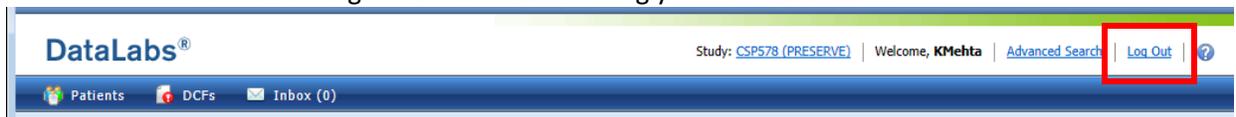




How do I log out of DataLabs?

1. When logging out of DataLabs, ensure that you click the “Log Out” button at the top of the screen.

Note: Closing the browser will not log you out of DataLabs



How do I add a patient to DataLabs?

1. Log into DataLabs with your username and password.
2. Click on “Add Patient” on the Actions Palette on the left hand side of the screen.

Patient ID	Status	Last Event	DCFs	Signed	Frozen	Locked
137-0001-BC	Enrolled	ConfirmatoryBloodDraw	✗	✗	✗	✗
137-0002-CD	Enrolled	Safety	✗	✗	✗	✗
881-1005-AC	Enrolled	Safety	✗	✗	✗	✗
999-1002-BN	Enrolled	Baseline	✗	✗	✗	✗
999-1005-PI	Enrolled	ConfirmatoryBloodDraw	✗	✗	✗	✗
999-1006-TI	Enrolled		✓	✗	✗	✗
999-1007-TG	Screened		✓	✗	✗	✗
999-1009-BS	Screened		✓	✗	✗	✗
999-1010-TE	Enrolled	Safety	✗	✗	✗	✗
999-1011-GU	Screened		✓	✗	✗	✗
999-8001-AB	Enrolled	Safety	✗	✗	✗	✗
999-9001-AC	Enrolled	Safety	✗	✗	✗	✗

3. Enter the 7-digit participant ID and the Patient’s Initials (i.e., first letter of patient’s first name and first letter of patient’s last name only; **do not include middle initial** and use all CAPITAL letters) in the format of ###-####-AB.
 - a. Patients who are consented in order to obtain a screening creatinine and then are found to be ineligible do not need to be entered into DataLabs.

4. Enter or Select the Screening Date (i.e., the date the patient signed the consent)
5. Click on “Save and Enter Data”
6. Note that the icon color for the patient is Yellow.
7. ONCE THE PATIENT IS RANDOMIZED, click on “Enroll Patient” on the Actions Palette on the left hand side of the screen. **Enter ONLY the 7-digit ID (format of ### - ####, without participant initials)** and the date the patient signed the consent. Click on “Save” button. The patient icon color will change to Blue.
 - a. Note: Data will not be entered in DataLabs for ineligible, non-randomized patients.

The screenshot shows the DataLabs interface for a patient with ID 999-1011-GU. The patient's status is 'Screened' and the protocol is 'CSP578 (v1.0)'. The primary investigator is 'rferguson'. The interface includes a search bar, a patient ID field, and an 'Actions' palette on the left. The 'Enroll Patient' action is highlighted with a red box. Below the actions palette is a table of events and their completion status.

Event	Date	CRFs	DCFs	Signed	Frozen	Locked
Safety	<none>	✘	✔	✘	✘	✘
ConfirmatoryBloodDraw	<none>	✘	✔	✘	✘	✘
Common	--	✔	✔	✘	✘	✘

How do I enter initial form data?

1. Click on the applicable Patient ID and ‘event’ (e.g., Baseline, 4dayPostProcedure, etc.).
2. Click on the applicable form name (e.g., Form 05. Blood Pressure and Weight).
3. Click ‘**Check Out**’ button at the bottom (right-hand side) of the form.

DataLabs® Study: CSP578 (PRESERVE) | Welcome, KMehta | [Advanced Search](#) | [Log Out](#) | ?

Patients DCFs Inbox (0)

99999-Test All Patients » 999-1002-BN Site Portal

Patient ID: 999-1002-BN Status: Enrolled Protocol: CSP578 (v1.0) Primary Investigator: rferguson

CRFs	DCFs	Signed	Frozen	Locked
Form 04. Military History	✓	✗	✗	✗
Form 05. Blood Pressure and Weight	✓	✗	✗	✗
Form 06. Pre Procedure	✗	✗	✗	✗
Form 07. Demographics	✓	✗	✗	✗
Form 08. Pre Procedure Non-study Medications	✓	✗	✗	✗
Form 09. Medical History	✓	✗	✗	✗
Form 10. Pre Procedure Non-Study IV Fluid	✓	✗	✗	✗
Form 11. Procedure Related Data	✓	✗	✗	✗

DataLabs® Study: CSP578 (PRESERVE) | Welcome, KMehta | [Advanced Search](#) | [Log Out](#) | ?

Patients DCFs Inbox (0)

99999-Test All Patients » 999-9001-AC » Form 05. Blood Pressure and Weight Site Portal

Patient ID: 999-9001-AC Event: Baseline CRF: Form 05. Blood Pressure and Weight

Study: CSP578 Protocol: CSP578 (v1.0) Primary Investigator: rferguson

VA CSP #578 PRESERVE
PREVENTION OF SERIOUS ADVERSE EVENTS FOLLOWING ANGIOGRAPHY (PRESERVE):
FORM 05: BLOOD PRESSURE AND WEIGHT

1.	Was a blood pressure measurement noted in the medical record within 72 hours of the angiography procedure?	[Blank]
2.	Date blood pressure measured [Record the date of the measure most proximate to the index angiography and within 72 hours of the procedure]	[Blank]
3.	Systolic blood pressure (mmHg)	[Blank]
4.	Diastolic blood pressure (mmHg)	[Blank]
5.	Weight (kg):	[Blank]
6.	Source of weight measurement:	[Blank]
7.	Specify the "other" source of weight measurement:	[Blank]
8.	Date form completed:	[Blank]

Baseline/Form 05. Blood Pressure and Weight **Check Out** Cancel

- Use the mouse to click on the question you wish to answer. If the question contains a "Code List," a list of choices will drop down. If the question requires that you enter data directly onto the form, a cursor will appear in the data field.
- Enter the data into each field using the Facts for Form Completion document (appendix 12 in the Operations Manual) and the appropriate paper Case Report Form as your guides.
- When all questions on the form have been answered, scroll to the bottom of the screen and click on the 'Save' button.
- The system will check the form back in and save the data if there are no existing queries associated with any of the data fields.

- If there are queries, it is recommended that you correct them immediately** by selecting the “Continue” button on the Query Warning Page, then checking out the form again.
- If there are outstanding queries and you wish to instead continue on to the next form**, please click on the “Continue” Button on the Query Warning Page and continue with your data entry.

How do I make changes to data I entered?

- Click on the applicable Patient ID and ‘event’ (e.g., Baseline, 4dayPostProcedure, etc.).
- Click on the applicable form name (e.g., Form 07 Demographics).
- Click **‘Check Out’** button at the bottom (right-hand side) of the form.
- Click on the answer that you wish to change. The question and answer will expand so that you may change the answer and record a reason for your change.
- Enter or Select a new answer
- Select a reason for change – either Data Clarification Form (DCF) or Self Evident Correction (SEC). Use ‘DCF’ for data queries that the system generates. Use ‘SEC’ for changes you decide to enter based on new information. The ‘SOR’ option is only used by the CSPCC.
- Add any additional comments that you may want
- Click **‘Save.’**

The screenshot displays the DataLabs interface for a patient with ID 999-1002-BN at the Baseline event. The form is 'Form 07: Demographics' for the study 'CSP578'. A notification indicates the CRF was checked out by KMehta on 05/14/2014. The form title is 'VA CSP #578 PRESERVE PREVENTION OF SERIOUS ADVERSE EVENTS FOLLOWING ANGIOGRAPHY (PRESERVE)'. The form is currently in a 'Check Out' state. A red box highlights the editing interface for the question 'What is the participant's sex?'. The 'Enter new value' dropdown is set to '[Blank]', the 'Reason for change' dropdown is set to '[Select]', and there is an 'Additional Notes' text area. The form also includes questions about the participant's date of birth (09/06/2013) and race (American Indian or Alaskan Native, Asian).

How do I enter and edit data in a table?

Tables are special structures that can handle multiple events. Adverse Events are a good example – zero, one, or many events could occur at a visit. Entering and editing data in tables is similar to the process in other CRF forms.

1. Click on the CRF form
2. To enter data, click **Check Out** to check out the table
3. To add a record, click **Add New Row**. The form will be open for data entry. Click the **OK** button at the bottom to close the row.
4. You can then add as many new rows as applicable. Note that you can only edit/enter data on one row as a time. You must click OK to close a row before editing/entering a new one.
5. To edit a record after you have saved the form, select the event record you want to edit
6. Click the question response for which you would like to edit data
7. Enter or select the new value
8. Select the **Reason for Change** (“DCF” or “SEC”)
9. Click **OK** to close event and Click **OK** to close form
10. Click **Save** to check in the table and save your work.

The screenshot shows a web-based CRF form for 'VA CSP #578 PRESERVE'. The form is titled 'FORM 20: ENDPOINT_SAE FORM / F21: Follow-Up'. It displays a table of adverse events (SAE) with columns for Onset Date, Event reported, Initial Outcome, Date of follow-up, and Follow-up Outcome. The first row shows a heart attack event reported on 09/03/2013, with a fatal initial outcome and a follow-up outcome of fatal on 09/17/2013. A red box highlights the 'Enter new value' field for the onset date, which currently shows '09/03/2013'. A black box highlights the 'Reason for change' dropdown menu, which is currently set to '[Select]'. The form also includes a sidebar with search and actions, and a top navigation bar with patient and study information.

1. SAE (Click to add new row):	Onset Date	Event reported	Initial Outcome	Date of follow-up	Follow-up Outcome
1.1.	09/03/2013	heart attack	Fatal	09/17/2013	Fatal
1.1.1.	Date Site Investigator became aware of the event:		09/11/2013		
1.1.2.	Onset Date:	Enter new value: <input type="text" value="09/03/2013"/> <small>mm/dd/yyyy</small> Reason for change: [Select] Additional Notes: <input type="text"/>			
1.1.3.	Event being reported:		heart attack		
1.1.4.	Did the event result in death?		Yes		
1.1.5.	Date of death:		09/04/2013		
1.1.6.	Is this date an estimate?		No		

Checking out records in a table is like checking out a medical record. It is important that when you are finished with a table record that you check the table back in by hitting the **Save** button.

When would I ‘discontinue’ a patient in DataLabs?

Discontinue a participant if the Site Investigator determines the participant is no longer appropriate for the study or if the participant withdraws from the study prior to completing the 90 day post-procedure assessment.

To discontinue a patient:

1. Click on “Discontinue Patient” on the Actions Palette on the left hand side of the screen.
2. Enter the discontinued date and click Save.
3. Complete Form 22 (Early Participant Withdrawal) in the ‘Common’ section in DataLabs.
4. The patient icon color will change to Orange.

The screenshot shows the DataLabs interface for patient 999-1005-PI. The 'Discontinue Patient' option is highlighted in the Actions palette on the left. The main area displays a table of events and their completion status.

Event	Date	CRFs	DCFs	Signed	Frozen	Locked
Baseline	<none>	✓	✗	✗	✗	✗
96HrPostProcedure	<none>	✓	✗	✗	✗	✗
Day5PostProcedure	<none>	✓	✓	✗	✗	✗
Day35PostProcedure	<none>	✓	✓	✗	✗	✗
Day90PostProcedure	<none>	✓	✓	✗	✗	✗
Safety	<none>	✓	✓	✗	✗	✗
ConfirmatoryBloodDraw	<none>	✓	✓	✗	✗	✗
Common	--	✓	✗	✗	✗	✗

How do I answer data queries (DCFs)?

1. Log into DataLabs.
2. Click on the ‘DCF’ tab at the top of the screen.
3. Click on the ‘Patient ID.’
4. Click on the ‘DCF ID’ number.
5. Click on ‘Answer’ on the left of your screen
 - a. If you need to change the data on the form, click the link to the “related form(s)” (e.g., Form05.Blood Pressure and Weight). Click on ‘Check Out.’ Click on the answer that you wish to change. The question and answer will expand so that you may change the answer and record a reason for your change. Enter or Select a new answer. Select reason for change = DCF. Click ‘Save.’
 - b. If you have a data query that asks you a question about the data you have entered but does not require you to change your data, then click ‘Answer’ again and type in a description as to why the data you initially entered is correct. (Ex: patient truly weighs 425 lbs but the system only allows a weight range between 100 and 400 lbs.)

Study: CSP578 (PRESERVE) | Welcome, KMehta | [Advanced Search](#) | [Log Out](#) | ?

Patients | **DCFs** | Inbox (0)

99999-Test | All Patients | Site Portal

Patient ID	Status	Received	Viewed	Answered	Resolved	Closed
137-0001-BC	Enrolled	64	0	0	0	7
137-0002-CD	Enrolled	62	0	0	0	0
881-1005-AC	Enrolled	2	1	0	0	0
999-1002-BN	Enrolled	6	0	4	0	4
999-1005-PI	Enrolled	24	0	1	0	3
999-1006-TI	Enrolled	0	0	0	0	0
999-1007-TG	Screened	0	0	0	0	0
999-1009-BS	Screened	0	0	0	0	0
999-1010-TE	Enrolled	7	4	0	0	5
999-1011-GU	Screened	0	0	0	0	0
999-8001-AB	Enrolled	138	3	0	0	4
999-9001-AC	Enrolled	17	2	0	0	0

Site Summary

Received: 320
Viewed: 10
Answered: 5
Resolved: 0
Closed: 23
Aging Avg: 190.7

Study: CSP578 (PRESERVE) | Welcome, KMehta | [Advanced Search](#) | [Log Out](#) | ?

Patients | **DCFs** | Inbox (0)

99999-Test | All Patients > Viewed > DCF | Site Portal

Patient: 881-1005-AC | Primary Investigator: rferguson | Created By: System
DCF ID: 2811 | DCF Status: Viewed | Query Reference: SysBP_3/4847/

Related Form(s) | Event | Reference | Original Value | Current Value
Form 05, Blood Pressure and Weight | Baseline | 3: Systolic blood pressure (mmHg) | 1000 | 1000

Query Description: Value exceeds the maximum length for this item.
Action Request: Enter fewer Digits

[Confidential These records should be retained through 12/31/2222] Cancel

Workflow

DCF ID	Action	Query Information	Date/Time	User
2811	Viewed		02/26/2014 06:53:18 PM GST	nbest (EOCRRWEBMAVE1\Nbest)
2811	Received	Query Description: Value exceeds the maximum length for this item. Action Request: Enter fewer Digits	02/26/2014 06:52:21 PM GST	System (System\System)

Site Summary

Received: 320
Viewed: 10
Answered: 5
Resolved: 0

How do I show that I am deliberately skipping a question in DataLabs?

Sometimes data may not be available for a particular field. For example, a participant may not be willing to provide data OR data may not be available for a participant. In DataLabs one can use the **Mark Question Not Answered** Option to flag data that's not available.

1. **Check Out** the CRF Form
2. Right Click on the question you would like to mark not answered. A box will appear
3. Click **Mark Not Answered**
(This will put a telephone icon next to the question and will clear any DCF related to the response)
4. Click **Save** to check the form back in.

Patient ID: Go

Study: CSP578 Protocol: CSP578 (v14.4) Primary Investigator: None

CRF Checked Out - Christopher Donnelly on 10/31/2012 02:55:16 PM EDT

VA CSP #578 PRESERVE

PREVENTION OF SERIOUS ADVERSE EVENTS FOLLOWING ANGIOGRAPHY (PRESERVE):

Form 07: Demographics

1.	What is the participant's date of birth?	10/22/1994	?
2.	What is the participant's sex?	Male	?
What is the participant's race? (Check all that apply. For example, if the participant is of mixed race, check all races that apply.)			
3.	Is the participant American Indian or an Alaskan Native?	No	?
4.	Is the participant Asian?	No	?
5.	Is the participant Black or African American?	No	?
6.	Is the participant considered an Indigenous Australian (including Aboriginal and Torres Strait Islander)?	No	?
7.	Is the participant Native Hawaiian, Pacific Islander or Maori?	No	?
8.	Is the participant White or Caucasian?	No	?
9.	Did the participant specify another race?	No	?
10.	Specify other race:	[Blank]	?
11.	What is the participant's ethnicity? (Check only one)	Cuban	?
12.	Date form completed:	9/30/2012	?

[Confidential] These records should be retained through 07/02/2076

Save Cancel

Note #1: Using this mechanism does not eliminate the need for a protocol deviation if a data element was required. We recommend against using this option unless requested by the Coordinating Center (e.g. after review of a DCF).

Note #2: Marking a question **Mark Not Answered** is reversible if the data becomes available at a later date. Simply edit the data as you would for any change in data on a form.

How do I show that I am deliberately skipping a form in DataLabs?

Sometimes a form may not be completed (e.g., if patient misses a visit or is unable to complete all required forms at a visit). In DataLabs one can use the **Mark CRFs Not Collected** Option to handle forms that are not completed.

1. Click on the patient with the missing form
2. Click the **Mark CRFs Not Collected** command in the Actions Palette. This will take you to a new screen where each form is listed by visit.
3. If an entire visit was not conducted, click on **Omit All** for that visit.
4. If just one form was not collected, click on the check box next to the form that was not collected at that visit.
5. Scroll to the bottom of the page and click **Save**.
6. A red "x" will appear on each form that was marked not collected.

The screenshot shows the DataLabs interface for patient 999-1002-BN. The patient is enrolled in protocol CSP578 (v1.0). The 'Request Signature' option is highlighted in the Actions menu. The table below shows the status of various events:

Event	Date	CRFs	DCFs	Signed	Frozen	Locked
Baseline	<none>	🟡	❌	❌	❌	❌
96HrPostProcedure	<none>	❌	✅	❌	❌	❌
Day5PostProcedure	<none>	❌	✅	❌	❌	❌
Day35PostProcedure	<none>	❌	✅	❌	❌	❌
Day90PostProcedure	<none>	❌	✅	❌	❌	❌
Safety	<none>	❌	✅	❌	❌	❌
ConfirmatoryBloodDraw	<none>	❌	✅	❌	❌	❌
Common	--	🟡	✅	❌	❌	❌

Note#1: Using this mechanism does not eliminate the need for a protocol deviation if a particular form was required. We recommend against using this option unless requested by the Coordinating Center.

Note#2: Marking a form not completed is reversible if the data becomes available at a later date. Simply check out and form and enter data as you normally would.

What if I accidentally enter data on the wrong form?

If you realize you are entering data on the wrong form, you can click the “Cancel” button at the bottom right (instead of the “Save” button) and the form changes will not be saved. If you have already saved the data and the form is submitted, you will need to open the form and edit the data for each question.

When and how would I use a flag to track the progress of a patient?

The flags in DataLabs give you a visual cue with respect to the progress of patients and case report forms (CRFs). Specifically, a green check (✅) means there is progress or completion, a red X (❌) means there is no progress or there are issues to address, a yellow recycle symbol (🔄) means that there is at least one CRF flagged, and an orange flag (🚩) means at least one flagged CRF has been changed since being flagged.

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Patients DCFs Inbox (0)

99999-Test All Patients Site Portal

Patient ID	Status	Last Event	DCFs	Signed	Frozen	Locked
137-0001-BC	Enrolled	ConfirmatoryBloodDraw	✘	✘	✘	✘
137-0002-CD	Enrolled	Safety	✘	✘	✘	✘
881-1005-AC	Enrolled	Safety	✘	✘	✘	✘
999-1002-BN	Enrolled	Baseline	✘	✘	✘	✘
999-1005-PI	Enrolled	ConfirmatoryBloodDraw	✘	✘	✘	✘
999-1006-TI	Enrolled		✔	✘	✘	✘
999-1007-TG	Screened		✔	✘	✘	✘
999-1009-BS	Screened		✔	✘	✘	✘
999-1010-TE	Enrolled	Safety	✘	✘	✘	✘
999-1011-GU	Screened		✔	✘	✘	✘
999-8001-AB	Enrolled	Safety	✘	✘	✘	✘
999-9001-AC	Enrolled	Safety	✘	✘	✘	✘

Search Patient ID: Go

Actions > Add Patient

Site Summary

- Screened : 3
- Failed : 0
- Enrolled : 9
- Discontinued : 0
- Completed : 0
- Signed : 0
- Frozen : 0
- Locked : 0

When and how would I complete a patient in DataLabs?

All participants should have their status changed to “completed” once they meet the following criteria:

- 1) Form 18 (90 Days Post-Procedure) has been completed
- 2) If applicable, results from a confirmatory blood test (Serum Creatinine) at 90 days post-procedure have been obtained from the Central Laboratory
- 3) If applicable, follow-up information has been collected and entered for all unresolved SAEs (Form 21: Endpoint_SAE Follow-up).

Note: unresolved related AEs are only followed for 35 days after the initial angiography (unless the AE turns into an SAE) whereas all SAEs must be followed until the event is considered resolved. Remember that updates on ongoing SAEs must be entered into DataLabs at least every 30 days.

To complete a patient:

1. Click on “Complete Patient” on the Actions Palette on the left hand side of the screen.
2. Enter the completed date and click Save.
3. The patient icon color will change to Green.

The screenshot shows the DataLabs interface for a patient with ID 999-1002-BN. The patient is enrolled in the CSP578 (v1.0) protocol. The 'Complete Patient' option is highlighted in the Actions menu. The following table represents the data shown in the interface:

Event	Date	CRFs	DCFs	Signed	Frozen	Locked
Baseline	<none>	⚠	⊗	⊗	⊗	⊗
96HrPostProcedure	<none>	⊗	✓	✓	⊗	⊗
Day5PostProcedure	<none>	⊗	✓	✓	⊗	⊗
Day35PostProcedure	<none>	⊗	✓	✓	⊗	⊗
Day90PostProcedure	<none>	⊗	✓	✓	⊗	⊗
Safety	<none>	⊗	✓	✓	⊗	⊗
ConfirmatoryBloodDraw	<none>	⊗	✓	✓	⊗	⊗
Common	--	⚠	✓	✓	⊗	⊗

How does a Site Investigator electronically sign completed case report forms in DataLabs?

1. The data coordinating center will email you as to which patient casebooks are ready for signature by the Site Investigator.
2. Open the patient who has CRFs ready for signature.
3. Click on “Sign Casebook” command from the Actions Palette on the left hand side of the screen. The sign casebook page appears listing all of the forms ready for signature.
 *Note: If “Sign Casebook” is not an option on Action Palette, make sure that signatures have been requested by using the “Request Signatures” command on the Actions Palette. Once signatures have been requested, the “Sign Casebook” command becomes active.
4. Click on the “All” Button in the “Accept” column to indicate that you want to certify the data contain on the CRFs.
5. To sign the CRFs, type your Username and Password into the appropriate field.
6. Click on Submit.
7. Note that the “Sign” column now has green check marks for every form signed.

99999-Test | All Patients » 999-1010-TE | Site Portal

Search Patient ID: Go

Actions:

- Discontinue Patient
- Complete Patient
- Request Signature**
- Review CRFs
- D-Review CRFs
- Mark CRFs Not Collected
- View Unpublished Forms

Patient: 999-1010-TE Status: Enrolled Protocol: CSP578 (v1.0) Primary Investigator: rferguson

Event	Date	CRFs	DCFs	Signed	Frozen	Locked
Baseline	<none>	✘	✔	✘	✘	✘
96HrPostProcedure	<none>	✘	✔	✘	✘	✘
Day5PostProcedure	<none>	✔	✔	✘	✘	✘
Day35PostProcedure	<none>	✘	✔	✘	✘	✘
Day90PostProcedure	<none>	✘	✔	✘	✘	✘
Safety	<none>	✔	✘	✘	✘	✘
ConfirmatoryBloodDraw	<none>	✘	✔	✘	✘	✘
Common	--	⚠	✔	✘	✘	✘

Checking in/Saving forms:

Q: What happens if the form is not ‘saved’ or ‘checked in’ after it has been ‘checked out’?

A: If data entry personnel forget to ‘check in’ a form prior to logging off, the form will remain idle and will not be accessible by other site staff until the form is ‘saved’ and ‘checked-in’. Take note that no information will be lost if this occurs, the site staff can always return to ‘check in’ the form without losing any information.

Q: How can we easily see the forms which we have left ‘checked out’?

A: Users can go to the ‘Inbox’ tab at the top of the screen and click on the ‘Work Queue’ button to see any forms that have not yet been checked in.

DataLabs® | Study: CSP578 (PRESERVE) | Welcome, KMehta | Advanced Search | Log Out | ?

Patients | DCFs | **Inbox (1)**

CSP#578 PRESERVE Facts for Form Completion

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General Instructions for Data Collection & Form Completion

All CSP#578 trial data is first recorded on paper source document worksheets at each study visit. Completed source document worksheets are signed by the site investigator, filed in the Participant's Study Binder, and subsequently entered into one of two electronic systems: Interactive Web Response System (IWRS) or DataLabs. Determination of patient eligibility, randomization, and drug assignment will be managed using the IWRS (see Forms 01, 02a, 02b). Form 03 (Participant Contact Information) will be completed on the CSP#578 SharePoint site and faxed to MAVERIC's secure fax line. All other participant data collected during the course of the study will be entered into DataLabs (i.e., Forms 04 – 24). Ensure that all forms are accurately completed and entered into DataLabs in a timely fashion (*recommended time is within 5 working days of the visit, and no later than 10 working days after the visit*).

Participant ID

Record the 7-digit Participant ID in the header of all source document worksheets in the format of ###-####. The first 3 digits represent your site ID and the last 4 digits correspond to the patient ID (sequentially assigned by each site beginning with 1001).

Forms 01, 02a, and 02b – Eligibility, Randomization, and Drug Assignment

Forms 01, 2a, and 2b will be entered in the IWRS system. Please refer to the IWRS User Manual for detailed instructions. Please be sure to print a completed copy of Form 02a and Form 02b and give to your site research pharmacist.

Note: For Form 01, Q5 and Q6 (re: patient's diabetic status and eGFR measurement), both questions cannot be answered "yes." If the system detects that both questions are answered "yes", you will receive an error message and will be directed to change your answers. Check your answers and resubmit the form.

Q: For Form 01, Q9: If a potential participant has a pending serum creatinine (Scr) prior to the angiography, how should I answer Q9?

A: Q9 should be answered based on all available Scr results at the time the patient is consented. Pending Scr values will not make a participant ineligible. If the result of a pending Scr value reveals unstable Scr post-randomization, this will not be considered a protocol deviation.

Q: For Form 01, Q16: If a potential female participant is of childbearing age, should I obtain a pregnancy test to determine her eligibility?

A: We require that potentially eligible female subjects who are able to have children (not considered post-menopausal [i.e., had a menstrual period within previous 12 months], not had tubal ligation, a hysterectomy or bilateral oophorectomy) and are sexually active, have a negative urine pregnancy test before being enrolled in the study.

Form 03 – Participant Contact Information

Site coordinators will complete the form on SharePoint and fax the completed form to MAVERIC's secure fax line. Form 03 is initially completed at the Baseline visit.

Q. What is the process for completing and submitting this form?

A: Here are step-by-step instructions that you should follow:

1. Open form by going to your CSP578 SharePoint site – the Source Documents Forms Library.
2. Complete the form by typing the required information into each field.
 - a. No hand-written forms or required fields with missing information will be processed.
3. Information for at least 1 contact other than the participant is required, preferably someone not living with the participant.
4. Print the completed Contact Form.
5. FAX both pages of Contact Information Form to MAVERIC at 857-364-4009 using the CSP578 FAX Coversheet.
 - a. Completely fill out the Fax Coversheet; hand-written forms are acceptable.
 - b. The Informed Consent Signature Form Page and HIPAA Form may be faxed with the Contact Information Form.
6. File the printed copy of Form 03 Contact Information Form in the Participant's Study Binder.

Q: Can multiple phone numbers and email addresses be listed?

A: Multiple phone numbers and email addresses should be collected for each participant to provide the most robust contact information and to ensure adequate patient follow-up. Space is provided on the Contact Information Form to capture multiple phone numbers and email addresses. Please check the "preferred" box to indicate a participant's preferred method of contact.

Q: If a participant informs me of a change in his/her contact information, how do I update this in the electronic system?

A: Please complete a new Form 03 on SharePoint with the updated participant contact information and fax the form to MAVERIC at 857-364-4009.

Form 04 – Military History

Form 04 data will be submitted via DataLabs. You will first enter the data on the Form 04 source document worksheet and then enter the data electronically in DataLabs. Form 04 is collected at the Baseline study visit.

Q: Should I enter military history if a participant was/is on reserve duty?

A: No, only enter military history for *active duty* service.

Q: Do I need to provide the exact dates of service for a potential participant?

A: If the research participant remembers only the year of service but not the exact date, please enter January 1st of that year. If the participant knows the month and year, please enter 1st of that month. You can also look into research participant's CPRS → Reports → Health Summary → Ad Hoc Reports → Demographics to find participant's military history. There is also an option within DataLabs to check "Mark Not Answered" to indicate that information is unavailable.

Form 05 – Blood Pressure and Weight

Form 05 data will be submitted via DataLabs. You can look up the blood pressure measurement in the participant's electronic medical record (within 72 hours of the angiography) and record the data on the Form 05 source document worksheet. The data should be entered electronically in DataLabs. Form 05 is collected at the Baseline study visit.

Q: For Q1 on Form 05, is it considered a protocol deviation if a participant does not have blood pressure (BP) measured within 72 hours before the angiography?

A: Since we are not having the study coordinator measure BP and we are only asking for data from the patient chart, this would not be considered a protocol deviation. However, it would be a major deviation from the standard of care to have a patient undergo an angiography procedure (particularly a cardiac catheterization) and not have a pre-procedure BP checked by the clinical team before the procedure.

Q: For Q5-Q6, what are the acceptable methods and permissible time period for obtaining a participant's weight?

A: Obtain the participant's weight from the electronic medical record if it was obtained during the last 72 hours. If a weight is not available within the last 72 hours, the coordinator will need to obtain the weight so that IV fluids can be calculated accurately. If a weight is not recorded in the medical record within 72 hours, and a scale is not available, the participant should be asked their weight. Please enter the weight in kilograms.

Form 06 – Pre Procedure Laboratory Values

Form 06 data will be submitted via DataLabs. You will first enter the data on the Form 06 source document worksheet and then enter the data electronically in DataLabs. Form 06 is collected at the Baseline study visit.

Q: For Q7-Q24, is it a protocol deviation if a participant does not have one of these labs done within 30 days? (Hgb, glucose, CO2, Na, K, BUN)

A: Since we are relying on existing labs (and not ordering these as part of the study protocol), their absence would not constitute a protocol deviation (unlike for question 1, which are protocol specified tests – urine albumin and urine creatinine). Once again, it is highly likely (although not absolutely certain) that these tests will be available.

Q: What should I do if my lab only reports baseline urine albumin and urine creatinine as a combined urine albumin to creatinine ratio (UACR)?

A: Please report the combined UACR in question 3A and check in the box if the value is greater than the upper limit value. If the UACR ratio is greater than the upper limit value (or if the participant has dipstick proteinuria and the lab is unwilling to run urine albumin), please order a urine total protein and urine creatinine on the current urine specimen and make sure to answer questions 5-6b.

Form 07 – Demographics

Form 07 data will be submitted via DataLabs. You will first enter the data on the Form 07 source document worksheet and then enter the data electronically in DataLabs. Form 07 is collected at the Baseline study visit.

Q: For Q3-Q9, what should I do if a participant refuses to provide his/her race?

A: On the source document worksheet, the Site Coordinator should add a note to indicate the participant did not report his/her race, and initial and date the note. In DataLabs, there will be a drop-down option for 'Participant Chose Not to Answer' for each race category.

Form 08 – Pre Procedure Non-Study Medications

Form 08 data will be submitted via DataLabs. You will first enter the data on the Form 08 source document worksheet and then enter the data electronically in DataLabs. Form 08 is collected at the Baseline study visit.

Q: How should I handle discrepancies between the list of medications in the electronic medical record and medications reported by the participant?

A: The electronic medical record will be considered the primary source for obtaining medications and reconciliation with the participant is not required. If information is obtained from the participant that indicates a discrepancy with the medications listed in the medical records, use the participant's report for data entry.

Form 09 – Medical History

Form 09 data will be submitted via DataLabs. You will first enter the data on the Form 09 source document worksheet and then enter the data electronically in DataLabs. Form 09 is collected at the Baseline study visit.

Q: Please clarify the preferred source of documentation for the medical history data: participant vs. medical record review.

A: Q1-Q6 should be answered using the medical record. Q7 should be obtained by participants' self-report of their smoking history.

Form 10 – Pre Procedure Non-Study IV Fluid

Form 10 data will be submitted via DataLabs. You will first enter the data on the Form 10 source document worksheet and then enter the data electronically in DataLabs. Form 10 is collected at the Baseline study visit.

Form 11 – Procedure Related Data

Form 11 data will be submitted via DataLabs. You will first enter the data on the Form 11 source document worksheet and then enter the data electronically in DataLabs. Form 11 is collected at the 0-12 hours post-angiography study visit.

Q: What sources of information will be used to determine the answers to questions on Form 11?

A: The coordinator needs to speak with the team performing the angiography procedure (e.g., nurse/angiography tech/physician) to obtain details of the procedure that cannot be ascertained from medical record review.

Q: How do you define “outpatient”?

A: A patient presenting solely for the procedure or who presents with an acute problem leading to the performance of the angiogram that day and who is discharged within 23 hours should be considered an outpatient.

Form 12 – Study IV Fluid Administration

Form 12 data will be submitted via DataLabs. You will first enter the data on the Form 12 source document worksheet and then enter the data electronically in DataLabs. Form 12 is collected at the 0-12 hours post-angiography study visit.

Note: The **CSP#578 PRESERVE STUDY IV FLUID FLOWSHEET** will travel with the participant from the time they are started on study IV fluids (IVF) until the time study IVFs are discontinued. Information will be obtained and entered on this form by the nurses and technicians caring for the patient (Pre angiogram, during angiogram, and following angiogram). The information should be obtained by the unit staff as well as the angiography team.

Q: Should I include non-study IV fluid boluses in the total volume in Questions 6, 10, and 17?

A: No. Record only study IVF boluses (should not exceed 250 mL during the procedure) that are administered. Non-study fluids given during the angiographic procedure are recorded in Question 20.

Form 13 – Post Procedure Urine pH

Form 13 data will be submitted via DataLabs. You will first enter the data on the Form 13 source document worksheet and then enter the data electronically in DataLabs. The urine specimen should be collected on the participant approximately two hours following the angiography procedure. Be sure to record the urine pH results on Form 13 and enter in DataLabs.

Form 14 – 12 Hours Post Procedure

Form 14 data will be submitted via DataLabs. You will first enter the data on the Form 14 source document worksheet and then enter the data electronically in DataLabs. Form 14 is collected at the 0-12 hours post-angiography study visit.

Q: For Q2 and Q3 on Form 14, is it considered a protocol deviation if NAC/placebo are administered greater than or less than 1hr prior to angiography and/or greater than or less than 1hr post angiography?

A: No, this is not considered a protocol deviation. The study protocol states that the drug will be given APPROXIMATELY 1 hour pre procedure (1st dose) and approximately 1 hour post procedure (2nd dose). It will be a deviation if the drug is not given pre or post procedure, but if the precise timing is off it will not be a deviation.

Form 15 – Hospitalizations within 4 days Post Procedure

Form 15 data will be submitted via DataLabs. You will first enter the data on the Form 15 source document worksheet and then enter the data electronically in DataLabs. Form 15 is collected at the >12 hour-4 days post-angiography study visit.

Q: How will I know if a participant is hospitalized?

A: At the time of randomization, site coordinators will distribute an informational card (i.e., “Participant Study ID Card”) to the PRESERVE participants informing them to call the coordinator if admitted to a hospital. A release of information form is available as an appendix in the Operations Manual to obtain information from a non-VA facility (see Appendix 13). However, some hospitals may require specific release of information forms.

Q: For Q1, is it an SAE if the participant remains in the hospital beyond 12hrs following the angiography?

A: Not specifically – it depends on the reason for staying in the hospital. If the patient is found to have a medical condition that is identified within the first 12 hours following angiography that requires continued hospitalization (pulmonary edema, need for CABG and/or Valve Surgery), this would represent an SAE. However, if the patient has another planned or non-medical reason for remaining in the hospital beyond 12 hours (e.g., transportation issues, continued IV fluids, etc.) this would not be considered an SAE.

Q: For Q7, if participant had more than 1 radiological procedure, where should that information be entered?

A: Study coordinators should use another page 2 of Form 15 (source document worksheet) to collect information on additional radiological procedures. Multiple worksheets on additional procedures should be lettered/numbered sequentially (i.e., 2A, 2B, 2C, etc.). DataLabs will accommodate entry of multiple radiological procedures.

Q: For Q8.2, what if it is unknown whether the radiological procedure was planned or unplanned?

A: Information should be obtained from the primary clinical team to make this determination. Mark ‘yes’ if this was a staged procedure and mark ‘no’ if it was not planned or unknown.

Q: For Q 10.2, what if the type of surgical procedure is unknown?

A: If the type of surgical procedure is unknown, check “other reason”, and place “Unknown” in the specification area of Q10.3

Form 16 – 5 Days Post Procedure

Form 16 data will be submitted via DataLabs. You will first enter the data on the Form 16 source document worksheet and then enter the data electronically in DataLabs. Form 16 is collected at the 5 Days post-angiography study visit.

Q: Define an acceptable window of time for the completion of this form.

A: The window of time acceptable for form completion is 5 to 8 days post angiography. However, due to the importance of the required data, the data should be obtained even if this window has lapsed.

Q: How should it be handled if a participant is hospitalized at a different location?

A: If the patient is hospitalized at another hospital, Form 16 may not be completed in its entirety; question 4 will be “NO” and an SAE form and Protocol Deviation Form (form 23) must be completed. State in the justification section that the patient was hospitalized and unavailable for interview.

If patient is not available for interview at 5 days post-procedure, this information should be obtained from the participant after discharge.

Q: If this form is not completed will I need to complete a protocol deviation?

A: If this form is not completed, a protocol deviation will need to be completed.

Form 17 – 35 Days Post Procedure

Form 17 data will be submitted via DataLabs. You will first enter the data on the Form 17 source document worksheet and then enter the data electronically in DataLabs. Form 17 is collected at the 35 Days post-angiography study visit.

Q: Define an acceptable window of time for the completion of this form.

A: The window of time acceptable for form completion is 35 to 49 days post angiography. However, due to the importance of the required data, the data should be obtained even if this window has lapsed.

Q: Will a protocol deviation need to be completed if the data is collected outside of the acceptable window of time?

A: If the data is collected outside of the acceptable window of time, a protocol deviation will not be necessary if there is a progress note to file documenting the attempt to schedule collection of data during the recommended time frame.

Form 18 – 90 Days Post-Procedure

Form 18 data will be submitted via DataLabs. You will first enter the data on the Form 18 source document worksheet and then enter the data electronically in DataLabs. Form 18 is collected at the 90 Days post-angiography study visit.

Q: Define an acceptable window of time for the completion of this form.

A: The acceptable window of time for form completion is 90 to 104 days post angiography. However, due to the importance of the required data, the data should be obtained even if this window has lapsed.

Q: Will a protocol deviation need to be completed if the data is collected outside of the acceptable window of time?

A: If the interview is performed outside of the acceptable window of time, a deviation will not be necessary if there is a progress note to file documenting the attempt to schedule the collection of data during the recommended time frame. However, if the 90-day blood sample is collected outside of the window of time, a protocol deviation **will** have to be completed.

Form 19 – Adverse Event (AE)

Q: For Q1.1.14, when an adverse event is marked as “Recovering/Resolving”, why is Q1.1.16 (“Is this date an estimate?”) still shown as required. How should this be answered?

A: This question should remain blank given that the “date resolved” is not relevant in this case. The team has taken note of this issue and it will be dealt with prior to the release of the next version of DataLabs. Any DCFs that occur because of this programming error should be ignored.

1.1.13.	What action was taken with the study drug capsule following the AE?	Temporarily Interrupted
1.1.14.	AE Outcome:	Ongoing - Recovering/Resolving
1.1.15.	Date resolved:	<input type="text"/> mm/dd/yyyy
1.1.16.	Is this date an estimate?	[Blank]
1.1.17.	Date form completed:	<input type="text"/> mm/dd/yyyy

Q: What dates are acceptable for the site investigator to sign this form?

A: The source document worksheet (Form 19) should be signed once completed by the coordinator and prior to entering data in DataLabs (per the Ops Manual). If there is a lengthy delay in obtaining the Investigator signature, please enter data in Datalabs in a timely manner and edit entries as needed after Investigator review.

Q: For Q14, how should I decide which category of AE outcomes is most appropriate. (e.g., the difference between ongoing and not recovered)?

A: AE Outcome (Check one)

- Recovering/Resolving** (Ongoing - the participant has a good prognosis and is in the process of recovering or the problem is being resolved)
- Recovered/ Resolved**
- Recovered/Resolved with Sequelae** (no change expected)
- Not recovered/not resolved** (The participant has not recovered yet and the prognosis is unsure or the problem has not been resolved and the resolution is unclear)

Form 20 – Endpoint_SAE Form

Q: When should I report an SAE to the Study Chair’s Office and CSPCRPCC (Study Pharmacist)?

A: SAEs need to be reported within 72 hours of the time the investigator becomes aware of the event (your answer to Q1 on the form).

Q: For Q16 on Form 20, how do I select the best primary discharge diagnosis given the overlap between the first three entries (acute coronary syndrome, STEMI, NSTEMI)?

A: Select primary discharge diagnosis as documented in the medical record or discharge summary. The overlapping categories will be collapsed and grouped appropriately prior to data analysis.

Q: When should I obtain the site Investigator's signature for this form?

A: The investigator should sign the source document worksheet (Form 20) at the time it is completed – within 72 hours of learning of the event. If this is not possible, the investigator should sign as soon as possible after that timeframe, but lack of signature *should not* delay reporting to CSPCC and CSPCRPCC.

Form 21 – Endpoint_SAE Follow-up

Complete SAE Follow-up information on the Form 21 source document worksheet, and attach this completed paper form to the corresponding completed Form 20 (SAE_Endpoint) source document worksheet. In DataLabs, the SAE follow-up form data should be added under the 'Safety' event in Form 20 Endpoint_SAE beginning with question 1.1.39.

For Q2 and Q5, "Not applicable" should be considered a "no".

Q: For Q16, if the follow up outcome is Fatal, what should I put for Q17 Date Resolved?

A: Use the date of death for Q17 if the event outcome is fatal.

Q: When should the SAE follow-up be completed?

A: A follow-up must be completed in the following situations:

1. Events with outcomes that are ONGOING (**recovering/resolving** or **not recovered/not resolved**). Follow-up reports should be completed every 30 days, or sooner if new information becomes available.
2. For events that are **recovering/resolved** or **recovered/resolved with sequelae** AND for which additional information becomes available that changes one or more elements on the initial SAE form, follow-up should be completed at the time the new information becomes available. (30-day rule does not apply)

*For all SAE outcomes, if within 72 hour reporting timeframe and new information becomes available, then the initial SAE form can be modified.

Q: How do I enter follow-up information for an ongoing SAE?

A: Complete the following steps:

1. When initially answering Question #39 on Form 20 when the event is reported, you will select **NO** from the dropdown list and click on **OK** when the rest of the data in the form has been completed to your satisfaction
2. When you go back into the form later on to complete the follow-up information, you will again select **F20. EndpointSAE_F21Fu.**
3. When you return to question 39 to update that there is Follow-up information, you will click on the **No** link which will then allow you to edit the fields. From **Enter new value**, you will select **Yes** and for **Reason for change** you will select **SEC**. As it is an SEC, there is no need to provide additional notes at this time. Finally you will select **OK** to return to the rest of the form

4. When you indicate that there is follow-up, this then activates other required fields related to follow-up data. You will need to complete these fields or DCFs will be generated. When everything has been completed/answered as necessary, select **OK**. Please note that the DCFs will be gone/disappear when they are completed correctly. When you return to the main menu, click **Save and Close**

Q: How should follow-up reports for events occurring at 90 days post angiography be handled?

A: Data on related SAEs will not be collected after the Day 35 post-angiography visit. However, study personnel may learn of unrelated SAEs that occurred between 35-90 days at the Day 90 phone contact. Since a patient's participation ends at 90 days (or at the time of the confirmatory blood draw), study sites should complete Form 20 Endpoint_SAE to record events that occurred up until the Day 90 end of study contact.

Note: if an SAE is still unresolved at Day 90, it may be necessary to obtain follow-up information from discharge summaries or progress notes even after the patient's study participation ends. For any unresolved SAEs at Day 90, study sites are advised to consult the Study Pharmacist in Albuquerque regarding whether follow-up is needed on unresolved events.

Q: When should I obtain the site Investigator's signature for this form?

A: As with initial SAE reports, signature should be obtained at the time the source document worksheet is completed. Lack of signature should not delay entry into DataLabs and reporting to the Study Chair's Office and CSPCRPCC (Study Pharmacist).

Form 22 – Early Participant Withdrawal

Q: When would someone qualify as early withdrawal? Only if they didn't complete the 90-day interview?

A: This is anytime between randomization and 90-day follow-up (or confirmation blood work visit, if needed) if the patient withdraws or needs to be exited from the protocol for cause. Submitting an SAE or protocol deviation does not *a priori* require early withdrawal from the study.

Q: Can I check more than 1 reason for withdrawal?

A: No, please select **one** primary reason for withdrawal.

Form 23 – Protocol Deviation

Q: Is it considered a protocol deviation if the participant didn't take all of their study drug?

A: As it states on Q2 of this form, participant non-compliance with study drug is *not* considered a protocol deviation. However, if study drug was incorrectly administered or prescribed, that would constitute a deviation.

Q: How should I handle multiple protocol deviations throughout the course of the trial?

A: A new form must be completed for each protocol deviation completed.

Q: When should I obtain the site Investigator's signature for this form?

A: As with any form requiring a signature, best practice is to obtain the signature at the time the source document worksheet is completed. Lack of signature should not delay reporting of the deviation.

Form 24 – Study Blood Specimens

Form 24 must be completed at the time of submission of study blood specimens at the following visits: baseline, 4 days following angiography, and 90 days following angiography. Specimens should be submitted and forms completed as soon as possible after the specimen is available, which will depend on whether the patient returns to the center for the collection or has it done by the mobile collection agency. This form should also be completed if a confirmatory blood draw is needed following the 90-day post-procedure assessment (see Q/A below for details). You will first enter the data on the Form 24 source document worksheet and then enter the data electronically in DataLabs.

Q: How should I enter the specimen ID?

A: The specimen ID should be the participant ID followed by a dash and the Type of Blood specimen (from Q2). Remember to include a dash between the site number and patient ID as well. For example, if the participant ID is 123-4567 and the type of blood specimen is 4 days, then the specimen ID should read: 123-4567-04.

Q: When would I select “confirmatory” as the specimen type?

A: Please reference the Operations Manual section regarding the 90-day post-procedure assessment. If a participant has a $\geq 50\%$ increase in SCr between their baseline and 90 day measurements, a confirmatory SCr measurement will be obtained.

Q: Should this form be sent with the lab sample?

A: No, the form remains at the site, but it is important that you affix a specimen label to the form so that you know the sample ID of each specimen.

APPENDIX 8: CSP Guidelines (hyperlink)

https://vaww.ord.research.va.gov/CSP/Boston/csp578/Operations%20Manual/APPENDIX%207_CSP%20Guidelines%202013.pdf

Guidance for Industry

Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)**

**Procedural
October 2009**

Guidance for Industry Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects

*Additional copies are available from:
Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
(Tel) 301-827-4573*

<http://www.fda.gov/cder/guidance/index.htm>

or

*Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
<http://www.fda.gov/cber/guidelines.htm>.
(Tel) 800-835-4709 or 301-827-1800*

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Center for Devices and Radiological Health
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Tel: 1-800-638-2041
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Contains Nonbinding Recommendations

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Guidance for Industry¹ Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides an overview of the responsibilities of a person who conducts a clinical investigation of a drug, biological product, or medical device (an *investigator* as defined in 21 CFR 312.3(b) and 21 CFR 812.3(i)). The goal of this guidance is to help investigators better meet their responsibilities with respect to protecting human subjects and ensuring the integrity of the data from clinical investigations. This guidance is intended to clarify for investigators and sponsors FDA's expectations concerning the investigator's responsibility (1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties and (2) to protect the rights, safety, and welfare of study subjects.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. OVERVIEW OF INVESTIGATOR RESPONSIBILITIES

In conducting clinical investigations of drugs, including biological products, under 21 CFR part 312 and of medical devices under 21 CFR part 812, the investigator is responsible for:

- Ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs, including biological products, or agreement for clinical investigations of medical devices, the investigational plan, and applicable regulations
- Protecting the rights, safety, and welfare of subjects under the investigator's care
- Controlling drugs, biological products, and devices under investigation (21 CFR 312.60, 21 CFR 812.100)

¹ This guidance has been prepared by the Investigator Responsibilities Working Group, which includes representatives from the Office of the Commissioner, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

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Although specific investigator responsibilities in drug and biologics clinical trials are not identical to the investigator responsibilities in medical device clinical trials, the general responsibilities are essentially the same. This guidance discusses the general investigator responsibilities that are applicable to clinical trials of drugs, biologics, and medical devices.

An investigator's responsibilities in conducting clinical investigations of *drugs* or *biologics* are provided in 21 CFR Part 312. Many of these responsibilities are included in the required investigator's signed statement, Form FDA-1572 (see Attachment A) (hereinafter referred to as 1572). Note that although the 1572 specifically incorporates most of the requirements directed at investigators in part 312, not all requirements are listed in the 1572. Investigators and sponsors should refer to 21 CFR Parts 11, 50, 54, 56, and 312 for a more comprehensive listing of FDA's requirements for the conduct of drug and biologics studies.²

An investigator's responsibilities in conducting clinical investigations of a *medical device* are provided in 21 CFR Part 812, including the requirement that there be a signed agreement between the investigator and sponsor (see 21 CFR 812.43(c)(4) and 812.100). The medical device regulations do not require use of a specific form for an investigator's statement; and there are additional requirements not listed above (see Attachment B). Investigators and sponsors should refer to 21 CFR Parts 11, 50, 54, 56, and 812 for a more comprehensive listing of FDA's requirements for the conduct of device studies.

Nothing in this guidance is intended to conflict with recommendations for investigators contained in the International Conference on Harmonisation (ICH) guidance for industry, *E6 Good Clinical Practice: Consolidated Guidance* (Good Clinical Practice Guidance).³

III. CLARIFICATION OF CERTAIN INVESTIGATOR RESPONSIBILITIES

This section of the guidance clarifies the investigator's responsibility to supervise the conduct of the clinical investigation and to protect the rights, safety, and welfare of participants in drug and medical device clinical trials.

A. Supervision of the Conduct of a Clinical Investigation

As stated above, investigators who conduct clinical investigations of drugs, including biological products, under 21 CFR Part 312, commit themselves to personally conduct or supervise the investigation. Investigators who conduct clinical investigations of medical devices, under 21 CFR Part 812, commit themselves to supervise all testing of the device involving human subjects. It is common practice for investigators to delegate certain study-related tasks to employees, colleagues, or other third parties (individuals or entities not under the direct supervision of the investigator). When tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

² As a reminder, some investigators may be responsible for submitting certain clinical trial information to the National Institutes of Health clinical trials data bank under 42 U.S.C 282(j), 402(j) of the Public Health Service Act. Although not all investigators will be expected to meet this requirement, go to www.clinicaltrials.gov for further information about potential responsibilities.

³ Guidances, including ICH guidances, are available on the Agency's Web page. See the Web addresses on the second title page of this guidance.

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In assessing the adequacy of supervision by an investigator, FDA focuses on four major areas: (1) whether individuals who were delegated tasks were qualified to perform such tasks, (2) whether study staff received adequate training on how to conduct the delegated tasks and were provided with an adequate understanding of the study, (3) whether there was adequate supervision and involvement in the ongoing conduct of the study, and (4) whether there was adequate supervision or oversight of any third parties involved in the conduct of a study to the extent such supervision or oversight was reasonably possible.

1. What Is Appropriate Delegation of Study-Related Tasks?

The investigator should ensure that any individual to whom a task is delegated is qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task. Appropriate delegation is primarily an issue for tasks considered to be clinical or medical in nature, such as evaluating study subjects to assess clinical response to an investigational therapy (e.g., global assessment scales, vital signs) or providing medical care to subjects during the course of the study. Most clinical/medical tasks require formal medical training and may also have licensing or certification requirements. Licensing requirements may vary by jurisdiction (e.g., states, countries). Investigators should take such qualifications/licensing requirements into account when considering delegation of specific tasks. In all cases, a qualified physician (or dentist) should be responsible for all trial-related medical (or dental) decisions and care.⁴

During inspections of investigation sites, FDA has identified instances in which study tasks have been delegated to individuals lacking appropriate qualifications. Examples of tasks that have been inappropriately delegated include:

- Screening evaluations, including obtaining medical histories and assessment of inclusion/exclusion criteria
- Physical examinations
- Evaluation of adverse events
- Assessments of primary study endpoints
- Obtaining informed consent

The investigator is responsible for conducting studies in accordance with the protocol (see 21 CFR 312.60, Form FDA-1572, 21 CFR 812.43 and 812.100). In some cases a protocol may specify the qualifications of the individuals who are to perform certain protocol-required tasks (e.g., physician, registered nurse), in which case the protocol must be followed even if state law permits individuals with different qualifications to perform the task (see 21 CFR 312.23(a)(6) and 312.40(a)(1)). For example, if the state in which the study site is located permits a nurse practitioner or physician's assistant to perform physical examinations under the supervision of a physician, but the protocol specifies that physical examinations must be done by a physician, a physician must perform such exams.

The investigator should maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated.⁵ This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks

⁴ Guidance for industry, *E6 Good Clinical Practice: Consolidated Guidance*, section 4.3.1.

⁵ *Ibid*, section 4.1.5

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(e.g., can refer to an individual's CV on file), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.

2. What Is Adequate Training?

The investigator should ensure that there is adequate training for all staff participating in the conduct of the study, including any new staff hired after the study has begun to meet unanticipated workload or to replace staff who have left. The investigator should ensure that staff:

- Are familiar with the purpose of the study and the protocol
- Have an adequate understanding of the specific details of the protocol and attributes of the investigational product needed to perform their assigned tasks
- Are aware of regulatory requirements and acceptable standards for the conduct of clinical trials and the protection of human subjects
- Are competent to perform or have been trained to perform the tasks they are delegated
- Are informed of any pertinent changes during the conduct of the trial and receive additional training as appropriate

If the sponsor provides training for investigators in the conduct of the study, the investigator should ensure that staff receive the sponsor's training, or any information (e.g., training materials) from that training that is pertinent to the staff's role in the study.

3. What Is Adequate Supervision of the Conduct of an Ongoing Clinical Trial?

For each study site, there should be a distinct individual identified as an investigator who has supervisory responsibility for the site. Where there is a subinvestigator at a site, that individual should report directly to the investigator for the site (i.e., the investigator should have clear responsibility for evaluating the subinvestigator's performance and the authority to terminate the subinvestigator's involvement with the study) and the subinvestigator should not be delegated the primary supervisory responsibility for the site.

The investigator should have sufficient time to properly conduct and supervise the clinical trial. The level of supervision should be appropriate to the staff, the nature of the trial, and the subject population. In FDA's experience, the following factors may affect the ability of an investigator to provide adequate supervision of the conduct of an ongoing clinical trial at the investigator's site:

- Inexperienced study staff
- Demanding workload for study staff
- Complex clinical trials (e.g., many observations, large amounts of data collected)
- Large number of subjects enrolled at a site
- A subject population that is seriously ill
- Conducting multiple studies concurrently
- Conducting a study from a remote (e.g., off-site) location
- Conducting a study at multiple sites under the oversight of a single investigator, particularly where those sites are not in close proximity

The investigator should develop a plan for the supervision and oversight of the clinical trial at the site. Supervision and oversight should be provided even for individuals who are highly qualified

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and experienced. A plan might include the following elements, to the extent they apply to a particular trial:

- Routine meetings with staff to review trial progress, adverse events, and update staff on any changes to the protocol or other procedures
- Routine meetings with the sponsor's monitors
- A procedure for the timely correction and documentation of problems identified by study personnel, outside monitors or auditors, or other parties involved in the conduct of a study
- A procedure for documenting or reviewing the performance of delegated tasks in a satisfactory and timely manner (e.g., observation of the performance of selected assessments or independent verification by repeating selected assessments)
- A procedure for ensuring that the consent process is being conducted in accordance with 21 CFR Part 50 and that study subjects understand the nature of their participation and the risks
- A procedure for ensuring that source data are accurate, contemporaneous, and original
- A procedure for ensuring that information in source documents is accurately captured on the case report forms (CRFs)
- A procedure for dealing with data queries and discrepancies identified by the study monitor
- Procedures for ensuring study staff comply with the protocol and adverse event assessment and reporting requirements
- A procedure for addressing medical and ethical issues that arise during the course of the study in a timely manner

4. *What Are an Investigator's Responsibilities for Oversight of Other Parties Involved in the Conduct of a Clinical Trial?*

a. Study Staff Not in the Direct Employ of the Investigator

Staff involved directly in the conduct of a clinical investigation may include individuals who are not in the direct employ of the investigator. For example, a site management organization (SMO) may hire an investigator to conduct a study and provide the investigator with a study coordinator or nursing staff employed by the SMO. In this situation, the investigator should take steps to ensure that the staff not under his/her direct employ are qualified to perform delegated tasks (see section III.A.1) and have received adequate training on carrying out the delegated tasks and on the nature of the study (see section III.A.2), or the investigator should provide such training. The investigator should be particularly cautious where documentation needed to comply with the investigator's regulatory responsibilities is developed and maintained by SMO staff (e.g., source documents, CRFs, drug storage and accountability records, institutional review board correspondence). A sponsor who retains an SMO shares responsibility for the quality of the work performed by the SMO.

The investigator is responsible for supervising the study tasks performed by this staff, even though they are not in his/her direct employ during the conduct of the study (see section III.A.3). This responsibility exists regardless of the qualifications and experience of staff members. In the event that the staff's performance of study-related tasks is not adequate

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and cannot be made satisfactory by the investigator, the investigator should document the observed deficiencies in writing to the staff member's supervisor(s) and inform the sponsor. Depending on the severity of the deficiencies, the clinical trial may need to be voluntarily suspended until personnel can be replaced.

b. Parties Other than Study Staff

There are often critical aspects of a study performed by parties not involved directly in patient care or contact and not under the direct control of the clinical investigator. For example, clinical chemistry testing, radiologic assessments, and electrocardiograms are commonly done by a central independent facility retained by the sponsor. Under these arrangements, the central facility usually provides the test results directly to the sponsor and to the investigator. Because the activities of these parties are critical to the outcome of the study and because the sponsor retains the services of the facility, the sponsor is responsible for ensuring that these parties are competent to fulfill and are fulfilling their responsibilities to the study.

Less frequently, a study may require that investigators arrange to obtain information critical to the study that cannot be obtained at the investigator's site. For example, if the study protocol requires testing with special equipment or expertise not available at the investigator's site, the investigator might make arrangements for an outside facility to perform the test. In this case, the results are usually provided directly to the investigator, who then submits the information to the sponsor. If the investigator retains the services of a facility to perform study assessments, the investigator should take steps to ensure that the facility is adequate (e.g., has the required certification or licenses). The investigator may also institute procedures to ensure the integrity of data and records obtained from the facility providing the information (e.g., a process to ensure that records identified as coming from the facility are authentic and accurate). Procedures are particularly important when assessments are crucial to the evaluation of the efficacy or safety of an intervention or to the decision to include or exclude subjects who would be exposed to unreasonable risk.

Investigators should carefully review the reports from these external sources for results that are inconsistent with clinical presentation. To the extent feasible, and considering the specifics of study design, investigators should evaluate whether results appear reasonable, individually, and in aggregate, and they should document the evaluation. If investigators detect possible errors or suspect that results from a central laboratory or testing facility might be questionable, the investigator should contact the sponsor immediately.

c. Special Considerations for Medical Device Studies

Field clinical engineers (device sponsor employees) have traditionally played a role in some investigational device procedures (e.g., cardiology, orthopedics, and ophthalmology) by providing technical assistance to the device investigator. The field clinical engineer should be supervised by the investigator because the field clinical engineer's presence or activities may have the potential to bias the outcome of studies, may affect the quality of research data, and/or may compromise the rights and welfare of human subjects. The field clinical engineer's activities should be described in the protocol. If the field engineer has

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face-to-face contact with subjects or if the activities of the field engineer directly affect the subject, those activities should also be described in the informed consent.

B. Protecting the Rights, Safety, and Welfare of Study Subjects

Investigators are responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial (21 CFR 312.60 and 812.100). This responsibility should include:

- Providing reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention
- Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, when specialized care is needed)
- Adhering to the protocol so that study subjects are not exposed to unreasonable risks

The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and the subject agrees to the primary physician being informed.

1. Reasonable Medical Care Necessitated by Participation in a Clinical Trial

During a subject's participation in a trial, the investigator (or designated subinvestigator) should ensure that reasonable medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial participation. If the investigator does not possess the expertise necessary to provide the type of medical care needed by a subject, the investigator should make sure that the subject is able to obtain the necessary care from a qualified practitioner. For example, if the study involves placement of a carotid stent by an interventional neuroradiologist and the subject suffers a cerebral stroke, the neuroradiologist should assess the clinical status of the subject and arrange for further care of the subject by a neurologist. Subjects should receive appropriate medical evaluation and treatment until resolution of any emergent condition related to the study intervention that develops during or after the course of their participation in a study, even if the follow-up period extends beyond the end of the study at the investigative site.

The investigator should also inform a subject when medical care is needed for conditions or illnesses unrelated to the study intervention or the disease or condition under study when such condition or illness is readily apparent or identified through the screening procedures and eligibility criteria for the study. For example, if the investigator determines that the subject has had an exacerbation of an existing condition unrelated to the investigational product or the disease or condition under study, the investigator should inform the subject. The subject should also be advised to seek appropriate care from the physician who was treating the illness prior to the study, if there is one, or assist the subject in obtaining needed medical care.

2. Reasonable Access to Medical Care

Investigators should be available to subjects during the conduct of the trial for medical care related to participation in the study. Availability is particularly important when subjects are receiving a drug that has significant toxicity or abuse potential. For example, if a study drug has potentially fatal toxicity, the investigator should be readily available by phone or other electronic communication 24 hours a day and in reasonably close proximity to study subjects (e.g., not in

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another state or on prolonged travel). Study subjects should be clearly educated on the possible need for such contact and on precisely how to obtain it, generally by providing pertinent phone numbers, e-mail addresses, and other contact information, in writing. Prior to undertaking the conduct of a study, prospective investigators should consider whether they can be available to the extent needed given the nature of the trial.

During any period of unavailability, the investigator should delegate responsibility for medical care of study subjects to a specific qualified physician who will be readily available to subjects during that time (in the manner a physician would delegate responsibility for care in clinical practice). If the investigator is a non-physician, the investigator should make adequate provision for any necessary medical care that the investigator is not qualified to provide.

3. Protocol Violations that Present Unreasonable Risks

There are occasions when a failure to comply with the protocol may be considered a failure to protect the rights, safety, and welfare of subjects because the non-compliance exposes subjects to unreasonable risks. For example, failure to adhere to inclusion/exclusion criteria that are specifically intended to exclude subjects for whom the study drug or device poses unreasonable risks (e.g., enrolling a subject with decreased renal function in a trial in which decreased function is exclusionary because the drug may be nephrotoxic) may be considered failure to protect the rights, safety, and welfare of the enrolled subject. Similarly, failure to perform safety assessments intended to detect drug toxicity within protocol-specified time frames (e.g., CBC for an oncology therapy that causes neutropenia) may be considered failure to protect the rights, safety, and welfare of the enrolled subject. Investigators should seek to minimize such risks by adhering closely to the study protocol.

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ATTACHMENT A: COPY OF FORM 1572

<p>DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION</p> <p>STATEMENT OF INVESTIGATOR <i>(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)</i> (See instructions on reverse side.)</p>	<p>Form Approved: OMB No. 0910-0014. Expiration Date: May 31, 2009. See OMB Statement on Reverse.</p> <p>NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).</p>
1. NAME AND ADDRESS OF INVESTIGATOR	
2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.	
<input type="checkbox"/> CURRICULUM VITAE <input type="checkbox"/> OTHER STATEMENT OF QUALIFICATIONS	
3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED	
4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.	
5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE	
6. NAMES OF THE SUBINVESTIGATORS (<i>e.g., research fellows, residents, associates</i>) WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).	
7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.	

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<p>8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:</p> <p><input type="checkbox"/> FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.</p> <p><input type="checkbox"/> FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.</p>	
<p>9. COMMITMENTS:</p> <p>I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.</p> <p>I agree to personally conduct or supervise the described investigation(s).</p> <p>I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.</p> <p>I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.</p> <p>I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.</p> <p>I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.</p> <p>I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.</p> <p>I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.</p> <p>I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.</p>	
<p>INSTRUCTIONS FOR COMPLETING FORM FDA 1572 STATEMENT OF INVESTIGATOR:</p>	
<ol style="list-style-type: none"> 1. Complete all sections. Attach a separate page if additional space is needed. 2. Attach curriculum vitae or other statement of qualifications as described in Section 2. 3. Attach protocol outline as described in Section 8. 4. Sign and date below. 5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION. 	
<p>10. SIGNATURE OF INVESTIGATOR</p>	<p>11. DATE</p>
<p>(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)</p>	
<p>Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p>	

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this application to this address.

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**ATTACHMENT B: INVESTIGATOR RESPONSIBILITIES
FOR SIGNIFICANT RISK DEVICE INVESTIGATIONS**

This document is intended to assist investigators in identifying and complying with their responsibilities in connection with the conduct of clinical investigations involving medical devices. Although this guidance primarily addresses duties imposed upon clinical investigators by regulations of the Food and Drug Administration (FDA), investigators should be cognizant of additional responsibilities that may derive from other sources (such as the study protocol itself, the investigator agreement, any conditions of approval imposed by FDA or the governing institutional review board, as well as institutional policy and state law).

GENERAL RESPONSIBILITIES OF INVESTIGATORS (21 CFR 812.100)

1. Ensuring that the investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations
2. Protecting the rights, safety, and welfare of subjects under the investigator's care
3. Controlling devices under investigation
4. Ensuring that informed consent is obtained from each subject in accordance with 21 CFR Part 50 and that the study is not commenced until FDA and IRB approvals have been obtained.

SPECIFIC RESPONSIBILITIES OF INVESTIGATORS (21 CFR 812.110)

1. Awaiting IRB approval and any necessary FDA approval before requesting written informed consent or permitting subject participation
2. Conducting the investigation in accordance with:
 - a. The signed agreement with the sponsor
 - b. The investigational plan
 - c. The regulations set forth in 21 CFR Part 812 and all other applicable FDA regulations
 - d. Any conditions of approval imposed by an IRB or FDA

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3. Supervising the use of the investigational device. An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under 21 CFR Part 812 to receive it.
4. Disposing of the device properly. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

MAINTAINING RECORDS (21 CFR 812.140)

An investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

1. Correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA
2. Records of receipt, use or disposition of a device that relate to:
 - a. The type and quantity of the device, dates of receipt, and batch numbers or code marks
 - b. Names of all persons who received, used, or disposed of each device
 - c. The number of units of the device returned to the sponsor, repaired, or otherwise disposed of, and the reason(s) therefore
3. Records of each subject's case history and exposure to the device, including:
 - a. Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent
 - b. All relevant observations, including records concerning adverse device effects (whether anticipated or not), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests;
 - c. A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.
4. The protocol, with documents showing the dates of and reasons for each deviation from the protocol
5. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation

INSPECTIONS (21 CFR 812.145)

Investigators are required to permit FDA to inspect and copy any records pertaining to the investigation including, in certain situations, those which identify subjects.

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SUBMITTING REPORTS (21 CFR 812.150)

An investigator shall prepare and submit the following complete, accurate, and timely reports:

1. To the sponsor and the IRB:
 - Any *unanticipated adverse device effect* occurring during an investigation. (Due no later than 10 working days after the investigator first learns of the effect.)
 - *Progress reports* on the investigation. (These reports must be provided at regular intervals, but in no event less often than yearly. If there is a study monitor, a copy of the report should also be sent to the monitor.)
 - Any *deviation from the investigational plan* made to protect the life or physical well-being of a subject in an emergency. (Report is due as soon as possible but no later than 5 working days after the emergency occurs. Except in emergency situations, a protocol deviation requires prior sponsor approval; and if the deviation may affect the scientific soundness of the plan or the rights, safety, or welfare of subjects, prior FDA and IRB approval are required.)
 - Any use of the device *without obtaining informed consent*. (Due within 5 working days after such use.)
 - A *final report*. (Due within 3 months following termination or completion of the investigation or the investigator's part of the investigation. For additional guidance, see the discussion under the section entitled "Annual Progress Reports and Final Reports.")
 - Any *further information* requested by FDA or the IRB about any aspect of the investigation.

2. To the Sponsor:
 - *Withdrawal of IRB approval* of the investigator's part of an investigation. (Due within 5 working days of such action).

INVESTIGATIONAL DEVICE DISTRIBUTION AND TRACKING

The IDE regulations prohibit an investigator from providing an investigational device to any person not authorized to receive it (21 CFR 812.110(c)). The best strategy for reducing the risk that an investigational device could be improperly dispensed (whether purposely or inadvertently) is for the sponsor and the investigators to closely monitor the shipping, use, and final disposal of devices. Upon completion or termination of a clinical investigation (or the investigator's part of an investigation), or at the sponsor's request, an investigator is required to return to the sponsor any remaining supply of the device or otherwise to dispose of the device as the sponsor directs (21 CFR 812.110(e)). Investigators must also maintain complete, current, and accurate records of the receipt, use, or disposition of investigational devices (21 CFR 812.140(a)(2)). Specific recordkeeping requirements are set forth at 21 CFR 812.140(a).

PROHIBITION OF PROMOTION AND OTHER PRACTICES (21 CFR 812.7)

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The IDE regulations prohibit the promotion and commercialization of a device that has not been first cleared or approved for marketing by FDA. This prohibition is applicable to sponsors and investigators (or any person acting on behalf of a sponsor or investigator) and encompasses the following activities:

1. Promotion or test marketing of the investigational device
2. Charging subjects or investigators for the device a price larger than is necessary to recover the costs of manufacture, research, development, and handling
3. Prolonging an investigation beyond the point needed to collect data required to determine whether the device is safe and effective
4. Representing that the device is safe or effective for the purposes for which it is being investigated

APPENDIX 10: Protocol (hyperlink)

<https://vaww.ord.research.va.gov/CSP/Boston/csp578/centralfile/Protocol%20and%20Supporting%20Documents/Forms/AllItems.aspx?RootFolder=%2FCSP%2FBoston%2Fcsp578%2Fcentralfile%2FProtocol%20and%20Supporting%20Documents%2F01%2E%20Approved%20Protocol%20Versions%20and%20Approved%20Amendments&View=%7b117FD8A4%2dEBDE%2d4ED6%2d84F2%2d5FBCE4BA1BA2%7d>

APPENDIX 11: Volunteering in Research Pamphlet

Veterans'
Participation in
Research

**VOLUNTEERING
IN RESEARCH**

Here are some things
you need to know.

R&D Communications (12)
103 South Gay Street, Ste. 517
Baltimore, MD 21202
(410) 962-1800 x223
research.publications@va.gov



DISCOVERY INNOVATION ADVANCEMENT

DISCOVERY INNOVATION ADVANCEMENT



What questions should I ask before volunteering?

If you are asked to participate in a research project, you might want to ask the questions on this tear out to help you decide whether or not you want to take part in the study.

Tear this page out and take it with you to remind yourself of some of the questions to ask.

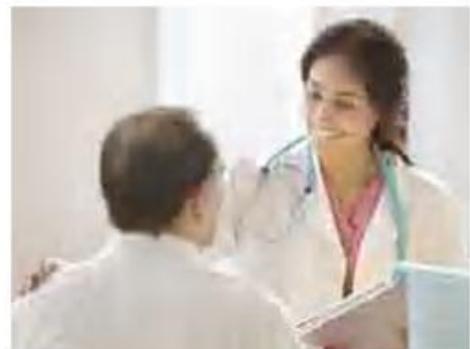


DISCOVERY INNOVATION ADVANCEMENT

Who will answer my questions?

If you have any questions, concerns, or complaints about VA research, or if you would like to talk to someone about the VA Research program, please contact your local Research & Development office at:

The VA Office of Research & Development's Center On Advice and Compliance Help (COACH) offers free educational materials to help assure that veterans receive adequate information when they consider participating in VA research. You can order additional copies of this brochure and other brochures, a video on VHS tape or DVD-ROM, and posters at: <http://www.research.va.gov/programs/pride/resources/order.cfm>





Here are some things you need to know



The Department of Veterans Affairs (VA) ranks as one of the nation's leaders in health research. Thousands of studies are conducted at VA medical centers, outpatient clinics, and nursing homes each year. This research has significantly contributed to advancements in health care for veterans and other Americans from every walk of life.

For example, VA researchers have:

- Used microelectronics and microchips (very small electronic components), as well as robotics, to create artificial limbs (prostheses) that look, feel, and work more like real arms and legs.
- Developed the nicotine patch to help people stop smoking.
- Invented the cardiac pacemaker.
- Performed the first successful liver transplant.
- Played a major role in the development of the CAT (or CT) scan.
- Tested new drugs and treatments for diseases such as AIDS, diabetes, Alzheimer's, and osteoporosis.

These important health care advances are only possible because veterans volunteered to take part in research projects.

What is a research study?

A research study is an organized way of learning more about a problem or answering a question. A research study may be done to:

- Understand health needs, concerns, or feelings people have about an illness or their general health.
- Test if a product, such as a drug or piece of equipment, is safe and effective.
- Determine the best way to treat or prevent an illness.
- Find out what health care practices work best.

Like your medical record, the information in your research record will be kept confidential.

Are there benefits to being in a research study?

There may or may not be a direct benefit to your health or health condition if you take part in a research study. No one can predict the exact outcome of a research study or how it might affect you. The study may not help you personally, but your participation may provide information that will improve the lives of others in the future.



What questions should I ask before volunteering? If you are asked to participate in a research project, you might want to ask the following questions to help you decide whether or not you want to take part in the study: *tear this page out and take it with you.*

What is informed consent?

Informed consent is the process of learning important facts about the research study before you decide whether or not to volunteer. If you agree to volunteer, it should be based on a clear understanding of what will take place in the study and how it might affect you.

Informed consent begins when the research staff explains the study to you. These facts include details about the study, tests or procedures you may receive, the benefits and risks that could result, and your rights as a research volunteer.

Once your questions have been answered and you fully understand the facts about the research study, you will be asked to sign an "informed consent form." You should take your time when you read the informed consent form. If you have any questions, ask the research staff to explain. It may be helpful to talk with family members, friends, or your health care providers before you make a decision.

What if I do not want to take part in a research study?

- If you decide to take part in a study, you do so as a VOLUNTEER. This means YOU decide.
- If anyone asks you to take part in a research study, you have the right to say "no."
- Your decision will not affect your VA health care or benefits.
- You need to weigh both the potential risks and potential benefits of the study.
- You can change your mind and leave a research study at any time without losing any of your VA health care benefits.

- Who is doing this study and what questions might it answer?
- Who reviewed or approved this study?
- What could happen to my health, good or bad, if I take part in this study?
- Is it possible that I will receive a placebo (inactive substance)?
- What tests or procedures will I have during the study?
- How long will this study last?
- If I decide to participate, how will it affect my daily life?
- Will I have to make extra trips to the VA?
- Could my condition get worse during the study? What happens if it does?
- Will I be charged anything or paid anything to be in this study?
- Who will be in charge of my care? Can I continue seeing my own doctor?
- Who will be told I am taking part in this study? What information will they receive?
- What happens to any specimens that I give?
- What happens after the study ends?
- Will I be told the results of the study?
- How do I end my participation in the study if I change my mind?
- What other options do I have if I decide not to take part in this study?
- Whom do I contact for questions and information about the study?

APPENDIX 12: Drug Treatment and Handling Plan (DTHP)

VA COOPERATIVE STUDY #578

"The Prevention of Serious Adverse Events Following Angiography
(PRESERVE)"

DRUG TREATMENT
AND
HANDLING PROCEDURES

IND #: 116,882

December 2013

Prepared by:

THE DEPARTMENT OF VETERANS AFFAIRS
COOPERATIVE STUDIES PROGRAM CLINICAL RESEARCH PHARMACY
COORDINATING CENTER (151-I)

2401 Centre Ave., SE
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DRUG TREATMENT AND HANDLING PROCEDURES (DTHP)

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1. INTRODUCTION

Each site investigator (SI) and participating pharmacy is responsible for a complete and accurate accounting of all study drugs received and dispensed by the site. The VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) in Albuquerque, New Mexico, will provide forms, instructions and assistance as necessary to assure proper use of and accountability for all study drugs. The CSPCRPCC will monitor the performance of each participating site in this regard. In addition, each site must observe local policies and applicable state and federal regulations concerning custody, dispensing, and disposition of study drugs.

2. RESPONSIBILITIES OF PHARMACY SERVICE

Note: This study is sponsored by the United States Department of Veterans Affairs (VA) Cooperative Studies Program (CSP) and will have VA sites. Although the Site Investigator at each site is ultimately responsible for the conduct of the study in all health care settings, within the VA system Pharmacy Service is responsible for certain functions, which are detailed below.

VA Pharmacy Service is responsible for the following:

A. Storage of Study Drugs:

Providing secure storage for the study drugs in the Pharmacy or elsewhere at the site, local policy permitting.

B. Drug Accountability:

1. Maintaining complete and accurate records showing the receipt and disposition of study drug supplies. Records should contain information regarding quantities received, quantities dispensed to and returned by participants, and the disposition of returned and unused drug supplies.
2. Providing to the Site Investigator (SI) a complete account of the receipt and disposition of the study drug supplies. The records provided to the SI should contain information regarding quantities received, quantities dispensed to and returned by participants, and the disposition of returned and unused drug supplies.

C. Informed Consent Verification:

Verifying that informed consent has been obtained from each participant before any study drug is dispensed or administered. Veterans Health Administration Handbook 1108.04, "Investigational Drugs and Supplies," §10.d(4), requires the initial order or prescription for each new subject on a study drug must be accompanied by a signed informed consent or written assurance, by the provider, that the signed consent is available for viewing and printing in the electronic medical record. NOTE: *Pharmacy does not need to physically have a copy of the consent if it can be viewed in the electronic medical record. If there is not a physical copy of the*

consent maintained in pharmacy there must be a mechanism by which the pharmacist can document that the signed consent was seen before dispensing to the subject for the first time. SMART has developed a GCP Tool – “Pharmacy Service – Record of Informed Consent Verification” that is available at: <https://vaww.ord.research.va.gov/CSP/SMART/default.aspx>.

D. Drug Dispensing:

Dispensing study drug only upon the written order (e.g., prescription or inpatient order form) of the SI or a sub-investigator authorized to prescribe the study drug at the site.

E. Drug Information:

Providing the clinic with a copy of the three CSP #578 Investigational Drug Information Records (VA Form 10-9012) for inclusion in VA research record of each participant randomized into the trial when appropriate.

3. RESPONSIBILITIES OF SITE INVESTIGATOR

The Site Investigator (SI) is responsible for:

A. Providing the Site Pharmacy with:

1. VA Form 10-9012 (when appropriate):

The completed and approved “Investigational Drug Information Record” (VA Form 10-9012) for each study drug. CSPCRPCC provides a partially completed VA Form 10-9012 for each drug to the SI. The SI completes this document, obtains required approvals (Chairs of the VA Central IRB and Research & Development Committee), and submits it to the Site Pharmacy before the study begins.

2. Informed Consent:

The initial order or prescription for each randomized participant receiving an investigational drug must be accompanied by a signed informed consent or written assurance, by the SI, that the signed consent is available for viewing and printing in the electronic medical record by the Site Pharmacy.

3. Prescriptions:

A written or electronic prescription or physician's order signed by the SI or sub-investigator authorized to prescribe the study drugs at the site.

4. Sub-investigators:

The names of clinicians authorized to prescribe the study drugs at the site.

B. Drug Accountability:

Maintaining adequate drug accountability records, including the quantity received from the sponsor (CSP), the quantity used or returned by participants and the quantity destroyed or returned to the sponsor (CSPCRPCC). This responsibility may be delegated to Pharmacy Service, but all drug accountability records (originals or copies) must be archived with the SI's study files when the study is completed or terminated early.

C. Record Retention:

Retaining all study-related documents until notified by the CSP Coordinating Center concerning the disposition of these documents.

CSP studies remain active for five years after the last participant follow-up.

D. Drug Information:

Ensuring that a copy of each Investigational Drug Information Record (VA Form 10-9012) is included in the participant's VA research record when appropriate.

E. Representations Regarding Study Drugs:

The SI, any sub-investigator, and any other personnel associated with the study will not represent that any individual study drug or combination of study drugs used in CSP #578 are safe or effective for the purpose for which they are being investigated.

F. Control of the Study Drug:

The SI may prescribe or administer the study drugs only to participants under the SI's personal supervision or under the supervision of a sub-investigator responsible to the SI. The study drugs may be dispensed and administered to participants only for the purposes of this study.

4. DESCRIPTION OF STUDY DRUGS

The following study drugs will be distributed by the CSPCRPCC.

Table 1. CSP #578 Study Drugs

Study Drug	Strength (active)	Drug Code	Manufacturer/ Packager
Blinded Sodium Chloride (NaCl)	0.9% IV (154 mEq/L)	NaCl/NaHCO₃-578	Baxter/CSPCRPCC
Blinded Sodium Bicarbonate (NaHCO ₃)	1.26% IV (150 mEq/L)		
Blinded N-acetylcysteine (NAC) or Placebo	300 mg cap	NAC-578	CSPCRPCC

5. DESCRIPTION OF TREATMENT REGIMENS

5.01. *Study Objective and Overview*

Background: Acute kidney injury (AKI), which is characterized by an abrupt drop in renal function, has multiple etiologies. One of the most common causes of AKI is the intravascular administration of iodinated radiocontrast. Past research has confirmed that contrast-induced acute kidney injury (CIAKI) is associated with serious adverse outcomes. Studies have demonstrated a 2 to 7 fold increase in in-hospital mortality associated with CIAKI, while length of hospital stay and healthcare costs rise more than 100% among some patients who develop this condition. Research on preventive interventions for CIAKI has focused in large part on intravenous (IV) fluids (NaCl, NaHCO₃) and N-acetylcysteine (NAC). It is believed that peri-procedural IV fluid prevents CIAKI and that isotonic fluid provides greater protection than hypotonic fluid. Since an initial study by Tepel et al. published in 2000 found NAC to be efficacious for the prevention of CIAKI, there have been dozens of trials and several meta-analyses investigating this agent. Despite data suggesting a benefit with the use of NaHCO₃ and NAC, there continues to be clinical equipoise on the effectiveness of these interventions. While studies have shown that small increases in serum creatinine (SCr) following angiography are associated with an increased risk for in-hospital death, it is unknown whether the purported effect of NaHCO₃ and NAC to prevent CIAKI translates into a reduction in serious adverse outcomes. To address the clinical equipoise that exists on the effectiveness of NaHCO₃ and NAC and establish a sound evidence basis for the use of these two interventions to prevent serious adverse outcomes, an adequately powered, multi-center, randomized clinical trial is clearly needed.

Study Hypothesis: The primary hypotheses to be tested are that NaHCO₃ is more effective than NaCl and that NAC is more effective than placebo for the prevention of serious morbidity and mortality following coronary and non-coronary angiography in high-risk Veterans.

Study Endpoints:

Primary endpoint

To assess the effectiveness of IV NaHCO₃ compared to IV NaCl and oral NAC compared to placebo for the prevention of 90-day adverse outcomes (i.e., death, need for acute dialysis, or persistent decline in kidney function within 90 days following angiography) in high-risk Veterans undergoing coronary or non-coronary angiography

Secondary and Tertiary endpoints

1. CIAKI defined by an increase in SCr of ≥ 0.5 mg/dL and/or $\geq 25\%$ from the pre-procedure value at 96 hours following angiography.

2. Hospitalization with acute coronary syndrome, heart failure, or cerebrovascular accident within 90 days following the index angiographic procedure.
3. All-cause hospitalization within 90 days of the index angiographic procedure.
4. Development of end-stage renal disease within one year following angiography.
5. Death within one year following angiography.

Study Design: The comparative effectiveness study is a multicenter, randomized, double-blind clinical trial that will use a 2 x 2 factorial design to assess the effectiveness of IV NaHCO₃ compared to IV NaCl and oral NAC compared to placebo for the prevention of serious, adverse outcomes in high-risk Veterans undergoing coronary or non-coronary angiography. Veterans will be enrolled if, at the time of angiography, they have underlying chronic kidney disease with an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m² and a diagnosis of diabetes mellitus, or an eGFR <45 ml/min/1.73 m² regardless of whether or not they have diabetes mellitus.

Participants will be randomized to one of four treatment combinations: NaCl + NAC, NaHCO₃ + NAC, NaCl + matching placebo for NAC, or NaHCO₃ + matching placebo for NAC. The administration of IV fluids will be pseudo-protocolized to deliver at least 3 mL/kg of study fluid over at least 1 hour at an infusion rate of not less than 1 mL/kg per hour and not more than 3 mL/kg per hour prior to the angiographic procedure; 1 to 1.5 mL/kg per hour during angiography; and at least 6 mL/kg of study fluid over at least 4 hours post-angiography at an infusion rate of not less than 1 mL/kg per hour and not more than 1.5 mL/kg per hour. The maximal fluid administration will be 12 mL/kg over a duration of up to 12 hours pre-angiography and 12 mL/kg over a duration of not more than 12 hours post-angiography. This strategy will ensure the provision of a minimum necessary volume of IV fluid, yet will permit providers to administer additional study IV fluid as they deem appropriate for individual participants. NAC or placebo will be administered in a dose of 1200 mg orally approximately 1 hour prior to and 1200 mg approximately 1 hour post procedure and then 1200 mg twice daily for 4 days. (See **Table 3.**)

References:

See Protocol

5.02 *Study Treatments and Blinding*

A. General

All study medications (NaCl, NaHCO₃, and NAC) will be blinded and given drug code names to maintain the blind. NaCl and NaHCO₃ will be blinded to one another and oral NAC and placebo for NAC will be blinded to one another.

B. Study Drug Code Names

Table 2. CSP #578 Study Drug Code Names

Study Drug Code	Drug Name	Strength	Route of Admin	Packaged	Kit Size
NaCl/NaHCO₃-578	Sodium Chloride (NaCl)	0.9% (154 mEq/L)	IV	1000 ml/ bag	12 bags/kit
	OR Sodium Bicarbonate (NaHCO ₃)	1.26% (150 mEq/L)			
NAC-578	N-acetylcysteine (NAC) or matching placebo	300mg/capsule or placebo	PO	48 caps/ bottle	12 bottles/kit

C. Administration of Study Drug

All participants meeting all inclusion and exclusion criteria will receive either NaCl or NaHCO₃ and either NAC or matching placebo according to the following drug administration schedule:

Table 3. CSP #578 Treatment Groups Summary

Administration Period	NaCl/NaHCO ₃ -578	NAC-578
Pre-angiography	3-12ml/kg over 1-12 hours	4 capsules 1 hour prior to procedure
During angiography	1-1.5ml/kg/hour	N/A
Post angiography	6-12 ml/kg over 4-12 hours	4 capsules 1 hour post procedure
Days 1-4 post angiography	N/A	4 capsules TWO times a day

It is recommended that **NaCl/NaHCO₃-578** be administered through a dedicated IV line, however, under certain circumstances this may not be feasible and the site personnel should consult with the local site pharmacist to determine the compatibility of the additional IV fluid with the study drug, **NaCl/NaHCO₃-578**.

D. Participant Enrollment, Treatment Period, and Study Drug Dispensing Schedule

- An estimated 7680 participants will enter this study during a 2.5 year enrollment period. Thirty three VA medical centers will participate. There will be a 90 day follow-up period after angiography. Each participant will be treated with **NaCl/NaHCO₃-578** 1 to 12 hours prior to; during; and 4 to 12 hours after procedure and treated with **NAC-578** for 5 days and then evaluated for primary study endpoints up to 90 days.
- While the participant is in the hospital, participants will be administered **NAC-578** twice daily at pre-specified time points. The

participant will be dispensed the remaining **NAC-578** doses upon discharge from the hospital. **Note:** Each bottle has an additional eight (8) capsules to provide coverage for misplaced capsules during the 5 day course of therapy. Fluid administration will not be protocolized, but the recommended infusion rate and duration of **NaCl/NaHCO₃-578** is 3 to 12 mL/kg over 1 to 12 hrs prior to, 1 to 1.5 mL/kg per hour during, and 6 to 12 mL/kg over 4 to 12 hrs following the procedure. Dispensing of study drugs is described in **Section 9**.

5.03 *Supply of Study Drug*

All study drugs listed in **Table 1** will be provided to site pharmacies by the CSPCRPCC. **NaCl/NaHCO₃-578** will be provided in bulk kits (not participant specific kits) containing 12 IV bags per kit. **NAC-578** will be provided in bulk kits (not participant specific kits) containing 12 bottles per kit. **NAC-578** will be provided in bottles containing 48 capsules/bottle. The correct IV bag of **NaCl/NaHCO₃-578** and bottle of **NAC-578** for each individual participant must be assigned by the CSPCRPCC using the PRESERVE Interactive Web Response System (IWRS) as described in the **Sections 8 and 9**.

6. CUSTODY, STORAGE AND STABILITY OF STUDY DRUGS

6.01 *Study Drug Storage*

The local Pharmacy Service is responsible for the secure storage of study drugs at the site. CSPCRPCC centrally monitors stability/expiration dating of each blinded study drug it supplies to assure the drugs will be stable from time of receipt to actual participant utilization. Provision of lot numbers and expiration dates for blinded study medication may contribute to un-blinding of treatment assignment in a blinded clinical trial, therefore, the lot numbers and expiration dates for blinded study medications will NOT be provided to the study site or pharmacy.

Study sites will be contacted and instructed to ship all outdated study drug to CSPCRPCC (See **Section 11.03**) in the event that drug expiration occurs prior to use during the course of the study.

NaCl/NaHCO₃-578 and **NAC-578** should be stored below 30°C (86°F) and protected from freezing and excessive heat.

7. ORDERING STUDY DRUGS AND RELATED ITEMS FROM CSPCRPCC

7.01 *Study Drug Ordering*

A predetermined number of study drug bottles and IV bags will be maintained at each site (e.g. par level). The CSPCRPCC will monitor inventory levels at each site centrally and automatically send additional shipments as required. Manual drug orders should normally not be required. CSPCRPCC will notify the site Study Coordinator (SC) each time drugs are shipped to the site to enable the SC to monitor drug supplies currently on hand.

The CSPCRPCC must be notified if enrollments and randomizations are occurring more rapidly than expected and a shortage of drugs becomes a concern. In this situation the site par levels for study drugs will be increased. Individual sites are responsible for ordering extra study drugs to meet unexpectedly high enrollment and randomization rates. These orders can be emailed, phoned, or faxed depending upon the urgency of the request.

7.02 *Study Drug Shipment Documents*

Each shipment of study drugs will be accompanied by a:

1. Shipping Notice (form DTHP-4) listing each IV bag and bottle and its unique identification number. The receiving Pharmacist should verify that the shipment is complete, sign and date the Shipping Notice, and file with the pharmacy study regulatory documents.
2. Receiving, Dispensing and Disposition of Study Drugs (form DTHP-1) for each box of study drug. The CSPCRPCC will pre-print on the form the site number and the IV bag and bottle identification numbers. The form will be used to track the disposition of each study IV bag and bottle.

7.03 *Non-Study Drug Supplies*

A supply of participant study identification cards will be shipped at the initiation of each site. Additional participant identification cards are also available from the CSPCRPCC upon request.

8. **ENROLLMENT, RANDOMIZATION, AND ASSIGNMENT OF STUDY DRUGS**

Procedures for obtaining informed consent as well as participant enrollment and randomization are outlined in detail in the Study Operations Manual. Following the completion of the informed consent process, enrollment, randomization and study drug assignment will be accomplished by the SC at each study site via the PRESERVE IWRS.

8.01 *User ID and Password Assignment*

A user ID and password will be assigned to study personnel authorized to perform participant enrollment, randomization and study drug assignment procedures. This user ID and password are needed to access the PRESERVE IWRS. Study personnel must only use their unique user ID and password to access the PRESERVE IWRS.

8.02 *PRESERVE Interactive Web Response System (IWRS)*

The PRESERVE IWRS is a computerized system that will allow authorized study personnel to enroll and randomize participants, obtain study drug assignments, and record all study drugs that are dispensed. SCs must register on the PRESERVE IWRS to obtain their user ID and password prior to screening their first participant.

Assignments for multiple participants can be made during one logon. The PRESERVE IWRS can be accessed 24 hours/day, 7 days/week. Prior to accessing the PRESERVE IWRS to perform enrollment, randomization or study drug assignment procedures, the user must have the following information:

- User ID number and password
- Participant ID Number and (after randomization) Randomization Number to obtain study drug assignments
- The appropriate study form to record the study drug IV bag/bottle identification numbers assigned and dispensed.

8.03 *Initial Study Drug Assignment*

The SC will complete Form 01 Eligibility and Randomization and enter the information into the PRESERVE IWRS. If the participant meets all specified inclusion/exclusion criteria the system will show a message to the SC informing them that the participant may be randomized. The PRESERVE IWRS will assign a unique randomization number to the participant associated with one of the four treatment arms of the study. If the participant does not meet all specified inclusion/exclusion criteria, the PRESERVE IWRS will show a message to the SC informing them that the participant is ineligible and will therefore not be randomized (screen failure).

Once the randomization number has been assigned to an eligible participant the SC will complete Form 02a Initial Study Drug Assignment, again via PRESERVE IWRS. The SC will enter the participant ID number and randomization number and select "Request Study Medication".

The PRESERVE IWRS will then provide the SC with the unique bottle number for **NAC-578** and a unique IV bag number for **NaCl/NaHCO₃-578**. The SC should print out two (2) copies of the drug assignment certificate on a local printer. One copy should be given to the site pharmacist and the other should be retained by the SC. The site pharmacist and SC should record the study drug bottle number and IV bag number to be dispensed on the appropriate study form and on the study medication order or prescriptions.

8.04 *Additional/Replacement Study Drug Assignments*

In the event that additional study drugs are required following the initial assignment (i.e., additional study IV fluid bag(s) needed, participant loses their study drug bottle, etc.) the SC will complete Form 02b "Additional or Replacement Study Drug Assignment." After logging onto the PRESERVE IWRS, the SC will enter the participant ID number, randomization number and specify their request type (**NaCl/NaHCO₃-578** or **NAC-578**).

The PRESERVE IWRS will provide the SC with the bottle number for **NAC-578** and/or IV bag number for **NaCl/NaHCO₃-578**. The SC should print out two (2) copies of the drug assignment certificate on a local printer. One copy should be given to the site pharmacist and the other should be retained by the SC. The site pharmacist and SC should record the study drug bottle number and IV bag number to be dispensed on the appropriate study form and on the study medication order or prescriptions.

8.05 *Manual Randomization and Study Drug Assignments*

In rare situations, the PRESERVE IWRS may be unavailable at a time when a site needs to complete enrollment, randomization and/or study drug assignment procedures for a participant. Instructions for what to do in this situation are outlined in the Study Operations Manual in Appendix 5.

9. DISPENSING STUDY DRUGS

9.01 *Dispensing Overview*

Participants who meet protocol criteria will be randomized to one of four treatment combinations: **1.) NaCl + NAC, 2.) NaHCO₃ + NAC, 3.) NaCl + matching placebo for NAC, or 4.) NaHCO₃ + matching placebo for NAC.** Infusions of **NaCl/NaHCO₃-578** will be dispensed by the site study pharmacist. These infusions will not be protocolized, but the recommended duration and rate are listed in **Table 3**. One bottle of **NAC-578** containing 48 capsules of either 300 mg of NAC or matching placebo will dispensed by the site study pharmacist. **Note:** Each bottle has an additional eight (8) capsules to provide coverage for misplaced capsules during the 5 day course of therapy. While in the hospital, study personnel will administer **NAC-578** at a dose of 1200 mg (four capsules) 1 hour prior to the procedure and 1200 mg (four capsules) 1 hour after the procedure and then 1200 mg (four capsules) twice daily for four days. Upon discharge, participants will receive directions to take **NAC-578** at a dose of 1200 mg (four capsules) twice daily for a total of 5 days of therapy including days of therapy while hospitalized.

9.02 *Dispensing of Study Medication*

Upon enrollment of the participant into the study, the SC will request from the pharmacy a unique IV bag and bottle number of **NaCl/NaHCO₃-578** and **NAC-578** to be dispensed (see **Section 8**). Dispensing of the study drugs supplied by CSPCRPCC must be logged by the site research pharmacist on Form DTHP-1, "Receiving, Dispensing and Disposition of Study Drugs". Participants should be instructed to bring their **NAC-578** bottles with them to follow-up appointments or mail them to the SC. SCs will count remaining capsules to determine participant adherence and return used bottles to the site pharmacy.

9.03 *Receiving, Dispensing and Disposition of Study Drug Form (DTHP-1)*

As noted in **Section 7.02**, the CSPCRPCC will pre-print on the Receiving, Dispensing and Disposition of Study Drugs form (DTHP-1) the site number and the study drug ID Numbers. The form will be used to track the disposition of study drug supplied. The form will allow the pharmacist to account for the initial dispensing of an IV bag or bottle, the return of each (with count of the capsules remaining in bottles at return for **NAC-578**), and the final disposition of the IV bags/bottles (**NAC-578**-return to CSPCRPCC for destruction, **NaCl/NaHCO₃-578**-destroy locally). The original of this form must be retained as part of the site's Drug Accountability Records. See **Section 11** which includes information on disposition of returned or unused study drug.

9.04 *Study Drug Dose Adjustments*

Dosage adjustments for **NAC-578** will not be permitted. Adjustments to the duration and rate of **NaCl/NaHCO₃-578** will be at the discretion of the prescribing physician. **Table 3** lists the recommended rate and duration for **NaCl/NaHCO₃-578**.

9.05 *Prescriptions for Study Drugs*

All **NaCl/NaHCO₃-578** study drugs will be ordered using the standard inpatient medication order or prescription procedure for the facility (electronic or paper). Each time **NaCl/NaHCO₃-578** is to be dispensed, an order or prescription will be generated by the SI or other authorized prescriber.

- The medication orders for **NaCl/NaHCO₃-578** should include the following:
 - Participant's name, VA ID number, and hospital location/room number as appropriate
 - Study name: VA Cooperative Studies Program #578
 - Participant Identification Number
 - Drug name: **NaCl/NaHCO₃-578**
 - Bag Number [assigned by the CSPCRPCC study website, located on the overwrap of the IV bag of **NaCl/NaHCO₃-578**]
 - Dispense one IV bag
 - Directions:
 - [Will not be protocolized. See **Table 3** for recommended rate and duration]
 - Signature of SI or other authorized prescriber
 - Date medication order is generated/written

All **NAC-578** study drug will be ordered using the standard inpatient medication order or prescription procedure for the facility (electronic or paper). Each time

NAC-578 is to be dispensed, an order or prescription will be generated by the SI or other authorized prescriber. If the participant is discharged prior to completion of **NAC-578**, then the remaining supply of **NAC-578** will be dispensed to the participant with an outpatient prescription label.

- The medication order/prescription for **NAC-578** should include the following:
 - Participant's name, VA ID number, and hospital location/room number or current address as appropriate
 - Study name: VA Cooperative Studies Program #578
 - Participant Identification Number
 - Drug code name: **NAC-578**
 - Box Bottle [assigned by the PRESERVE IWRS]
 - Dispense one bottle (48 count)
 - Directions:
 - Take 4 capsules by mouth 1 hour prior to procedure and 4 capsules by mouth 1 hour after procedure, then 4 capsules by mouth twice daily for 4 days
 - Signature of SI or other authorized prescriber
 - Date medication order/prescription is generated/written

All medication orders and prescriptions for study drugs should contain any additional information required by site policy or current VA regulations.

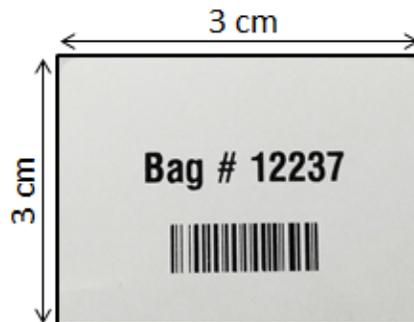
9.06 Pharmacy Dispensing Labels

The dispensing pharmacist must affix a dispensing label to each IV bag of **NaCl/NaHCO₃-578** and each bottle of **NAC-578** study drug. Please do not cover the investigational drug label applied to NaCl/NaHCO₃-578 and NAC-578 study drug supplied by the CSPCRPCC. In addition, the removable label contained on the overwrap of each IV bag of **NaCl/NaHCO₃-578** must be removed and placed on the IV bag prior to dispensing. The first lot of IV bags will contain a label on the overwrap that is not removable. For these labels, the IV bag number must be contained on the dispensing label. See pictures below of the two labels.

Figure 1. **NaCl/NaHCO₃-578** Label on First Lot



Figure 2. NaCl/NaHCO₃-578 Removable Label on Subsequent Lots



Each pharmacy dispensing label for **NaCl/NaCO₃-578** or **NAC-578** must contain the following information:

- Site's name, address and telephone number
- Prescription number and date prescription was written
- Participant's name and Participant Identification Number
- Drug code name (**NaCl/NaHCO₃-578**, **NAC-578**), or blinded drug name (NaCl or NaHCO₃; N-acetylcysteine or placebo), concentration and total dose (as if active drug)
- If **NaCl/NaHCO₃-578**, Bag Number [assigned by the PRESERVE IWRS, located on the overwrap of the IV bag of **NaCl/NaHCO₃-578**]
- Quantity and directions for use
- VA Cooperative Studies Program #578
- Prescriber's name
- Any other information required by site policy or current VA regulations
- If **NAC-578** "REMAINING DRUG MUST BE RETURNED TO THE STUDY COORDINATOR".

9.07 Replacement Study Drug Assignments

Additional IV bags of **NaCl/NaHCO₃-578** may be required during study IV fluid administration. As described in Section 8.04, the SC may log onto the PRESERVE IWRS to assign an additional IV bag of **NaCl/NaHCO₃-578**. Study personnel must log onto the study website for each assignment. Do not dispense any study drug without first getting a proper assignment. Dispensing of an additional IV bag should be recorded on the Receiving, Dispensing and Disposition of Study Drug form (DTHP-1). The form will be used to track the disposition of each IV bag of **NaCl/NaHCO₃-578**. The original of this form must be retained as part of the site's Drug Accountability Records. See **Section 11**,

which includes information on disposition of returned or unused study drug.

In the event a participant loses a bottle of **NAC-578** or is admitted to a hospital without his **NAC-578**, the participant can be assigned a replacement bottle to replace the one lost. As described in Section 8.04, the SC may log onto the PRESERVE IWRS to assign a replacement bottle of study drug. Study personnel must log onto the study website for each assignment. Do not dispense any study drug without first getting a proper assignment. Dispensing of a replacement bottle should be recorded on the Receiving, Dispensing and Disposition of Study Drug form (DTHP-1). The form will be used to track the disposition of each bottle of **NAC-578**. The original of this form must be retained as part of the site's Drug Accountability Records. See **Section 11**, which includes information on disposition of returned or unused study drug.

10. EMERGENCY BREAKING OF THE BLIND

10.01 24-hour emergency call service

The CSPCRPCC will not provide Emergency Code Envelopes to the Research Pharmacy for CSP #578. Emergency unblindings will be managed through the 24-hour emergency call service (505-248-3203). This number is also listed on the participant ID cards given to each patient participating in CSP #578. The system managed by the CSPCRPCC will electronically capture up-to-date study drug assignment information gathered from the PRESERVE IWRS.

10.02 Authorization to Break the Blind

Under unusual circumstances, chiefly related to participant safety, unblinding may be necessary. This is usually done after consultation with the Study Chair, Steven Weisbord MD, MSc or Study Co-Chair, Paul Palevsky MD. If Dr. Weisbord and Dr. Palevsky are unavailable, the CSPCRPCC Clinical Research Pharmacist (Todd Conner PharmD) or the Study Director (James Kaufman, MD) should be contacted. Current telephone numbers are listed in the study personnel directory on the CSP #578 Main SharePoint Site.

In life-threatening emergencies, the CSPCRPCC will be available through the 24-hour emergency call service. If the CSPCRPCC receives a request for unblinding information from anyone other than the SI or SC, the CSPCRPCC will refer the requester to the SI or SC or, in his or her absence, the CSPCRPCC will confer with the parties above. If unblinding is required in an emergency, the Site Investigator or Site Coordinator must contact the CSPCRPCC through the 24-hour emergency call service to obtain study drug assignment information. The CSPCRPCC will notify the Study Chair's Office and the MAVERIC CSPCC by telephone as soon as possible after an unblinding has occurred.

11. DISPOSITION OF UNUSED STUDY DRUG

11.01 Study Drugs Returned by Participants

At 5-8 days post-angiography, the SC will call the participant to determine if they took all of the prescribed **NAC-578** capsules. **Note:** Each bottle has an additional eight (8) capsules to provide coverage for misplaced capsules during the 5 day course of therapy. If the participant has any remaining **NAC-578** capsules, then the SC will send a mailer with a pre-printed shipping label to the participant. The SC should instruct each participant to place the unused study drug in the original bottle insert it in the mailer and place it in the mail. If the participant does not have any remaining **NAC-578** capsules, then the SC will instruct the participant to discard the empty bottle. If mailing is unavailable, the participant may also bring the **NAC-578** bottle into the SC.

11.02 Returning Study Drugs to Pharmacy Service

All unused and unopened **NaCl/NaHCO₃-578** IV bags and all returned **NAC-578** bottles are to be returned to Pharmacy Service by the SC. Pharmacy will record the IV bag and bottle numbers of returns on the Receiving, Dispensing and Disposition of Study Drugs form (DTHP 1).

11.03 Final Disposition of Study Drugs

At least annually (but not more frequently than semi-annually) throughout CSP #578, sites should return to CSPCRPCC all **NAC-578** bottles for participants who have completed the study and for whom all dispensed bottles have been accounted for on the Receiving, Dispensing and Disposition of Study Drugs form. All unused **NaCl/NaHCO₃-578** IV bags that have expired or cannot be re-assigned will be destroyed **onsite** after being instructed to do so by the CSPCRPCC. Used **NaCl/NaHCO₃-578** IV bags will be returned and disposed of according to local policies and procedures. The date of return or destruction will be noted on the Receiving, Dispensing and Disposition of Study Drugs form as the date of final disposition. At the time of disposition, the form must be signed by the responsible pharmacist and a **copy** of the **signed** Receiving, Dispensing and Disposition of Study Drugs form should be returned to CSPCRPC.

The original signed Receiving, Dispensing and Disposition of Study Drugs form should be retained as part of the site's Drug Accountability Records.

12. ANCILLARY SUPPLIES:

The following items will be provided by the CSPCRPCC directly to the study site at site initiation:

- Participant Identification (ID) wallet cards: The ID cards will be completed for each participant randomized into the study. The wallet-sized ID card should be given to the participant with instructions to present the card to any physician seen for medical treatment while participating in CSP #578.
- Pre-addressed mailers for returning of **NAC-578** from participant to study site.

Additional supplies will be sent upon request of the SC.

13. DISTRIBUTION AND USE OF CSPCRPCC STUDY DOCUMENTS AND ANCILLARY SUPPLIES

Instructions for the use and routing of forms, documents and items provided by the CSPCRPCC:

ITEM #	NAME	MAINTAINED OR USED BY	ORIGINAL	COPY 1	COPY 2
Form VA 10-9012	Study Drug Information Record	Pharmacy and Study Personnel	Route to Pharmacy	Essential Documents Binder	
Form DTHP-1	Receiving, Dispensing and Disposition of Study Drugs	Pharmacy	Pharmacy	Essential Documents Binder	Mail to CSPCRP CC upon request or at the end of the study
Form DTHP-2	Participant ID Card	Study Personnel	Give to participant	---	---
Form DTHP-3	Shipping Notice	Pharmacy	Pharmacy	Essential Documents Binder	
N/A	Pre-addressed Mailer	Study Personnel	N/A	N/A	N/A
Note: Forms are not illustrated in this document					

APPENDIX 13: Release of Information



DEPARTMENT OF VETERANS AFFAIRS

In Reply Refer To:

I hereby authorize the above named health care entity to release my protected health information as indicated below to the Department of Veterans Affairs. The purpose of the disclosure is to assist Veterans Health Administration (VHA) clinical staff with my continuity of treatment or to assist VHA investigators in conducting an approved VA research protocol for which I am a subject. Any radiology films or laboratory slides will be returned after review.

Information to be released: From _____ to _____ or as specified below.

- Discharge Summary _____
- History and physical exam _____
- Laboratory Information _____
- Radiology Reports _____
- Other: EKGs, cardiac imaging studies (e.g., echocardiogram, angiography)

I understand that this health information may include HIV-related information and/or information relating to diagnosis or treatment of psychiatric disabilities and/or substance abuse and that by placing my initials next to the condition, I am specifically authorizing the release of the information relating to:

- Substance Abuse (including alcohol/drug abuse _____ (initials)
- Mental Health _____ (initials)
- Psychotherapy Notes _____ (initials)
- HIV related information (including HIV related testing) _____ (initials)

- I certify that this request has been made freely, voluntarily and without coercion and that the information given above is accurate and complete to the best of my knowledge
- I understand that the health entity identified above may not condition treatment, payment, enrollment or eligibility for benefits upon my signing this authorization.
- I understand that I may revoke this authorization in writing to the health care entity at any time except to the extent that action has already been taken to comply with it.
- Without my express revocation, this consent will automatically expire after the requested information has been supplied to VA. I understand that I will receive a copy of this form after I sign it.
- I understand that redisclosure of my health records by those receiving the authorized information may be accomplished without my further written authorization and may no longer be protected by Federal laws or regulation.

(Signature of Patient or Authorized Representative)

(Date)

Print Patient Name or Authorized Representative)

(Status of Authorized Representative :
Guardian/POA)

NOTE: Please send a copy of this request along with the health information requested to the above VA address.

FL 10-212
OCT 2011

APPENDIX 14: Template for Research Enrollment Note

CSP#578 Research Enrollment Note Template

(to be entered into the participant's medical record):

<insert participant's name> was identified as potentially eligible for participation in CSP#578 ("Prevention of Serious Adverse Events Following Angiography") and the study was introduced to the patient by *<insert name>*. Based on medical record review and interview, patient meets study inclusion criteria and appears capable of understanding the consent form and consenting process. The CSP#578 protocol and informed consent form were reviewed with *<insert participant's name>* on *XX/XX/XXXX*. The possible risks, benefits, and alternative treatment options were discussed with *<insert participant's name>* by *<insert name of person obtaining consent>*. *<insert participant's name>* read the informed consent form and was given the opportunity to ask questions. *<insert participant's name>* agreed to participate in CSP#578, and signed the consent form and the HIPAA authorization form on *<insert date (dd/mm/yyyy) and time (24-hour clock) when patient signed consent form>*. The consent process was completed and signatures were obtained prior to the performance of any study related procedures. *<insert participant's name>* was given a copy of the signed informed consent and the signed HIPAA document as well as a copy of the VHA "Volunteering in Research" brochure.

* If the participant is screen failed, please update the progress note accordingly.

APPENDIX 15: pH Analyzer Use and Handling Procedures

pH Analyzer Instructions & Calibration Log

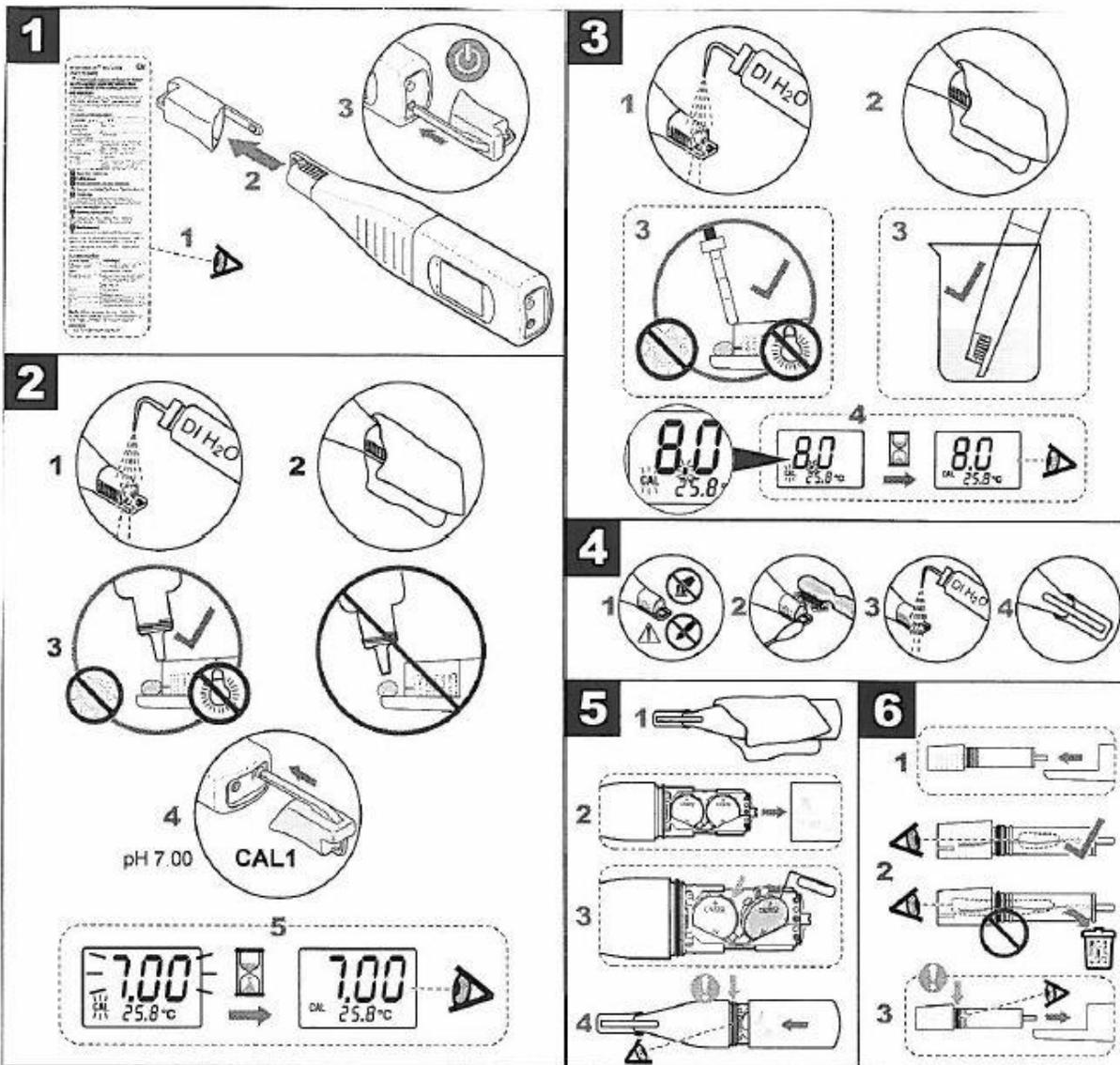
The Hach H130 miniLab is a portable waterproof pH meter with an ion-sensitive field transistor (ISFET) pH sensor for pH measurements.



Technical Information: Hach H130 miniLab

Calibration Points	1 Point
Auto Buffer recognition	pH 7.00
Temperature compensation	Automatic
pH range	Urine pH range: 4.5 to 8; meter range 2 to 12
Temperature range	5° to 40° C (40° to 105° F)
Power	Auto Shut Off, 3 V lithium batteries (2x) CR2032
Electrode	product #: 9316900
Buffer solution	product #: 2283536
Cleaning solution	product #: 2964349

STEP BY STEP INSTRUCTIONS



1. Turn the meter on

- Remove the cap from the sensor.
- Turn the meter on using the the cap by pressing the on/off button on the meter base (left button).

2. Calibration:

- To change the buffer set or the temperature units, push and hold the CAL 1 button and then push the power button. Push the CAL 1 button again to toggle between the parameters.
- Rinse the sensor with deionized water. Deionized water should be available in your clinical laboratory or dialysis unit.
- Dry the sensor.
- Place a drop of calibration fluid onto the sensor taking care that the droplet is nestled in the angle of the sensor. Do not expose to sunlight or bright lights.
- Push the CAL1 button on the base of the meter.
- Read: pH reading once image has stopped flashing =7.00

3. Measurement

- a) Rinse the sensor with deionized water.
- b) Dry the sensor.
- c) Either immerse the sensor into a container of urine OR place a drop of urine onto the angle of the sensor pad. Do not expose to sunlight or bright lights.
- d) Read after image stops flashing: Normal Urine pH value = 4.5-8.

4. Maintenance and storage

- a) For protein deposits, the manufacturer recommends an enzymatic cleaning solution.
- b) Clean the sensor with a soft brush (e.g., toothbrush) and/or cotton swab.
- c) Rinse with deionized water.
- d) Dry, and cover the sensor with the cap.

5. Battery Replacement

- a) *ALWAYS DRY THE METER FIRST*
- b) Slide off the meter cover to expose the 2 button batteries.
- c) Replace with fresh batteries (meter takes two (2) CR2032 lithium button cell 3-volt batteries).
- d) Replace the meter cover, ensuring the O ring is intact.

6. Reference electrode replacement

AVOID DIRECT CONTACT WITH THE pH SENSOR



a) Remove the electrode unit from the meter

b) Observe the liquid level.

c) When the liquid in the reference electrode is decreased, replace the electrode (9316900).

TROUBLESHOOTING

Error Code	Definition
Battery Icon	< 10 hours battery life
BAT	Replace the battery
0.00 or 14.00	Make sure that the probe is properly immersed in the sample
E06	Slope error
E07	Voltage error
E08	Calibration time out
E13	Temperature sensor error

NOTE: When an error occurs, clean the probe and calibrate again.

ORDERING SUPPLIES

- **Reference Electrode Replacements:**

If you need to replace the meter's electrode, you can order a 'Replaceable Reference Electrode for H130, H135 & H138 miniLab Models' (product #: 9316900) via the Hach website.

Link: <http://www.hach.com/replaceable-reference-electrode-for-h130-h135-h138-minilab-models/product?id=7664031406&callback=qs>

- **Calibration/Buffer Solution:**

A bottle of calibration or buffer solution is provided to each site initially by MAVERIC, but sites will need to reorder as needed. You can use the manufacturer's buffer solution 'Hach Buffer Solution, pH 7.00 (NIST), color-coded yellow, 15 mL' (product #: 2283536), or you can choose to order a compatible generic buffer solution from other sources. Please note that the buffer solution expires three months after opening.

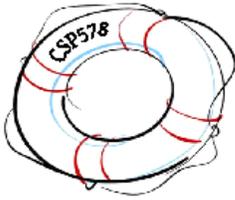
Link: <http://www.hach.com/buffer-solution-ph-7-00-nist-color-coded-yellow-15-ml/product?id=7640205086&callback=qs>

- **Cleaning Solution:**

Sites will need to order their own cleaning solution for the pH meter initially, and then reorder as needed. Please use only the manufacturer's cleaning solution 'Hach Probe Cleaning Solution for Samples that Contain Proteins, 500mL' (product #: 2964349).

Link: <http://www.hach.com/probe-cleaning-solution-for-samples-that-contain-proteins-500-ml/product?id=7640518303&callback=qs>

APPENDIX 16: Lab Supply Request Sheet



VA PRESERVE (CSP 578) Supplies Order Form

FAX TO: MAVERIC Biorepository

Fax: 857-364-6678

Phone: 857-364-5664

DATE: _____

Please send:

_____ Complete ExaktPak Shippers

_____ 4 ml CryoVials

_____ Specimen Labels

Specify: (i.e. labels for 50 patients starting with 101-0050) _____

-or-

Please send the following supplies: _____

Site # _____

Site Name: _____

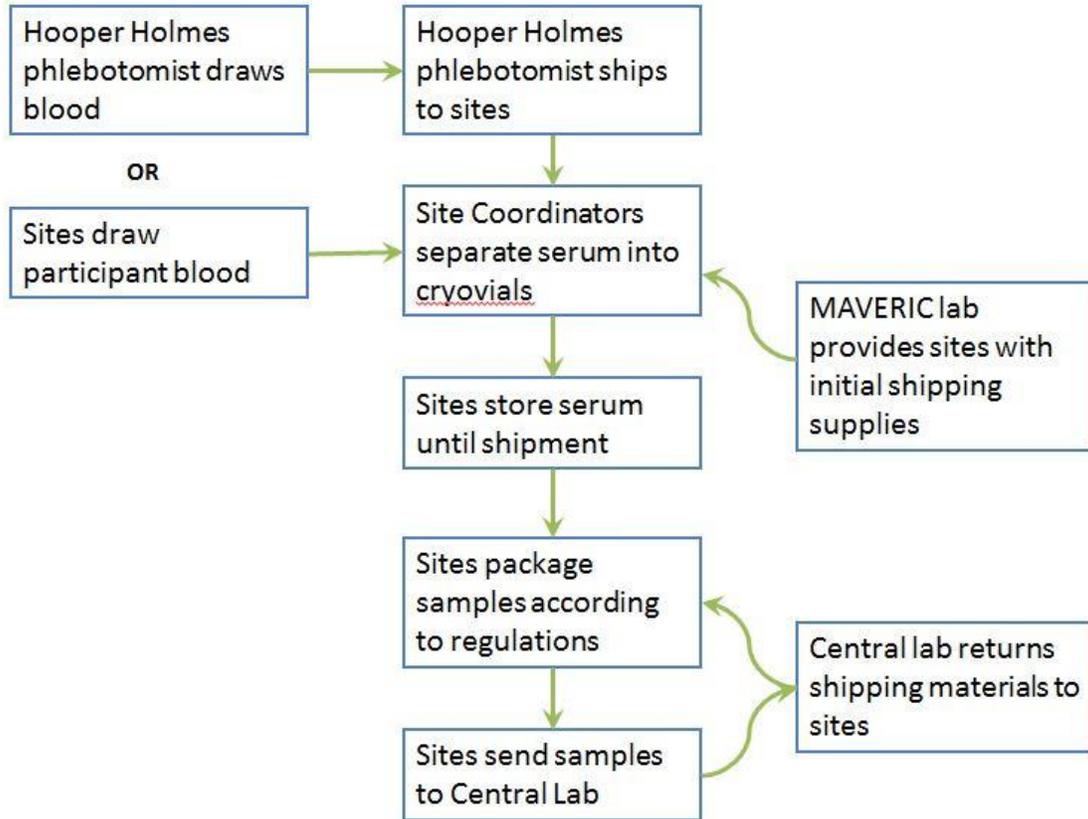
Study Coordinator: _____

Shipping Address:



Comments:

APPENDIX 17: Blood Collection Flowchart



APPENDIX 19: Study Reports Overview

REPORT TITLE	DESCRIPTION	FREQUENCY
Participant Calendar	Listing of all participants that are both consented and randomized into the trial. All visit dates are available for site coordinators to use for scheduling purposes.	Weekly
Enrollment	Table of expected vs. actual number of participants, with a graphical representation of enrollment by site.	Weekly
Site Performance	Overall performance of the site. Report includes 5 parts: (1) Forms Completion – Monitors overall form completion for Baseline & Follow-up forms (2) Missing Visits - listing of participants who have missed a visit or a visit that was not entered electronically. (3) Data Clarification Form (DCF) Management - listing of open DCFs that need to be addressed by the sites. (4) Average time from randomization to form completion (5) Missing Teleform ‘Contact Forms’	Weekly
Informed Consent Form Completion	Highlights any important missing elements on the Informed Consent Form.	Weekly
Safety Event Tracking	Listing of all Adverse and Serious Adverse Events in which the event outcome is on-going (i.e. requires follow-up)	Weekly
Missing 90-Day Blood Draw	List of any participants missing a 90-Day blood draw and if the missed blood draw requires a Protocol Deviation (Form 23)	Weekly

APPENDIX 20: Pre-Screening and Participant Consent Logs

PRE-SCREENING

Server Read-Only This workbook was opened from a server in read-only mode. [Edit Workbook](#)

C6

Instructions for CSP#578 PRE-SCREENING LOG

This log is a tool to help you identify potentially eligible patients as you review medical charts and records. A patient is eligible if:

- they are undergoing coronary or non-coronary angiography with iodinated contrast
- the screening eGFR is 45-59.9 ml/min with diabetes or the screening eGFR is 15-44.9 with or without diabetes
- **AND** the answers to all of the **GREEN** questions below are 'No'

DIRECTIONS: Save the log to your secure research drive and include your site ID number at the top of the form. Fill out a row for each patient undergoing an angiogram. If a patient is potentially eligible, but does not enroll it is necessary to provide the reason the person did not enroll.

EVERY FRIDAY: Remove the first column (column A) that contains patient initials and last 4 digits of their SSN, and send the log to Lee.Mandich@va.gov.
~DO NOT EMAIL THIS FORM UNTIL YOU HAVE REMOVED PATIENT INITIALS AND LAST 4 SSN DIGITS~

* Non cardiac angiography includes angiograms in which iodinated contrast is injected into an artery other than the coronary arteries. Examples include: pulmonary angiogram, cerebral and peripheral extremity angiogram (arm/leg), and aortoangiogram. Computed Tomography (CT) scans and CT angiography do **NOT** meet eligibility criteria.
 † Dialysis includes intermittent hemodialysis, peritoneal dialysis, continuous renal replacement therapy, or sustained low efficiency dialysis.

Site ID #	PRE-SCREENING LOG FOR CSP#578											
	Patient Initials & Last 4 Digits of SSN	Date Pre-Screened	Undergoing coronary or non-coronary angiogram?*	Diabetic?	eGFR Value	Under 18 years of age?	On dialysis? †	On IV inotropes, vasopressors, or vasodilators?	Known allergy to iodinated contrast?	Potentially Eligible?	Did Patient Enroll?	Why not enroll (for potentially eligible)
6												
10												
11												
12												
13												
14												
15												
16												
17												
18												
19												
20												

Hyperlink to Location on SharePoint:

<https://vaww.ord.research.va.gov/CSP/Boston/csp578/case%20report%20forms/Forms/AllItems.aspx>

PARTICIPANT CONSENT TRACKING LOG

Once a participant is consented, Study Coordinators will fill out the Participant Tracking Log (Form 00 in the Source Document Worksheets library on the CSP578 Study Sharepoint site) according to the following directions:

1. Save a copy of the Participant Tracking Log on your local drive where only CSP578 research staff can access it
2. In the upper left corner of the spreadsheet, enter your site ID #

The screenshot shows a Microsoft Excel spreadsheet titled "00_Participant Consent Log [Read-Only] - Microsoft Excel". The spreadsheet is in read-only mode. The title bar indicates "Server Read-Only This workbook was opened from a server in read-only mode." The spreadsheet has a blue header row with the title "Participant Tracking Log". The columns are labeled as follows: Patient Initials, Date Consented, Date Randomized, Randomization #, Patient ID, Angiography Date, 96 hour post Angio, 5 Days post angio Range, Appt Date, Medication Returned, 35 Days post angio Range, Appt Date, 90 Days post angio Range, Appt Date, Date Terminated, and Reason not Randomized or Terminated. The "Site ID #" cell is highlighted with a red box. The spreadsheet contains data for Patient IDs 1001 through 1028.

Patient Initials	Date Consented	Date Randomized	Randomization #	Patient ID	Angiography Date	96 hour post Angio	5 Days post angio Range	Appt Date	Medication Returned	35 Days post angio Range	Appt Date	90 Days post angio Range	Appt Date	Date Terminated	Reason not Randomized or Terminated
				0 - 1001											
				0 - 1002											
				0 - 1003											
				0 - 1004											
				0 - 1005											
				0 - 1006											
				0 - 1007											
				0 - 1008											
				0 - 1009											
				0 - 1010											
				0 - 1011											
				0 - 1012											
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				0 - 1019											
				0 - 1020											
				0 - 1021											
				0 - 1022											
				0 - 1023											
				0 - 1024											
				0 - 1025											
				0 - 1026											
				0 - 1027											
				0 - 1028											

3. Enter the participant initials, date consented, date randomized, and randomization number
4. In the column titled "Angiography Date", enter the procedure date scheduled for the participant
 - a. By doing this, the spreadsheet will automatically fill in the remaining follow-up dates as required by the protocol. Use this spreadsheet to keep track of dates.

Participant Tracking Log

Patient Initials	Date Consented	Date Randomized	Randomization #	Patient ID	Angiography Date	96 hour post Angio	5 Days post angio Range	Appt Date	Medication Returned	35 Days post angio Range	Appt Date	90 Days post angio Range	Appt Date	Date Terminated	Reason not Randomized or Terminated
				0 - 1001	9/22/2014	9/26/2014	27-Sep-14 30-Sep-14			27-Oct-14 10-Nov-14		21-Dec-14 4-Jan-15			
				0 - 1002											
				0 - 1003											
				0 - 1004											
				0 - 1005											
				0 - 1006											
				0 - 1007											
				0 - 1008											
				0 - 1009											
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				0 - 1021											
				0 - 1022											
				0 - 1024											
				0 - 1025											
				0 - 1026											
				0 - 1027											
				0 - 1028											

5. After each follow-up is completed, enter in the actual appointment dates in the appropriate columns.

Participant Tracking Log

Patient Initials	Date Consented	Date Randomized	Randomization #	Patient ID	Angiography Date	96 hour post Angio	5 Days post angio Range	Appt Date	Medication Returned	35 Days post angio Range	Appt Date	90 Days post angio Range	Appt Date	Date Terminated	Reason not Randomized or Terminated
				0 - 1001	9/22/2014	9/26/2014	27-Sep-14 30-Sep-14			27-Oct-14 10-Nov-14		21-Dec-14 4-Jan-15			
				0 - 1002											
				0 - 1003											
				0 - 1004											
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				0 - 1024											
				0 - 1025											
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				0 - 1027											
				0 - 1028											

6. When the participant follow-up is complete, enter the termination date of the participant

7. If the participant was not randomized or terminated, indicate the reason by selecting one of the 6 drop-down options in the final column.

The screenshot shows a Microsoft Excel spreadsheet titled "00_Participant Consent Log [Read-Only] - Microsoft Excel". The spreadsheet is in "Server Read-Only" mode. The main content is a "Participant Tracking Log" table with the following columns:

Site ID #	Patient Initials	Date Consented	Date Randomized	Randomization #	Patient ID	Angiography Date	96 hour post Angio	5 Days post angio Range	Appt Date	Medication Returned	35 Days post angio Range	Appt Date	90 Days post angio Range	Appt Date	Date Terminated	Reason not Randomized or Terminated
1					0 - 1001	9/22/2014	9/26/2014	27-Sep-14	30-Sep-14		27-Oct-14	10-Nov-14	21-Dec-14	4-Jan-15		
2					0 - 1002											
3					0 - 1003											
4					0 - 1004											
5					0 - 1005											
6					0 - 1006											
7					0 - 1007											
8					0 - 1008											
9					0 - 1009											
10					0 - 1010											
11					0 - 1011											
12					0 - 1012											
13					0 - 1013											
14					0 - 1014											
15					0 - 1015											
16					0 - 1016											
17					0 - 1017											
18					0 - 1018											
19					0 - 1019											
20					0 - 1020											
21					0 - 1021											
22					0 - 1022											
23					0 - 1023											
24					0 - 1024											
25					0 - 1025											
26					0 - 1026											
27					0 - 1027											
28					0 - 1028											

The dropdown menu for the "Reason not Randomized or Terminated" column is open, showing the following options:

- eGFR ineligible
- Procedure cancelled
- Withdrawn
- Pregnant
- Death
- Other

APPENDIX 21: Participant Medication Diary

CSP#578 Participant Study Medication Diary

Use the table below to help you remember when you took your CSP#578 study drug capsules. In this study you are asked to take 4 capsules in the morning and 4 capsules in the evening every day for 4 days following your angiography procedure.

It is important that you take the correct number of study capsules each day as directed. This means if you are going to be away from home, you should take your study medication with you. If you have to return to the hospital, you should take your study medication with you.

Keep this diary handy. About 5 days after your angiography procedure, you will be called by a member of the study team who will ask about how you are feeling and the study drug capsules you have been taking. Having this diary filled out will help you answer the questions you'll be asked.

Day	Date	Number of study capsules taken	
		AM	PM
1			
2			
3			
4			

CSP#578 PRESERVE
Subject Study Medication Diary v1.0
4/13/2012

APPENDIX 23: Source Document Worksheets by Study Event

- 1. Eligibility & Randomization**
 - a. Form 01: Eligibility and Randomization (IWRS)
- 2. Study Drug Assignment**
 - a. Form 02a: Initial Study Drug Assignment (IWRS)
 - b. Form 02b: Additional or Replacement Study Drug Assignment (IWRS)
- 3. Baseline (Angiography Procedure)**
 - a. Form 03: Participant Contact Information (fax Form to MAVERIC)
 - b. Form 04: Military History
 - c. Form 05: Blood Pressure and Weight
 - d. Form 06: Pre-Procedure Laboratory Values
 - e. Form 07: Demographics
 - f. Form 08: Pre-Procedure Non-Study Medications
 - g. Form 09: Medical History
 - h. Form 10: Pre-Procedure Non-Study IV Fluid
 - i. Form 24: Study Blood Specimens
- 4. 0- 12 Hours Post Procedure**
 - a. Form 11: Procedure Related Data
 - b. Form 12: Study IV Fluid Administration
 - c. Form 13: Post-Procedure Urine pH
 - d. Form 14: 12 Hours Post-Procedure
- 5. 4 days Post Procedure**
 - a. Form 15: Hospitalizations within 4 days Post-Procedure
 - b. Form 24: Study Blood Specimens
- 6. Day 5 Post Procedure**
 - a. Form 16: 5 Days Post Procedure
- 7. Day 35 Post Procedure**
 - a. Form 17: 35 Days Post Procedure
- 8. Day 90 Post Procedure**
 - a. Form 18: 90 Days Post Procedure
 - b. Form 24: Study Blood Specimens
- 9. Safety**
 - a. Form 19: Adverse Event (AE)
 - b. Form 20: EndPoint_SAE Form
 - c. Form 21: Endpoint_SAE Follow-up
- 10. Confirmatory Blood Draw**
 - a. Form 24: Study Blood Specimens
- 11. Common**
 - a. Form 22: Early Participant Withdrawal
 - b. Form 23: Protocol Deviation

APPENDIX 24: Telephone Scripts

APPENDIX 22:

Telephone Scripts

CSP#578 PRESERVE

Phone Script – First Contact

Depending on circumstances, study personnel may make initial contact with a patient over the phone or in person at the time of the patient's angiogram procedure. The phone script below would be used by study personnel if contacting the patient by phone after the study has been introduced to the patient by someone involved in their care and they have agreed to be contacted.

Hello Mr(s) _____. My name is _____. I am a research coordinator at the <insert name of VA Medical Center>. I understand that you will be having an angiogram at our facility and that your provider asked you if it would be okay if we spoke with you about a VA research study currently going on at our facility involving patients who are having an angiogram procedure. Is that correct?

If No → The conversation will end and the coordinator will speak with the treating provider

*If Yes → Can I tell you a little more about this study now? I don't think this should take more than 5-10 minutes. <If no, the coordinator will skip to *> The name of this research study is the PRESERVE study and we're looking for patients who are having an angiogram procedure to participate. When you have an angiogram you are given a dye through a tube placed in one of your blood vessels to see whether that blood vessel is clogged. Some patients who have an angiogram can have complications such as kidney damage from the dye used, especially if their kidneys weren't working well before the procedure. The purpose of this research study is to find out how to best prevent complications caused by the dye used during angiography. Doctors often give IV fluids or a medicine called N-acetylcysteine or NAC to patients who need an angiogram to help prevent complications caused by the dye. This study is trying to determine whether one IV fluid is better than another for preventing complications caused by the dye and also whether NAC is helpful in preventing complications.*

** Would it be alright if we see you when you arrive at the hospital for your angiogram to talk some more about this study and to see if you would be interested in participating?*

If No → The coordinator will thank the patient and the conversation will end.

If Yes → Would you like me to mail you additional information about the study and a copy of the study's informed consent form to look over before we see you when you arrive for your angiogram? <This will depend on how much time there is prior to the patient's angiogram>

For patients who agree to have us speak with them at the time they arrive for their angiogram, we will complete the informed consent process and conduct necessary screening procedures in person at that time.

CSP#578 PRESERVE
Phone Script – First Contact v1.0

CSP#578 PRESERVE
Phone Script – 5 days post procedure

The phone script below would be used by study personnel when contacting participants by phone 5 days following their angiography procedure. If the participant was not discharged from the hospital following their angiography or was readmitted to the VA where their angiography had been done, these questions will be asked in-person.

Hello Mr(s) xxx. My name is _____ and I am the study coordinator for the VA PRESERVE study in which you're participating. I would like to ask you a few follow up questions. I don't think it should take more than 10-15 minutes. Is now a good time?

<If the participant was to return to the VA where his/her angiography took place for the 96 hour blood draw>

Were you able to return to <insert name of VA Medical Center> for your blood draw? Did you have any questions about travel reimbursement?

<If the participant was to utilize the mobile specimen collection service for the 96 hour blood draw>

How did your blood draw visit at home go?

Now I'd like to ask you about the study drug capsules you were taking. It may be helpful to look at the study medication diary you were given to help answer these questions. Would you like to get it?

Let's review how many study drug capsules you took on each day since you had your angiography procedure.

Were you able to take all of your study drug capsules as directed?

If No → *Why didn't you take all of your study drug capsules as directed?*

I'd like to take this time to remind you to return your study drug bottle with any capsules you didn't take to our study's pharmacy coordinating center in the mailer which you were given when you left the hospital after your angiography.

As you know, when you were enrolled in this study, you were given either N-acetylcysteine or placebo capsules to take for 5 days. Can you tell me whether you think you were given N-acetylcysteine or placebo capsules?

You were also given either intravenous saline or intravenous sodium bicarbonate at the time of your angiogram. Can you tell me whether you think you were given saline or sodium bicarbonate?

Did you experience any change in or worsening of your medical condition that required you to seek medical care while taking the study capsules?

CSP#578 PRESERVE
Phone Script – 5 Days Post Procedure v1.0

If Yes → Can you tell me what happened? Where did you receive care? <If the participant received care outside of the VA, the coordinator will ask for their permission to obtain their records from the hospital and send them VA Form 10-212>

Since the time of your angiogram at the start of the study, have you been admitted to the hospital?

If Yes → Can you tell me what happened? Where did you receive care? <If the participant received care outside of the VA, the coordinator will ask for their permission to obtain their records from the hospital and send them VA Form 10-212>

Since the time of your angiogram at the start of the study, have you needed to receive dialysis?

If Yes → Can you tell me what happened? Where did you receive care? <If the participant received care outside of the VA, the coordinator will ask for their permission to obtain their records from the hospital and send them VA Form 10-212>

CSP#578 PRESERVE

Phone Script – 35 days post procedure

The phone script below would be used by study personnel when contacting participants by phone 35 days following their angiography procedure. If at this time the participant is hospitalized at the VA where their angiography had been done, these questions will be asked in-person.

Hello Mr(s) xxx. My name is _____ and I am the study coordinator for the VA PRESERVE study in which you're participating. I would like to ask you a few follow up questions. I don't think it should take more than 10-15 minutes. Is now a good time?

Have you experienced any change in or worsening of your medical condition over the past month that required you to seek medical attention?

If Yes → Can you tell me what happened? Where did you receive care? <If the participant received care outside of the VA, the coordinator will ask for their permission to obtain their records from the hospital and send them VA Form 10-212>

Have you been admitted to the hospital in the past month?

If Yes → Can you tell me what happened? Where did you receive care? <If the participant received care outside of the VA, the coordinator will ask for their permission to obtain their records from the hospital and send them VA Form 10-212>

Have you received dialysis in the past month?

If Yes → Can you tell me what happened? Where did you receive care? <If the participant received care outside of the VA, the coordinator will ask for their permission to obtain their records from the hospital and send them VA Form 10-212>

Were you able to return your study drug bottle with any capsules you didn't take to our study's pharmacy coordinating center?

Yes _____ No _____

If No → Please use the mailer which you were given _____ when you left the hospital after your angiography to return your study drug bottle with any capsules you didn't take to our study's pharmacy coordinating center.

CSP#578 PRESERVE
Phone Script – 35 Days Post Procedure v2.0

**CSP#578 PRESERVE
Phone Script – 90 days post procedure**

The phone script below would be used by study personnel when contacting participants by phone 90 days following their angiography procedure. If at this time the participant is hospitalized at the VA where their angiography had been done, these questions will be asked in-person.

Hello Mr(s) xxx. My name is _____ and I am the study coordinator for the VA PRESERVE study in which you're participating. I would like to ask you a few follow up questions. I don't think it should take more than 10-15 minutes. Is now a good time?

<If the participant was to return to the VA where his/her angiography took place for the 90 day blood draw>

Were you able to return to <insert name of VA Medical Center> for your blood draw? Did you have any questions about travel reimbursement?

<If the participant was to utilize the mobile specimen collection service for the 90 day blood draw>

How did your blood draw visit at home go?

Since the last time you were contacted in <insert month>, have you been admitted to the hospital?

If Yes → Can you tell me what happened? Where did you receive care? <If the participant received care outside of the VA, the coordinator will ask for their permission to obtain their records from the hospital and send them VA Form 10-212>

Since the last time you were contacted in <insert month>, have you received dialysis?

If Yes → Can you tell me what happened? Where did you receive care? <If the participant received care outside of the VA, the coordinator will ask for their permission to obtain their records from the hospital and send them VA Form 10-212>

As we talked about at the start of the study when we reviewed the informed consent form, we may need to contact you again to schedule another blood draw in the next few weeks. It will depend on the test results related to your kidney function we get back from the blood samples you've already provided. If we do need to schedule another blood draw we will call you. If we do not need to schedule another blood draw, we will not call you and your active participation in this study will be over. In about nine months we will review your medical records to track how your health has been, but we will not need to contact you directly again.

Do you have any questions?

CSP#578 PRESERVE
Phone Script – 90 Days Post Procedure v1.0

CSP#578 PRESERVE

Phone Script – Confirmatory blood draw

The phone script below would be used by study personnel when contacting participants by phone to schedule a confirmatory blood draw. Confirmatory blood specimens are required for participants with a => 50% increase in Scr between their baseline and 90 day measurements.

Hello Mr(s) xxx. My name is _____ and I am the study coordinator for the VA PRESERVE study in which you're participating. I would like to ask you a few follow up questions related to the study. I don't think it should take more than 10-15 minutes. Is now a good time?

We would like to ask you to return to <insert name of VA Medical Center> to provide another blood sample. We would like to test this blood to measure how well your kidneys are working. If you are unable to return to our facility we can schedule a time for the blood sample to be taken at your residence. Which option would you prefer?

If the results of this test show that your kidneys are not functioning properly, we will notify your provider of the results and he/she will be responsible for determining your care. After your blood draw is completed, your active participation in this study will be over. A year after your angiography procedure we will review your medical records to track how your health has been since the procedure, but we will not need to contact you directly again.

CSP#578 PRESERVE
Phone Script – Confirmatory Blood Draw v1.0

APPENDIX 25: Study IV Fluid Administration Table

STUDY IV FLUID ADMINISTRATION PRIOR TO THE ANGIOGRAM		
Total Volume	<i>Minimum</i>	3 ml/kg [‡]
	<i>Maximum</i>	12 ml/kg [‡]
Duration of Infusion	<i>Minimum</i>	1 hour [‡]
	<i>Maximum</i>	12 hours [‡]
Recommended infusion rate*	<i>Outpatient</i>	3 ml/kg per hour for 1 hour
	<i>Inpatient</i>	1 ml/kg per hour for 6-12 hours
STUDY IV FLUID ADMINISTRATION DURING THE ANGIOGRAM		
<i>Starting when the participant enters the procedure room and ending when they leave</i>		
Recommended infusion rate*	<i>Minimum</i>	1 ml/kg/hour [‡]
	<i>Maximum</i>	1.5 ml/kg/hour [‡]
Note: If a bolus is needed > 250 ml, do not use study IVF's		
STUDY IV FLUID ADMINISTRATION AFTER THE ANGIOGRAM		
<i>Starting when the participant leaves the procedure room</i>		
Total Volume	<i>Minimum</i>	6 ml/kg [‡]
	<i>Maximum</i>	12 ml/kg [‡]
Duration of Infusion	<i>Minimum</i>	2 hours [‡]
	<i>Maximum</i>	12 hours [‡]
Recommended infusion rate*	<i>Outpatient</i>	1.5 ml/kg per hour for 4 hours
	<i>Inpatient</i>	1 ml/kg per hour for 6-12 hours

APPENDIX 26: Participant Withdrawal Guidelines

Participant Termination Prior to Expected End of Study Participation

Once consented and enrolled, a participant should be followed and all study procedures should be performed according to the approved protocol, unless any one of the following occurs:

1. The participant does not have a creatinine measurement within 30 days of procedure and a creatinine is drawn to determine eligibility, but is outside the acceptable range.
 - a. Complete early withdrawal form
2. Participant revokes consent.
 - a. Complete early withdrawal form and all required study procedures up to the point the participant revokes consent.
3. Study medications not administered **AND** procedure not performed **AND** will not be rescheduled.
 - a. Complete early withdrawal form.
4. Death of participant that occurs anytime between randomization and completion of 90 day blood draw or the confirmatory blood draw.
 - a. Complete Endpoint/SAE Form to record the cause of death.

Examples When and When Not to Withdraw a Participant from the Study

Participant enrolled; Study IV Fluids and NAC-578 not given; Procedure is cancelled, but rescheduled ≤ 30 days from date of original consent.

1. Early withdrawal? **No** (Unless repeat screening creatinine outside acceptable range)
2. Informed Consent Form
 - a. Original Consent Form can be used.
3. Screening eGFR
 - a. Original screening eGFR is valid if ≤ 30 days from date of procedure, but the eGFR most proximate to rescheduled procedure should be used to determine eligibility.
 - b. If repeat screening creatinine outside of acceptable range, then:
 - i. participant should **not** receive study drug.
 - ii. complete early withdrawal form.
4. Study medications
 - a. Overwrap of the Study IV Fluids has not been opened
 - i. The originally assigned study IV fluids can be set aside in the pharmacy to be dispensed prior to rescheduled procedure.
 - b. Overwrap of the Study IV Fluids has been open:
 - i. **Less than 24 hours**- The originally assigned Study IV Fluids can be dispensed prior to rescheduled procedure.
 - ii. **Greater than 24 hours**- The originally assigned Study IV Fluids must be discarded and a new bag must be assigned and dispensed prior to rescheduled procedure.

- c. Originally assigned NAC-578 can be set aside opened or unopened to be dispensed and administered prior to rescheduled procedure **OR** a new unopened bottle of NAC-578 can be assigned.
5. Blood sample collection
- a. Collect a new baseline blood sample and send to Central Lab on the day of the rescheduled procedure and prior to administration of study fluids.
 - b. Collect day 4 and day 90 blood samples.

Participant enrolled; Study IV Fluids and NAC-578 not given; Procedure is cancelled, but rescheduled > 30 days from date of original consent **OR** date of rescheduled procedure is unknown.

1. Early withdrawal? **Yes**
 - a. Send email to MAVERIC prior to rescheduled procedure to rescind withdrawal to allow participant to become active in the study again.
2. Informed Consent
 - a. A new Consent Form must be signed prior to commencing study procedures.
3. Screening eGFR
 - a. Original screening eGFR is valid if ≤ 30 days from date of procedure, but the eGFR most proximate to rescheduled procedure should be used to determine eligibility.
 - b. If repeat screening creatinine outside of acceptable range, then:
 - i. participant should **not** receive study drug.
 - ii. complete early withdrawal form.
4. Study medications
 - a. Overwrap of the Study IV Fluids has not been opened
 - i. The originally assigned study IV fluids can be set aside in the pharmacy to be dispensed prior to rescheduled procedure.
 - b. Overwrap of the Study IV Fluids has been open:
 - i. **Less than 24 hours**- The originally assigned Study IV Fluids can be dispensed prior to rescheduled procedure.
 - ii. **Greater than 24 hours**- The originally assigned Study IV Fluids must be discarded and a new bag must be assigned and dispensed prior to rescheduled procedure.
 - c. Originally assigned NAC-578 can be set aside opened or unopened to be dispensed and administered prior to rescheduled procedure **OR** a new unopened bottle of NAC-578 can be assigned.
5. Blood sample collection
 - a. Collect a new baseline blood sample and send to Central Lab on the day of the rescheduled procedure and prior to administration of study fluids.
 - b. Collect day 4 and day 90 blood samples.

Participant enrolled; Study IV Fluids not given due to clinical status of participant; Procedure completed.

1. Early withdrawal? **No**
2. Study medications
 - a. Continue to give NAC-578.
3. Blood sample collection
 - a. Collect day 4 and day 90 blood samples.

Participant enrolled; Study IV Fluids and NAC-578 given pre-procedure; Procedure cancelled and not rescheduled.

1. Early withdrawal? **No**
2. Study medications
 - a. Stop administration of both Study IV Fluids and NAC-578.
3. Blood sample collection
 - a. Collect day 90 blood sample.

APPENDIX 27: Form Completion Guide: Common Scenarios

Common Scenarios						
Forms	Consented but not Randomized	Randomized, did not initiate study meds and did not have angiogram	Randomized, initiated Study Meds, but did not have angiogram	Randomized, did not have study meds but did undergo angiogram	Randomized, initiated Study Meds, had angiogram, but terminated before 90 days	Randomized, initiated Study Meds, had angiogram, and completed 90 days
IWRS FORMS						
Form 01. Eligibility and Randomization	X	X	X	X	X	X
Form 02a. Initial Study Drug Assignment		X	X	X	X	X
Form 02b. Additional or Replacement Study Drug Assignment			if needed	if needed	if needed	if needed
DATALABS						
Common: Screened	X	X	X	X	X	X
Common: Enrolled		X	X	X	X	X
Form 03. Participant Contact Information			X	X	X	X
Form 04. Military History			X	X	X	X
Form 05. Blood Pressure and Weight			X	X	X	X
Form 06. Pre Procedure			X	X	X	X

Laboratory Values						
Form 07. Demographics			X	X	X	X
Form 08. Pre Procedure Non-study Medications			X	X	X	X
Form 09. Medical History			X	X	X	X
Form 10. Pre Procedure Non-Study IV Fluid			X	X	X	X
Form 11. Procedure Related Data				X	X	X
Form 12. Study IV Fluid Administration			X	X	X	X
Form 13. Post Procedure Urine pH Results				X	X	X
Form 14. 12 Hours Post Procedure			X	X	X	X
Form 24. Study Blood Specimens (BASELINE)			X	X	X	X
Form 15. Hospitalizations Within 96 Hours Post Procedure			X	X	X (depends when terminated)	X
Form 24. Study Blood Specimens (Day 4)				X	X (depends when terminated)	X
Form 16. 5 Days Post Procedure			X	X	X (depends when terminated)	X
Form 17. 35 Days Post Procedure			X	X	X (depends when terminated)	X
Form 18. 90 Days Post Procedure			X	X	X (depends when terminated)	X
Form 24. Study Blood Specimens			X	X	X	X

(Day 90)						
Form 24. Study Blood Specimens (Confirmatory)			If needed	If needed	If needed	If needed
Form 19. Adverse Event	if needed					
Form 20 Endpoint_SAE/Form 21 Endpoint_SAE Follow-up	if needed					
Common: Form 22. Early Participant Withdrawal		X	if needed	if needed	X	
Common: Form 23. Protocol Deviation			X	X	if needed	if needed