

LOUIS STOKES CLEVELAND VA MEDICAL CENTER
Medical Research Service
SOP Cover Page

Effective Date: August 1, 2007

SOP Title: Collection and Storage of Regulatory Documentation

SOP Number: HSP-006

SOP Version: .01

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Signature _____ Date 8-1-07

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Signature _____ Date 8/2/2007

LOUIS STOKES CLEVELAND VA MEDICAL CENTER
Medical Research Service
Standard Operating Policy and Procedure (SOP)

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1. PURPOSE. To describe the methods for the collection and storage of complete and accurate regulatory documentation for research studies approved by the Louis Stokes Cleveland Department of Veteran Affairs Medical Center (LSCDVAMC Research & Development (R&D) Committee and Institutional Review Board (IRB). The documentation requirements as detailed in this SOP are designed to meet the Office of Human Research Protection (OHRP), Food and Drug Administration (FDA), federal regulations, Good Clinical Practices (GCP) and VA policies and procedures for documentation required for research studies performed at the LSCDVAMC.

2. RESPONSIBILITIES

- a. The Principal Investigator (PI) is responsible for maintaining the required documentation for his/her research studies at the site.

- b. The PI and/or research coordinator is responsible for:
 - (1) Obtaining and storing all required documentation for each study,
 - (2) Maintaining records of study administrative activities and data from each study subject
 - (3) Collecting and filing study documents in the study regulatory file and/or notebook.

- c. The PI may delegate certain study-related responsibilities to the study coordinator or study team personnel. This delegation of duties and their training must be clearly documented.

3. PROCEDURES

a. **Study Regulatory File:** Copies of all documents related to the study will be kept in the study regulatory file in chronological order. These documents must be maintained in a safe, secure place during the study and for the required retention period.

- (1) All studies require the following items to be kept in the study regulatory file:

- (a) IRB & R&D initial approval letters with VA Form 10-1223
- (b) IRB submissions, approvals, and correspondence.
- (c) All protocol versions and all amendments
- (d) Consent forms (blank copy of every IRB approved, and date stamped, consent form)
- (e) IRB approved recruitment materials
- (f) Log of all consented subjects (sample attached)
- (g) Serious adverse events/safety reports (sample SAE log attached)
- (h) Unanticipated problem reports
- (h) Investigator agreements
- (i) Curriculum Vitae for all study personnel
- (j) Site signature log (sample attached)
- (k) Education and training records for all research personnel
- (l) Correspondence and notes to file (sample attached)
- (m) Originals of all case report forms (CRF's) and any other data forms
- (n) Copies of any abstracts or manuscripts regarding the results of the study
- (o) DSMB letters and reports

(2) FDA regulated studies require these additional documents to be kept in the study regulatory file:

- (a) Investigator Brochures and/or package inserts
- (b) IRB membership list or Federal Wide Assurance (FWA) documentation
- (c) Signed Form FDA 1572 and/or FDA Form 1571
- (d) Laboratory certification and normal values
- (e) Test article accountability records (please note that if the test article is an investigational drug, this record will be kept in pharmacy until the completion of the study)
- (f) Screening logs
- (g) Study monitoring log
- (h) Drug/device log for investigational drug/device
- (i) Drug/device shipment and retrieval documents
- (j) IND/IDE FDA approval letter

b. Subject Data Requirements. Documentation must also include a case history or subject study file. Federal guidelines and regulations require the PI to maintain adequate and accurate record for each subject in a research study. This record is known as the subject case history or subject study file. This file includes the following documents but are not limited to:

- (1) Subject signed informed consent document
- (2) Case report forms (protocol-specific data collection tools; a vehicle used to convey the study information confidentially from the source document to the Sponsor) or data collection forms
- (3) Medical history records

- (4) Physical exam results
- (5) Results of laboratory tests
- (6) Research notes including study subject clinical management information, observations on the study subject's condition, and any information collected for the study.
- (7) Memos of correspondences with the study subject
- (8) Memos to file indicating any particular circumstance(s) with that study subject

c. **Source documents** are the original patient information as first recorded. These can be in either paper or electronic format and can be found in the VA medical record and/or clinic chart. The following principles of source documentation are consistent with GCP and recommended in all VA research projects:

- (1) All data points on case report forms (CRF) are supported by source documents unless the Sponsor specifies otherwise.
- (2) Primary source documents are the subject's medical record (Computerized Patient Record System (CPRS)) and are generated in the course of routine medical care.
- (3) The subject file, maintained by the study team, should contain a copy of the source documents or clearly indicate where the source documents can be found.
- (4) The CRF is not appropriate as a source document and will be used as such only if so specified in the study protocol or by other instructions from the Sponsor and allowed by the LSCDVAMC Research Office.
- (5) Source entries are timely (written at the time of the event or identified as late entry).
- (6) Entries are signed and dated by the author.
- (7) Every subject contact is documented.

d. **Investigational drug record requirements.** The PI, or designee, and the research pharmacist must maintain accurate and complete accounting of all clinical study materials received, dispensed, and returned to the Sponsor. These records must be kept with other study records and for the same retention time.

e. **Investigation device record requirements.** The PI, or designee, maintains accurate and complete accounting of all clinical study materials received, dispensed, and returned to the Sponsor. These records must be kept with other study records and for the same retention time.

f. **Documentation in the Medical Record (CPRS).** VHA requires that specific research progress notes be placed in the medical record to document the informed consent process, study enrollment, study visits, and study termination. This will require a progress note: (See SOP HSP-003 "Documentation in Patient's Medical Record of Enrollment Contact, Actual Enrollment and End of Study Participation").

- (1) **Informed Consent Progress Note:** A progress note documenting the informed consent process must be placed in the subject's medical record. At a minimum, the progress note must include:

- (a) The name of the study
- (b) The person obtaining the subject's consent
- (c) A statement that the subject or the subject's legally-authorized representative was capable of understanding the consent process
- (d) A statement that the study was explained to the subject
- (e) A statement that the subject was given the opportunity to ask questions.

- (2) Enrollment Note: An entry must be placed in the progress note when the human subject is actually entered into the study.
- (3) Termination of Enrollment Note: An entry must be place in the progress note when the human subject's participation is terminated.
- (4) Exceptions to this procedure are outlined in Medical Research Service SOP HSP-017 "Exception to the Requirement for CPRS Documentation."

4. REFERENCES: Human Research Protection Program Standard Operating Procedures; Medical Center Policy "Investigational Drugs"; Medical Center Policy 151-015 "Investigational Devices"; Good Clinical Practice Guidelines; Medical Research Service SOP HSP-017 "Exception to the Requirement for CPRS Documentation."

5. RESCISSION: Medical Research Service SOP HSP-006 dated September 1,2004 was rescinded. The review date for this SOP is August 1, 2007.

6. FOLLOW-UP RESPONSIBILITY: Research Compliance Officer

7. APPENDICES: A: Required Documentation Study File Notebook/Regulatory Binder; B: Irregularities/non-Compliance Form; C: Signatures and Delegated Responsibilities; D: Subject Log; E: SAE Log; F: Detailed Information Regarding Regulatory Document Collection

REQUIRED DOCUMENTATION STUDY FILE NOTEBOOK/ REGULATORY BINDER

*Required

**Required for FDA regulated studies

+ Optional

Documents **Filed/Not Filed** Comments

Copy of the Principal Investigator's CV* with state license information
Copy of the Investigator's Certification(s) +
Copy of other Research Staff CV +
Copy of Research staff certification(s) +
Final signed 1572
All amended FDA 1572s
Copy of Original Research Protocol*
Investigator's Brochure (if applicable)
Copy of the IRB original and other approved/stamped versions of Informed Consent Form (s) *
Copy of protocol amendments*
Copy of IRB protocol approval letter*
Approval of protocol amendments*
Copy of IRB approved advertisements +
Copy of approved modifications"
Copy of protocol continuing review approval(s)*
Copy of Serious Adverse Event (s) reporting ^x
Copies of IRB Correspondence, progress report and termination letter *
Copies of all internal/external communications related to the study: Letters, memos, phone contacts +
Copy of Research and Development (R&D) Committee approval letter*
R&D Committee communication*
Laboratory certification and lab normal values (if applicable)
Original or copy of investigational drug device log, equipment and copies of drug device shipment and retrieval documents **
Copies of any information related to the investigational drug/device
Screening log
Enrollment log
SAE report log
Sponsor's Communication
At end of study, copy of drug/device randomization codes
Monitoring visits reports

Note-To-File:

Investigator: _____
Patient #: _____
Date: _____

GCP and PROTOCOL
Irregularities / Non-Compliance

Check all of the following that apply:

- Informed Consent Document signed after patient started study procedures
- Safety labs not collected as specified by the protocol
- Inclusion/Exclusion criteria violated
- Patient in simultaneous interventional trials
- Required source data documentation could not be obtained
- Serious Adverse Event not reported appropriately to sponsor (see operations manual)
- Serious Adverse Event not reported appropriately to IRB (see local IRB guidelines)
- Drug accountability issue
- Patient took excluded medication
- Patient did not return study drug
- Patient did not take medication as directed or received wrong drug
- Patient was seen outside the allowed visit interval
- Required study procedure not completed
- Other

Description of irregularity or non-compliance:

Record of notifying Sponsor (if applicable):

Date Sponsor notified: _____
Name of representative contacted: _____
Person who contacted representative: _____

Study Coordinator: _____ Date: _____
(Signature)

Investigator: _____ Date: _____
(Signature)

(Also file note in the patient's record if related to specific patient)

SITE PERSONNEL

SIGNATURES & DELEGATED RESPONSIBILITIES

Investigator: _____ Project: _____

Study Site: _____ Sponsor: _____

NAME (PRINT OR TYPE)	TITLE OR POSITION	Task* Codes	Signature	INITIALS	A. B. (OF WORK ON STUDY)
					From: To:

Delegated Responsibilities*	A = Make eligibility/termination decisions E = Evaluate adverse events (cause/severity)		Other Tasks*
	B = Obtain informed consent	F = Prescribe study drugs/devices	I= _____
	C = Direct medical care of subject (treatment decisions)	G = Label and dispense study drug	J= _____
	D = Make data entries and corrections on CRFs	H = Maintain drug accountability records	K = _____
			L = _____

**List all other key protocol tasks, e.g., administer study drug, draw bloods, physical exams, etc.

TO BE SIGNED AT SITE CLOSURE:

I confirm that this list accurately reflects the delegation of responsibilities during the trial.

Investigator Signature: _____

Date:

					2	0	0	
D	D	M	M	M	Y	Y	Y	Y

SERIOUS ADVERSE EVENTS LOG

(SAEs occurring at this site)

Investigator: _____ Project: _____

Study Site: _____ Sponsor: _____

Date SAE Occurred	Date Learned of Event	Patient Number	Event	SAE Form Completed (Y/N)	Date Reported to Sponsor*	Date Reported to IRB**	IRB Acknowledged (Y/N)
*If required by the Sponsor (see protocol for Sponsor requirements) **If required by the IRB (see IRB requirements on SAE reporting, i.e., definitions & timeframes)							

Detailed Information Regarding Regulatory Document Collection

Regulatory documents are a critical piece of the research process. These vital documents serve the following functions:

- They are used as a tool for the assessment of conduct in a trial
- They documents establish investigator, sponsor and monitor compliance with the standards of Good Clinical Practice (GCP)
- They validate the data management of a trial.

These documents also have the highest potential for being audited by the sponsor and/or a regulatory authority. The following table pertains to regulatory documents used for all types of Sponsored trials. All regulatory documents should be filed in a regulatory binder. Many times this binder is provided by the sponsor and has dividers for specific sections (i.e. correspondence, IRB approvals, Laboratory information, etc).

Regulatory documents are involved in all three phases of a trial.

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Phase	Title	Provided by	Comment
	<p>Statement of the Investigator, FDA Form 1572 (FDA initiated and sponsor provided)</p> <p>(Maybe also get the FDA forms from the VA website soon)</p>	<p>Comes from Sponsor or obtained on-line from FDA Website and completed by site</p>	<p>Purpose: <i>Used for drug trials only:</i> Signed by the PI and specifies the investigator's ultimate responsibility for carrying out the trial in accordance with the protocol, the institution and federal regulations; registers the investigator under the investigational new drug (IND); includes material about the trial, investigator, Co-investigator~key responsibilities and study site(s).</p> <p><u>What do I do with this?</u> Complete (2) forms as directed and have the PI sign/date both copies. Send (1) to the sponsor and keep (1) for your files.</p>
	<p>Biographical Sketch</p>	<p>PI and all Co-investigators</p>	<p><u>What do I do with this?</u> Used for federally funded trials & replaces the 1572 Form. This can be retrieved from the internet and is part of the NIH grant submission packet. The original goes to FDA and a copy is kept at the site.</p>
	<p>Investigator Agreement</p>	<p>Sponsor</p>	<p>Purpose: <i>Used for device trials only.</i> Pursuant to 21 CFR 812.43 (c), it includes Investigator's Curriculum Vitae (CV), an account of related experience, dates, locations, extent; details of study termination.</p> <p><u>What do I do with this?</u> Complete (2) as directed and have PI sign/date both copies. Send (1) to the sponsor and keep (1) for your files.</p>
	<p>Financial Disclosure Form</p>	<p>Industry Sponsor and IRB</p>	<p>There are (2) different types that need to be completed: (1) originating from the IRB and (1) originating from the sponsor.</p> <p><u>Purpose:</u> Verifies the equity interest in the sponsor for all involved in the study.</p> <p><u>What do I do with this?</u> Have each study personnel, i.e. all investigators, complete, sign and date (1) original and make (2) copies of each. Originals of each go to the sponsor and a copy goes to the IRB. The other copy is for your files.</p>

Phase	Title	Provided by	Comment
S T A R T U P	Curriculum Vitae and Medical License	Investigator(s)	<p><u>Purpose:</u> This demonstrates to the sponsor that study personnel are qualified to carry out the terms of the protocol.</p> <p><u>What do I do with this?</u> All study personnel listed within the 1572 and/or investigator's agreement needs to provide his/her recent (within 1 year) signed and dated CV. Make a copy for your files and send the original to the sponsor.</p>
	Informed Consent Document	Model from Sponsor	<p><u>Purpose:</u> Pursuant to 21 CFR 54, to provide the subject with information regarding the research project and allow him/her to ask questions,</p> <p><u>What do I do with this?</u> Obtain the model from the sponsor. Format it into the IRB's recommended wording. Ensure that study-related events are explained in lay-man's terms (6th grade level). Return to sponsor for approval. Once approved by sponsor, submit to IRB for review and approval. When the IRB has approved and stamped it, send a copy of the approval letter and approved consent form to the sponsor. Keep the originals in your files. Please note: IRB requested changes to the informed consent form must be reviewed by the sponsor prior to resubmitting to the IRB.</p>
	IRB Approval Letter	Participating Site	Valid for the continuing review interval determined by the IRB. All studies require continuing review.
	IRB Approved Informed Consent Document	Participating Site	Valid for the interval determined by the IRB.. Approval interval appears on each page of the informed consent form. The IRB will provide a newly stamped informed consent form indicating the approval period at the time of continuing review.
	IRB Membership Roster	Participating Site	List of IRB members and consultants This roster is available in a printer friendly format on the IRB Website. Need to discuss this at the next IRB meeting. Presently we do not provide names.

	<p>Laboratory Certification-CLIA (Clinical Laboratory Improvement Amendments) and/or CAP (College of American Pathologist). The VA does not fall under the jurisdiction of CLIA.</p>	<ol style="list-style-type: none"> 1. Central lab (i.e. Covance) 2. Local lab (i.e. participating site) 	<ol style="list-style-type: none"> 1. The Sponsor provides this if using a Central lab. 2. Call general laboratory number for Pathology and they will fax it to you
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Phase	Title	Provided by	Comment
S T A R T U P	Director's CV and Medical License (if applicable)	<ol style="list-style-type: none"> 1. Central lab (if one is being used) or Participating Site upon request of sponsor 2. Local Lab 	<ol style="list-style-type: none"> 1. The Sponsor provides this. 2. Call _____ to request a copy (Ki Ho Kwon, MD is the Chief Pathology and Laboratory)
	Current lab Normal Values-Guide to Laboratory Services Pathology & Laboratory Medicine	<ol style="list-style-type: none"> 1. Central lab (if one is being used) or Participating Site upon request of sponsor 2. Local Lab 	<ol style="list-style-type: none"> 1. The Sponsor provides this. 2. Copy from lab manual or obtain from _____
	Human Research Subject Protection Training Certificate	Participating Site for each person involved in the study	Prior to participating as a researcher on any clinical trial, one must take the VA mandated combined educational on-line training. This is a web-based test and directions can be found contacting David Burkhart in the IRB at ext. 4658.
	Documentation of a VA-approved Tissue Bank, if applicable If you need to seek VA approval of the tissue bank to be used in the study and have questions, please contact the Research Compliance Officer at 4625.	PI or Sponsor	I This is to certify that VACO has approved the tissue bank that is to be utilized in the prospective study. <u>What do you do with this?</u> Forward to the R&D Committee and then it will be forwarded to the IRB. Keep a copy for your files.

Phase	Title	Provided by	Comment
A C T I V E S T U D Y	Maintain all versions of the protocol including amendments.		File In Binder
	Keep any revisions to the following: Informed Consent FDA Form 1572 Advertisements All written material given to subjects		
	Keep all communication to/from IRB regarding: Approval of amendments Annual or continuing reviews Approval of ICF Approval of advertisements Adverse Event correspondence Safety reports		
	Keep any CV's and medical licenses of additional sub-investigators		
	Keep expired documents such as: Annual IRB approval of protocol and informed consent Outdated CV's and medical licenses Outdated laboratory licenses Outdated IRB Roster		
	Keep all communication to document agreements or significant discussions pertaining to: -trial administration -protocol violations -trial conduct -AE reporting -patient issues -meeting notes -newsletters -phone logs -in-service documentation -monitoring visit reports -subject screening logs -enrollment logs -signature logs -drug accountability logs - courier airbills		File In Binder

Phase	Title	Obtain on IRB Website	Comment
S T U D Y C O M P L E T I O N	Final report to the IRB/Project completion (cc to sponsor)	Participating Site and copy to sponsor	The Project Completion Form is completed and submitted to the IRB listing final enrollment, AE summary log, any new findings or relevant information learned during the course of the study, and any publications of study data to date.
	IRB Project Completion acknowledgment (cc to sponsor)	Participating Site and copy to sponsor	Once the IRB acknowledges and approves the Projection Completion Form, a copy of the approval letter is sent to the sponsor and the original is filed in the IRB correspondence.

Note:

All documentation requested by the sponsor returns to the sponsor. The FDA 1572 Form is a government required document which may be provided by the sponsor with study specific information completed or can be accessed on line and completed by the site. The sponsor needs an executed 1572 for their files and the site keeps a copy for their study file.