

_____ Sutter Health Sacramento Sierra Region

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Approved: Linda Marks, Director, SIMR Operations

SUTTER INSTITUTE FOR MEDICAL RESEARCH STANDARD OPERATING PROCEDURES

INTRODUCTION

Following are the standard operating procedures (SOP) that SIMR follows to conduct clinical studies. This is a living document and is updated as procedures are added and revised.

SOPs	Most recent revision
CO-SS.01 to CO-SS.10	August 1, 2007
CO-SM.01 to CO-SM.08	August 1, 2007
CO-SS.11, QA-PO.01, and QA-PO.02	August 1, 2007
CO-SS.12	August 1, 2007

INTRODUCTION

All research involving human subjects conducted at Sutter Health Sacramento Sierra Region (SHSSR) facilities should be reviewed and approved by the Sutter Institute for Medical Research (SIMR) Office of Research Administration (ORA) prior to its implementation. The process includes administrative, clinical, legal and financial review and approval before the research can be initiated (Figure 1, Appendix A). Currently, these SOPs apply to research that is managed through SIMR.

TERMINOLOGY

Following is a list of acronyms that are repeatedly used in these SOPs,

- Adverse event (AE)
- Centralized Institutional Review Committee (IRC)
- Clinical Research Organization (CRO)
- Clinical research associate (CRA)
- Clinical research coordinator (CRC)
- Dietician
- Good clinical practice (GCP)
- Human subjects compliance specialist (HSCS)
- Principal investigator (PI)
- Informed consent form (ICF)
- Investigational drug service (IDS) pharmacist
- Laboratory technician
- Office of research administration (ORA)
- Regulatory compliance technician
- Serious adverse event (SAE)
- Sutter Institute for Medical Research (SIMR)
- Sub-investigator (Sub-I)
- Sutter Health Central Institutional Review Committee (SHCIRC)

CLINICAL OPERATIONS

PURPOSE

This policy establishes the study start-up, study management, and study closure procedures required to ensure proper placement and clinical operations management within SHSSR.

CO-SS STUDY STARTUP

Study startup may include visits by the sponsor for screening and site selection (pre-start-up), preliminary startup, and study initiation following study approval (prior to enrollment of the first subject).

APPLICABLE REGULATIONS AND GUIDELINES

The following regulations and SOPS apply to all procedures regarding study startup.

21 CFR 312.32	IND safety report
21 CFR 312.33	Annual report
21 CFR 312.60	General responsibilities of investigators
21 CFR 312.62	Record keeping and record retention (investigator)
21 CFR 312.64	Investigator reports
21 CFR 312.66	Assurance of IRC review
45 CFR 46.109	IRC review of research
E6 GCP 3.1	IRC/IEC - Responsibilities
E6 GCP 3.3	IRC/IEC - Procedures
E6 GCP 3.4	IRC/IEC - Records
E6 GCP 4.4	Investigator - communication with the IRC/IEC
E6 GCP 5.11	Sponsor – Confirmation of review by IRC/IEC
NIH – HPPERT – 11/02 Chapter 4	IRC Review
REFERENCES TO SIMR SOPs	
CO - SS.06	Study Preparation
CO - SM.06	Drug Accountability

CO-SS.01 PROTOCOL FEASIBILITY

POLICY

Each study submitted to SIMR ORA will be evaluated to determine the feasibility of undertaking the study.

PROCEDURE

01.01 Site surveys and Confidentiality Agreements (CDA) are reviewed by CRCs, MD, and DSO for study feasibility. Surveys for studies that are feasible are completed by appropriate CRC and potential Principal Investigator

01.02 Upon receipt of the protocol synopsis, the CRCs and PI review study again for feasibility. If study is determined to be feasible, the appropriate SIMR staff proceeds with sponsor requirements. If site is approved by sponsor, study startup phase begins. All CDAs are signed by Medical Director, except if sponsor's requirements conflict with this policy.

01.03 Studies will be evaluated according to the following guidelines:

- Scientific and clinical merit
- Subject safety
- Subject population
- Necessary resources for the study
- Adequate financial compensation
- History of similar studies

CO-SS.02 REGULATORY SUBMISSION PROCESS

APPENDIX A

Appendix A contains the following attachments that are referenced in the SOPs regarding submissions to SHCIRC: All of these forms are accessible on the SHIRC Website

www.shirc.org

- a. Full Committee Review Application Protocol Summary
- b. Protocol Summary
- c. IRC Consent Form – Plain (Form C)
- d. Consent Full Guide
- e. Checklist
- f. Safety table report
- g. Continuing review / Study Close out (Form J)
- h. Adverse Event Report (Form H)
- i. Form X-Administrative Compliance (Form X)
- j. IRC Fee Form
- k. Amendment Form – 8
- l. Amendment Fee Form
- m. Amendment Expedited Review Requested
- n. FDA Form 1572

POLICY

The SHCIRC executes the regulatory review process. The SHCIRC exists to protect the rights and welfare of human research subjects in accordance with regulatory guidelines established by the United States Department of Health and Human Services, Office of Human Research Protection, State of California, and the United States Food and Drug Administration (FDA). The HSCS reports the activity of SHCIRC to SHSSR CMO.

Investigators must obtain approval from SHCIRC to conduct research involving Sutter subjects. However, investigators conducting research studies that involve outpatients that are not in the Sutter Health system may submit studies to a centralized IRC. The HSCS informs investigators of all decisions and administrative processes, and returns disapproved protocols to the investigator.

The FDA requires an IRC to review and approve new protocols for clinical trials. There are different processes for submission to the SHCIRC versus a centralized IRC.

PROCEDURE-SHCIRC

New protocols – Forms available on IRC Website www.shirc.org

- 02.01** Prepare sponsor regulatory documents to include, protocol signature page, investigators brochure cover page, financial disclosure statement and FDA Form 1572, and obtain PI's signature on all forms .
- 02.02** Revise CV in SIMR template, have PI/Subs sign. Must be updated every 2 years. Obtain copy of medical license.
- 02.03** Complete full committee review application. The PI is required to review and sign this form.
- 02.04** Complete – Protocol Summary.

- 02.05** IRC Consent form plain to include: Sutter HIPAA authorization form, and California Experimental Bill of Rights. This will be used to create a consent form implementing sponsors information. The consent must be reviewed and approved by the CRC and PI if possible, then sent to the study sponsor before it can be submitted to the SHCIRC.
- 02.06** Complete SHCIRC fee form. The fee form is the tool the Financial Analyst uses to initiate billing for SHCIRC services provided. available on website referenced above
- 02.07** Complete Form X indicating level of Sutter resources required for study. Signature of Department Administrator and PI is required. available on website referenced above
- 02.08** Complete SHCIRC application checklist Copy the requested number of SHCIRC documents and assemble the application as requested on the SHCIRC application checklist. Include all recruitment materials.
- 02.09** Submit completed SHCIRC application packet to: Sutter Health Central Area Institutional Review Committee 2801 Capitol Avenue, Suite 400 Sacramento, CA. 95816-6000.
- 02.10** IRC coordinator will schedule presentation date and time. . PI will present for 10-15 minutes to the SHCIRC Committee.
- 02.11** Protocol amendments
- 02.12** Complete SHCIRC fee form I. The fee form is the tool the Financial Analyst uses to initiate billing for SHCIRC services provided.

02.13 Amendment Form – 8. Complete form. PI reviews and signs this form. If the amendment requires revisions to the consent form, this needs to be reviewed and approved by the study sponsor prior to IRCIRC submission. Submit original amendment form and updated documents to the IRCIRC and file a copy in the regulatory binder.

02.14 Contingent approval – the study will be contingent upon IRC requested changes to the consent or other IRC requests listed on the IRC contingent letter. These changes to the consent must first be approved by the study sponsor before resubmission to the IRC for final approval. The IRC will review the consent for accuracy and grant final approval. All study documents and approvals must be sent to the study sponsor via fax, or email and filed in the regulatory binder.

IND safety reports

02.15 Submit IND safety reports signed and dated by the PI and safety summary table. Original documents are filed in the regulatory binder.

Continuing reviews

02.16 Regulatory Technician and CRC prepare and submit reports for continuing review for each study to the SHCIRC at least annually, or more frequently if requested by the SHCIRC. PI signs original document. s

02.17 Attach a clean copy of the current consent and the consent signed by the last subject enrolled in the study. .

02.18 Original signed forms are sent to the IRC in the submission packet. A copy of the submission packet is filed in the regulatory binder.

Close out reports

- 02.19** Schedule a study closure visit with the study sponsor.
- 02.20** Complete and have PI review and sign Form J.
- 02.21** Review the regulatory binder and all CRFs and correct any outstanding issues.
- 02.22** File "Records Management" form in the regulatory binder.
- 02.23** Submit Form J to the SHCIRC only after the study sponsor completes a study closure visit. A permanent closure letter is sent by the SHCIRC.
- 02.24** Send the IRC close out letter to the sponsor.. Archive regulatory and study documents as noted in

Consent revisions

- 02.25** The sponsor may request a revision of the consent for the following reasons:
- Protocol revisions (amendment)
 - Updated investigator brochures
 - Changes in subject stipend
- 02.26** Document reasons for consent revisions.
- 02.27** Provide the SHCIRC with a copy of the updated document and a copy of the letter from the sponsor outlining the requested changes to the consent.
- 02.28** Use track changes to indicate requested changes to the consent.
- 02.29** Change the footer on the consent to reflect a new version.

02.30 Submit an updated version and a clean copy of the consent to the sponsor for approval. You must have received sponsor approval before submission to the IRC.

02.31 Submit the revised consent to the SHCIRC after the sponsor has approved the revisions. The SHCIRC will generate a new date-stamped consent after the consent revisions have been reviewed and approved.

02.32 Use the most recent approved version as the current ICF.

Study transfer

A study transfer is defined as the transfer of a study from one site to another.

02.33 RT and CRC complete Form J and PI reviews and signs.

02.34 Submit Form J to the SCHIRC after the clinical trial has been reviewed and approved by the new site's IRC.

02.35 Schedule a study transfer visit with the study sponsor for the current site where the regulatory binder and all CRFs are reviewed and all outstanding issues completed.

02.36 File "Records Management" form in the regulatory binder

02.37 Submit SHCIRC letter of transfer and file a copy in the regulatory binder and send a copy to the new site.

02.38 Retain a copy of the regulatory binder at the original site.

02.39 Send the original regulatory binders and the original CRF binders to the new site. This officially closes the study at SIMR.

PROCEDURE-CENTRAL IRC

Central IRCs usually meet twice a week. Following are the procedures used for submission of all types of documents that may be submitted to a central IRC.

New Protocols

02.40 Prepare regulatory documents and obtain PI's signature on the following:

- FDA Form 1572
- Protocol signature page
- PI's and Sub-I's CV and medical license
- Financial disclosure statement
- IRC questionnaire (site specific)

02.41 Submit the following documents:

- Protocol
- Investigational drug brochure
- Standardized informed consent
- Site specific IRC questionnaire
- Recruitment materials
- PI's and Sub-I's CV, medical license, and financial disclosure statement
- Local laboratory documents (if required)

02.42 SIMR is required to submit other requested documents (per central IRC requirements) and consent revisions with SHCIRC (required language (Form C)).

02.43 Upon study approval, the central IRC will notify the SIMR clinical trials office.

Protocol amendments and addendums

- 02.44** Revise the consent to reflect the updated revised protocol for the PI to review.
- 02.45** The study sponsor may use a CRO when submitting a new protocol to the central IRC. The CRO submits the protocol to the central IRC on behalf SIMR. SIMR is required to submit other requested documents (per central IRC requirements) and consent revisions with SHCIRC language (Form C). The revised consent is sent for sponsor approval and then to the central IRC for review.
- 02.46** A hard copy of the approved documents will be mailed following review. File approved documents in the regulatory binder

IND safety reports

- 02.47** Write a letter stating the date that the safety reports were sent to the central IRC following review and signature by the PI.
- 02.48** For study sponsors using a central IRC, the study sponsor is responsible to submit IND safety reports on SIMRs behalf. Continuing review
- 02.49** Complete continuing review form and attach any requested documents.
- 02.50** The PI for the study completes signs and dates the continuing review form. If the study is still open to enrollment, a copy of the consent form of the last enrolled subject is included. All forms are returned to the RT. The central IRC may request the return of the original document but a copy is retained in the regulatory binder.
- 02.51** Documentation from the IRC is sent to the site after continuing review is granted.

Close out reports

- 02.52** Schedule a study closure visit with the study sponsor. The regulatory binder is reviewed, and outstanding issues resolved.

02.53 Write a close out letter on and include the following:

- Date of study closure. This date is usually the day of the last sponsor monitoring visit.
- The number of subjects who were enrolled in the study
- The number of subjects who completed the study
- Any unreported IND safety reports

02.54 Request a letter of acknowledgement from the IRC that the study has closed. This letter should be filed in the regulatory binder.

Consent revisions

02.55 The sponsor may request consent revisions for the following reasons:

- Protocol revisions
- Updated investigator brochures
- Changes in subject stipend
- Study administrative changes

02.56 Document the reason for the consent revision and provide the IRC with a copy of the updated document and a copy of the letter from the sponsor outlining the requested changes to the consent.

02.57 Highlight old and strikethrough new requested changes to the consent and change the footer of the consent to reflect a new version.

02.58 Submit the revised version of the ICF and a clean copy of the ICF to the sponsor for their approval.

- 02.59** Submit the revised ICF to the IRC after the sponsor has approved the revisions. The IRC will generate a new date-stamped consent after the revisions have been reviewed and approved.
- 02.60** Use the updated approved version as the current ICF.
- 02.61** The CRO submits updated documents and consent revisions, and a hard copy of the approved documents to the central IRC if applicable. Approved documents will be mailed to SIMR.

Study Transition

A study transition is defined the transfer of a study from one site to another.

- 02.62** Schedule a study transfer visit with the study sponsor. The regulatory binder and all outstanding issues are resolved.
- 02.63** File the form “Records Management” with the regulatory technician.
- 02.64** Submit a letter of transfer to the IRC, if applicable and file a copy of this letter in the regulatory binder.
- 02.65** Request a letter from the sponsor that states the date that the transfer takes effect.
- 02.66** Retain a copy of the regulatory binder at the original site.
- 02.67** Send the original regulatory binders and the original CRF binders to the new site.
- 02.68** The transfer of the regulatory binders closes the study at SIMR.

CO-SS.03 MAINTAINENCE AND STORAGE OF REGULATORY DOCUMENTS

POLICY

The regulatory binder is maintained throughout the clinical study. The binder contains pre-study documents and all forms and reports completed during the course of the study. Appendix B contains forms associated with maintenance, storage, and destruction of study documents.

PROCEDURE

Contents of the regulatory binder

03.01 Include the following materials in the regulatory binder if applicable:

- Pre-study documents
- Form FDA 1572
- Signed and dated financial disclosure form and medical license for the PI and Sub-I
- Current (within 2 years) CV for PI, Sub-I and laboratory director
- Laboratory certification
- IND safety reports
- Protocol (including signature page and synopsis)
- IRC membership list
- IRC approval
- Approved informed consent form
- Advertising material
- Investigators brochure
- Test article inventory and drug accountability record
- Delegation of Authority Form
- CRFs and AE Forms
- Site visit log
- Telephone log
- Master subject list
- Original source documents
- All correspondence to and from the sponsor including additional documents as the study progresses. These may include but are not limited to:
 - a. Updated documents (amendments, addenda, investigator brochures, revised consents)
 - b. Shipping invoices for all test materials, returned goods forms.
 - c. All correspondence pertaining to the study.

Archiving regulatory documents

03.02 All study regulatory documents are stored for a period of 1 year at the SIMR Clinical Trials Office: 2801 Capitol Avenue, Suite 410, Sacramento, CA 95816.

03.03 After 1 year, records are archived at the Sutter Health Records Management at 1650 Cebrian Street, West Sacramento, CA. 95691 for 25 years.

03.04 Appendix B contains the forms that need to be completed when archiving documents

CO-SS.04 PRE-STUDY STARTUP SITE SELECTION VISIT

POLICY

Each study submitted to SIMR ORA will be evaluated with the sponsor to identify issues that may need to be addressed prior to study placement within SHSSR system facilities.

PROCEDURE

- 04.01** The sponsor submits a study protocol or protocol synopsis to ORA or the prospective PI for the study.
- 04.02** The sponsor may request a screening site selection visit, which is arranged with ORA and/or CRC.
- 04.03** The ORA identifies and facilitates study coordination with ORA and CRC
- 04.04** Arrange for a tour of the sites where the research is conducted. Areas visited may include:
- Exam rooms
 - Laboratory facilities
 - Special procedure rooms
 - Drug storage facilities
 - Study material storage, including CRFs and source documents
 - Location of regulatory binders
- 04.05** A meeting is arranged between the PI, the sponsor, and CRC to discuss clinical issues, answer questions, and present requirements by ORA for protocol review.
- 04.06** The sponsor notifies ORA and/or PI if the site has been awarded the study.
- 04.07** If SIMR is awarded the study, the sponsors notify the PI, the CRC and/or the ORA, of locations and dates of required investigator meetings.

04.08 Upon SIMR selection as a study site, the sponsor provides the necessary regulatory documents for IRC submission.

APPLICABLE REGULATIONS AND GUIDELINES

21 CFR312.60	General responsibilities of investigator
21 CFR 312.50	General responsibilities of sponsor
21 CFR 312.55	Informing investigator
21 CFR 312.57	Record keeping and record retention (sponsor)
E6 GCP 5.1	Sponsor – Quality Assurance and Quality Control
E6 GCP 5.12	Sponsor – Information on Investigational Product(s)
E6 GCP 5.14	Supplying and Handling Investigational Product(s)
E6 GCP 8.2	Essential Documents for the Conduct of a Clinical Trial – Before the Clinical Phase of the Trial Commences
REFERENCES TO SIMR SOPs	
CO - SS.05	Study Site Initiation Visit
CO - SS.06	Study Preparation

CO-SS.05 STUDY SITE INITIATION VISIT

POLICY

The details of a study protocol are given to the PI, CRC, IDS pharmacist and other research team members at the sponsor study site initiation visit. The details of the SIMR internal study activity including but not limited to, finance, billing compliance, budget, regulatory, and recruitment are discussed at the study start up meeting.

SPONSOR SITE INITIATION

PROCEDURE

- 05.01** Members of the research team may include the PI, CRC, IDS pharmacist and other ancillary staff. The team is notified of the location, date, and time of the visit. The CRC reminds the study team one day in advance of the visit.
- 05.02** Copies of the research protocol are made available to study team members. For protocols that include investigational drugs, a complete protocol and investigator's brochure is forwarded to the IDS.
- 05.03** The sponsor meets with the PI and research team to review the protocol, roles, and responsibilities as well as GCP guidelines.
- The sponsor reviews the CRF with the CRC.
- 05.04** ORA contracts office addresses funding for additional supplies or equipment that need to be provided
- 05.05** Exceptions:
- (1) The investigator meeting if attended by the PI and CRC, may take the place of the study initiation visit.

- (2) When drug is shipped directly to the PI (not located within a Sutter Hospital), the IDS Pharmacist is not involved in the initiation visit

SIMR INTERNAL STUDY START UP MEETING

PROCEDURE

05.06 Following sponsor site initiation visit, the CRC schedules an internal study start up meeting. The team for this meeting should include finance, billing compliance, contract/budget, recruitment, regulatory,

05.07 The team shares pertinent information including but not limited to :

1. Study Summary – study period, study site, participant issues
2. Study Team information – Investigator issues, names of PI, sub I, backup CRC.
3. Contract/Budget – patient target, budget breakdown, patient stipend, investigator contract, start up fees.
4. Finance Review – Investigator compensation, worksheet
5. Billing Compliance – Form K, and billing instructions
6. Recruitment – various methods of recruitment that will be used including, print and radio advertisement, physician referral, call center, database queries.
7. Regulatory – consent review

05.08 Meeting information is summarized and forwarded to the SIMR general staff.
This is general notification of study startup.

CO-SS.06 STUDY PREPARATION

Study preparation time is used to address issues identified during the study initiation visit and prior to study startup.

POLICY

ORA facilitates the preparation for study startup, advertisement, promotion and recruitment of study subjects from SHSSR hospitals, clinics, and the community.

PROCEDURE

- 06.01** The CRC confirms the IRC approval date and reviews any protocol amendments or changes to the consent.
- 06.02** The SIMR contract department confirms the contract and budget approval with the sponsor and solidifies arrangements with off-site subcontractors.
- 06.03** The SIMR contract department solidifies the contract with participating physicians and vendors.
- 06.04** CRC trains a back-up coordinator.
- 06.05** The CRC and regulatory technician resolve any issues regarding storage space or transportation of study materials.
- 06.06** Develop and implement recruitment plan to identify potential subjects. Confirm the date that enrollment starts from the sponsor. Recruitment plans that include direct patient marketing must have approval from an IRC prior to implementation.
- 06.07** In-service and training required by ancillary staff is completed and documented. Ancillary staff may include:
 - Office staff
 - Pharmacy staff

- Off-site facility staff

06.08 Confirm and record receipt of study drug. Store and file study supplies and IRC study specific approved literature advertisements.

06.09 Purchase and store additional study specific materials or equipment.

APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 56.109	IRC Review of research
21 CFR 56.111	Criteria for IRC approval of research
21 CFR 312.21	Phases of an investigation
21 CFR 312.23	IND content and format
21 CFR 312.60	General responsibilities of investigators
21 CFR 312.68	Inspection of investigator's records and reports
	REFERENCES TO SIMR SOPs
CO-SS.05	Study Site Selection Visit
CO-SM.04	Drug Accountability

CO-SS.07 ADULT INFORMED CONSENT

POLICY

Informed consent will be administered according to GCP, CFR and HIPAA regulations.

PROCEDURES

07.01 The consent form used must be approved by an IRC and includes SHSSR HIPAA authorization, and a California Experimental Subjects Bill of Rights.

07.02 Study sponsors and their representatives are not involved in the ICF process.

07.03 The PI or the CRC meets with the subject to review each page of the ICF. The following topics must be addressed in the ICF and discussion:

- Purpose of the study
- Number of subjects involved in the trial
- Medication or device involved and probability for random assignment to each treatment
- Description of study procedures and how long subjects will be in the study
- Experimental aspects of the trial
- Risks and benefits
- Alternatives to the study
- Voluntary nature of the study
- Right to withdraw
- Compensation and/or treatments available if the subject is injured
- California Experimental Subjects Bill of Rights
- Expenses from subject participating in the study
- Who to contact for information on rights of trial participants if injury occurs during study
- Stipends for participation
- HIPAA authorization to disclose subjects' information
- A statement regarding how new information about the study will be conveyed to potential subjects
- Questions and concerns of potential study subject

- 07.04** The ICF is written in a language that potential subjects or subjects' representatives understand.
- 07.05** The PI and CRC review the ethical and legal consideration for potential study participants whose first language is not English.
- 07.06** Potential subjects are instructed to read the consent completely and to not sign or date the ICF until questions, comments, and discussions between the PI or designee and potential study subject are addressed.
- 07.07** Potential subjects read the consent alone in a quiet and confidential atmosphere, or are encouraged to take it home and discuss it with family members.
- 07.08** Signatures are obtained on the ICF only when subjects are completely comfortable with the study requirements and have no reservations with signing.
- 07.09** Each page of the consent form is initialed and the last page signed by subjects or subjects' representative. The California Experimental Subject Bill of Rights and the HIPAA authorization form are also be signed and dated.
- 07.10** If required, the informed consent process is witnessed. The witness signing the ICF cannot be the person who obtained the consent.
- 07.11** The CRC documents the informed consent process in the in the source documents and notes that a signed copy of the ICF was given to the subject prior to commencement of the study.
- 07.12** If stipends are provided, subjects complete a W-9 form.
- 07.13** Subjects are given a copy of the signed ICF, California Experimental Subject's Bill of Rights, HIPAA authorization form, and the W-9 form, if applicable.
- 07.14** If study amendments necessitate revision of the ICF (study procedures are changed, or serious adverse event information becomes available), re-consenting subjects is required. Additional consents need to be obtained as outlined above.

APPLICABLE REGULATIONS AND GUIDELINES

T45 CFR 46.116	General requirements for informed consent
45 CFR 46.117	Documentation of informed consent
50 Subpart B CFR 50.20-50.27	Informed consent of human subjects
E6 GCP 4.8	Investigator – Informed Consent of Trial Subject
http://ohrp.osophs.dhhs.gov/	
http://www.fda.gov/oc/ohrt/IRCs/faqs.html	
45 CFR 46.116	General requirements for informed consent
45 CFR 46.117	Documentation of informed consent

CO-SS.08 SURROGATE CONSENT

POLICY

Surrogate consent is administered according to the guidelines provided by the Sutter Health Legal Advisory and SHCIRC. Appendix C contains a Sutter Health advisory memo regarding surrogate consent.

PROCEDURES

The following procedures apply to the non-emergency room environment, emergency room environment, and to mentally alert potential subjects unable to sign a consent form.

- 08.01** Research staff conducting the consent discussion must go outside the area to find an impartial 3rd party to witness the consent process. When potential subjects indicate they want to participate in the study, the 3rd party signs the ICF for subjects.
- 08.02** The 3rd party must document their own name (legibly written) and an explanation regarding why they signed the ICF for the subject.
- 08.03** An The Coordinator and/or PI signs and verifies why the subject couldn't sign the ICF when available.
- 08.04** Subjects who are able, indicate they have agreed to participate in the research study by making a mark on the ICF.

APPLICABLE REGULATIONS AND GUIDELINES

The following regulations and guidelines apply to CO-SS.08, CO-SS.09, and CO-SS.10

50 Subpart D CFR 50.50-50.56	Additional Safeguards for Children in Clinical Investigations
REFERENCES TO SIMR SOPs	
CO – SS.07	Adult Informed Consent

CO-SS.09 PEDIATRIC INFORMED CONSENT

POLICY

For research subjects under the age of 18, informed consent is obtained from the minor's parent or legal guardian as described in the Adult Informed Consent SOP. Assent should be sought when in the judgment of the IRC; children are capable of understanding the nature of their participation in the research. The following guidelines are used when obtaining pediatric informed consent.

GUIDELINES

- 09.01** Minors may participate in research when the IRC finds the study meets one of the following criteria:
- a. Does not involve greater than minimal risk to the minor.
 - b. Involves greater than minimal risk but presents the prospect of direct benefit to the individual subject,
 - c. Involves greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- 09.02** The parent(s) or legal guardian must be at least 18 years old or an emancipated minor.
- 09.03** The parent(s) or legal guardian must be capable of understanding the research study.
- 09.04** Consent from only one parent or legal guardian is required if the research involves no more than minimal risk.

- 09.05** Consent from only one parent or legal guardian is required if the research involves greater than minimal risk but presents the prospect of direct benefit to the individual subject.
- 09.06** Consent from both parents or legal guardians is necessary only if the research involves greater than minimal risk and does not hold out the prospect of direct benefit to the individual subject. This is likely only to occur in oncology studies.
- 09.07** Study materials must be provided in a language understood by the parent or legal guardian.

CO-SS.10 PEDIATRIC ASSENT

POLICY

Pediatric assent is required when in the judgment of the IRC, children are capable of understanding the nature of their participation in the research. The NIH National Commission recommends that assent generally be obtained from children who are seven years of age or older.

GUIDELINES

- 10.01** Pediatric assent is not required if the research directly benefits the subject and the intervention is available only through research.
- 10.02** Information must be given to child in age-related and developmentally appropriate language where the format is simple and short.

CO-SS.11 CONTRACT PREPARATION AND MANAGEMENT

PURPOSE

The purpose of this SOP is to document the process for completion of a clinical research site contract.

POLICY

It is the policy of Sutter Health that all studies conducted on the premises or involving a Sutter facility within the SHSSR are managed through SIMR. All contracts are reviewed by a contracts specialist (CS) according to Sutter Health guidelines and are processed in a timely manner. The CS works with a contracts team that may include the PI, CRCs, DO, regulatory technician, compliance and contract coordinator, Sutter's Risk Services Department, and Sutter's legal counsel.

BUDGET REVIEW

The budget and contract may occur simultaneously or consecutively. The sequence of events is dependent upon the sponsor. An agreement with the sponsor can be signed before a budget is in place. However, in accordance with the Stark law, payments to physicians must be agreed upon prior to signing a contract with physicians.

PROCEDURE

- 11.01** Receive notification of a new study and obtain sponsor contact information from the regulatory technician, CRC, PI, CRO, sponsor.
- 11.02** The CS reviews study schema with members of the contracts team to determine billable hours for each visit and other potential costs associated with the protocol such as labs, diagnostic tests, other medical personnel, or equipment needed.

11.03 If subcontracts are needed to conduct the study The CS and members of the contracts team review the contract to determine:

- a. The estimated number of screen failures.
- b. The difficulty of meeting the enrollment goals.
- c. An appropriate budget for patient stipends and advertising.
- d. PI fee structure and payment schedule.
- e. Start-up fees from fee schedule. (Attachment)
- f. Other per patient fees that may include equipment, pharmacy, labs, or procedures.

11.04 The CS:

- a. Works with members of the contracts team to ensure non-billable procedures are in the budget.
- b. Reviews the study requirements and budget with members of the contract team to determine whether or not SIMR should accept the study.
- c. Negotiates the budget with the study sponsor.
- d. Ensures CCC initiates billing compliance procedures for any project utilizing Sutter hospital services and/or resources.

CONTRACT REVIEW

The CS reviews the sponsor's draft contract with the Sutter's legal department and makes required changes to reflect Sutter Health policies. Sutter's legal department strives to respond to a request for contract review within 1-5 working days. This is dependent upon the legal complexity of the issue being addressed. Contract development is dependent upon the number of changes required by the sponsor as well as Sutter Health. As a result, the contract may go through several revisions until it satisfies the needs of the sponsor and Sutter Health. The CS evaluates the risks and determines when to involve other members of the contract team. SIMR maintains a total turnaround time of not more than 20 working days- whenever possible. A copy of the fully executed contract is given to the CCC to be scanned into Tract Manager. Tract manager number is entered onto the lower right hand corner of first page of contract in red. The CCC gives scanned contract to finance analyst for billing purposes. Finance Analyst returns document to CS for filing.

PROCEDURE

- 11.05** The CS obtains sponsor agreement or provides Sutter's Clinical Trials agreement if requested by sponsor.
- 11.06** The CS reviews the sponsor agreement for format, standard language, accurate identification of parties, mutual and sufficient indemnification, ambiguous statements, governing law, limitations of liability, payment schedules, and other elements of the contract.
- 11.07** The CS submits a revised contract to the sponsor for review after Sutter changes have been made. Several rounds of review may be required between SIMR and the sponsor before both parties agree on the contract.

PHYSICIAN SERVICE CONTRACTS

- 11.08** Working with the approved sponsor budget, the CS prepares a sub-contract and budget for the physician service components of the study.

11.09 The CS and specified members of the contracts team meet with the PI to review the investigator budget.

11.10 The CS sends the subcontract to the PI for signature and executes the contract for SIMR.

11.11 A copy of the executed agreement is sent to all appropriate parties. ----

CONTRACT COMPLETION

11.12 Once the sponsor and Sutter Health have agreed on the contract language and study specifics, the contract is forwarded to the PI and ED for signatures and promptly returned to sponsor for countersignature.

11.13 The CS and specified members of the contracts team reviews the contract and investigator budget to discuss milestones for billing and invoicing.

11.14 One original is filed in the contract folder along with all correspondence, notes, subcontracts, and physician agreements.

CO-SS.12 SUBJECT RECRUITMENT

Effective recruitment methods provide rapid enrollment of qualified research subjects into a clinical research study. For each clinical research study, a plan is developed using a wide range of recruitment methods. Recruitment methods are implemented according to GCP and HIPAA regulations (Appendix F: SHSSR Policy On Use and Disclosure of Protected Health Information (PHI) for Research Under HIPAA)

POLICY

A variety of recruitment methods are used to assist with subject recruitment to meet sponsor-required timelines. The research team develops a recruitment plan that is specific for each research study. Recruitment goals are established, reviewed, and revised on an ongoing basis throughout the course of the study. Only IRC approved recruitment materials are used to for subject recruitment. Subject recruitment activities are conducted in compliance with state and federal laws, GCP, IRC requirements and HIPAA. Effective April 14, 2003, SHSSR research personnel uses and discloses potential research patients PHI with proper authorization

SIMR implements recruitment strategies designed to meet individual site needs. SIMR utilizes the SIMR Call Center, direct advertising such as radio and print ads and community networking in addition to querying databases of patients treated at SHSSR facilities to market currently available clinical trials.

PROCEDURES

- 12.01** During the protocol feasibility stage SIMR determines whether or not SHSSR has the patient population to successfully meet enrollment goals for a clinical trial. Sutter Medical Foundation (SMF) lab, pharmacy, and/or billing databases may be used to determine an appropriate Sutter PI for the study and to determine if Sutter has a patient population with the medical condition required for the study. At this stage only the number of patients with a particular medical condition are queried.

12.02 Prior to study enrollment, the research team develops a recruitment plan. Brainstorming sessions among the clinical research team are conducted to generate recruitment strategies.

12.03 The research team creates recruitment and screening forms, physician to patient letters, and phone screen questionnaires. These are submitted to the IRC and the sponsor for approval prior to use.

Methods of subject recruitment may include:

- Call Center
- Advertising
- Accessing SHSSR PHI
- Accessing the SMF lab, pharmacy, and/or billing databases
- Performing chart screens at outpatient SHSSR facilities
- Performing chart screens at inpatient SHSSR facilities
- Performing chart screens at non-SHSSR facilities
- Accessing SIMR's Research Database,
- Inviting other physicians, and office staff to participate in subject recruitment and enrollment

Direct Advertising

12.04 The availability of funds for direct advertising and sponsor-approved recruitment materials is confirmed with the sponsor.

12.05 The research team contacts Sutter Health Marketing to assist in the recruitment campaign.

12.06 The sponsor, IRC, and Sutter Health Marketing approve the recruitment materials prior to distribution.

12.07 Direct advertising methods may include:

- Newspaper ads
- Radio scripts
- Television scripts
- Public service announcements
- Press releases
- Posters and flyers,
- Sutter Health Regional Update
- Sutter Insights Newsletter
- Newspaper human interest and medical columns
- SIMR and other appropriate website listings
- Participation in local health fairs and trade shows.

Recruitment of patients treated at SHSSR facilities

12.08 The SIMR research team follows the SHSSR Policy on Use and Disclosure of PHI for Research Under HIPAA during all recruitment activities

12.09 Recruitment of patients treated at SHSSR facilities may include:

- Accessing the SMF lab, pharmacy, and/or billing databases
- Performing chart screens or accessing an electronic medical record (EMR) at outpatient SHSSR facilities
- Performing chart screens or accessing an EMR at inpatient SHSSR facilities
- Performing chart screens at non-SHSSR facilities
- Accessing SIMR's Research Database
- Inviting site physicians office staff members to participate in subject recruitment and enrollment
- Reviewing the PI and Sub-I's daily schedules for patients who may meet study criteria

Recruitment at non-SHSSR facilities

12.10 SIMR staff may review the medical records' of potential research subjects' at non-SHSSR facilities with proper authorization from the treating physician.

12.11 Treating physicians at non-SHSSR facilities are required to follow the facility's HIPAA policy.

APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 50.2021	General requirements for informed consent
21 CFR 56.10921	IRC review of research
21 CFR 312.60	General responsibilities of investigators
21 CFR 312.62	Investigator record keeping and record retention
	SSHR Policy on Use and Disclosure of PHI for Research, August 2004
45 CFR 160 & 164	US department of HHS/ Health Insurance Portability and Accountability Act of 1996 (HIPAA)

CO-SM STUDY MANAGEMENT

Standard operating procedures outlined below provide continuity and guidelines during the conduct of clinical studies. These policies include sponsor-initiated monitoring visits, reporting AEs, progress reports, and drug accountability requirements.

APPLICABLE REGULATIONS AND DOCUMENTS

The following regulations and guidelines apply to all SOPs that address study management.

21 Subpart D CFR 312.50 – 312.70	Responsibilities of Sponsors and Investigators
E6 GCP 4.6	Investigator – Records and Reporting
E6 GCP 4.9	Investigator – Progress Reports
E6 GCP 5.18	Sponsor – Monitoring
E6 GCP 5.15	Sponsor – Record Access
E6 GCP 8.3	Essential Documents for the Conduct of a Clinical Trial – During the Clinical Conduct of the Trial

CO-SM.01 RECORDS AND CASE REPORT FORMS

POLICY

The PI is responsible for all data reported on CRFs. CRCs or designee completes CRFs using the following guidelines.

PROCEDURES

- 01.01** CRFs should be completed using a black or black ink pen (if paper).
- 01.02** Data reported on CRFs, which are derived from source documents (HP, lab results, imaging reports) should be consistent with the source documents, or the discrepancies should be explained.
- 01.03** Any change or correction to the CRF should be lined out without obscuring original entry, dated, initialed, and explained if necessary. Directions from the individual study sponsor should be followed.
- 01.04** Original source documents should be made available for comparison with the CRFs at monitoring visits.

CO-SM.02 SPONSOR MONITORING VISITS

POLICY

The ORA and CRCs will facilitate a monitoring visit in which all materials are accessible, complete, and accurate. A successful monitoring visit allows the site to reinforce or revise logistics according to the protocol and GCPs. ORA will provide adequate space for the proper conduct of the monitoring visit.

PROCEDURES

Prior to the monitoring visit, the CRC is responsible for:

- 02.01** Notification of all research team members, including the PI and regulatory technician, of monitoring visit date, time, and place.
- 02.02** Assurance of a space to work, phone, FAX, copy machine, and computer if requested.
- 02.03** Review of the CRF and all applicable documents for accuracy.
- 02.04** Notification of the IDS pharmacist of impending meeting and requesting copies of all required documentation to be forwarded to the CRC.

The monitoring visit consists of the following.

- 02.05** Reviewing the CRF with the study monitor.
- 02.06** A meeting between the PI and study monitor to sign required documents.
- 02.07** Addressing questions, corrections, and clarifications.

APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 312.50	General responsibilities of sponsors
21 CFR 312.56	Review of ongoing investigation
21 CFR 312.59	Disposition of unused supply of drug
21 CFR 312.60	General responsibilities of investigators
21 CFR 312.62	Investigator record-keeping and record retention
21 CFR 312.64	Investigator reports
21 CFR 312.66	Assurance of IRB review
21 CFR 312.68	Inspection of investigator's records and reports

CO-SM.03 ADVERSE EVENT REPORTING

POLICY

Adverse events (AEs) that occur during the course of a research study are reported to the IRB and the study sponsor.

PROCEDURE

- 03.01** An AE is defined as a medical complaint, change or possible side effect of any degree of severity that may or may not be attributed to the test article. AEs may or may not need to be reported to the sponsor.
- 03.02** Record AEs immediately in source documents, include the following information: start and stop date of adverse reaction, severity of adverse event, action taken, if any with start and stop dates; and causality.
- 03.03** The PI or Sub-I determines the causality between the AE and the study device or drug.
- 03.04** The severity of the AE is determined based on the criteria noted in the study protocol.

APPLICABLE REGULATIONS AND GUIDELINES

The following regulations and guidelines apply to CO-SM.03 and CO-SS.04

21 CFR 312.32	IND safety reports
21 CFR 56.108	IRB functions and operations
21 CFR 56.109	IRB review of research
21 CFR 56.115	IRB records
E6 GCP 4.11	Investigator – Safety Reporting
E6 GCP 5.16	Safety Information
E6 GCP 5.17	Adverse Drug Reaction Reporting
Clinical Safety Data Management	

CO-SM.04 SERIOUS ADVERSE EVENT REPORTING

POLICY

A serious adverse event (SAE) is defined as any untoward medical occurrence that results in death, is life threatening requires in-patient hospitalization or prolongs existing hospitalization; results in persistent or significant disability or incapacitation; or is a congenital anomaly/birth defect. An important medical event may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. An AE is considered an SAE when defined as any occurrence that is not consistent with the current investigator brochure or study protocol. SAEs are reported by the investigator to the IRB and study sponsor to comply with applicable regulations and sponsor requirements. The FDA and IRB require that SAEs be reported as soon as possible but not later than 10 days following notification of an event. Most sponsors require SAEs to be reported to them within 24 hours following notification of an event.

PROCEDURE

- 04.01** Access all medical information pertaining to SAE (i.e. medical records, statements, documentation)
- 04.02** Contact the sponsor within 24 hours of knowledge of an SAE or unexpected AE by phone or FAX, unless sponsor has provided different instructions. The sponsor is required to report unexpected AEs to the FDA within 24 hours of notification.
- 04.03** Complete SAE form provided by the sponsor and fax to sponsor and Central IRB (if applicable), within 24 hours of knowledge of serious or unexpected AE.
- 04.04** If applicable, complete Form H to report SAE and submit to SHCIRC within 10 business days of knowledge of serious adverse or unexpected event.
- 04.05** In a blinded study, the PI in conjunction with the sponsor determines whether the blind needs to be broken. The blind is not disclosed unless instructed by the sponsor.
- 04.06** Subjects with an SAE may or may not be removed from the study. Any subject who is unblinded will be removed from further participation in the study.

04.07 Removal of a subject with an SAE depends on the nature of the event and is determined by the PI and sponsor.

04.08 Submit follow-up reports or information to the sponsor and IRB as soon as possible.

CO-SM.05 DRUG ACCOUNTABILITY

The investigational drug service (IDS) pharmacy is responsible for the proper receipt, storage, distribution, accountability and disposition of study drug according to policies, state and federal requirements. This procedure describes the procedure for receipt, distribution, accountability, and disposition of drugs for outpatient studies. The Policy and Procedures on Investigational Drugs 121674-#001 (Appendix D) for hospitalized patients undergoing research through SIMR will be followed as applicable. Appendix D contains documents applicable to drug receipt, storage, delivery, and transfer.

POLICY

The IDS pharmacy, under the supervision of the IDS pharmacist, will participate as a voting member of the SHCIRC, and inform the medical staff, through the pharmacy and therapeutics committee of all approved investigational drug studies. The IDS pharmacist is responsible for the safe distribution and control of investigational drugs on protocols with SHCIRC/IRB approval and will develop ongoing educational programs for medical, nursing, pharmacy, and administrative staff in the dispensing, administration and associated clinical implications of study medications and agents. Exceptions to this policy will be discussed among the IDS pharmacist, CRC, and study sponsor prior to study start-up.

PROCEDURES

- 05.01** The IDS pharmacy assumes responsibility for investigational protocol agents, dispense to outpatient subjects per investigator's instructions or the entities listed under drug dispensing as applicable, maintain drug accountability logs, and obtain unused drug returns for final disposition.
- 05.02** The IDS pharmacist maintains and updates on a monthly basis a protocol list with drug, location of drug stock, and CRC who distributes drug to the study subject. This list is distributed throughout study drug locations and a copy sent to SIMR ORA.

05.03 The following addresses are used to receive drug shipments:

Sutter Memorial Hospital Pharmacy

5151 F Street

Sacramento, CA 95819

Sutter General Hospital Pharmacy

2801 L Street

Sacramento, CA 95816

Sutter Midtown Pharmacy

2800 L Street, Suite 450

Sacramento, CA 95816

Outpatient physician offices and clinics

Investigational drugs may also be shipped to the offices of PIs provided that they have adequate facilities for proper receipt, accountability, and storage of drug. All shipping information, along with the complete study protocol and investigator's brochure is copied and forwarded to the IDS pharmacist when drug is shipped to the office of PIs.

Documentation of Delivery

05.04 Notification of investigational drugs received by doctors' offices will be forwarded to the IDS by faxing or copying original documentation from the sponsor.

05.05 The following movement of drug shipment from the IDS pharmacy is documented:

- The time it is received
- Where and when it was dispensed
- To whom it was dispensed
- What was returned to the sponsor and destroyed (other than cancer chemotherapy drug).

05.06 If drug needs to be transported from IDS Pharmacy to a remote study site (i.e. Sutter Roseville, Infusion Center, etc) without the CRC or pharmacist, obtain approval from the study sponsor to use the current SHSSR delivery system (Appendix D).

05.07 All drugs are stored in a secure, locked cabinet or designated pharmacy with access only to authorized personnel. Each drug is stored separately by protocol. If a drug is used for more than one protocol, the drug is stored separately for each protocol.

Drug dispensing

05.08 Drug is dispensed from the IDS pharmacist or PI to:

- The CRC
- The Sutter satellite pharmacy servicing the clinic
- Directly to the hospital pharmacy servicing the subject's nursing unit
- Pediatric HMO infusion clinic
- Cancer center ambulatory infusion clinic

05.09 All required documentation and drug accountability logs are completed in black ink by all individuals handling investigational drugs and forwarded to the IDS pharmacy when completed.

Drug returns

05.10 The CRC is responsible for acquisition of any unused drug from the patient.

05.11 The IDS pharmacist is responsible for study drug accountability.

APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 312.50	General responsibilities of sponsors
21 CFR 312.59	Disposition of unused supply of drug
21 CFR 312.60	General responsibilities of investigators
21 CFR 312.61	Control of the investigational drug
21 CFR 312.62	Investigator record keeping and record retention
21 CFR 312.68	Inspection of investigator's records and reports
21 CFR 312.69	Handling of controlled substances
E6 GCP 4.6	Investigator – Investigational Product (s)
E6 GCP 5.12	Sponsor – Information on Investigational Product(s)
E6 GCP 5.14	Sponsor – Supplying and Handling Investigational Product(s)

CO-SM.06 SPECIMEN PROCESSING

POLICY

It is the policy of SIMR to comply with all state and federal laws pertaining to the processing and shipping of laboratory specimens. Department managers determine the occupational exposure and required training for each employee.

PROCEDURE

- 06.01** “*Shipping Infectious and Diagnostic Specimens*” Certification is maintained by SIMR research staff involved with shipping lab specimens. Certification is updated every 2 years, as required by law.
- 06.02** Research staff receives yearly training regarding blood borne pathogens, as required by law. This training is included in the *Sutter Medical Center Annual Environment of Care (Safety) Education Checklist*.
- 06.03** Employees have access to the *Sutter Health Infection Control/Blood Borne Pathogen Manual*, as required by law. The SIMR safety officer maintains the manual and provides required training. The safety officer I also contacts the Sutter Health Safety Department to obtain yearly updates regarding blood borne pathogens and protocols.
- 06.04** Department managers update the employee occupational hazard classification annually.
- 06.05** Needlestick injuries are reported to Occupational Health (7:00-4:00) or the Emergency Department (for non-business hours). All follow-up visits are with Occupational Health.
- 06.06** Non-Needlestick injuries are reported to the regional disability manager the next business day
- 06.07** A report of injury log (*OSHA 300*) log is maintained and kept current within 14 days and is posted at each site for one month during the year.

APPLICABLE REGULATIONS AND GUIDELINES

29 CFR 1910.1030	Bloodborne pathogens
	California Code of Regulations Title 17
	SHSSR – Environment of Care Manual
	SHSSR – Infection Control Manual
	SHSSR – Policy Guidelines for Work Related Employ Injuries
49 Subtitle B Parts 105-180	RESEARCH AND SPECIAL PROGRAMS ADMINISTRATION, DEPARTMENT OF TRANSPORTATION

CO-SM.07 STUDY RECORD RETENTION/DESTRUCTION

POLICY

SIMR ORA will retain study records in accordance with Title 21 CFR or sponsor's contractual agreement; whichever is more stringent (Appendix B).

PROCEDURE

07.01 All study records are delivered to the SIMR regulatory technician for processing in a Bankers box supplied by Sutter Health's records management department and includes:

- All patient CRFs
- Patient research charts
- Regulatory binder(s)
- Investigators' brochure (including all versions)
- Investigator's binder (if available)
- Blank CRF
- Copy of blank source documents

07.02 Insert a copy of the completed "Record of Deposit" form in the box and include the following:

- Sponsor, protocol number, PI and study close out date on the first line of each page. List only one study per page.
- An individual list of all contents of the box (include patient initials and patient number).

07.03 A label the end of the box with the following information:

- Facility name (location of research)
- Department
- Record types (i.e patient records)
- Sponsor and study name
- Protocol number (if available)
- Study close out date

07.04 Study records for closed studies will be maintained on-site for a minimum of one year.

07.05 After a minimum of one year, study records are retained off- site by Sutter Health Records Management, for a period of 25 years.

CO-SM.08 STUDY CLOSURE

PROCEDURE

- 08.01** Collect drugs or devices from subjects, inventory supplies, and reconcile drug or device accountability log for each patient.
- 08.02** Follow sponsors' instructions on destruction of study drugs. IDS pharmacy provides these services, or sponsor will have drug shipped back to them at their expense for destruction.
- 08.03** Study sponsor conducts close- out visit.
- 08.04** When all queries have been resolved, the sponsor provides a letter closing the study. If no letter is received, the CRC contacts the sponsor to confirm all data have been received and documents the contact.
- 08.05** PI sends letter to IRB closing the study.

APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 312.50	Review of ongoing investigations
21 CFR 312.56	General responsibilities of sponsors
21 CFR 312.56	General responsibilities of sponsors
21 CFR 312.59	Disposition of unused supply of drug
21 CFR 312.60	Investigator record keeping and record retention
21 CFR 312.62	Investigator report
21 CFR 312.64	Investigator reports
21 CFR 312.66	Assurance of IRB review
E6 GCP 4.13	Investigator Final Report(s)
E6 GCP 4.22	Sponsor – Clinical Trial/Study Reports
E6 GCP 8.4	Essential Documents for the Conduct of a Clinical Trial – After Completion of Termination of the Trial
REFERENCES TO SIMR SOPs	
CO-SM05	Drug Accountability

QUALITY ASSURANCE

INTRODUCTION

Clear quality standards, operating processes and procedures, and oversight procedures have been established to provide guidance for SIMR to meet its goal of promoting and ensuring quality in all aspects of its operations.

The purpose of this policy is to describe the procedures in place that demonstrate SIMR's practices to ensure adherence to the policies and regulations mandated by the ICH Good Clinical Practice guidance and FDA regulations.

QA-PO PROGRAM OVERSIGHT

Program oversight includes the oversight procedures SIMR has put in place to maintain billing compliance and monitor the quality of the studies conducted at SIMR.

QA-PO.01 BILLING COMPLIANCE

POLICY

Any claim for services rendered to a participant of a clinical trial must be compliant with federal regulations and policies. To obtain this objective, departments, coordinators, and principal investigators must cooperate with SIMR Administration, provide any necessary documentation, and strictly follow any written instructions throughout the course of the clinical trial.

PURPOSE

The purpose of this policy is to describe the process that allows for the accurate processing of claims involving inpatient charges for services rendered to patients enrolled in clinical trials at SIMR. The policy also ensures that Sutter remains compliant with applicable regulations pertaining to the processing of claims for clinical trial participants.

PROCEDURE – PREPARATION FOR BILLING COMPLIANCE

- 01.1** A copy of the study budget, protocol or study schema, and Form X is obtained from the contracts and compliance coordinator or designee. The CCC collects the information from the specific department including SHC IRC administrative office, regulatory technician (RT), PI and/or CRC. If information is omitted or not properly completed on the Form X, this form is returned to the CRC for further processing.
- 01.2** For an investigational device exemption (IDE) the CCC is required to notify Sutter's fiscal intermediary (FI) prior to billing for costs associated with the clinical study.
- 01.3** The PI includes the FDA approval letter in the submission to the IRB. The FDA approval letter includes the category of the device. The categories of devices are as follows:
- Category A (experimental)
 - Category B (non-experimental)

- 01.4** Category A (experimental): The safety and effectiveness of Category A devices are not established and cannot be billed to Medicare.
- 01.5** Category B (non-experimental): The safety and effectiveness of Category B devices are assured and can be covered by Medicare.
- 01.6** For Category B devices only, the CCC submits required information to Sutter's FI, United Government Services (UGS) for approval. UGS requires the following information:
- FDA approval letter (either conditional or final/full approval letter)
 - Device Category B (specified in the first letter issued by the FDA)
 - Name of device (both trade, common or usual name, and classification name)
 - Narrative description of the device
 - Action taken to confirm to any applicable FDA special controls
 - Statement that indicates how the device is similar to and/or different from other comparable device(s)
 - Provider's protocol for obtaining the patient's informed consent specific to clinical trial
 - The SHCIRC authorization/approval letter
 - Name of the facility and it's Medicare provider number where the clinical trial will be conducted

PROCEDURE – BILLING COMPLIANCE PROCEDURES

- 01.7** The CCC writes specific requirements for billing for these studies. This includes using the appropriate revenue code and including the IDE number. The device is included on the bill either as a non-covered charge or as a covered charge depending upon the determination.

- 01.8** The specific billing requirements accompany the approval letter sent from the FI after processing the provider's submission.
- 01.9** Investigational new drug studies (IND) are automatically qualified and it is not necessary to notify the FI for these studies.
- 01.10** CCC or designee determines the non-billable or protocol induced procedures from the information in the protocol document. The PI, CRC, other appropriate personnel, and CBO are included in this process to accurately complete this task.
- 01.11** The CCC or designee creates clear and precise billing instructions using the billing instruction and Form K templates. This information is distributed to the CRC and applicable staff within each department involved in the study.
- 01.12** The CCC or designee adds SIMR (3108) as a primary payer code upon receipt of each Form K in the "billing revisions screen" in MS4 (Sutter's primary billing system). In the "insurance verification screen", the CCC or designee adds SIMR (3108) as the primary carrier by moving the patient's insurance(s) into the secondary, tertiary or fourth carrier slots. The CCC or designee updates notes in the "patient account notes screen" by informing CBO that SIMR has been designated as the primary payer and that the patient is a participant in SIMR clinical trial. CBO is instructed to follow the billing instructions pertaining to the trial.
- 01.13** If the patient's bill is not received within 10 business days after their discharge date, the CCS or designee follows up with CBO.
- 01.14** Upon receipt of the patient bill, the CCC removes any protocol that includes labs, x-rays, or procedures ordered specifically for the clinical trial from the patient's bill prior to submitting it to the insurance company.
- 01.15** Study related charges are removed regardless of whether or not the sponsor's budget covers the cost of these items. If the device is provided at no charge, then it cannot be included on the patient's bill. Other sponsor provided supplies are coded appropriately and are not billed to the patient's insurance.

- 01.16** If the sponsor does not supply the device and the provider has the approval from the FI, then insurance can be billed for the device. The charge must be comparable to that of an approved device serving the same medical purpose.
- 01.17** If the FI determined that the trial was not “qualified” and did not approve billing for the study, then the device and any related services required in preparation, use, and aftercare of the device is not billable to insurance.
- 01.18** Qualified Clinical Trials include:
- Trials funded or supported by the National Institutes of Health (NIH), Center for Disease Control (CDC), Agency for Health Care Quality (AHRQ), Center for Medicare and Medicaid Services (CMS), Department of Defense (DOD), Veterans Administration (VA).
 - Investigational New Drug Application (IND) reviewed by the FDA.
 - An IND Exemption under 21 CFR 312.2 [b], are considered “deemed” until qualifying and certifying processes are in place.
- 01.19** If the provider is receiving funds for standard of care through the study budget, these items or services cannot be included on the patient bill.
- 01.20** The CCC or designee removes study related procedures from the bill, makes a copy of the bill, sends one copy to CBO and one copy to SIMR’s financial analyst. CBO invoices all remaining charges to the patient’s insurance company.
- 01.21** To ensure billing instructions are followed, accounts are audited as per CO-QA.2.

APPLICABLE REGULATIONS AND GUIDELINES

42 CFR 405-207	Services Related to a Non-covered Device
42 CFR 405-209	Payment for a Non-experimental /Investigational (Category B) Device
42 CFR 411.406	Procedures for Medicare Contractors in Making Coverage Decisions
National Coverage Decision	Section 30-1, Routine Costs of Clinical Trials
Medicare Bulletin 402 (Clinical Trials-Medical Devices)	
Transmittal AB-00-89 (Claims Processing Instructions for Carriers, DMERCS, Intermediaries and Regional Home Health Intermediaries (RHHs) for Claims Submitted for Medicare Beneficiaries Participating in Medicare Qualifying Clinical Trials	
Transmittal AB-01-142 (Revised Guidelines for Processing Claims for Clinical Trial Routine Care Services	
REFERENCES TO SIMR SOPs	
CO-QA.2	Auditing Study Quality

QA-PO.02 AUDITING STUDY QUALITY

PURPOSE

The National Institutes of Health (NIH) require all institutions conducting clinical research to establish an internal mechanism by which their research conduct and data collection is reviewed and confirmed as meeting federal regulations and International Conference on Harmonization GCP. The Research Compliance Officer (RCO) has the responsibility of conducting institutional audits on clinical trials conducted at SHSSR. The categories of audits are:

- Protocol Compliance
- Billing Compliance
- Informed Consent
- Regulatory Compliance

The RCO is supported by the SIMR Medical Director (MD), Director, SIMR Operations (Dr) ,, and IDS pharmacist,. The RCO that will have the knowledge and ability to audit all of the above processes. The RCO will contact the personnel required in order to conduct the audit and will make arrangements to spend an appropriate amount of time auditing the selected study. Personnel contacted may include the PI, CRC, and appropriate study staff.

During the audit, the RCO refrains from discussing findings with the PI, CRC and/or the RT. However, if vital information is not available it is appropriate for the RCO to question the PI, CRC, and/or the RT to confirm its existence.

Protocol Selection Process

Any category of audit may be conducted on a study. The RCO along with the MD and DO determines the protocols selected for an audit. The three types of audits that may be performed are: 1) For cause, 2) Random selection, and 3) Directed selection.

- For cause: An audit for cause is performed for studies that are identified as having grave study conduct issues defined to be in violation of the ICH GPC guidance.
- Random selection: Any open study is subject to be selected for a random audit.
- Directed selection: A directed selection audit may be conducted on studies that are complex due to the nature of the patient population of study, standard of care, or research billing configuration.

Patient Selection Process

A random sample of 10% of the patient population is selected for auditing. When a 10% sample is less than 5 patients, the percentage is increased to include at least 5 patients in each audit sample. If a study has enrolled less than 5 patients, all patients are audited.

PROTOCOL COMPLIANCE AUDIT

The purpose of the protocol compliance audit is to ensure the study has been conducted appropriately and adheres to the federal regulations and GCP including verification that the study conduct corresponds to the protocol and all amendments as written.

PROCEDURE

Once a study has been selected for auditing, the RCO:

- 02.1** Notifies the PI and CRC of the intent to audit the study via a formal letter and e-mail. The PI and CRC are asked to assist the auditors to provide information that might not be readily available or to make known the location of study specific data that might not be obvious to the RCO..

- 02.2** Notifies the RT of the intent to audit the study via e-mail. The RT is asked to provide the protocol and all amendments to the auditor to document the evolution of the study.
- 02.3** Creates audit forms to collect the study's required information. Customized audit forms are created for each study. The exception to this is the regulatory audit, which has a standard audit form available to the auditors (Appendix E).
- 02.4** The IRB, PI, and sponsor are immediately notified when major violations are found during an audit.

BILLING COMPLIANCE AUDIT

The purpose of the billing compliance audit is to ensure that charges for study related procedures, exams, or tests generated during the study are billed to the appropriate party.

PROCEDURE

- 02.5** When a study has been selected for an audit, the RCO or designee notifies the SIMR Contracts and Compliance Specialist (CCS) of the intent to audit the study via a formal letter and e-mail.
- 02.6** The RCO can obtain a copy of the Form K, billing instructions and patient invoices for the study period.
- 02.7** The CRC, CCC and the Central Billing Office (CBO) are notified immediately when billing compliance issues are identified.

INFORMED CONSENT AUDIT

The purpose of the informed consent audit is to ensure that the consent forms were signed and dated appropriately by the patient or patient representative and a valid study consentor. This audit also compares the date of the consent against the study start date to confirm that the patient was consented prior to initiation of the research.

PROCEDURE

- 02.8** The RCO notify the PI and CRC of the intent to audit the study via a formal letter and e-mail. The PI and CRC may be asked to assist the auditors in providing information about the filing of the consent form.
- 02.9** The RCO obtain study start information to verify that the consent was signed prior to the study intervention.
- 02.10** Protocol regulatory information is obtained to ensure that study participants have signed the correct version of the consent.
- 02.11** The signature of the person conducting the consent process is validated.

REGULATORY COMPLIANCE AUDIT

The purpose of the regulatory compliance audit is to ensure all appropriate and required regulatory documentation is available in the regulatory binders, all protocol amendments are consistent between the sponsor and the IRB submissions, and that all information in the regulatory binder is updated and current.

PROCEDURE

- 02.12** The RCO notifies the PI, CRC, and the RT of the intent to audit the study via e-mail and formal letter.
- 02.13** The RCO obtains a standard regulatory audit form and modifies this as needed.
- 02.14** The RCO requests a date, time and place to review the regulatory binder from the RT.
- 02.15** The IRB, PI, and sponsor are notified when major violations are identified.

AUDIT FINDINGS

- 02.16** The results of all audits are summarized in an audit report prepared by the RCO (Appendix E). The report is signed and dated by the RCO and DO.
- 02.17** An audit findings letter and report is sent to the PI for review and comments.
- 02.18** The PI is given the opportunity to respond to the findings within a specified period of time.
- 02.19** The PO reviews the PI's responses and signs and dates a final letter and issues it to the PI, MD, and IRB.
- 02.20** The IRB keeps the RCO and DO informed of actions and outcomes directly related to the information provided by the audit.
- 02.21** All information provided by the IRB is documented and included in the study's audit file.
- 02.22** The results of all audits are included in the semiannual report to the Medical Policy Committee.

APPLICABLE REGULATIONS AND GUIDELINES

ICH GCP 4.5	Protocol Compliance
ICH GCP 4.8	Informed Consent of Trial Subjects
ICH GCP 4.9	Records and Reports
ICH GCP 4.11	Safety Reporting
ICH GCP 8.1	Essential Documents – Before the Clinical Phase of Trial Commences
ICH GCP 8.2	Essential Documents – During the Clinical Conduct of Trial
ICH GCP 8.3	Essential Documents – After Completion or Termination of the Trial
21 CFR 50.20	General Requirements of the Informed Consent (IC)
21 CFR 50.23	Exceptions from General Requirements (IC)
21 CFR 50.27	Documentation of the Informed Consent (IC)
REFERENCES TO SIMR SOPs	
CO-SS.02	Regulatory Submission Process
CO-SS.07	Adult Informed Consent
CO-SS.08	Surrogate Consent
CO-SS.09	Pediatric Informed Consent
CO-SS.10	Pediatric Assent
CO-SM.01	Records and Case Report Forms
CO-SM.03	Adverse Event Reporting
CO-SM.03	Serious Adverse Event Reporting
CO-QA.01	Billing Compliance