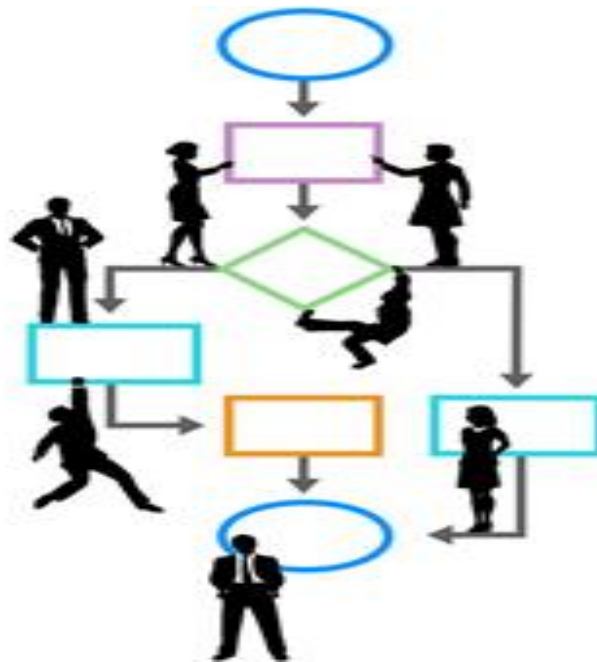


Upcoming Trainings from CRRO

- Informed Consent Regulations and Procedures workshop, **Oct. 15** (3 hours)
- FDA Drug and Device Application workshop, **Oct. 23**
- DSMPs and AE monitoring and reporting for biomedical research workshop, **Nov. 12** (3 hours)
- Fundamentals in the Conduct of Clinical Research, **Dec. 7 and Dec. 14** (2 half days)
- The PI Role, **a ½-day in Feb (tbd)**

Sign up for early-bird notification on CRRO website.



Standard Operating Procedures in Clinical Research

Mary-Tara Roth, RN, MSN, MPH

Director, Clinical Research Resources Office (CRRO)

BU Medical Center

Overview of the Session

- What are Standard Operating Procedures (SOPs)?
- SOPs and MOPs
- Regs and guidance on SOPs
- Components of SOPs
- How to write an SOP



Standard Operating Procedures

- One key objective in conducting clinical trials is the generation of quality data
 - Quality has to be built into a protocol from the outset.
- Another objective is to keep research subjects safe by minimizing risks.
- The SOP is a tool used to **document the processes adopted for the initiation, conduct, and reporting of clinical trials**
 - Ensuring compliance with regs, policies, guidance, best practices

SOPs ... Definitions

- ICH GCP promotes the development and maintenance of SOPs and defines them as: “Detailed instructions to achieve uniformity of performance of a specific function.” ICH GCP 1.55
- FDA regs pertaining to cGMPs: “..... written procedures that accurately describe and detail essential job tasks.” DC Peterson, 9/2/06 BioPharm International
- “...written instructions that identify the activities and responsibilities needed to achieve a standard, controlled procedure that ensures compliance to GCP and applicable regulatory requirements and reflects business needs in support of clinical research.” S. Prokscha in Writing and Managing SOPs for GCP

Regulatory Requirements for SOPs

- FDA:
 - SOPs not a stated requirement for investigators in regs
 - IDE (device) regs require sponsors to have written procedures for monitoring of device trials
 - 21 CFR 812.25(e)
 - IND (drug) regs only say that sponsors must have monitoring procedures
 - 21 CFR 312.50 and 21 CFR 812.40
 - However: written procedures are inferred for sponsors and investigators....
 - Stated requirements of investigators and sponsors should have processes to back these requirements up

Regulatory Requirements for SOPs

- FDA guidance on Investigator Responsibilities (Oct. 2009) has as multiple references to procedures for “adequate supervision for the conduct” of a trial:
 - The **investigator should develop a plan for supervision and oversight of the clinical trial at the site**..... A plan might include the following elements.....: a procedure for the timely correction and documentation of problems identified by study personnel, outside monitors or auditors, or other parties involved in the conduct of a study
 - A **procedure** for documenting or reviewing the performance of delegated tasks in a satisfactory and timely manner...
 - A **procedure** for ensuring that the consent process is being conducted in accordance with 21 CFR part 50 and that study subjects understand the nature of their participation and the risks
 - A **procedure** for ensuring that source data are accurate, contemporaneous, and original
 - **Procedures** for ensuring study staff comply with the protocol and adverse event assessment and reporting.....

Regulatory Requirements for SOPs

- OHRP:
 - IRB requirements for written procedures
 - 45 CFR 46.108, 46.103 (b)(4), and 46.103 (b)(5)
 - Guidance on Written IRB Procedures (7/1/11)

Regulatory Requirements for SOPs

- ICH GCP:
 - “The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs....” Section 5.1.1
 - This is guidance; however if it is written in your protocol that you must follow GCP
- NIH Policy:
 - Stipulates that a system be in place for appropriate oversight and monitoring to ensure the safety of participants and the validity and integrity of the data in all NIH-supported or conducted trials
 - Also requires MOPs for multicenter trials (recommended for single center)

Why SOPs?/Benefits of SOPs

- In some cases they are a regulatory requirement
- Provides a written record of processes used to conduct the trial
- Promotes consistency/reproducibility: within sites and between sites
- Enhance reliability of data
- Helps sites follow protocol-specific parameters (which might be different from clinical procedures)
- Increases confidence (of staff and sponsor); enhanced performance of staff; increased quality of data
- Aids in training of new staff
- Reduces supervisory time and effort
- Serves as a historical record
- Demonstrates compliance with applicable regulations, guidance (such as Good Clinical Practice (GCP)), institutional policies, etc.

- Sajdak et al. 2013 J Nucl Med Technol

- S. Proksha in Writing and Managing SOPs for GCP

Components of SOP

- Make a template:
 - Intro/Purpose: why is policy needed; background
 - Scope: What is covered? What are limitations or exceptions?
 - Definitions/Abbreviations
 - Applicable regs and guidelines
 - Responsible parties
 - Process/Procedures
 - Title, header, footer, version #, signatures (author and authorizing individual), dates original version, revision, effective, approved, etc.)
 - References (including other SOPs and regulations)
 - Appendix/Attachments

Clinical Translational Research Center TraCS Institute	Approved by: Administrative Director and Nursing Director
SOP Title and #: Guidelines for Urine Pregnancy Testing in the CTRC	Revisions:
Effective Date: 4/1/2009	Page 1 of 2

- I. **Purpose:** This Standard Operating Procedure (SOP) describes the activities and identifies the individuals responsible for urine pregnancy testing at the Clinical and Translational Research Center (CTRC).
- II. **Scope:** This SOP applies to the procedures for urine pregnancy testing and documentation of the findings at the CTRC.
- III. **Applicability:** Female subjects participating in research studies performed on the CTRC are frequently required to have pregnancy testing performed prior to study entry, performance of a study procedure, or medication administration. Urine pregnancy testing performed on the CTRC will help facilitate the start of studies and could decrease a patient's length of stay on the CTRC. All CTRC nursing staff will be trained on the proper urine testing procedure as outlined in the UNC Hospital policy and procedure manual. The policy and procedure manuals of the McLendon Laboratory may be accessed at http://intranet.unchealthcare.org/policies/mclendon_policies_general
- IV. Annual competency testing will be provided by the Point-of-Care Committee to assure all CTRC nurses can competently and accurately perform urine pregnancy testing. Accurate specimen collection and proper handling of such specimens is imperative for all research studies in order to avoid any errors or protocol deviations that could occur. The CTRC will continue to offer serum beta hCG testing if required by sponsor.
- V. **Responsible Parties:** CTRC nursing staff and dietary staff trained in the procedure of urine pregnancy testing and quality assurance who will be using the hospital provided equipment and follow UNC Health Care policy and procedure guidelines.
- VI. **Procedures:**
 - A. Industry sponsored studies providing their own urine pregnancy kits should be performed by the study staff. Only study staff will be allowed to perform urine pregnancy testing using sponsor provided kits. The CTRC staff cannot perform any urine pregnancy testing by kits, which are not approved by McLendon Laboratory.
 - B. If a CTRC staff member is performing a procedure that includes risk to a fetus, women of childbearing potential must have a urine pregnancy test performed by CTRC nursing staff or a pregnancy test performed by UNC Hospitals McLendon Laboratories, with results confirmed as negative, prior to having the a procedure performed. Such procedures include, but are not limited to, DEXA scans and dosing of certain medications.
 - C. CTRC trained staff will only perform urine pregnancy testing using hospital approved equipment (Bayer Clinitek) and supplies (pregnancy test cartridges from central distribution order # 050435) Therefore, study staff must get sponsor permission to use hospital supplied testing materials if CTRC staff are to perform the test.



Policy #:	39.04.462
Issued:	April 2014
Reviewed:	
Revised:	
Section:	39 Research

Research Participant Compensation

Purpose:

This policy is to establish guidance and outline the process for obtaining compensation for human subjects participating in research and provide guidelines to establishing an appropriate incentive payment to participants. The goal is to provide efficient and cost effective means of providing compensation while maintaining internal controls and compliance with Internal Revenue Service (IRS) laws.

Policy Statement:

Research Participants may be compensated for time and inconvenience associated with participation in a clinical study, with the payments in the form of cash or non-cash. While it is not required that all participants receive compensation for their participation, the IRB recognizes that participants do incur costs when involved in research studies. Compensation is mainly used to offset expenses due to travel, meals, time and/or lost revenue and must be appropriate. Excessive compensation may be viewed as inducement and can place unnecessary pressure on the participant to participate/remain in the clinical study.

Reimbursement:

Payment to a research participant for expenses incurred as a result of their participation in a study (ex. Parking, transportation, meals, lodging, etc.). Reimbursements must be processed via check requisitions with receipts or other valid documentation attached. Reimbursements for actual expenses are not considered taxable income. Parking vouchers are recommended whenever possible so participants do not need to be reimbursed at a later date. Contact the parking office (x8-4915) to purchase vouchers.

Compensation/Incentive:

Payment to research participants for participation in studies is considered a recruitment incentive. Compensation may be in the form of cash or cash equivalent and is considered taxable income. Compensation is a predetermined amount defined within the project for time, effort, inconvenience and general expense to participate in a research study

MOPs

- MOP = Manual of Procedures

(some say Manual of Operations and Procedures)

- Handbook that details a study's conduct and operations as well as facilitates consistency in protocol implementation and data collection across study participants and sites
- Transforms protocol into a guideline that describes each step of the study and how it is to be executed.
- (See NIA Toolkit link at end with excellent templates for MOP development)



SOPs vs MOPs

- SOPs are based on applying regs, guidance, best practices, institutional policies to a certain topic....
- MOP is based on detailing the protocol
- SOPs outline general processes applicable to all studies
- MOP details processes in one protocol
- SOPs change infrequently
- MOP changes frequently, following life of study

The SOP Development Process

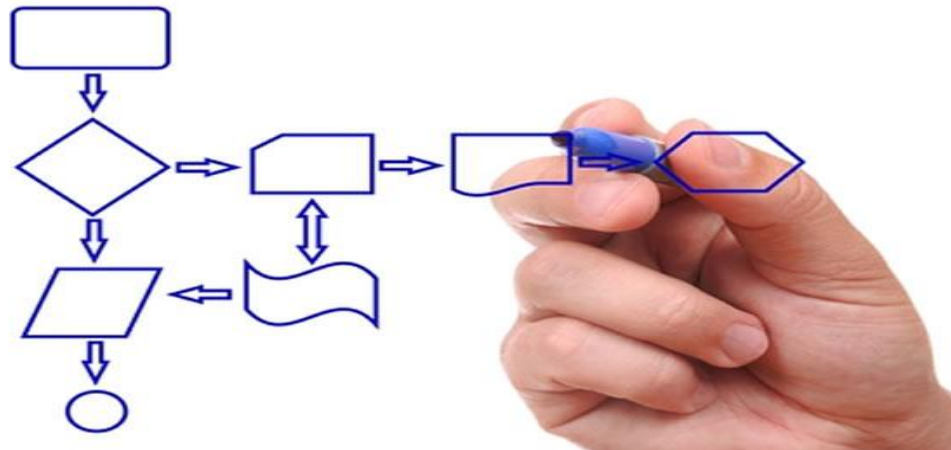
- Identify the people who will be responsible for oversight and development
- Figure out what processes you need to document with an SOP
- Spend time defining your processes
 - Develop a process flowchart (“Process mapping”)
- Make sure to cover:
 - review times,
 - how you’ll handle SOP exceptions and deviations,
 - how SOP review and approval will be handled
- Define standard SOP format and process
 - SOP on SOPs

Developing SOPs

- ID task...
- ID relevant regs, guidance, policies, best practices for which the SOP is designed to ensure compliance
- ID purpose of SOP
- ID responsible parties who will follow SOP
- Process mapping
- Write high-level instructions (consider end-user as author)
- List other SOPs, work instructions, or forms that may be related
- Ensure title, header, footer, version #, effective date are correct
- Review, sign, date by person(s) in authority
- Communicate: distribute and train on SOPs, (document!)
- Review SOPs as needed and w/in predetermined timeframe

Process Mapping

- Lay out the steps in the process
- Analyze the process with goal of making it more efficient/easier to follow
- Involve all individuals who do the task in the mapping exercise
- Identify primary steps to the process
- Identify secondary details to ensure consistency when needed
- Add responsible individuals at each step (use titles, roles, not names)
- Convert to outline form
- This is the basis of your Process/Procedures section of the SOP document



KE Woodin, CRC's Guide to Coordinating Clinical Research, 2009

Makin' the Coffee



What process needs to be followed to get this result every time?

KE Woodin, CRC's Guide to Coordinating Clinical Research, 2009

Writing SOPs

Think: Baby Bear....



Not too much detail

Not too little detail

Juuuuuust the right amount of detail

Can someone who is new to the process/procedure complete the process/procedure successfully when on their own?

(And not be overwhelmed by too much detail?)

Writing SOPs

- Keep language concise
- Step-by-step description
- Plain language
- Use active voice
- Use titles instead of names

Keep in mind/Best Practices

- SOPs are different than guidance and best practices; they are auditable
 - FDA, OHRP, IRB audits will all hold study teams accountable to their SOPs
 - Provide sufficient detail but allow for expected variations
- Make an SOP on your SOP development and maintenance process
- Make your SOPs easy to access by those who need to follow them
- Make sure you have a version control process to ensure that staff are following the correct processes! (This can be described in your SOP on SOPs)
- An existing, beautifully written, SOP \neq Compliance:
 - **Communication, training, easy access are key!**
- Keep all outdated versions
 - And stamp them as such so they are not used in place of current versions!

Sometimes SOPs are created in response to identified problems....

- Don't waste your time if you're not going to do it right....



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

In your September 12, 2013, written response to the Form FDA 483, you did not provide any explanation for the delay in this subject's visit. However, you did acknowledge that problems with scheduling occurred. You noted that you have taken corrective action and that, as part of that corrective action, you hold weekly meetings with study staff and include the study staff in your weekly meetings with clinic staff. You also stated that you have Standard Operating Procedures (SOPs) on assessments, and that you, as well as the study staff, were retrained on this SOP.

Your response is inadequate because you have not provided documentation of any extraordinary events, or of any discussion with the medical monitor to determine maximum visit-window deviation in this case. In addition, you have not provided sufficient details about your corrective action plan. You have not provided a copy of the SOP on assessments, which you indicated that you have in place and on which you and your staff have been retrained, nor have you provided any details about that training. Without those details, we are unable to determine whether your corrective action is adequate to prevent similar violations in the future.

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Specifically, you failed to adequately supervise individuals to whom you delegated study tasks. Your failure to adequately supervise the conduct of the studies referenced above led to many of the violations noted in this letter. These violations include, but are not limited to, enrollment of ineligible subjects in Protocols (b)(4) and (b)(4) and failure to take adequate precautions to prevent theft or diversion of the investigational drug (b)(4), a Schedule II controlled substance. Had you provided adequate oversight, you may have been able to prevent many of these violations from occurring.

In your June 3, 2013 written response to the Form FDA 483, you explained that one probable cause of the protocol violations was lack of proper supervision due to lack of or limited clinical investigator experience and supervision in delegating responsibilities to unqualified staff. You also noted that you increased your supervision of clinical research, that you and your staff were retrained, and that you implemented new standard operating procedures about delegation of responsibilities, investigator and sub-investigator responsibilities, investigator review of essential study documents, source document and case report form creation, pharmacy operations and pharmacy diversion policy.

Your written response is inadequate because your corrective action plan is not sufficient to prevent similar violations in the future. Specifically, we find your Standard Operating Procedures (SOPs) insufficient and note that you did not provide details regarding the training that you and your staff underwent.

Your SOP titled "Principal Investigator and Sub-Investigator Responsibilities" does not address how you personally will ensure adequate oversight of study procedures, activities of study coordinators and protocol training for you and your study staff. In addition, your SOP lists some responsibilities of a clinical investigator, and states that it is not an all-inclusive list. However, please note that you are responsible for compliance with all regulations applicable to your conduct as a clinical investigator, not just those which are listed as responsibilities in your SOP.

Regarding the training that you and your staff underwent, you did not provide details regarding the training. Without having the details of this training, we are unable to determine whether it appears adequate to help prevent similar violations in the future.

As the clinical investigator, it was your ultimate responsibility to ensure that these studies were conducted properly and in compliance with FDA regulations to protect the rights, safety, and welfare of study subjects and ensure the integrity of study data. Your lack of supervision and oversight over the clinical studies raises significant concerns about the adequacy of your protection of study subjects enrolled at your site in the studies mentioned above, and also raises concerns about the integrity of the data generated at your site.



WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

During the inspection, you stated:

"[A]ll study related records and source data pertaining to protocol (b)(4) at our site were shredded, including, but not limited to: signed informed consent forms, subject diary cards, records of screening results, documentation of assessments at additional study related visits, and laboratory test results. This data is not retrievable and was not available for inspection. Due to the destroyed study records, [the FDA investigator] was not able to verify the study data for protocol (b)(4), or the existence of signed informed consent forms during the inspection."

During the inspection, your study coordinator provided Investigator Babbitt with a copy of a Standard Operating Procedure (SOP), signed by you and with an effective date of October 30, 2008, for study-record retention. We are concerned that this SOP appears to be insufficiently detailed to prevent similar violations in future studies. Of note, based on the description you provided during the inspection, the boxes of study records that were shredded were labeled with pertinent identifying study information, such as sponsor, date range of the study, subject numbers, and protocol number. Your SOP for study-record retention does not address how you will ensure that boxes of study records that are appropriately labeled will not be shredded erroneously in the future.

Failure to retain study records as required by FDA regulations compromises the validity and integrity of data significantly. Because you failed to retain drug accountability records and case histories for both studies, we consider the data generated at your site for Protocols (b)(4) and (b)(4) unreliable in support of a research or marketing application.

In CRRO website go to Regulatory Tools and Resources, then to Study Documentation: Regulatory Binder, and there is a list of templates of assist you in documentation.

Study name: [Redacted]
 Study ID #: [Redacted]

Study PI: [Redacted]

Staff Member Training Log

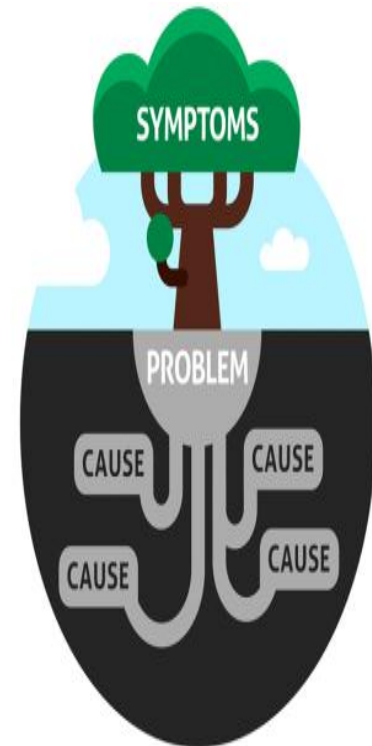
This log documents training of individual staff members. To record specific training for an entire group (if easier) refer to "Staff Training Log for Groups."

Study Staff Member Name: [Redacted]

Date Training	Description of Training	Expiration date (if applicable)	Initials

If creating an SOP in response to identified problems....

- Make sure you have done due diligence to understanding the root cause(s)
- Make sure to develop your CAP based on your root cause analysis
- Make sure that your SOP properly details procedures to ensure that the problem is fixed
- Make sure to **document** that you have communicated this SOP and new procedures through formal training of staff
- Audit your procedures to ensure that the CAP is successful (and **document** the results!)



Examples of Clinical Research SOPs

- SOP on SOPs
- AE assessment documentation and reporting
- Protocol deviation assessment documentation and reporting
- Informed consent process and documentation
- Screening and recruitment
- Specific study procedures
 - e.g. Exercise tolerance test; measurement of BP
- Data entry of CRFs to electronic database
- Drug/device accountability
- Recruitment material review process
- Loss to follow-up procedures and documentation
- Study staff training
- Audits: Sponsor, CRO, internal, FDA, etc.
- Form control
- IRB submissions
- Study documentation and corrections
- Storage and destruction of research records

For more info try these great sites:

- Writing SOPs for Clinical Trials:
<https://www.michr.umich.edu/services/projectmanagement/clinicalresearchmanagement/resourcecenter/sops> (Michigan Institute for Clinical & Health Research)
- SOPs for Clinical Trials:
<http://globalhealth.duke.edu/standard-operating-procedures-clinical-trials-sops> (Duke Global Health)
- SOPs:
<https://hub.ucsf.edu/sops> (UCSF)
- MOP Outline and Guidelines:
<https://www.nia.nih.gov/research/dgcg/clinical-research-study-investigators-toolbox/startup> (NIA)

Questions?