Establishment of a Quality Systems approach to Clinical Site Management – An Overview of Standard Operating Procedures (SOPs)

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Learning Objectives:

- Define what a “Quality System” is
- Understand what role SOP’s Play in Site Management
- Understand the “How-To” of SOP’s
- Learn the Pitfalls of SOP’s and Best Practices
Quality System Approach to Clinical Site Management

- Examples of Regulations and Guidelines that embody the principles of the Quality System;
  - 21 CFR Part 820 Regulation for Medical Devices
  - ISO 13485 Standard for Manufacturers of Medical Devices
  - ICH Guideline E6 for Good Clinical Practice
  - ICH Guideline Q10 Pharmaceutical Quality System
What is a Quality System???

A systematic written program of Standard Operating Procedures that define the controls for a given process or set of processes.
The Process of Conducting Clinical Trials involves among other things:

- Protocol Adherence
- Informed Consent
- IRB Approval of Research
- Institutional Policies
- Drug Supply Handling and Accountability
- Adverse Event Reporting
- Safety Reporting
- Budgets / Contracts
Benefits of SOP’s

- Provides a standard method for executing key tasks
- Inserts a level of control over a given process
- Requires periodic review to manage change
- Can be used as a training vehicle for new employees
Periodic (Quality System) Review

- Management review of the effectiveness of SOP’s (At least every 2 years)
  - Review CAPA’s
  - Complaint files
  - Results of Audits
  - Monitoring visits
Periodic Review (continued)

- Based on review of the aforementioned data make informed decisions on improving methods (SOP’s);
  - Adding Additional controls
  - Relaxing some controls
  - Assess adequacy of the existing Quality System.
How to make it happen

- Must take full ownership of the SOP’s (Live them).
- SOP’s are no good if they are not followed.
- Failure to follow the SOP’s are a frequent audit finding.
Standard Operating Procedures
Standard Operating Procedures (SOPs)

- SOPs should be considered for all aspects of running clinical trials
- Need centrally by the organization managing the overall conduct of the study, at the site level, and by all vendors (central lab, ECG, electronic diaries)

Ref: Good Clinical Practice: Standard Operating Procedures for Clinical Researchers; by Josef Kolman, Paul Meng, and Graeme Scott (Kindle Edition - Jun 15, 1998)
Purpose for having SOPs

- Ensures standardized approach for completing same tasks by all employees responsible
- Ensures compliance with regulations; sets framework for adhering to GXPs
- Ensures comprehensive training of new staff
Typical Site SOPs

- Development and Administration of Standard Operating Procedures
- Managing Regulatory Inspections (FDA, Health Canada etc....)
- Managing Sponsor Audits (e.g. pharmaceutical, NIH, etc)
- Training and Personnel Training Records
- Archiving, Retention, Retrieval and Security of Study Documents
- Process for IRB Submission
- Participation in a Monitoring Visit
- Set up and Maintenance of the Investigator Site File (ISF)
- Adverse Events/Serious Events Reporting Process
- Informed Consent/Consenting Process
- Site Signature Log - Delegation of Authority
- Physical Exams (document who can do them, sign off etc.)
- Investigational Product Accountability
- Documentation for Receipt, Transfer and Return of Investigational Product
- Temperature Monitoring of Investigational Product
Typical Site SOPs

- Documenting Study Specific Contacts
- Subject Stipends Subject
- Lost to Follow-up (SOP documents all the action taken by site to attempt to get subject to come in for the final visit etc...how many calls, and certified letters must be sent before the site considers the subject LTFU)
- Leave Against Medical Advice (if an inpatient study and the patient leaves prior to completion study and they leave against medical advice, what is the process and what form does the patient sign releasing the PI, institution from responsibility)
- Maintenance of Equipment (inspections, calibration, cleaning etc....details for each piece of equipment used in a trial..including scales, BP equipment, ECG machines, DEXA machines etc.)
- Protection of Subject Personal Data
- Information Systems (general infrastructure, security, passwords protection etc.)
- CAPA Corrective and Preventive Actions
Standard Operating Procedures

SOP Best Practices and Challenges
Value of Quality System (SOP) Development

- Our CMSU Quality System provides the framework that assures:
  - cGMP compliance
  - Individual and team effectiveness
  - Controlled processes
  - Client assurance and confidence
  - Delivery of consistently accurate results
SOP Best Practices

- SOP Author should be process expert
- Approvers must include upper mgt.
- Review by users as well as approvers
- Reduce the number of “touches”:
  - Place WORD doc. in a central electronic folder so all reviewers comment on same file
  - Use tracked changes feature of WORD for input during review process
SOP Best Practices

Once approved:

- Original WORD doc. must have limited access
- Final Draft can be used for training
- SOP becomes effective AFTER training
- Make current approved SOP available to users in (pdf format)
Where Do You Begin?

- CMSU currently has 55 SOPs
- Clinical Sites: approximately 20 (see slides 13 & 14)
- CMSU SOPs are divided into applic.areas
  - SU - Supply Unit (general CMSU SOP that applies across all functional groups)
  - CS - Clinical Supply Operations
  - QA - Quality Assurance
  - IT - Information Technology
# Develop a Training Matrix

<table>
<thead>
<tr>
<th>SOP-QA-016</th>
<th>Transfer of Clinical Supplies from One Site for Use by Another</th>
<th>Executive Director Strategic Initiatives, CTCC</th>
<th>Regulatory &amp; Technical Affairs, Director</th>
<th>QA Associate Director, CMSU</th>
<th>Clinical &amp; Business Affairs, Director</th>
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<th><strong>Temp/Clerical</strong></th>
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Where Do You Begin?

- First Step….Develop an SOP for SOP’s

Example: SOP-SU-001 CMSU Document Management, Change Control and Training Procedure

Describes the Process for:

- Creating
- Approving and Controlling
- Training
- Maintaining (revisions, version control)
- Periodic Review (Insures cont. compliance)
STANDARD OPERATING PROCEDURE

SOP TITLE Here

Approvals:

Author:

Joan Woodcook
Associate Director, QA, CMSU

Approved By:

Tim Hackett
Director, Regulatory & Technical Affairs, CMSU

Approved By:

Patrick Bolger, R.Ph., MBA
Director, Clinical & Business Affairs, CMSU

Approved By:

Cornelia Karn
MBA Executive Director Strategic Initiatives, CTCC

NOTE:

+ Document is released for training on the Issue Date (date of final QA signature)
+ Document becomes the official version for use on the Effective Date
+ Document must undergo review every two years (ref SOP-SU-001)

Table of Contents

1 Purpose
   1.1 This section specifies the purpose of the SOP

2 Scope
   2.1 This section describes the scope of the SOP.

3 Responsibilities
   3.1 The Manager of the Quality Assurance Unit is responsible for

4 Applicable Standards, Regulations and Guidelines
   4.1 21 CFR

5 Definitions and Abbreviations
   5.1 CMSU: Clinical Materials Services Unit

6 Materials (if applicable)
   6.1

7 Procedure
   7.1 Fill in the procedure here.
      7.1.1 Fill in sub-steps here.
      7.1.2 Fill in sub-steps here.

8 SOPs and Forms referenced in this Document
   8.1

9 Version History

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<th>Effective Date</th>
<th>Changed By</th>
<th>Change Description</th>
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Std. Table of Contents for SOPs

- 1 Purpose
- 2 Scope
- 3 Responsibilities
- 4 Applicable Standards, Regulations and Guidelines
- 5 Definitions and Abbreviations
- 6 Materials (if applicable)
- 7 Procedure
- 8 SOPs and Forms referenced in this Document
- 9 Version History
What YOUR SOP-XX-001 Structure Can Look Like:

1. Purpose

- To provide a process for the creation, review, approval, training, control of changes and maintenance of the Standard Operating Procedures critical to the Process of Conducting Clinical Trials.
What YOUR SOP-XX-001 Structure Can Look Like:

2. Scope e.g.

- SOP applies to controlled docs. which are critical to the mgt. of study activities at Clinical Study Site XXXX.

- This procedure includes instructions for: document preparation, numbering, formatting, change control, reviewing, approval, access, implementation, training, deleting, and archiving.
Cont. 2. SCOPE

ADD A STATEMENT REGARDING CONFIDENTIALITY:

These documents are confidential and proprietary Site XXX documents, therefore, distribution to parties not directly involved in the relevant study and/or to third parties (e.g., external auditors) must be controlled.
3. RESPONSIBILITIES:

- Must Define Who:
  - Ensures content reflects current practices of the department
  - Must comply with SOP
  - Ensures SOP is followed and that all relevant personnel are trained
  - Manages the process defined in this SOP and insures that the site is current and compliant with GXPs and other applicable standards.
4. APPLICABLE STANDARDS, REGULATIONS AND GUIDELINES FOR CLINICAL SITES

- Add references to any applicable Institutional Policies and Procedures
- ICH Guideline E6 for Good Clinical Practice
- ICH Guideline Q10 Pharmaceutical Quality System
5. DEFINITIONS & ABBREVIATIONS

- The Clinical Study world is full of acronyms and abbreviations
- Staff need to speak the same “language”
- Define unique institutional language
- Very valuable to new personnel

6. Materials – reference if applicable
7. PROCEDURE

- 7.1 Creation, Review and Approval of New SOPs
- 7.2 Document Revision Process
- 7.3 Training
- 7.4 Implementation and Distribution
- 7.5 Periodic Review
- 7.6 Deletion
- 7.7 Numbering System
- 7.8 Format
- 7.9 Administration and Records
7.1 Creation, Review and Approval of New SOPs

- Describe Who (*use job titles*) Can/Should Create SOPs
- Who will oversee the SOP development process and provide guidance as needed.
- Who the signatories/approvers are
- What the draft file name structure is and where it should be saved so reviewers can access it
- How Review Period duration is determined
- How Author and Reviewers notify each other of progress
- How reviewer comments are addressed and final signature draft is prepared and circulated for signature
7.2 Document Revision Process

- Describe how *major* and *minor* changes to an SOP can be effected
- How to document changes (e.g. Change of Document form, COD)
- Who reviews and how changes are approved
- Describe file name structure and version control
7.3 Training

- Define who conducts training and what kind of training is needed
  - Live group session for new SOPs, SOPs with significant revisions
  - Read and Understand self-directed training for minor changes
- How training is documented
- Approvers are exempt from training but may want to attend live sessions to address ?s
7.4 Implementation and Distribution

- Describe how the “wet ink” copy is handled and filed
- Describe how the Final Approved WORD file is saved and stored electronically
- Describe how to handle superseded versions (both hard copy and WORD files)
- Describe how hard copies are distributed and controlled.
- Describe how to control the master list of SOPs
7.5 Periodic Review

- Quality system calls for routine review of SOPs to insure they are current.
- Typical cycle is every 2 years
- This section describes how that is accomplished and documented
Sections 7.6 – 7.9

- 7.6 Deletion: Process for retiring SOPs
- 7.7 Numbering System: Process for assigning SOP numbers (maintaining assignment log)
- 7.8 Format: Describes where SOP/document templates are stored electronically
- 7.9 Administration and Records: describes who is responsible for archiving, filing, maintaining and destroying all files
Last Sections:

8. SOPs/Forms referenced in this SOP
   - List which allows you to determine what other docs. may be affected by changes to this SOP

9. Version History
   - Simple table to capture: versions, date effective, who made changes, brief description of changes and reason(s) for changes
SOP CHALLENGES

- Time Available to Create and Manage:
  - Must have site management support
  - Management must be *publically* supportive
  - Must have staff fully invested

- How Much Detail?
  - Too much = too complex
  - Too little = insufficient guidance
  - BOTH lead to Non-Compliance
SOP CHALLENGES

- Availability of Reviewers to complete review within designated time-frame
- Ensuring Periodic Reviews are completed in a timely manner
  - Very common audit finding
- Controlling Distribution
  - How to make current SOPs accessible
  - How to insure no old versions are in use
BENEFITS

- SOPs provide training materials to ensure comprehensive and consistent training
  - Fresh eyes provide continuous improvement suggestions and ideas
- Provide the framework to ensure compliance to GXPs
- Common understanding of what has to be done, how to do it and why it is important
BENEFITS

- Seamless Audits!
- All lead to High Team Performance!
thank you!