THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

# SOP-18: Clinical Research Audits

## 1. Objective

To ensure that the Principal Investigator (PI) and all research team members assisting in the conduct of clinical research are informed about their obligations and responsibilities as they pertain to Good Clinical Practices (GCP), the investigational plan, applicable regulations, guidances, and institutional policies. This Standard Operating Procedure (SOP) applies to the written procedures followed by all members of a clinical research team involved in the conduct of human subjects' research at The Ohio State University Wexner Medical Center (OSUWMC), hereafter called the investigational site. These detailed instructions promote compliance in conducting clinical research.

**SOP-18** describes the process for preparing and participating in an audit (including internal, sponsor, IRB or FDA) for clinical research. Attachment templates include:

**A: Audit Preparation Checklist**
**B: FDA Inspection Notification Form**

## 2. Responsibility

The College of Medicine Clinical Trials Management Organization (COM-CTMO) develops, implements, and maintains SOPs. The need to write a new or revise an existing SOP is based upon changes to federal regulations, guidelines, institutional policies, or procedures. These documents will be provided to departments and research teams conducting human subjects' research. Departments or research teams may develop additional research SOPs or a Research Procedure Addendum (RPA) to expand on an existing SOP, however this need should be limited.

The PI is ultimately accountable for all clinical research activities and is responsible for the appropriate delegation of tasks to individuals with adequate training and education to perform such tasks. It is the responsibility of all members of the clinical research team involved in supervising, managing, or conducting study-related activities to follow the SOPs. The clinical research team may include but is not limited to the following members:

**Research Team Members**

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|---|---|
| Principal Investigator (PI) | Clinical Research Coordinator (CRC) |
| Sub-Investigator (Sub-I) | Clinical Research Assistant (CRA) |
| Clinical Research Manager (CRM) | Other Research Staff as appropriate |
| Clinical Research Specialist (CRS) | Administrative and Support Staff |

## 3. Definitions

Please refer to the SOP Glossary document for detailed definitions of commonly used clinical research terminology.

## 4. Procedures

### A. Preparing for an Audit

The PI and delegated research team members will permit monitoring and auditing by the sponsor, the IRB, and all appropriate regulatory authorities, including the FDA. The PI and delegated research team members will maintain a list of appropriately qualified persons to whom the PI has delegated significant clinical research study-related duties. The investigational site will work with the auditor or inspector to arrange a mutually agreed upon date and time to conduct the audit.

If the investigational site is notified of an audit, the PI or delegated research team member should obtain, at a minimum, the following information:

- Purpose of the audit
- Contact information of auditor(s)
- Planned number of auditor(s)
- Anticipated number of days or duration of audit

The investigational site will schedule an appropriate room for the audit that is away from clinical activity and in a private setting. They will also schedule any meetings with key personnel requested by the auditor.

The primary research team member assigned to the clinical research study should be the main point of contact for scheduling and organizing the audit and will notify all appropriate members of the study team immediately (e.g., PI, Sub-investigators, other research team members engaged in the study, direct supervisor, Research Director and Medical Director, Office of Responsible Research Practices (ORRP) College of Medicine Office of Research (COMOR) and the IRB).

An agreement should be secured from all involved parties to ensure direct access to all clinical research study-related sites, source documentation, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by regulatory authorities.

The PI and delegated research team members will prepare for the scheduled auditing visit by ensuring that all clinical research study related documents are current, organized, complete and accurate prior to the visit. They will also ensure that all original, relevant source documents and all clinical research study related documents are requested and available to the auditor during the visit *(See Attachment A: Audit Preparation Checklist)*.

If necessary, the PI or delegated research team member will request auditor access to the electronic medical record to review source documents directly in the system. Please note that this request can take up to two weeks to process. However, if this is requested by a regulatory agency such as the FDA, the access process may be expedited by contacting the Privacy Office or COMOR. If direct access is not requested, copies of the electronic source documents will be made available to the auditors on the day of the visit.

The PI and delegated research team members will be prepared for the auditor to review and verify all of the following:

*General Site Review*

- The PI has adequate qualifications and resources and these remain adequate throughout the clinical research study period, and that the staff and facilities, including laboratories and equipment, are adequate to safely and properly conduct the clinical research study and these remain adequate throughout the clinical research study period.
- The PI and delegated research team members are adequately informed about the clinical research study.

- The PI and the delegated research team members are performing the specified clinical research study functions in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.
- The investigator and delegated research team members follow the approved protocol and all approved amendments, if any.

*Informed Consent*

- Each subject has consented to direct access to his/her original medical records for clinical research study-related monitoring, audit, IRB review, and regulatory inspection.
- Informed consent was obtained before each subject's participation in the clinical research study.
- The PI is enrolling only eligible subjects.

*Clinical Research Data/Documents*

- Source documentation, case histories, CRF entries and other clinical research study records are accurate, complete, current, and maintained.
- The PI provides all required reports, notifications, applications, and submissions, and these documents are accurate, complete, timely, legible, dated, and identify the clinical research study.
- Adverse events (AEs) are appropriately reported within the time periods required by the protocol, IRB, and applicable regulatory requirements.
- The PI and delegated research team members are maintaining the essential documents as outlined in the Essential Documents SOP.

*Investigational Product*

- The investigational product storage conditions are acceptable and supplies are sufficient throughout the clinical research study.
- The investigational products are supplied only to eligible subjects and at the protocol specified doses.
- Subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational products.
- The receipt, use, and return of the investigational products at the clinical research study site are controlled and documented adequately.
- The disposition of unused investigational products complies with applicable regulatory requirement and is in accordance with the sponsor's authorized procedures.

**B. During the Audit**

When the auditor arrives, the delegated research team member will request identification and orient them to the investigational site facilities. Sponsor auditors should sign the monitoring visit log, as applicable.

The research team member assigned to that clinical research study may be the main point of contact for the auditing visit. The research team member should provide the auditor with all clinical research study documents requested for review and check in with the auditors throughout the day to address any questions or arrange any requested meetings with key personnel.

If copies of source documents or CRFs are requested, the primary coordinator or delegated research team members will make a copy for the auditor or FDA investigator and make a copy for the investigational site records which will be maintained with all other relevant audit documents.

**C. Audit Exit Interview**

The PI and delegated research team members, at a minimum, will be present for the audit exit interview. Sub-investigators, direct supervisor and other research representatives may be present, if requested. The investigational site should be prepared for the auditor to discuss:

- Any deviations from the protocol
- Applicable regulatory requirements
- Signed Investigator Agreement
- SOPs and investigational site processes
- Case histories

- Record keeping or management of regulatory documents
- Inaccurate data entry or invalid data
- Inadequate accountability and management of investigational product
- Inadequate protection of human subjects
- Inadequate PI oversight or delegation of responsibilities, and recommendations to secure compliance

The auditor should provide the investigational site with a certificate of audit or formal audit summary that includes details on what the auditors reviewed and any significant findings, deviations, and deficiencies noted. Audit findings discussed in detail should also be documented by the investigational site.

The PI and delegated research team members will address all findings, deviations and deficiencies presented by the auditor within a specified timeline in a formal response to the audit report. Responses should be based on the requirements of the auditing body. The formal response will include a cover letter, a statement of acknowledgement of each audit finding, any additional supportive source documentation, and detailed summary of corrective actions that will be implemented to eliminate future deficiencies such as departmental SOPs, training and education initiatives, revised protocol and new policies. All corrective actions will be documented, filed appropriately, and implemented within the timeline specified in the audit response letter.

Audit findings and corrective actions implemented will be communicated to key entities notified of the initial audit.

**D. Additional Information Regarding FDA Inspections**
In addition to the processes in sections A, B and C above, the following information applies to FDA inspections.

The FDA conducts both announced and unannounced inspections of clinical investigator sites. Reasons for inspections include but are not limited to the following:

- To verify the accuracy and reliability of data that has been submitted to the agency (e.g., Data Integrity Audit, Sponsor Submission for FDA Approval of Drug or Device).
- As a result of a complaint to the agency about the conduct of a study at a particular investigational site (including concerns or complaints of a sponsor).
- Upon termination of the clinical site (e.g., high volume of protocol deviations, adverse events, etc).
- To verify the conduct of a clinical research study and protection of human subjects during an active study (e.g., Inspection for Safety and Efficacy Events).
- At the request of an FDA review division.
- In relation to specific classes of investigational products that the FDA has identified as products of special interest in its current work plan (e.g., targeted inspections based on current public health concerns).

*Announced Inspections*
An inspector will contact the PI to schedule an inspection. After the PI or research team member schedule the inspection, they must contact the Office of Responsible Research Practices, WIRB or IRB of record (if applicable), study sponsor and College of Medicine Office of Research with details of the inspection *(See Attachment B: FDA Inspection Notification Form)*. When the inspector arrives on site, he or she will present their credentials, identification and a copy of the *FDA Form 482: Notice of Inspection* for signature. The PI or research team member should request the documents if not presented.

*Unannounced Inspections*
If a FDA inspector arrives unannounced, the PI and delegated research team members must accommodate the request and follow the processes described above.

*Inspection Outcomes*

If deficiencies are found during an FDA inspection, the inspector will outline the issues in a written *FDA Form 483: Inspectional Observations*. These observations are typically based on FDA regulations 21 CFR 50, 54, 56, 312 and/or 812. If a FDA 483 form is issued, the PI is responsible for writing a formal response addressing how the deficiencies will be corrected and eliminated from occurring in the future. The response may be in collaboration with key clinical research stakeholders (e.g., ORRP, COM-Office of Research), if needed. This response will be sent to the appropriate FDA District Office within 15 business days of receiving the inspection results.

## 5. Applicable Regulations, Guidances and Policies

| Regulation/ Guidance/Policy | Title |
|---|---|
| **21 CFR 11** | Electronic Records; Electronic Signatures |
| **21 CFR 50** | Protection of Human Subjects |
| **21 CFR 54** | Financial Disclosure by Clinical Investigators |
| **21 CFR 56** | Institutional Review Boards |
| **21 CFR 312** | Investigational New Drug Application |
| **21 CFR 812** | Investigational Device Exemptions |
| **45 CFR 46** | Protection of Human Subjects |
| **45 CFR 160** | HIPAA Privacy Rule |
| **45 CFR 164 Subparts A and E** | HIPAA Privacy Rule |
| **OSU Office of Responsible Research Practices HRPP** | Additional Requirements for Clinical Research: ICH GCP |
| **OSU Office of Responsible Research Practices HRPP** | Data and Safety Monitoring |
| **OSU Office of Responsible Research Practices HRPP** | Documentation of the Informed Consent Process |
| **OSU Office of Responsible Research Practices HRPP** | Event Reporting |
| **OSU Office of Responsible Research Practices HRPP** | Informed Consent Process and the Elements of Informed Consent |

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| **OSU Office of Responsible Research Practices HRPP** | Noncompliance |
| **OSU Office of Responsible Research Practices HRPP** | Privacy and Confidentiality |
| **OSU Office of Responsible Research Practices HRPP** | Recruiting Methods, Recruitment Materials, and Participant Compensation |
| **OSU Office of Responsible Research Practices HRPP** | Research Involving Data and or Biological Specimens |
| **OSU Office of Responsible Research Practices HRPP** | Research Involving Human Subjects |
| **OSU Office of Responsible Research Practices HRPP** | Research Involving Investigational Drugs |
| **OSU Office of Responsible Research Practices HRPP** | Research Involving Medical Devices |
| **OSU Office of Responsible Research Practices HRPP** | Research Performance Sites and Collaborative Off-Site Research |
| **OSU Office of Responsible Research Practices HRPP** | Responsibilities of Principal Investigators, Co-Investigators, and Key Personnel |
| **OSU Office of Responsible Research Practices HRPP** | Review of Research by Convened IRB |
| **OSU Office of Responsible Research Practices HRPP** | Suspension and Termination of IRB Approved Research |
| **OSU Office of Responsible Research Practices HRPP** | Vulnerable Populations: Students, Employees, and Adults Unable to Provide Consent |
| **OSU Office of Research** | Research Data Policy |
| **OSU Office of Research Compliance** | Human Gene Transfer |
| **OSU Office of Research Compliance** | Research Misconduct |
| **OSU Office of the Chief Information Officer** | Institutional Data Policy |
| **OSUWMC** | Use of Patient Information by Hospitals and Medical Staff |
| **OSUWMC** | Patient Information & HIPAA Requirements |

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| **OSUWMC** | Information Security Policy |
| **OSUWMC Investigational Drug Services** | IDS Policies and Procedures |
| **COM Office of Human Resources** | Training & Assessment Requirements |
| **ICH GCP E6(R2)** | Guideline for Good Clinical Practice: E6 Integrated Addendum |
| **FDA Guidance for Industry** | Investigator Responsibilities- Protecting the Rights, Safety, and Welfare of Study Subjects, October 2009 |
| **FDA Guidance for Industry** | IRB Continuing Review after Clinical Investigation Approval, February 2012 |
| **FDA Guidance for Industry** | Screening Tests Prior to Study Enrollment- Information Sheet |
| **FDA Guidance for Industry** | FDA Inspections of Clinical Investigators- Information Sheet, June 2010 |
| **FDA Guidance for Industry** | Adverse Event Reporting to IRBs- Improving Human Subject Protection, January 2009 |
| **FDA Compliance Program Guidance Manual** | Program 7348.11 Bioresearch Monitoring: Clinical Investigators and Sponsor-Investigators |
| **FDA Guidance for Industry** | Oversight of Clinical Investigations- A Risk-Based Approach to Monitoring, August 2013 |
| **FDA Guidance for Industry** | Sponsor- Investigator- IRB Interrelationship- Information Sheet |
| **FDA Guidance for Industry** | Frequently Asked Questions- Statement of Investigator (Form FDA 1572), May 2010 |
| **FDA Guidance for Industry** | Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials, October 2008 |
| **FDA Guidance for Industry** | Electronic Source Data in Clinical Investigations |