

OFFICE OF COMPLIANCE
UNIVERSITY OF PUERTO RICO
MEDICAL SCIENCES CAMPUS



AUDIT STANDARD OF PROCEDURES

Office of Compliance

UPR Medical Science Campus

AUDIT STANDARD OF PROCEDURES

1.0 Introduction, Purpose and Objectives of Audits

1.1 Introduction

All institutions that conduct or support biomedical research involving human participants must, by federal regulation, have an IRB that initially approves and periodically reviews the research. Every clinical trial in the U.S. must be approved and monitored by an Institutional Review Board (IRB) to guarantee that risks are as low as possible and are worth any potential benefits. An IRB is an independent committee of scientists, non-scientists and community advocates, that ensures that a clinical trial is conducted in an ethical manner and the rights of the study participants are protected.

The Department of Health and Human Services requires that Institutions engaged in human subjects research, must provide an Assurance of Compliance describing the means that will be used to comply with federal regulations.

1.2 Purpose and Objectives

The purpose of the Office of Compliance is to provide information to faculty and staff on regulatory compliance and Good Clinical Practice (GCP) Guidelines concerning research with human participants, data collection and data management; verify that the rights and welfare of human subjects are met; to verify investigator compliance with the currently approved Institutional Review Board (IRB) protocol, and applicable regulatory requirements; to verify that reported study data are accurate, complete and verifiable from the source documents; and rarely, to investigate complaints and/or allegations of noncompliance with research regulations. In addition to comply with the Food and Drug Administration (FDA) regulations, U.S. Department of Health and Human Services Office of Human Research Protection and the University of Puerto Rico Institutional Review Board Policies and Procedures.

The objectives of the Audit process are to assure compliance with regulatory requirements and guidelines for the conduct of clinical trials and study data validity. In addition, the audit component provides education and support regarding research implementation to all institutional research staff. As part of the monitoring and oversight process the Audit staff will:

- Ensure that appropriate oversight mechanisms to ensure compliance with the determinations of the IRB have been implemented.
- Ensure that all research sites have and can document, appropriate mechanisms to protect human subjects.
- Ensure that IRB review arrangements are documented in writing according to established regulations and guidance.
- Ensure that all independent investigators, have documented, their commitment to the institution's human subjects protection requirements and to the IRB determinations.

2.0 The Office of Compliance Audit Process

The Office of Compliance will follow the ICH Guideline for Good Clinical practice (CPMP/ICH/135/95), and University of Puerto Rico Medical Science Campus IRB Policies and Procedures. The Office for Human Research Protection (OHRP), formerly the Office of Protections for Research Risks (OPRR) of the NIH, Code of Federal Regulations as established under the common rule (45 CFR 46) and 21 CFR 50, 21 CFR 56, 21 CFR 312.

A selection of programs managing research projects under the University Of Puerto Rico Medical Science Campus Office Of Compliance will be audited every year, but all the projects shall be ready for audit for at least any one-year. Programs can be selected for audit even if their research project is withdrawn or terminated during the last year. Selection of terminated programs for audit is at the discretion of the Office of Compliance.

The UPR MSC audit process consists of reviewing and evaluating some or all the following components:

- The approved research protocol and all IRB correspondence
- The informed consent document and process
- The Regulatory Binder and affiliated study correspondence
- Adherence to the inclusion/exclusion criteria
- Adherence to study procedures
- Occurrence and reporting of adverse events
- Drug and device accountability (if applicable)

The Audit Staff, Office of Compliance and IRBwise® Administrator will work directly to manage the audit program. Section 2.1 to 2.6 will outline the process of auditing enrollment including selection of sites, scheduling sites, scheduling audit process, selecting protocol cases, data points, reporting requirements, and providing follow up information.

2.1 Selection and Scheduling of Sites

The Audit Staff must work directly with the Office of Compliance and IRBwise® Administrator to identify which programs are due for audit and re-audit. Selection of sites will be determined by randomization of all the available clinical trials or based on one or more of the following criteria included in the determination are:

- Sponsor regulatory requirements for study conduct and reporting.
- Absence of external monitoring or oversight
- Risk/ Benefit Assessment – based on expected adverse events, type of study, or vulnerable population(s)
- Allegations of human subject’s violations or noncompliance with Federal regulations.
- Investigator experience- New investigators (under 5 years of experience) might need more assistance in the process and regulations.
- Failure to submit a IRB renewal application (IRB approval lapse)

2.1.1 Once determined the research program(s) to be audited, the Office of Compliance will coordinate the visit within the previous twenty to thirty days with the Principal Investigators (PI) and/or Clinical Trials Coordinator. The principal investigator or coordinator may contact with the Office of Compliance to resolve any questions it has in reference to the audit process.

2.1.2 Under special or specific circumstances that will require immediate action from the Office of Compliance, the audit process will initiate without previous notification with the Principal Investigators and/or Clinical Trials Coordinator.

2.2 Audit Process – General Instructions

2.2.1 The nature of audits makes unannounced visits to research sites impractical. Appointments to audit should, therefore, be made by telephone, unless otherwise instructed in special cases by the Director of Compliance.

2.2.2 If during the audit, access to records or copying of parts is refused for any reason, the auditor should call the supervisor and report the refusal, so that the principal investigator can be advised promptly by telephone. The same procedure should be followed when it becomes evident that delays instituted by the audited are such that they constitute a de facto refusal.

If actions by the person being audited take a form of a partial refusal to audit of documents or areas which the Office of Compliance under the UPR Medical Science Campus, is entitled under the institutional policies the Director of Compliance will immediately meet with the principal investigator for complete advice.

- 2.2.3 If deviations from the regulations and policies of the UPR Medical Science Campus, that might affect data validity, endanger human subjects health or welfare, are encountered during an inspection, the auditor will call the Director of Compliance so that a determination can be made as to whether the audit should be expanded to be more intensive or to include other research studies. The Office of Compliance will provide guidance on initiating an in-depth audit; however, the auditor should continue the audit process.

2.3 Audit Procedures

- 2.3.1 Before going to the site to be audited the Audit Staff will review the research documents that are available in the Office of Compliance and through IRB wise. The auditor will already have the information on the project to be audited, scope, eligibility criteria, amendments, etc.
- 2.3.2 IRB approvals, re-approvals, and all required amendment approvals for the audited protocol will be reviewed.
- 2.3.3 The approved consent form and amendments (if any) will be carefully reviewed and compared to the ones in the Office of compliance files.

2.4 Audit at the Research Site

- 2.4.1 The site to be audited must be prepared for the audit by gathering all the documentation pertaining to the research projects.
- 2.4.2 The principal areas that will be audited are: Compliance with inclusion / exclusion criteria, compliance with protocol amendments and/or modifications, Full record reviews (informed consent, inclusion/exclusion criteria, procedures, general data quality, case report forms, clinical data, etc.), consent forms revision, inspection of storage area and record room and electronic records procedures (when applicable).

- 2.4.3 For each selected case, the following records should be available (when required as part of the project) informed consent documents, protocol flow sheet, clinical charts, physician and research notes, outpatient and clinic records, correspondence, x-rays, scans, and other pertinent studies. The program can flag all key documents to expedite the review.
- 2.4.4 For the selected protocols, the following documents must be provided; (a) IRB approvals, (b) annual reports submitted to IRB, (c) current version of the protocol, including any amendment and informed consent currently in use at the research site.
- 2.4.5 The Principal Investigator or designee and his/her research staff should be available through the audit to answer any questions and help the auditor locate necessary information in the source documents.

2.5 On Site Audit Procedures Overview

2.5.1 Entrance Meeting

During the first day of the audit, the auditor will meet with the Principal Investigator and will present basic information on how the audit process will be conducted. The following items must be included in this meeting:

- Reason for Audit
- Expected Scope of the Audit
- Expected duration of audit
- Administrative Procedures
- How findings will be reported
- Discussion with management

2.5.2 Review of Source Documents

Source documents will be used independently to identify study data. Source documents may include, but are not limited to, the following:

- Informed consents and IRB documents
- Inpatient and outpatient medical records
- Investigator's records
- Progress Notes
- Diagnostic reports (x-ray, scans, etc)
- Laboratory data
- Study flow sheets

- Appointment books
- Encounter Log
- Enrollment- tracking sheets
- Subjects Diaries/ calendars
- Copies of study forms

2.5.3 Assessment of Audit Findings

All Components to be audited (IRB documents, inclusion/exclusion criteria, individual participant record, etc.) will be assessed under one of four categories; Category 1-No Findings, Category 2-Minor Findings, Category 3-Major Findings, and Category 4-Critical Findings, based on findings at the time of the audit. There is also a common system for assessing each component of an audit (audit checklist), and a standard audit report format.

2.5.3.1 Category 1- No Findings

No deviation of the regulations or any finding of non compliance was identified under the specific audit process.

2.5.3.2 Category 2- Minor Findings

Minor findings of non compliance or deviations were identified in the audit process. The findings under this category do not necessarily represent potential harm to the human subjects or course of the investigation. Depending on the Auditor criteria, and when determined by the auditor, these finding will not necessarily require a corrective action. Some of the findings under this category may include:

- Minor violations to the proposed project (visit out of schedule, one blood sample not taken as established by the protocol, etc).
- Incomplete or expired IRB documentation, but resolved before the closing of the audit.
- Incongruence in the accounting of medicines, but resolved before the closing of the audit.
- Documents related to the protocol missing in the Office of Compliance. This will be identified as a Deviation for the Office of Compliance, and will be documented in letter directed to the Director of Compliance.
- Medication or agents have been borrowed.

- Medications not stored separately by protocol.

2.5.3.3 Category 3- Major Findings

This category includes serious deviations that may affect the research process and/or the safety of human subjects involved in the protocol. A correction plan will be required for findings under this category. These findings will be classified under this category when there is not previous history of deviation or there is not data to evidence that this is a frequent deviation under the protocol. Findings classified under this category are:

- Serious violations to the protocol (may be related to inclusion/ exclusion criteria)
- Participants signed an incorrect consent form.
- Failure to obtain continuous IRB approvals, or as determined by the IRB.
- Failure to submit adverse events to the IRB and regulatory agencies.
- Clinical charts not available for the audit.
- No source documents available to support the information in the study binders.
- Research staff is not adequately qualified.
- Inconsistencies in the accounting of the protocol medications.
- Inadequate use of the study medication.
- Agents or medications stored in insecure dispensing area or not stored under proper conditions.
- Satellite records do not agree.
- Incorrect treatment, dose, dates or administration reflected.

2.5.3.4 Category 4- Critical Findings

The findings or deviations under this category may represent a major harm to the research process and/or the safety of human subjects involved in the protocol. An Immediate correction plan will be required for these findings, and a report of findings under this category will be sent to the Director of Compliance. Under this category the findings are:

- All the findings under the category 3 with a high level of frequency in the audited documents (2 or more times in the determined audit sample).

- Failure to comply with and complete the Informed Consent of the participants before enrollment and/or after any amendment of the consent.
- Failure to obtain IRB approval for the initial protocol and consent forms prior to the recruitment process.
- There are erasures or “whiteouts” in the official documents.
- Suspect of documents falsification and/or alteration like signatures, laboratories, etc.
- Violations to the protocol procedures that may represent risk to the safety of human subjects involved in the protocol.
- Violations on the selection process of human subjects (not following the instructions of the protocol).

2.6 Audit Reports

2.6.1 Preliminary Audit Report

On the last day of the audit and once completed the review process, the Auditor will meet with the Director of Compliance and discuss the initial findings. An initial Audit Report will be completed and signed by the Auditor and Officer of Compliance.

2.6.2 Exit Interview

At the conclusion of the Site Visit, the Human research Auditor of Clinical Research with Human Subjects will conduct an exit interview with the responsible investigator and all other appropriate staff. During this exit interview the preliminary findings and any other recommendation from the audit are discussed. This interview provides opportunity for education, immediate dialogue, feedback and clarification.

2.6.3 Report of Findings

2.6.3.1 Category 1 Findings

The initial report will be provided to the site during the exit interview. The principal investigator will answer the findings within the next ten (10) labor days. A correction plan will not be necessary, training issues and/or technical

assistance in specific areas will be consulted or recommended to PI.

2.6.3.2 Category 2 Findings

The initial report will be provided to the site during the exit interview. Generally for findings under this category a correction plan will not be necessary, unless specified.

2.6.3.3 Category 3 Findings

Findings under this category will be discussed with the Director of Compliance during the last day of the audit visit and previous to the closing of the initial report. After the meeting with the Director of Compliance, the Auditor will establish dated recommendations for the Principal Investigator responding to the findings under this category. The Director of Compliance will determine if further action will be taken.

2.6.3.4 Category 4 Findings

Findings under this category will require immediate action. The Auditor will send a letter to the Director of Compliance reporting the findings under this category. The Director of Compliance will determine the course of the actions to be taken to respond to these findings.

2.6.4 Reporting Requirements

2.6.4.1 Initial Findings Report

The initial report will be provided to the site on during the exit interview. The principal investigator will answer the findings within the next ten (10) labor days.

2.6.4.2 Letter to the Director of Compliance

When findings under category 4 are identified, the Auditor will send a letter to the Director of Compliance notifying of the findings. The Director of Compliance will determine the following actions to be taken.

2.6.4.3 Final Audit Report

Once received the answers to findings from the Principal Investigator, the Auditor will complete the Final Audit report, which is the integration of the findings of the audit and the answers that the Principal Investigator provided to those findings.

The Final Audit Report must be completed and sent to the PI within the next 30 labor days, after the answers from the PI are received. If the answers to the audit are not received within the established 10 labor days, the Auditor will proceed and complete the Final Audit report indicating that the Principal Investigator did not answered the findings.

The final Audit report will include:

- Reason for inspection - indicate the unit or division that issued the audit and requirements of compliance. Also state the purpose of the audit and dates.
- What was covered- Identify study, protocol number, sponsor, location of study, etc.
- Administrative Procedures- Indicate the Auditor and Supervisor's name, persons interviewed, prior audit history, etc.
- Individual Responsibilities- Identify study personnel and their responsibilities in the study. Indicate by whom the program is monitored.
- Inspectional Findings- Comparison of data in the Office of Compliance and Research Site, state the records that were covered, number of files reviewed, number of consent forms reviewed, adverse events, amendments
- Discussion with management at the exit meeting.

2.6.4.4 Correction Plan

The PI will submit to the Office of Compliance a correction plan after 30 labor days that will be attached to the Final Audit Report

2.6.5 Follow-Up Requirements

A re-audit is required for any component rated under categories three (3) and four (4). This re-audit will consider only the findings under these categories and will be issued within a 1 year period.