Are you Audit Ready?
Audit Ready?

A PRESENTATION BY:
TULANE CLINICAL TRANSLATIONAL UNIT

AND

TULANE HUMAN RESEARCH PROTECTION OFFICE
Are you Audit Ready?

Produced by:

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- The Research Compliance Office
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Presentation Outline

- Research Noncompliance
- Audit Readiness
- FDA Audits
- Pop Quiz!
- OHRP Audits
- NIH Clinical Trials Monitoring Audits
Are you Audit Ready?

Noncompliance Defined and Discussed
Noncompliance Definition

- Any failure to follow 45 CFR part 46 (Code of Federal Regulations - including any applicable subparts), the requirements or determinations of the IRB or the provisions of the IRB-approved research study

- Can occur as a result of performing an act(s) that violate(s) requirements

- Can also occur as a result of failing to act when required
### What are the types of Noncompliance?

<table>
<thead>
<tr>
<th><strong>Serious Noncompliance</strong></th>
<th><strong>Continuing Noncompliance</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Failure to follow regulations and policies per Tulane SOPs</td>
<td>- Pattern of Noncompliance (in the judgment of the RCO or convened IRB) that suggests a likelihood instances of noncompliance will continue without intervention</td>
</tr>
</tbody>
</table>
| - Failure to follow IRB determinations and (in the judgment of the convened IRB)  
  - increases risks to participants  
  - decreases potential benefits, or  
  - compromises integrity of the HRPO | - Includes failure to respond to a request to resolve an episode of Noncompliance |
| - Research conducted without prior IRB approval = Serious Non-Compliance | |

*Note:* The document includes a list of types of noncompliance, with specific examples and criteria for each type. It emphasizes the importance of compliance with regulations and policies to ensure the safety and integrity of research practices.
### Minor Noncompliance

- Actions or activities associated with conduct or oversight of research involving human subjects - fails to comply with either:
  - IRB-approved research plan,
  - or
  - federal regulations or institutional policies governing human subject research

**That Does Not /Did Not...**

- Harm or increase risk to subjects
- Cause negative change in subjects’ welfare
- Significantly impact integrity of the data
- Result from deliberate misconduct by member of research team
Examples of Minor Noncompliance

- Change in study team members without IRB approval (not including PI)
- Change in questionnaires without IRB approval
- Missed laboratory test, later obtained
- Changing schedule of study visits without IRB approval
- Essentially, protocol deviations
Serious Noncompliance

- Actions or activities associated with conduct or oversight of research involving human subjects - fails to comply with either
  - IRB-approved research plan, or
  - federal regulations or institutional policies governing human subject research

That Does...

- Harm or increase risk to subjects
- Cause a negative change in subjects’ welfare
- Significantly impact the integrity of the data
- Result from deliberate misconduct by a member of the research team
Examples of Serious Noncompliance

- Conduct of research involving interactions/interventions with human subjects without IRB approval
- Enrolling a subject failing to meet inclusion/exclusion criteria, placing subject at greater risk
- Allowing IRB approval of study to expire and continuing study activities during a period of expiration
- Failing to obtain or document informed consent
Examples of Serious Noncompliance/Continuing Noncompliance

- Failing to maintain copies of informed consent forms
- Conducting a procedure without IRB approval; failing to perform a procedure that may impact subject safety or data integrity
- Failure to follow safety monitoring plan
- Enrolling subjects after IRB approval has expired
- Failing to report serious adverse events or unanticipated problems to the IRB
- Multiple minor Noncompliance issues can be considered Continuing Noncompliance
Possible Consequences of Serious/Continuing Noncompliance

- Reporting to Federal agencies (OHRP and FDA) and funding agencies (NIH)
- Mandatory re-education, Independent certification of the PI and study team
- Removal of PI from study and/or all studies
- Tarnished reputations
- Loss of funding or sponsorship
- Debarment from research
Additional Issues

- Continuing Noncompliance
- Failing to follow reporting requirements
- Corrective Action Plans
- Preventive Action Plans
Audit Ready

Are You?
Audit Ready

- Who can audit my research? (as applicable)
  - FDA (U.S. Food and Drug Administration)
  - OHRP (Office for Human Research Protections, Department of Health and Human Services)
  - DOD (Department of Defense)
  - NIH (National Institutes of Health {and associated entities})
  - Other federal and state sponsoring agencies
  - VA (U.S. Department of Veterans Affairs)
  - DEA (Drug Enforcement Agency)
  - Private Sponsors
  - Local IRB/HRPO
  - Research Compliance Office
Be Prepared

- Research Study File Maintenance
  - Keep files organized at all times
  - Retain all correspondence from
    - Sponsor
    - Monitors
    - Study subjects
    - IRB
    - Letters, faxes, emails, memos, telephone contacts
  - Retain all test articles and accountability records
  - Retain shipping receipts, screening and enrollment logs, dispensing logs
  - Maintain regulatory binder

- Audits can be unannounced or scheduled: Always be Audit Ready
Be Prepared

- FDA Inspection Triggers (increase the chance of an FDA audit)
  - Studies with **High Enrollment**, where test article approval is pending
  - Studies with **Few or No Adverse Events**
  - PIs who have received a FDA form 483 in the past
  - Studies where other sites have had problematic inspections
FDA 1572

- Signing 1572: PI commitment...
  - ...to be responsible for the study by
    - Following federal guidelines for the protection of human subjects
    - Interactions with IRBs involved
    - Adhering to IND application regarding details of adverse event reporting and recordkeeping
  - Being **AUDIT READY**
FDA Form 1572

<table>
<thead>
<tr>
<th>1. NAME AND ADDRESS OF INVESTIGATOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Principal Investigator</td>
</tr>
<tr>
<td>Address 1</td>
</tr>
<tr>
<td>City</td>
</tr>
<tr>
<td>State/Province/Region</td>
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<tr>
<td>Country</td>
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<tr>
<td>ZIP or Postal Code</td>
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<tr>
<th>2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED (STATE ONE OF THE FOLLOWING.)</th>
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<tbody>
<tr>
<td>Curriculum Vitae</td>
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<tr>
<td>Other Statement of Qualifications</td>
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<thead>
<tr>
<th>3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED</th>
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<tbody>
<tr>
<td>Name of Medical School, Hospital, or Other Research Facility</td>
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<tr>
<td>Address 1</td>
</tr>
<tr>
<td>City</td>
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<tr>
<td>State/Province/Region</td>
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<td>Country</td>
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<tr>
<td>ZIP or Postal Code</td>
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<thead>
<tr>
<th>4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY</th>
</tr>
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<tbody>
<tr>
<td>Name of Clinical Laboratory Facility</td>
</tr>
<tr>
<td>Address 1</td>
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<tr>
<td>City</td>
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<tr>
<td>State/Province/Region</td>
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<td>ZIP or Postal Code</td>
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<thead>
<tr>
<th>5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of IRB</td>
</tr>
<tr>
<td>Address 1</td>
</tr>
<tr>
<td>City</td>
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<tr>
<td>State/Province/Region</td>
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<td>Country</td>
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<tr>
<td>ZIP or Postal Code</td>
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</tbody>
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<tr>
<th>6. NUMBER OF SUBINVESTIGATORS (If not applicable, enter &quot;None&quot;)</th>
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<tr>
<th>7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR</th>
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Most common cause: **Protocol Noncompliance**
(Failure to conduct in accordance with investigational plan)

- **Examples**
  - Missing safety labs
  - No documentation of reasons for missed subject visit/test
  - Failure to ensure and document eligibility criteria were met
  - Making changes to the protocol without first obtaining IRB approval
**Inadequate Case Histories** – Failure to maintain adequate and accurate case histories with respect to data or informed consent

- Examples
  - Failure to complete case report forms (CRFs)
  - Inadequate or non-existent source documentation to support data in CRFs
  - Lack of properly documented informed consent and lost records
  - Failure to document timely review of adverse events
FDA Warning Letters (2015)

• Failure to obtain informed consent in accordance with 21 CFR part 50
  ○ EXAMPLES
    - No consent before administration of test article
    - Missing consent forms
    - Participants did not sign and date consent
    - Most recent IRB-approved consent was not used
    - Re-consent was not obtained or not obtained in a timely manner
    - Consent did not contain required elements
    - Inappropriate time period between consent signature and first study procedure
    - No documentation of time of informed consent process (to show that the process took place before research procedures began)
    - Improper consent of non-English speaking subjects
First Rule of Medicine Applies to FDA Review

• If it wasn’t documented, it wasn’t done!
FDA Inspections

Intention of Inspections

- Determine compliance with federal regulations and adherence to guidelines
- Verify validity and integrity - clinical data submitted in applications for approval
- Assure that rights and welfare of subjects participating in clinical studies are being protected
In Case of a Notification of Audit

- Immediately review your institution’s Standard Operating Procedures (SOPs) for audits
- Contact the Human Research Protection Office (HRPO) and Research Compliance Office (RCO)
- Consult and adhere to your institutional departmental policies and procedures regarding impending audit
In Case of a Notification of Audit

- Retrieve and assemble requested trial-related records
- Notify study-delegated personnel about the date, time and occurrence of the inspection
  - PI
  - Department Representative
  - Sponsor Contact
  - Project Manager and/or Lead Study Coordinator
  - Contact the HRPO and RCO
  - Investigational Pharmacist

- PI must be available in person during the Inspection
- If the PI is unavailable on the scheduled inspection date, the inspection must be re-scheduled
- A request to re-schedule must be made in a timely manner
Preparing for the FDA Inspection

- You **must** cooperate with any FDA Inspection
- All study personnel must be available to answer questions for which they have direct knowledge
- Secure a room for the Inspection that can be locked and available for more than one day, if necessary
- Designate a “documents” person to assist in preparation for the Inspection and for the actual Inspection
Preparing for the FDA Inspection

- Lead Study Coordinator or Project Manager: retrieve and assemble all study-related records
  - SOPs
  - Regulatory records
  - CRFs, monitoring reports
  - Source records
  - Test article accountability records

- Lead Study Coordinator: organize all study-related files, arrange logistics, and prepare for the audit

- PI and department representative function as liaison/escort for FDA Inspectors, facilitating requests
Conducting the Inspection - Role of the PI

- Greet FDA Inspector(s)
- Verify ID/Credentials
- FDA Inspector should provide FDA 482 (unless this is a criminal investigation)
- If no FDA 482 is provided, notify General Counsel immediately
- Provide a tour of facility
- Assist as needed

- Provide requested records. Make 2 copies of each record requested – one for FDA, one for site
- Ensure that each question is answered by a knowledgeable person
- Accompany FDA inspector(s) at all times, unless they are in conference room, reviewing records
- Arrange for follow-up as required for unanswered questions or outstanding documents
FDA Form 482
Conducting the Inspection – Role of Liaison

- Take notes concerning progress of inspection
- Provide requested records, make photocopies for FDA and the clinical site
- Document any line of questioning pursued by PI and FDA Inspector, including issues that remain unresolved and steps taken to resolve
  - Try to resolve any such unresolved issues while the Inspection is still occurring
- Arrange any interviews requested by FDA inspector(s) and escort FDA Inspector(s) if they request to go to specific sites
- Document name and title of all persons interviewed by FDA and date and time of interview
Post-FDA Inspection

- PI or Liaison should request an end-of-day discussion during each day of inspection with FDA Inspector to review preliminary findings.
- Document any questions whose answer could not be provided along with follow-up to request appropriate information.
- If PI receives an FDA 483 (report of observations) after audit, PI should consult General Counsel on how to respond and provide sponsor with an opportunity to assist in response.
Citations, used for the 483, are maintained in a database and are reviewed, edited and updated on a periodic basis. Citations relate to a Code of Federal Regulations (CFR) reference, and there may be many citations for a single CFR reference. To create an FDA Form 483, citations are selected from the pre-established system or database. The Long Description is entered into the FDA Form 483, ensuring uniformity of presentation, then specific information related to the observation may be entered, and the citations may be ranked by significance on the 483.
<table>
<thead>
<tr>
<th>Center Name</th>
<th>483s Issued</th>
</tr>
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<tbody>
<tr>
<td>Biologics</td>
<td>123</td>
</tr>
<tr>
<td>Bioresearch Monitoring</td>
<td>283</td>
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<tr>
<td>Devices</td>
<td>1008</td>
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<tr>
<td>Drugs</td>
<td>678</td>
</tr>
<tr>
<td>Foods</td>
<td>2300</td>
</tr>
<tr>
<td>Human Tissue for Transplantation</td>
<td>81</td>
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<tr>
<td>Parts 1240 and 1250</td>
<td>66</td>
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<tr>
<td>Radiological Health</td>
<td>17</td>
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<tr>
<td>Veterinary Medicine</td>
<td>294</td>
</tr>
<tr>
<td>Sum Product Area 483s from System*</td>
<td>4850</td>
</tr>
<tr>
<td>Actual Total in System 483s**</td>
<td>4751</td>
</tr>
</tbody>
</table>

- FDA Form 483 notifies institutions’ management of objectionable conditions – not all-inclusive
- Institutions responsible for corrective action addressing cited objectionable conditions
- Form 483s are discussed with a management at conclusion of the inspection
Post-FDA Inspection

- PI or designee must send a copy of FDA 483 to sponsor’s project manager, HRPO, RCO, and General Counsel, as well as submitting the FDA 483 for IRB review via IRBNet.
- PI must arrange a meeting to discuss findings with General Counsel, HRPO, RCO, and other offices, as necessary.
- PI prepares a written response with input from appropriate persons to any observations noted in FDA 483; response should be sent to FDA within time specified (usually 15 days).
Post-FDA Inspection

- Include in PI’s response
  - Address each observation and steps implemented to remedy observation and prevent future occurrences
  - Response should be factual and should be respectful, professional and cooperative

- PI should attempt to obtain a copy of official FDA investigator’s field audit report under the Freedom of Information Act (FOIA) request
  - This request can be made at the conclusion of the 483 response
  - FDA does not normally respond to such requests until the matter is formally closed
  - Get help from RCO and Office of General Counsel
QUIZ: Are You Ready?

- What is the most common finding during a FDA Inspection?
- Failure to obtain informed consent in accordance with the regulations
- Failure to protect rights, safety and welfare of study participants under care of the principal investigator
- Failure of investigator to conduct a study according to protocol
- Failure to maintain adequate and accurate case histories

QUIZ: Are You Ready?

- Anything you talk about with the auditors is official discussion and can be used as part of the Establishment Inspection Report?

  - True
  - False

QUIZ: Are You Ready?

- You may offer your FDA Inspector lunch, validated parking, etc. as a courtesy when they are performing an investigation.

- True
- False

QUIZ: Are You Ready?

- What is the best way to prepare your study staff for a FDA Inspection?
- Have written SOPs that detail processes on all research procedures, documentation methods, and individuals responsible for each activity
- Routinely conduct “mock audits”
- Ensure that all study documents are organized, complete and current
- Identify which staff members are responsible for specific areas of the study
- Ensure staff understand the protocol completely
- All of these apply

QUIZ: Are You Ready?

- Your sponsor is a key resource during a FDA Inspection.
- True
- False

QUIZ: Are You Ready?

- What is **not** considered an obligation of the Principal Investigator, according to the FDA?
- Appropriate delegation
- Follows protocol
- Obtains required IRB approvals
- Patient recruitment
- Appropriate informed consent process and documentation

QUIZ: Are You Ready?

- What prompts a “for cause” FDA inspection?
- Complaints filed in question of whether the rights and safety of patients are at risk
- Complaints filed in question of whether integrity of study data has been compromised
- Sponsor concerns
- All of these apply

It is best to have one point person who will escort the inspector at all times and answer any questions.

True
False

OHRP Jurisdiction

- Research involving human subjects conducted or supported by U.S. Department of Health and Human Services that is not otherwise exempt

and

- Non-exempt human subject research covered by Assurance of Compliance
  - “HHS human subject protection regulations and policies require that any institution engaged in non-exempt human subjects research conducted or supported by HHS must submit a written assurance of compliance to OHRP. The Federalwide Assurance (FWA) is the only type of assurance of compliance accepted and approved by OHRP. FWAs also are approved by the Office for Human Research Protections (OHRP) for federalwide use, which means that other federal departments and agencies that have adopted the Federal Policy for the Protection of Human Subjects (also known as the Common Rule) may rely on the FWA for the research that they conduct or support. Institutions engaging in research conducted or supported by non-HHS federal departments or agencies should consult with the sponsoring department or agency for guidance regarding whether the FWA is appropriate for the research in question.”
## OHRP For Cause vs. Not for Cause

<table>
<thead>
<tr>
<th>For Cause</th>
<th>Not For Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Responds to substantive allegations or indications of non-compliance in HHS-supported research or under an applicable assurance; usually through correspondence (&gt;90%)</td>
<td>• Assesses institutional compliance with 45 CFR 46 in absence of specific allegations; can be partially “for cause” (previous compliance problems or vague allegations); often through site visit (~1/3)</td>
</tr>
</tbody>
</table>
OHRP Compliance Oversight Investigation – For Cause

- Receive allegation or indication of Noncompliance
- Determine whether or not OHRP has jurisdiction over the study
- OHRP to send written inquiry to appropriate institutional officials
- OHRP will review institution report and relevant IRB documents (sent by institutional officials/response)
- OHRP will communicate with institution as needed (correspondence/telephone interviews/site visit)
- OHRP will issue final determinations
OHRP Compliance Oversight Investigation – Not For Cause

- OHRP can investigate institutions within its jurisdiction
- OHRP will send written inquiry to appropriate institutional officials
- OHRP will review institutional report and relevant IRB documents (sent by institutional officials/response)
- OHRP will communicate with institution as needed (correspondence/telephone interviews/site visit)
- OHRP will issue final determinations
Possible OHRP responses to initial institutional response
- OHRP may ask additional questions; express concerns
- OHRP may conduct phone interviews
- OHRP may conduct an on-site evaluation of human subject protections
Preparing for an OHRP Inquiry

- Notify Institutional Officials (IO, HRPO, RCO, and General Counsel)
- Re-review regulations, particularly the subparts
- Review OHRP guidance documents
- Review Institutional SOPs
- Ensure clear and consistent documentation of IRB activities
- Designate one contact person for compliance oversight coordinator who will coordinate requests, questions, etc.
## OHRP Site Visits - Two Types

<table>
<thead>
<tr>
<th>For Cause</th>
<th>Not For Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triggered by open compliance case</td>
<td>No open compliance case</td>
</tr>
<tr>
<td>Site visit team includes OHRP attorney, 2 – 5 OHRP staff, 2 – 4 outside consultants</td>
<td>Site visit team consists of 1 – 3 OHRP compliance staff, plus 1 – 3 outside consultants</td>
</tr>
<tr>
<td>Visit lasts 3 – 4 days</td>
<td>Visit lasts 2 – 3 days</td>
</tr>
<tr>
<td>Dual focus on allegations and systemic protections</td>
<td>Focus on systemic protections</td>
</tr>
</tbody>
</table>
OHRP’s Preparation for a Site Visit

- Request protocols and other documents to be reviewed
- Describe/name officials/groups to be interviewed
- Provide ample lead time to institution; work cooperatively to set schedule
After OHRP Site Visit

- OHRP will send a letter with official findings and additional questions/concerns within a few weeks.
- Institution will be asked to respond with corrective action plans in approximately 6 weeks.
- OHRP will evaluate adequacy of corrective action plans.
Compliance Oversight Investigation

Possible Determinations and/or Outcomes
Possible Determinations/Outcomes (1)

- Protections under an institution’s Assurance are in compliance
- Protections under an institution’s Assurance are in compliance, but recommended improvements have been identified
- Noncompliance identified, corrective actions required
- Noncompliance identified, Assurance restricted/suspended pending required corrective actions
Possible Determinations/Outcomes (2)

- Noncompliance identified, OHRP approvals of Assurance withdrawn
- OHRP may recommend to appropriate HHS officials or PHS agency heads that
  - An institution or investigator be temporarily suspended or permanently removed from participation in specific project
  - Peer review groups be notified of an institution’s or an investigator’s past noncompliance prior to review of new projects
Possible Determinations/Outcomes (3)

- OHRP may recommend that institutions or investigators be declared ineligible to participate in HHS-supported research (debarment). Debarment initiated in accordance with procedures specified at 45 CFR Part 76.
NIH Clinical Trials Monitoring Branch

Conducting the Audit
 NIH Clinical Trials Monitoring Branch

- One of the world’s largest publicly-funded sponsors of clinical trials
- NIH must ensure that research data generated under its sponsorship are of high quality, reliable and verifiable
- Auditing is conducted to determine whether trial-related activities were conducted, dates recorded, analyzed and accurately reported according to the protocol, sponsor’s SOPs, GCP and the applicable regulatory requirements
NIH Audit – Source Documents

- IRB documents and ICFs
- Drug accountability record forms/logs for imaging/radiopharmaceutical agents
- Inpatient and outpatient medical records
- Study flow sheets
- Protocol
- Enrollment tracking sheets
- Patient diaries/calendars
NIH Audit Findings

- Review and evaluate the following
  - Documentation and conformance to IRB and ICF requirements
  - Pharmacy operations and use of drug logs
  - Individual subject cases

- Each component will independently be assigned an assessment of
  - Acceptable
  - Acceptable; Needs Follow-up
  - Unacceptable – Re-audit Required
NIH Audit - Examples of Major Deficiencies

- **IRB-related Issues**
  - Protocol never approved by IRB
  - Initial IRB approval documentation missing
  - Registration and/or treatment of subject prior to full IRB approval
  - Registration of subject on protocol during period of delayed approval or during temporary suspension
  - Missing approval
  - Expired approval
  - Internal reportable adverse events reported late or not reported
  - Lack of documentation of IRB approval of amendment on greater than minimal risk research
  - Failure to submit timely external safety reports
NIH Audit - Examples of Major Deficiencies

- **Informed Consent**
  - Omission of one or more risks/side effects
  - Omission of one or more revisions per amendment
  - Omission of one or more required informed consent elements
  - Changes made to the informed consent not approved by IRB
  - Multiple cumulative effects of minor problems for a given ICF
NIH Audit Findings - Assessing Deficiencies

- **Acceptable**
  - No deficiencies
  - Few LESSER deficiencies
  - A major deficiency that was discovered and corrected prior to the audit

- **Acceptable; Needs Follow-Up**
  - Major deficiency identified during the audit but not addressed or corrected prior to the audit
  - Multiple lesser deficiencies
Assessing Deficiencies (cont’d)

- **Unacceptable**
  - Multiple major deficiencies identified
  - A single major flagrant deficiency found
  - Excessive number of lesser deficiencies identified
NIH Audit - Accountability of Investigational Agents and Pharmacy Operations

- **Control Dispensing Area/Pharmacy**
  - Direct receipt of agents
  - Appropriate storage and security
  - Dispensing as required by protocol
  - Overall inventory control
  - Final disposition of agents

- **Satellite Dispensing Area/Pharmacy** (same as above)

- **Imaging Studies**

- **Pharmacy Review** – based on compliance/non-compliance measures, due to complexity
NIH Audit - Review of Subject Case Records

- Approximately 10% of subjects reviewed for major and lesser deficiencies
  - Properly signed and dated consent forms
  - Established Eligibility (Inclusion/Exclusion criteria review for each subject)
  - Correct treatment and treatment sequence
  - Evaluation of disease outcome
  - Adverse events relative to treatment
  - General quality of data collected
NIH Audit - Major Deficiencies (examples)

- Informed Consent Document
  - Consent form document missing
  - Consent form document not signed and dated appropriately
  - Translated form not signed and dated by study participant
  - Consent form not signed by patient prior to enrollment
  - Consent form used not current IRB-approved version at time of registration
  - Consent form is not protocol-specific
  - Consent form does not contain updates or information required by IRB
  - Re-consent not obtained as required
NIH Audit Major Deficiencies (examples)

- Subject Eligibility
  - Review of documentation available at the time of audit confirms study participant did not meet all eligibility criteria and/or eligibility requirements were not obtained within the timeframe as specified by the protocol
  - Documentation is missing; unable to confirm eligibility
Major Deficiencies (examples)

- Treatment
  - Incorrect treatment/intervention used
  - Additional treatment used/not permitted by protocol
  - Dose deviations, modifications, or incorrect calculations
  - Dose modifications/treatment interventions not per protocol
  - Treatment/intervention incorrect or not documented adequately
  - Timing/sequencing of treatment/intervention not per protocol
  - Unjustified delays in treatment/intervention
Major Deficiencies (examples)

- **General Data Management Quality**
  - Recurrent missing documentation in study participant record
  - Protocol-specific laboratory tests not reported or documented
  - Protocol-specific diagnostic tests, including baseline assessments, not done/not reported/not documented
  - Frequent data inaccuracies
  - Errors in submitted data
  - Delinquent data submission
RESOURCES

- https://acrpblog.org/2016/04/18/auditing-your-site-vendors-and-other-pointers-for-pis-who-are-new-to-research/
- Title 21 CFR part 11
- Title 21 CFR parts 50 & 56
- Title 21 CFR part 312 & 312.62
- Title 21 CFR part 812 & 812.140
- ICH GCP Consolidated Guideline Part 4.9
- ICH GCP Consolidated Guideline Part 5.15
- http://www.yale.edu/hrpp/education/documents/Noncompliance_122012.ppt
RESOURCES

- FDA Compliance Program Guidance Manuals 7348.811 & 7348.810
- FDA Investigations Operations Manual
- [https://wwwwp.oakland.edu/Assets/upload/docs/Research/2--D--Elyse-Summers-Audits-Part-1-The-IRB.pdf](https://wwwwp.oakland.edu/Assets/upload/docs/Research/2--D--Elyse-Summers-Audits-Part-1-The-IRB.pdf)
- HRPO [Self Audit Tool](http://foreresearch.com/news/ready-fda-inspection-take-quiz/)
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