Are you **Audit Ready**?

Audit Ready?

A PRESENTATION BY:
TULANE CLINICAL TRANSLATIONAL UNIT

LA CaTS
LOUISIANA CLINICAL & TRANSLATIONAL SCIENCE CENTER

AND
TULANE HUMAN RESEARCH PROTECTION OFFICE

Tulane University

Are you **Audit Ready**?

- Produced by:
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  - The Tulane Human Research Protections Office
    - Director: Roxanne R. Johnson, MSPH, CHRC
  - The Research Compliance Office
    - Tulane Research Compliance Officer: Brian J. Weimer, Esq.

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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?

Serious Noncompliance

- Failure to follow regulations and policies per Tulane SOPs
- 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
- Research conducted without prior IRB approval = Serious Non-Compliance

Continuing Noncompliance

- Pattern of Noncompliance (in the judgment of the RCO or convened IRB) that suggests a likelihood instances of noncompliance will continue without intervention
- Includes failure to respond to a request to resolve an episode of Noncompliance

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

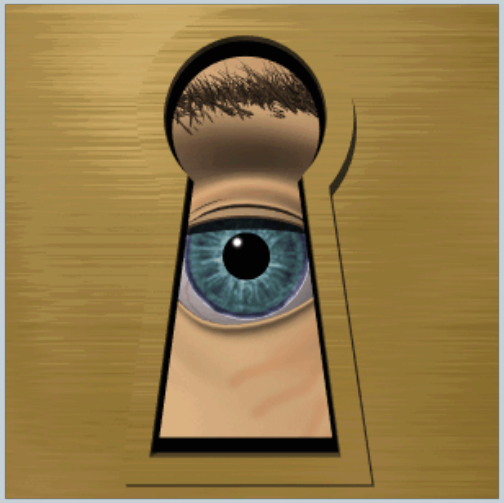
- Continuing Noncompliance
- Failing to follow reporting requirements
- Corrective Action Plans
- Preventive Action Plans

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

Food and Drug Administration

FDA

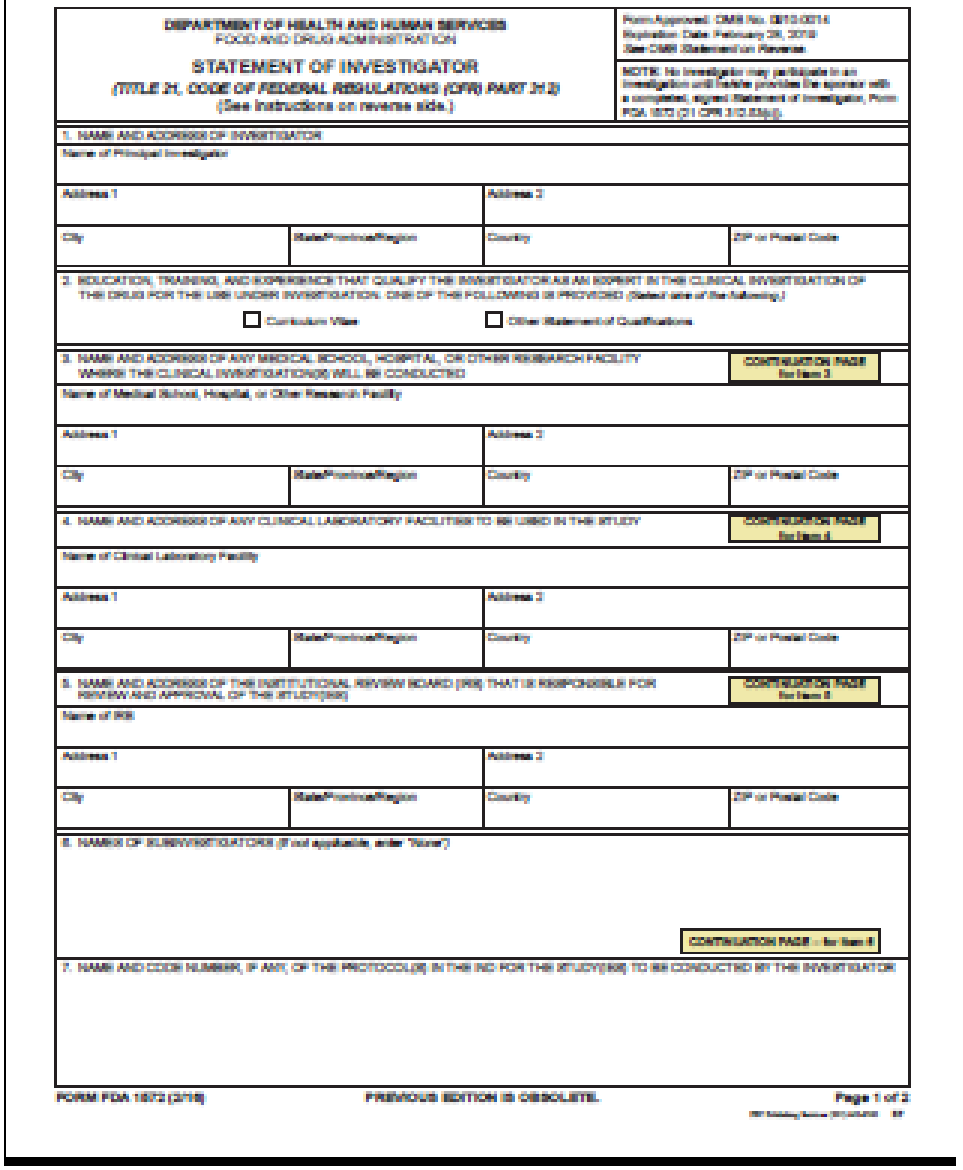
Be Prepared

- 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



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0014
Expiration Date: February 28, 2018
See OMB Statement on Reverse

STATEMENT OF INVESTIGATOR
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)
(See Instructions on reverse side.)

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

Name of Principal Investigator

Address 1 | Address 2

City | State/Province/Region | Country | ZIP or Postal Code

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THIS INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THIS DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED: *(Select one of the following.)*

☐ Curriculum Vitae ☐ Other Statement of Qualifications

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED

CONTINUATION PAGE for Item 3

Name of Medical School, Hospital, or Other Research Facility

Address 1 | Address 2

City | State/Province/Region | Country | ZIP or Postal Code

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY

CONTINUATION PAGE for Item 4

Name of Clinical Laboratory Facility

Address 1 | Address 2

City | State/Province/Region | Country | ZIP or Postal Code

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES)

CONTINUATION PAGE for Item 5

Name of IRB

Address 1 | Address 2

City | State/Province/Region | Country | ZIP or Postal Code

6. NAMES OF SUBINVESTIGATORS *(If not applicable, enter "None")*

CONTINUATION PAGE for Item 6

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THIS IND FOR THIS STUDY(IES) TO BE CONDUCTED BY THIS INVESTIGATOR

FORM FDA 1572 (3/18) PREVIOUS EDITION IS OBSOLETE. Page 1 of 2

FDA Warning Letters (2015)

- 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

FDA Warning Letters (2015)

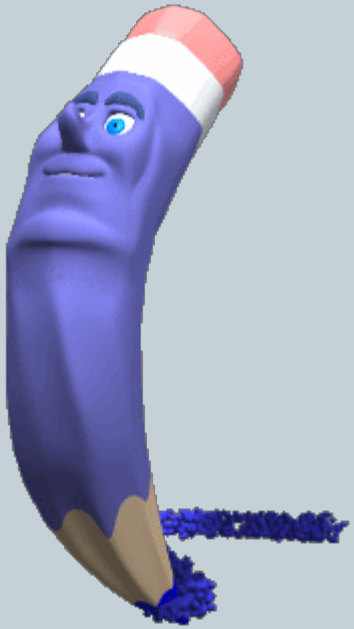
- Inadequate Case Histories – Failure to maintain adequate and accurate case histories with respect to data or informed consent
  - Examples
    - Failure to complete case report forms (CRFs)
    - Inadequate or non-existent source documentation to support data in CRFs
    - Lack of properly documented 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!

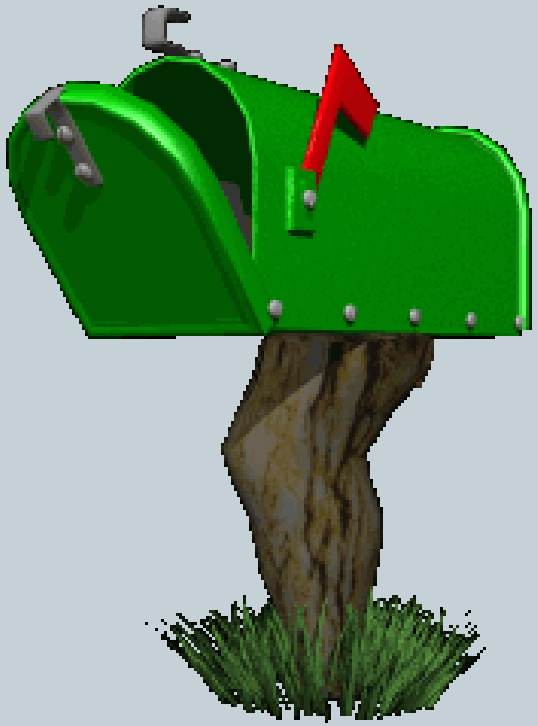


FDA Inspections

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 your 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

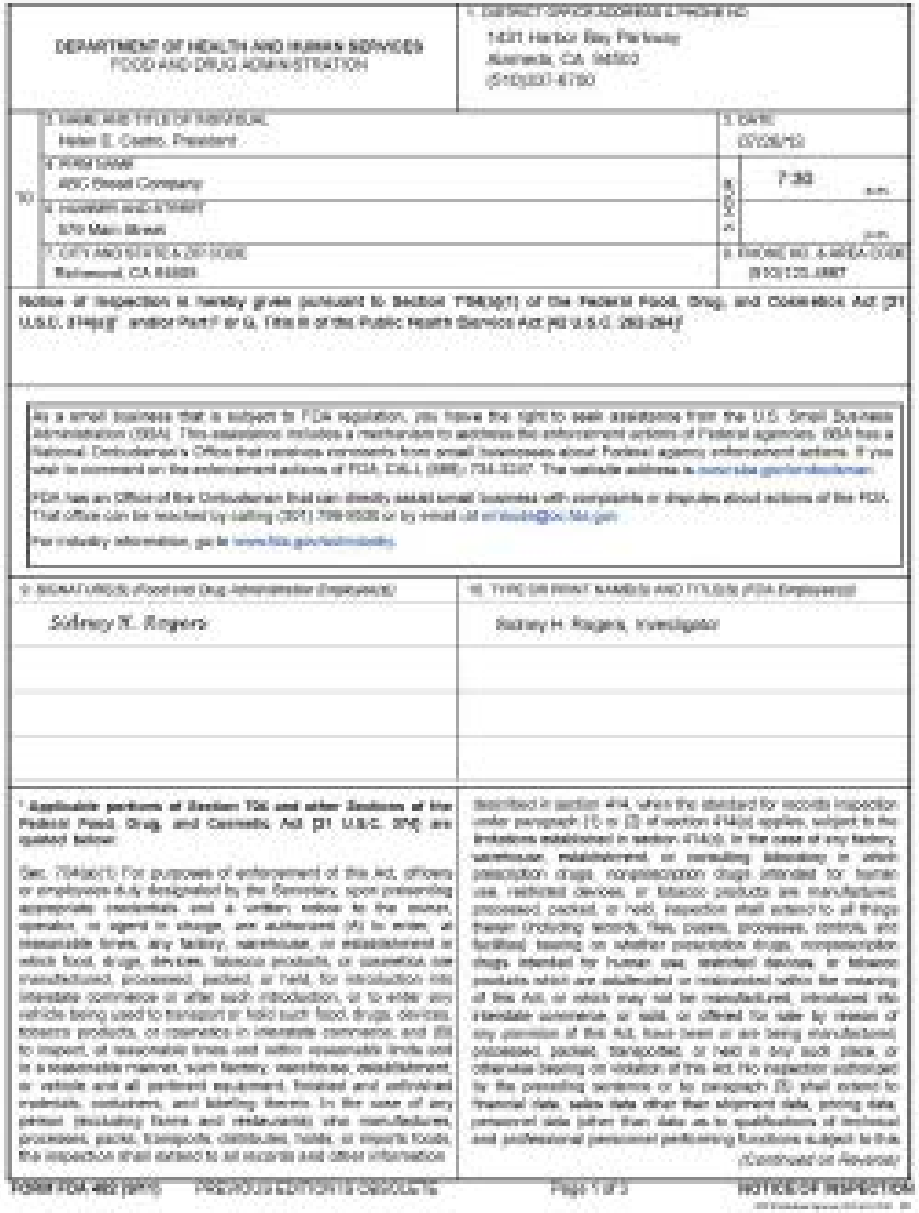
- Lead Study Coordinator: organize all study-related files, arrange logistics, and prepare for the audit
- PI and department representative function as liaison/escort for FDA Inspectors, facilitating requests

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



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

1431 Harbor Bay Parkway
Alameda, CA 94502
(510)337-6700

TO: Helen E. Castro, President
ABC Bread Company
679 Main Street
Richmond, CA 94809

DATE: 07/28/10
TIME: 7:30 a.m.

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 374(a)) and/or Part F of Q, Title III of the Public Health Service Act (42 U.S.C. 262-264).

As a small business that is subject to FDA regulation, you have the right to seek assistance from the U.S. Small Business Administration (SBA). This assistance includes a mechanism to address the enforcement actions of Federal agencies. SBA has a National Ombudsman's Office that receives comments from small businesses about Federal agency enforcement actions. If you wish to comment on the enforcement actions of FDA, call 1 (888) 734-3247. The website address is www.sba.gov/ombudsman.

FDA has an Office of the Ombudsman that can directly assist small business with complaints or disputes about actions of the FDA. That office can be reached by calling (301) 796-8538 or by e-mail at ombudsman@oc.fda.gov.

For industry information, go to www.fda.gov/smallbusiness.

SIGNATURE(S) (Food and Drug Administration Employee(s)): Sidney R. Rogers

TYPED OR PRINTED NAME(S) AND TITLE(S) (FDA Employee(s)): Sidney H. Rogers, Investigator

Applicable portions of Section 704 and other Sections of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 374) are quoted below:

Sec. 704(a)(1) For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, tobacco products, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, tobacco products, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein. In the case of any person (excluding farms and restaurants) who manufactures, processes, packs, transports, distributes, holds, or imports foods, the inspection shall extend to all records and other information described in section 414, where the standard for records inspection under paragraph (1) or (2) of section 414(a) applies, subject to the limitations established in section 414(b). In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products are manufactured, processed, packed, or held, inspection shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products which are adulterated or misbranded within the meaning of this Act, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this Act, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this Act. No inspection authorized by the preceding sentence or by paragraph (5) shall extend to financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualifications of technical and professional personnel performing functions subject to this

(Continued on Reverse)

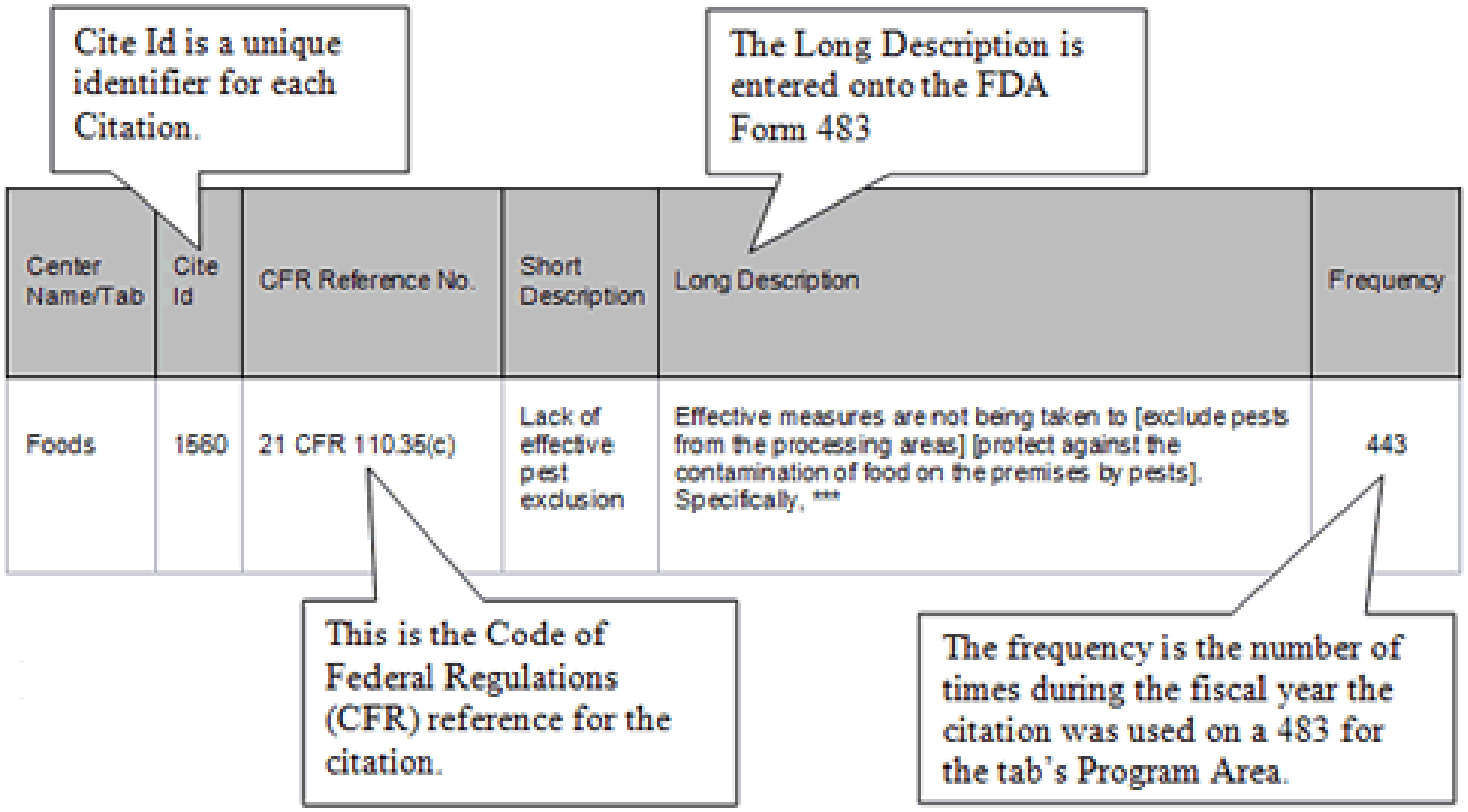
Conducting the Inspection – Role of Liaison

- 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.



483

Number of 483s Issued from the System* Inspections fiscal year 2015 Center Name	483s Issued
Biologics	123
Bioresearch Monitoring	283
Devices	1008
Drugs	678
Foods	2300
Human Tissue for Transplantation	81
Parts 1240 and 1250	66
Radiological Health	17
Veterinary Medicine	294
Sum Product Area 483s from System*	**4850**
Actual Total in System 483s**	**4751**

- 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)

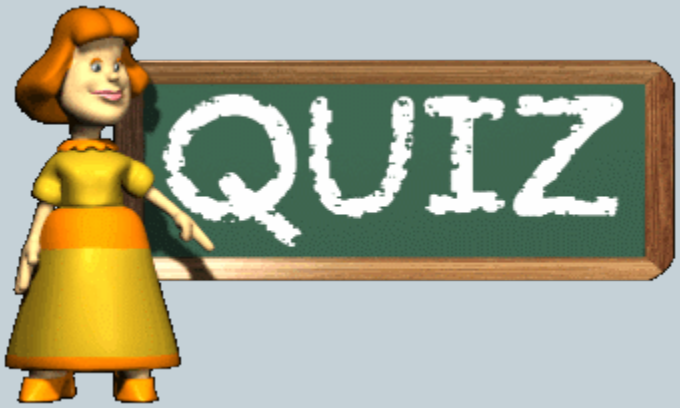
Post-FDA Inspection

- 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

http://foreresearch.com/news/ready-fda-inspection-take-quiz/

QUIZ: Are You Ready?

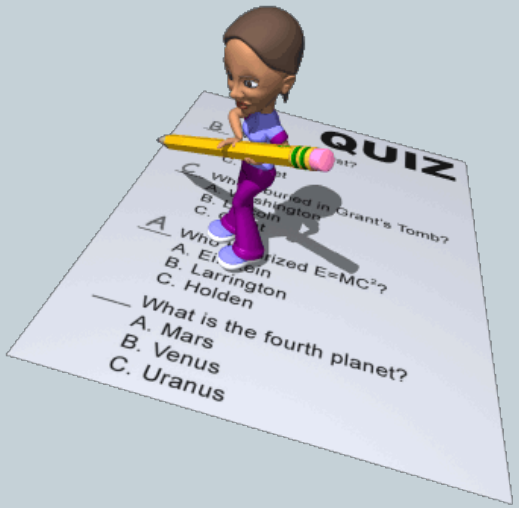
- Anything you talk about with the auditors is official discussion and can be used as part of the Establishment Inspection Report?

- True
- False

http://foreresearch.com/news/ready-fda-inspection-take-quiz/

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

http://foreresearch.com/news/ready-fda-inspection-take-quiz/

QUIZ: Are You Ready?

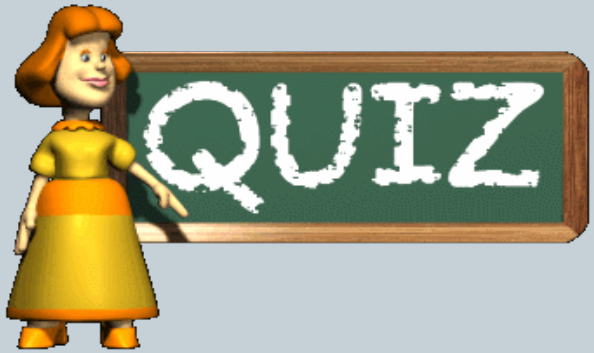
- What is the best way to prepare your study staff for a FDA Inspection?

- 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

http://foreresearch.com/news/ready-fda-inspection-take-quiz/

QUIZ: Are You Ready?

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

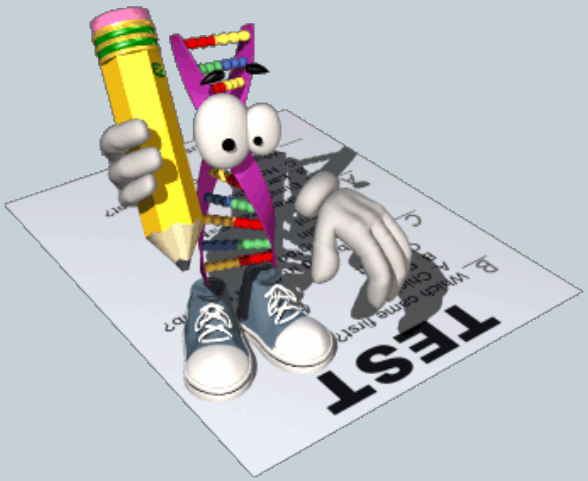


- True
- False

http://foreresearch.com/news/ready-fda-inspection-take-quiz/

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

http://foreresearch.com/news/ready-fda-inspection-take-quiz/

QUIZ: Are You Ready?

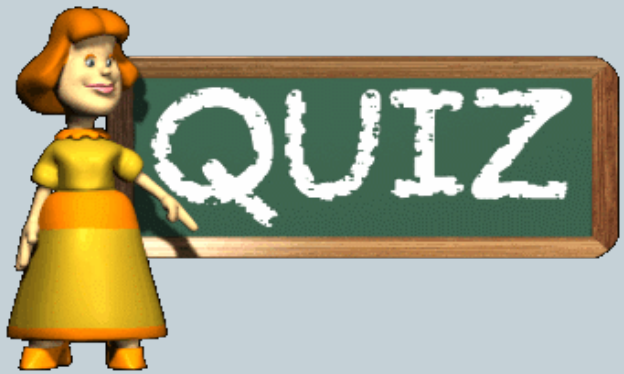
- What prompts a “for cause” FDA inspection?

- 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

http://foreresearch.com/news/ready-fda-inspection-take-quiz/

QUIZ: Are You Ready?

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



- True
- False

http://foreresearch.com/news/ready-fda-inspection-take-quiz/

HHS Office of Human Research Protections

OHRP

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

For Cause	Not For Cause
• Responds to substantive allegations or indications of non-compliance in HHS-supported research or under an applicable assurance; usually through correspondence (>90%)	• 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)

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

OHRP - Opening a Compliance Case

- 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)
- Review "OHRP Recent Compliance Oversight Determinations" http://www.hhs.gov/ohrp/compliance-and-reporting/determination-letters/2016/index.html
- 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

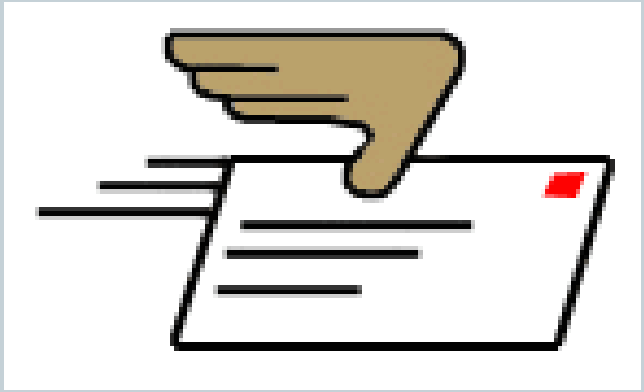
For Cause	Not For Cause
• Triggered by open compliance case • Site visit team includes OHRP attorney, 2 – 5 OHRP staff, 2 – 4 outside consultants • Visit lasts 3 – 4 days • Dual focus on allegations and systemic protections	• No open compliance case • Site visit team consists of 1 – 3 OHRP compliance staff, plus 1 – 3 outside consultants • Visit lasts 2 – 3 days • Focus on systemic protections

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

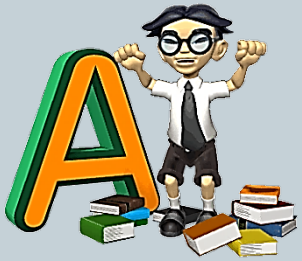


Compliance Oversight Investigation

Possible Determinations and/or Outcomes

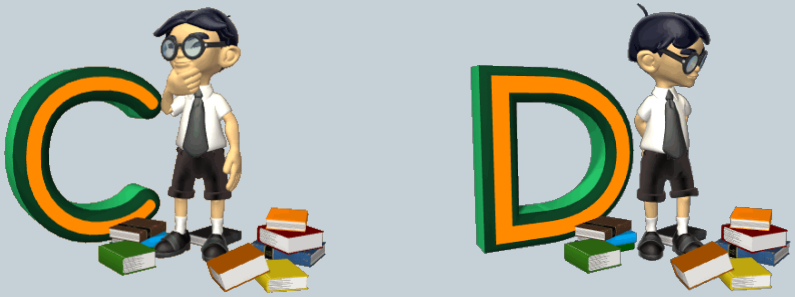
Possible Determinations/Outcomes (1)

- 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
- http://foreresearch.com/news/ready-fda-inspection-take-quiz/
- https://wwwp.oakland.edu/Assets/upload/docs/Research/2--D--Elyse-Summers-Audits-Part-1-The-IRB.pdf
- http://ctep.cancer.gov/branches/ctmb/clinicalTrials/docs/ctmb_audit_guidelines.pdf
- HRPO Self Audit Tool

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