FDA Audit Preparation Resource & Checklist

FDA Audit Preparation Guidance and Checklist for Clinical Investigations Using FDA Regulated Drug Products

ICTR Navigator
January 3, 2013
Version 1.0

The Johns Hopkins Institute for Clinical and Translational Research
ICTR—Where Science and People Connect
CTSA

JOHNS HOPKINS MEDICINE

TABLE OF CONTENTS

1.0 INTRODUCTION

FDA conducts clinical investigator and sponsor-investigator inspections to determine if clinical studies are being conducted in compliance with applicable statutory and regulatory requirements. Clinical investigators who conduct human subject's research with FDA-regulated investigational/approved drugs are required to permit FDA investigators to access, copy, and verify any records or reports made by the clinical investigator with regard to, among other records, the disposition of the investigational product and subjects' case histories.

Using regulatory references that include 21CFR50, 21CFR56, 21CFR312, ICH E:6, and policies of the Johns Hopkins Medicine Office of Human Subjects Research, the ICTR DDRS has developed this resource in order to help investigators prepare for an FDA audit.

Additional information is provided regarding suggested study team conduct during an FDA audit, what to expect upon completion of the audit, and points to consider regarding responses to FDA audit findings.

Please note that FDA does not require adherence to the International Committee on Harmonization (ICH) guidelines referenced later in this document. The Johns Hopkins guideline regarding ICH compliance may be found here. For those who are required to adhere to the ICH E:6 (e.g. commercial sponsors who require adherence, sponsor-investigators who elect to follow GCP, multi-center protocols that have sites in EU countries, etc.) they are provided here. For all others, they serve to promote best practices compliance.

If you have any questions regarding the information presented, please contact the ICTR Research Navigators at ICTR_Navigators@jhmi.edu or via telephone at 410-614-5383.

2.0 DEFINITIONS

Exhibit Log	Binder kept by the inspected site containing copies of all documents inspected and requested by the FDA during the inspection. The exhibit log is kept as a reference when drafting responses to any inspection findings.
External Audit	A periodic review performed by an Agency to ensure that a research study is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and applicable regulatory requirements. This does not include routine monitoring by a sponsor.
For-Cause (investigator related) Audit	A 'for-cause' audit may be performed because the study PI conducts studies outside of their area of expertise, the PI submits data that is inconsistent with other studies done under the IND, the study is highly-publicized in the media, the PI has been the recipient of a subject complaint, or the institution's IRB is notified of suspected fraud or misconduct.
Form FDA 482	Notice of Inspection Form. Officers or employees duly designated by the Agency, 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.
Form FDA 483	The FDA Form 483 notifies the site's management of objectionable conditions. At the conclusion of an inspection, the FDA Form 483 is presented and discussed with the site's senior management. Sites are encouraged to respond to the FDA Form 483 in writing with their corrective action plan and then implement that corrective action plan expeditiously.
Inspector	Refers to the representative of the Agency visiting the site. Some agencies may refer to this individual as an auditor.
Routine (study related) Audit	A routine audit may be done on sites that are randomly chosen, sites that have had a notably high or rapid enrollment, sites that are conducting multiple studies, or sites that are conducting large pivotal trials for which the majority of the investigational products claims are based.
Sponsor	Sponsor means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article [i.e., drug, biologic, device, or combination of the three] is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.
Sponsor-Investigator	Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

3.0 FDA and ICH GUIDANCE INFORMATION

Below are links to FDA and ICH guidance documents that may be useful with regard to preparing for a study related (routine) or an investigator-related ('for cause') FDA audit of a clinical protocol involving use of an investigational drug(s).

21CFR:	**312.68 Part 312 -- Investigational New Drug Application/Inspection of investigator's records and reports**
FDA:	**Bioresearch Monitoring: Clinical Investigators and Sponsor-Investigators Guidance for FDA staff**
FDA:	**Bioresearch Monitoring: FDA/ORA Bioresearch Monitoring Information Page**
FDA:	**Compliance Program Guidance Manual (CPGM)** ***(Chapter 48)***
FDA Guidance:	**Computerized Systems Used in Clinical Investigations**
FDA Guidance:	**FDA Inspections of Clinical Investigators**
FDA Guidance:	**Financial Disclosure by Clinical Investigators**
FDA:	**Form 483 Frequently Asked Questions**
FDA Information Sheet:	**Guidance for IRBs, Clinical Investigators, and Sponsors: FDA Inspections of Clinical Investigators**
ICH:	**International Committee on Harmonization (ICH) E: 6 Good Clinical Practices**
FDA:	**Investigations Operations Manual**
FDA Guidance:	**Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects**
FDA Guidance:	**Part 11, Electronic Records, Electronic Signatures – Scope and Application**
FDA:	**Preparing for a Clinical Investigator Inspection**
FDA:	**Regulatory Procedures Manual (RPM)**

4.0 AUDIT PREPARATION

FDA SITE INSPECTION PREPARATION CHECKLIST			
Administrative Activities[4]			
Initial Contact Information			
Staff member who received initial FDA contact:			
Contact/Notification Date:			
FDA Inspection Visit Information			
Visit Start Date:		Estimated Time of Arrival:	Expected Duration:
FDA inspector Contact Information:		Name:	
		Telephone:	
		Title:	
Additional FDA Inspectors' Names:			
Purpose of Inspection/Who and what are being inspected			
☐	Clinical trial(s):	Details:	
☐	Principal Investigator:	Details:	
☐	Sub-Investigator(s):	Details:	
☐	Routine (e.g., IND):	Details:	
☐	Directed (e.g., for cause):	Details:	
☐	Follow-up (e.g., 483; warning letters):	Details:	
☐	Other:	Details:	

Has FDA requested that specific personnel be available? If yes, please list. Use a separate sheet if needed.	
Who has been requested?	When must they be available?

Has FDA requested that specific documents be available? If yes, please list. Use a separate sheet if needed.	
Documents requested:	Check if requested prior to inspection:
	☐ Date:_____
	☐Date: _____
	☐Date: _____

If the FDA requests any documents be sent prior to the inspection obtain the following information		
Name of Recipient:	How?	☐ Overnight ☐ Registered ☐ Certified
Address of Recipient:	To be delivered by when?	Details:
Document any other details from the initial contact not noted above:		

After receiving a call from ANY governmental agency, notify the sponsor/sponsor-investigator without unnecessary delay and all involved personnel about the inspection. Notify additional relevant parties as appropriate			
	Notified/ Available	**Not notified/ Unavailable**	**Comments or check N/A if not applicable**
Sponsor/Sponsor-Investigator	☐	☐	
JHM IRB	☐	☐	
Principal Investigator	☐	☐	
Sub-Investigator(s)	☐	☐	
Study Coordinator(s)	☐	☐	
Medical Records	☐	☐	
JHM IRB Compliance Monitoring Program	☐	☐	
Investigational Pharmacy/IDS*	☐	☐	☐N/A
Clinical Laboratory(ies)	☐	☐	☐N/A
Reception Area Staff	☐	☐	☐N/A
Other (specify)			
***** *JHMIRB contacts the IDS Pharmacy to assist investigators with study document review and organization for drug studies. This is usual practice; especially if IDS has dispensed drug for the study.*			
If a SKCCC trial			**☐N/A**
PI should immediately send written notification of impending audit to appropriate IRB Chairman and IRB Regulatory Manager. This notification should include the name of the Agency requesting the inspection, the expected timeframe of the inspection (if given), the reason for the audit, and any potential problem areas or incidents of which the IRB was not already notified.	☐	☐	
PI has read and fully complied with SKCCC "**Preparing for a Regulatory or Cooperative Group Audit**" guidance.	☐	☐	
Designate an audit preparation team			
Identify one person as an "Inspection Coordinator" to coordinate preparations.	Designated "Inspection Coordinator"	:	
During the Inspection, one staff member ("the Escort") must always accompany/host the Inspection and takes notes during the entire process.	Designated to escort FDA personnel & take notes	:	
A staff member should be assigned to photocopy the exhibits being subjected to inspection and keep logs of those materials.	Designated to photocopy documents	:	

Assure that an area or room is designated for the audit. The area should include a table large enough for the auditor(s) to spread out several documents and be cleared of all documents relating to trials other than the one that is the subject of the inspection.	
Work space	Room #:
Telephone	Ext:
Desk/table	
Assure that a copy machine will be available for use during the audit.	
Copier	
NOTE: *Retain a site copy of all documents inspected and requested by the FDA during the inspection for future reference when responding to the inspection findings.* ***Photocopies for the FDA are to be done in 2 sets. One set is for the "Exhibit Log" and the other set for the FDA personnel****.*	
Review staff and clinic schedules	
Review staff schedules (vacations, appointments, miscellaneous time off, etc.) to ensure staff availability	
Reschedule non-essential visits/meetings if possible	
Retrieval of study records	
Retrieve (or be prepared to retrieve) all trial records and source documents from storage. If requesting files, (e.g. from Iron Mountain) assure that delivery of same will occur prior to audit date. The site should be prepared to produce research documentation as requested by FDA in advance or or during the inspection.	
Assure ready access to all study related materials that are exclusively stored electronically (e.g. imaging)	
Obtain and/or assure ready access to all hospital inpatient charts prior to audit date for all SAEs involving hospitalization during the trial.	
Assure that all records related to drug accountability are available prior to audit date, including records stored in the pharmacy or drug dispensing area, if separate from the site.	

Regulatory documentation[5]				
NOTE: If a SKCCC trial, upon notification of the CRO Quality Assurance Office, a QA auditor will be assigned to perform a pre-audit review to help ensure that all documentation is in order prior to the official audit. Study staff should notify the CRO QA office when all records are complete and available for pre-audit review. See SKCCC "Preparing for a Regulatory or Cooperative Group Audit" guidance for additional detail. For all other SOM studies, please notify the JH OHSR Compliance Monitoring Team, who may perform a pre-audit assessment of all regulatory documentation.				
	Regulatory Reference	**Completed/ Available**	**Incomplete/ Unavailable**	**Comments or check N/A if not applicable**
List of Principal Investigator's current active protocols	BIMO Compliance Program Guidance Manual, Chapter 48[-2]	☐	☐	☐N/A
Assure that copies of any signed agreement between involved parties (E.g. investigation and sponsor, investigation and CRO, Sponsor and CRO, etc. are available for inspection	ICH GCP 8.2.6	☐	☐	☐N/A
Protocol				
Make sure that all versions of the clinical protocol are available for inspection (dated and signed by the PI if required by the sponsor) Version_____ Version_____ Version_____ Version_____ Version_____ Version_____	21CFR§312.30 ICH GCP 8.2.2, ICH GCP 8.3.2	☐	☐	
Make sure that all protocol amendments and clarification memorandums are available for inspection Date_____ Date_____ Date_____ Date_____	21CFR§312.30 ICH GCP 8.2.2, ICH GCP 8.3.2	☐	☐	
Investigator's Brochure				
Have all versions of the Investigator's Brochure(s) and/or Package Insert(s) available for inspection (if applicable) Date_____ Date_____ Date_____ Date_____	21CFR 312.55; ICH GCP 8.2.1	☐	☐	☐N/A
Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure)	ICH GCP 8.2.14	☐	☐	☐N/A

	Regulatory Reference	Completed/ Available	Incomplete/ Unavailable (Provide comment)	Comments or check N/A if not applicable
Reports				
Obtain a complete list of IND Safety Reports. Check to ensure that all IND Safety Reports provided by the sponsor are present, organized, and available for inspection. IND Safety Report_____ IND Safety Report_____ IND Safety Report_____	21 CFR 312.50 21 CFR 312.32 (c)(1)(i) ICH GCP 8.3.18	☐	☐	☐N/A
DSMB summary report(s) and documentation of submission to the IRB	ICH GCP 8.3.17	☐	☐	☐N/A
Assure that all annual reports and the final report to the IRB are present (including interim reports, if applicable). Annual reports: _____ Final report: _____	21 CFR.109(f) ICH GCP 8.3.19	☐	☐	☐N/A
Consents				
Have the IRB approved Informed Consent Forms (all versions including screening consent forms and any translated versions as well) available for inspection Date_____ Date_____	21 CFR 312.60 ICH GCP 8.2.3 ICH GCP 8.3.2 FDA Information Sheets, "FAQ," #51, 1998 update, and "A Guide to Informed consent 1998 update.	☐	☐	

	Regulatory Reference	Completed/ Available	Incomplete/ Unavailable (Provide comment)	Comments or check N/A if not applicable
IRB Approval				
Have the original protocol IRB approval letter available for inspection IRB Approval Date_____	21 CFR 56.103(a), 21 CFR 56.109(e) ICH GCP 8.2.7 ICH GCP 8.3.3	☐	☐	☐N/A
If there is more than one IRB, all approval and notification documentation as noted above is required in regard to all involved IRBs for the site for this trial. Specify name(s) of IRBs: _____ _____	21 CFR 56.103(a), 21 CFR 56.109(e), ICH GCP 8.2.7 ICH GCP 8.3.3	☐	☐	☐N/A
IRB protocol amendment(s) approval letter(s) Date_____ Date_____ Date_____	21 CFR 56.103(a) 21 CFR 56.109(e), ICH GCP 8.2.7 ICH GCP 8.3.3	☐	☐	☐N/A
IRB continuing review approval letters	21 CFR 6.103(a), 21 CFR 56.109(e), ICH GCP 8.2.7 ICH GCP 8.3.3	☐	☐	☐N/A
IRB approval letter(s) for revised Informed Consent Forms including those translated from English to another language. Date of letter_____ Date of letter_____ Date of letter_____	21 CFR § 312.60 ICH GCP 8.2.3 ICH GCP 8.3.2	☐	☐	☐N/A
IRB approval of any subject compensation and documentation of all payments.	FDA Information Sheet, "Payment to Research Subjects," December 1999	☐	☐	☐N/A

	Regulatory Reference	Completed/ Available	Incomplete/ Unavailable (Provide comment)	Comments or check N/A if not applicable
IRB Approval				
IRB approval letter(s) for subject recruitment materials (advertisements, videos, handouts to participants, etc.) Ad approval date(s): _____ Ad approval date(s): _____	21 CFR § 56.109(a), FDA Information Sheet, "Recruiting Study Subjects," December 1999; ICH GCP 8.2.3	☐	☐	☐N/A
IRB approval letter(s) for case report forms (CRFs) *(if applicable)* CRF approval date(s): _____ CRF approval date(s): _____	ICH GCP 8.2.3 ICH GCP 8.2.7	☐	☐	☐N/A
Correspondence from Investigator to IRB				
Assure that a copy of **all letters from the investigator to the IRB** are present, including submission of all versions of the protocol (including Investigator's Brochure, annual reports, final report, interim reports if applicable, notification of premature discontinuation from the trial, clinical hold(s), and if a comparator drug was used in the trial, the package insert for that drug; all IND safety reports provided to the investigator by the sponsor, all site serious adverse events and any other adverse events submitted to the IRB/EC.	21 CFR 312.53 (c)(1)(vii) 21CFR 312.55 ICH GCP 8.3.17	☐	☐	☐N/A
Correspondence from Investigator to Sponsor/Sponsor-Investigator				
Assure that all correspondence between the investigator and the sponsor (and CRO, if applicable) is available, especially notification to the sponsor of site serious adverse events (SAEs), and including documentation of telephone conversations regarding the trial, hard copies of e-mails pertinent to the conduct of the study, notes to file, memoranda, documentation of transmittal of case report forms, letters from the monitor describing items to be addressed resulting from monitoring visits.	21 CFR § 312.64(b) ICH GCP 8.3.11 and 8.3.16	☐	☐	☐N/A

	Regulatory Reference	Completed/ Available	Incomplete/ Unavailable (Provide comment)	Comments or check N/A if not applicable
Acknowledgement Letters				
Assure that the original IRB letters are present, acknowledging receipt of SAE submission to the IRB	21 CFR 312.64(b) ICH GCP 8.3.11 ICH GCP 8.3.16	☐	☐	☐N/A
Assure that the original letters are present, acknowledging receipt of SAE submission to the sponsor	21 CFR § 312.64(b) ICH GCP 8.3.11 ICH GCP 8.3.16	☐	☐	☐N/A
Assure that the original letters are present, acknowledging identification and reporting of protocol violations/deviations to the IRB/sponsor per IRB and protocol requirements	21 CFR 312.64(b) ICH GCP 8.3.11 ICH GCP 8.3.16	☐	☐	☐N/A
Assure that the original letters are present, acknowledging receipt IND safety reports, site serious adverse events, and any other adverse event information submitted to the IRB, annual reports, periodic reports if applicable, and the final report.	ICH GCP 8.3.17	☐	☐	☐N/A
Logs				
Assure that the completed subject screening/ enrollment log (names of all participants screened including enrollment date and reason for screen failure if applicable; confirm that log is current and legible) is available for inspection. Updated/accurate Screening Log: _____ Updated/accurate Screening Log: _____	ICH GCP 8.3.20 ICH GCP 8.3.22	☐	☐	☐N/A
Assure that a completed site personnel log is present, including the name and signature of all staff authorized to make entries in case report forms and other trial related activities.	ICH GCP 8.3.24 Industry standard	☐	☐	☐N/A
Assure that a trial initiation monitoring visit report is available for inspection	ICH GCP 8.2.20	☐	☐	☐N/A
Signed and dated monitoring visit log	21 CFR312.53	☐	☐	☐N/A

	Regulatory Reference	Completed/ Available	Incomplete/ Unavailable (Provide comment)	Comments or check N/A if not applicable
Study Team				
Assure that a copy of all versions of Form FDA 1572 signed and dated by the principal investigator is present (two-sided). 1572(s) present: _____	21 CFR 312.53(c)(1)	☐	☐	☐N/A
Assure that all financial disclosure documentation is present for the principal investigator and all subinvestigators as listed on Form FDA 1572 in section 6, if applicable. Disclosure(s) for PI: _____ Disclosure(s) for Sub-I(s): _____ Disclosure(s) for Sub-I(s): _____ Disclosure(s) for Sub-I(s): _____ Disclosure(s) for Sub-I(s): _____	21 CFR 54.1(b) 21 CFR 54.4(3)(b) 21 CFR 12.53(c)(4) ICH GCP 8.2.4	☐	☐	☐N/A
Assure that a signed and dated Curriculum Vitae is available for the principal investigator and each subinvestigator listed on Form FDA 1572 evidencing their qualifications. Also any new subinvestigators added through the course of the trial. Signed CV for PI: _____ Signed CV for Sub-I: _____ Signed CV for Sub-I: _____ Signed CV for Sub-I: _____ Signed CV for Sub-I: _____	21 CFR 312.53(2) ICH GCP 8.2.10 ICH GCP 8.3.5	☐	☐	☐N/A
Licenses (Principal Investigator, Sub-Investigators, and other key staff members)	ICH GCP 8.2.10	☐	☐	☐N/A

	Regulatory Reference	Completed/ Available	Incomplete/ Unavailable (Provide comment)	Comments or check N/A if not applicable
Study Team				
Good Clinical Practice/ Human Subjects Protection training documentation for individuals listed on the Form FDA 1572 and any clinical research site personnel who have more than minimal involvement with the conduct of the research	ICH GCP 8.2.10 21 CFR 312.53	☐	☐	☐N/A
Assure that a signed and dated Curriculum Vitae is present for the study coordinator(s) involved in the trial evidencing their qualifications. Signed CV for SC: _____ Signed CV for other: _____	ICH GCP 8.2.10 Industry standard	☐	☐	☐N/A
Documentation of staff protocol training	ICH GCP 4.2.4 21 CFR 312.53	☐	☐	☐N/A
Documentation of additional staff training	ICH GCP 4.2.4 21 CFR 312.53	☐	☐	☐N/A
Other				
Documentation of protocol registration submission, approval, activation, and deregistration (if applicable)	FDAAA Section 801	☐	☐	☐N/A
Any other correspondence pertinent to the study	ICH GCP 8.3.11	☐	☐	☐N/A
If subjects were provided with any money related to their participation in the trial, assure that documentation of all payments is present. Note that provision of money to subjects should be clearly described in the IRB/EC approved informed consent/ PIS form(s). Ensure documentation of all payments is readily available.	FDA Information Sheet, "Payment to Research Subjects," December 1999	☐	☐	☐N/A
IRB Committee composition/roster for membership over the course of the trial.	ICH GCP 8.2.8	☐	☐	☐N/A
Assure that it is clear how the investigator could unblind study drug in the event of a medical emergency, if the study drug was blinded. Review the procedure w/the PI: _____ Check to confirm that randomization code envelopes or a randomization log is available for inspection: _____	ICH GCP 8.2.17 ; ICH GCP 8.2.18	☐	☐	☐N/A

Pharmacy[5]				
	Regulatory Reference	**Completed/ Available**	**Incomplete/ Unavailable**	**Comments or check N/A if not applicable**
Study Team				
CV of pharmacist(s) Signed CV for pharmacist: _____	ICH GCP 8.2.10 Industry standard	☐	☐	☐N/A
CVs of key pharmacy personnel	ICH GCP 8.2.10 Industry standard	☐	☐	☐N/A
Licenses of pharmacy personnel	ICH GCP 8.2.10	☐	☐	☐N/A
Label(s)				
Sample of label(s) attached to investigational product container(s)	21 CFR 312.6 ICH GCP 8.2.13	☐	☐	☐N/A
Logs/Records				
Signature list and/or Delegation log	ICH GCP 8.3.24	☐	☐	☐N/A
Investigational agent accountability logs	21 CFR 312.62(a) ICH GCP 8.4.1	☐	☐	☐N/A
Current IRB approved version of the protocol	ICH GCP 8.2.2,	☐	☐	☐N/A
Records of study product dispensation to appropriate staff member	ICH GCP 8.3.23	☐	☐	☐N/A
Shipping receipts and records for investigational product(s) and trial related materials	ICH GCP 8.2.15	☐	☐	☐N/A
Documentation of study drug transfers, returns, and destruction	21 CFR 312.62(a) ICH GCP 8.4.2	☐	☐	☐N/A
Temperature logs for applicable equipment (refrigerators, freezers, storage cabinets, etc.)	21 CFR 58.63	☐	☐	☐N/A
Calibration and maintenance records for all equipment (if applicable)	21 CFR 58.63	☐	☐	☐N/A
Investigators Brochure				
Most recent version of Investigator's Brochure(s) or Package Insert(s)	21CFR 312.55; ICH GCP 8.2.1	☐	☐	☐N/A
Certificates of Analysis				
Certificates of analysis of investigational product shipped	ICH GCP 8.2.16	☐	☐	☐N/A
Certificates of analysis for new batches of investigational products	ICH GCP 8.3.9	☐	☐	☐N/A

Clinical Laboratory[5]				
	Regulatory Reference	**Completed/ Available**	**Incomplete/ Unavailable**	**Comments or check N/A if not applicable**
Study Team				
CV of Laboratory Director(s) CV from Central lab: Yes _____ No_____ CV from local lab: Yes _____ No_____	ICH GCP 8.2.10 Industry standard	☐	☐	☐N/A
CVs of key laboratory personnel	ICH GCP 8.2.10 Industry standard	☐	☐	☐N/A
Licenses of laboratory personnel	ICH GCP 8.2.10	☐	☐	☐N/A
Laboratory Documentation				
Assure that documentation of CAP, CLIA, or State laboratory certification is present, for the entire period of the trial for each lab used. CAP (expiration dates): _____ CLIA (expiration dates) :_____ Other certifications : _____	ICH GCP 8.2.12 ICH GCP 8.3.7	☐	☐	☐N/A
Laboratory normal ranges of all labs used during the course of the study. Assure that dated lab normal ranges are present for all lab tests done and all lab facilities used by the site for the trial.	ICH E6 8.2.11	☐	☐	☐N/A
Updates to normal value ranges for medical laboratory/technical procedures or tests included in the clinical protocol	ICH GCP 8.3.6	☐	☐	☐N/A
Updates of medical/ laboratory/technical procedures/tests (e.g. laboratory certifications, accreditations, established quality control and/or external quality assessments, other validations (where required)	ICH GCP 8.3.7	☐	☐	☐N/A
Specimen logs	ICH GCP 8.3.25	☐	☐	☐N/A
Chain of Custody SOP (or similar process document)	Industry Standard	☐	☐	☐N/A

Clinical Equipment (If applicable) [5]				
	Regulatory Reference	**Completed/ Available**	**Incomplete/ Unavailable (Provide comment)**	**Comments or check N/A if not applicable**
Ensure temperature logs for applicable clinic equipment are complete and current (E.g. storage cabinets, refrigerators, freezers, etc.)	21 CFR 58.63	☐	☐	☐N/A
Ensure equipment maintenance & calibration records are available and current (E.g. electronic scales, electronic blood pressure cuff, etc.)	21 CFR 58.63	☐	☐	☐N/A
Research Lab (If applicable)[5]				
Temperature logs for applicable equipment (refrigerators, freezers, storage cabinets, etc.)	21 CFR 58.63	☐	☐	☐N/A
Calibration and maintenance records for all laboratory equipment (if applicable)	21 CFR 58.63	☐	☐	☐N/A
Other (please add any additional site-specific laboratory documents below) _____ _____		☐	☐	☐N/A

Locate, compile, organize, and review documents for accuracy and completeness[4]			
	Completed/ Available	**Incomplete/ Unavailable (Provide comment)**	**Comments or check N/A if not applicable**
Site Standard Operating Procedures	☐	☐	☐N/A
Source documents and medical records are available for each participant (Review for ALCOA: Ensure that all data is *Attributable, Legible, Contemporaneous, Original, Accurate*)	☐	☐	☐N/A
Completed Case Report Forms (CRFs) on file for each participant (signed dated and complete)	☐	☐	☐N/A
Documentation of CRF corrections to document all changes or additions made to the CRF after initial data was recorded *(i.e. proper correction conventions were followed: errant entry crossed out, new value entered, initialed by authorized study team member, and dated.).*	☐	☐	☐N/A
Inclusion/exclusion criteria for each participant have been met and documented	☐	☐	☐N/A
Original signed and dated Informed Consent Forms on file for each participant	☐	☐	☐N/A
All visits conducted within protocol windows	☐	☐	☐N/A
Correct volume of blood and correct tube type drawn at each visit	☐	☐	☐N/A
Protocol-required tests/evaluations have been completed and documented appropriately	☐	☐	☐N/A
All laboratory reports and other diagnostic test reports are on file and display correct participant identifiers	☐	☐	☐N/A
All laboratory results have been graded appropriately by the PI or designated medical officer protocol-requirements	☐	☐	☐N/A

Locate, compile, organize, and review documents for accuracy and completeness			
	Completed/ Available	**Incomplete/ Unavailable (Provide comment)**	**Comments or check N/A if not applicable**
Laboratory reports have been signed by the PI or designated medical officer (**NOTE**: Any clinical values outside the applicable reference range should be designated "Not Clinically Significant" or "Clinically Significant" by the PI or appropriate medical designee on the study team).	☐	☐	☐N/A
Concomitant/prohibited medications have been documented and reported appropriately	☐	☐	☐N/A
Adverse Events (AEs) have been identified and documented appropriately	☐	☐	☐N/A
All SAEs have been reported to the IRB	☐	☐	☐N/A
All AEs and SAEs have been reported to the sponsor per study requirements	☐	☐	☐N/A
Protocol endpoints have been identified and reported appropriately	☐	☐	☐N/A
Protocol violations/ deviations have been identified and documented appropriately with corrective and preventative action plans developed to minimize recurrence.	☐	☐	☐N/A
Premature discontinuations of participants are documented appropriately per study requirements	☐	☐	☐N/A
Ensure study product use by all participants has been documented	☐	☐	☐N/A
Study recruitment and retention plan	☐	☐	☐N/A

5.0 CONDUCT DURING THE AUDIT

5.1 Inspector credentials and Form FDA 482[-6]

When the FDA inspector arrives at the site, they will provide their identification/ID badge and present a **"Notice of Inspection" form FDA 482**

- The PI or his/her representatives should meet the inspector and receive and sign the FDA form 482 "Notice of Inspection"
- If not presented, request to see the inspector's identification
- Document all information from the inspector's identification as it is not permitted to make copies of the identification badges

NOTE: A representative of the IRB must be present for all FDA 'audit start-up' meetings and may request to be present for other Agency audits. Additionally, if a SKCCC trial, a member of the CRO audit team must be present for all audit start-up meetings as per the SKCCC "**Preparing for a Regulatory or Cooperative Group Audit**" guidance.

5.2 Requests for facility tour[-6]

FDA inspector may ask to be given a tour of the facility

- The designated escort should stay with the inspector at all times.

5.3 Requested document copies[-6]

If the inspector asks for copies of various documents:

- Be sure to remove subject identifiers from any copies given to the inspector
- Make a copy of the redacted copy and keep for your site in an Exhibit Log ('shadow binder')
- The copies given to the inspector should be marked or stamped 'Confidential' and the exhibit log (site copies) should be marked or stamped 'Copy'
- **Only give the inspector copies of documents that are specifically requested**

5.4 PI availability during the audit[-6]

The PI should make him/herself available to meet and speak with the inspector each day of the audit

5.5 Responses to inspector's questions[-6]

When answering questions posed by the inspector:

- Be concise; **Only answer only the question that was asked**
- Try to be as clear as possible
- Answer as honestly and openly as you can
- **DO NOT** volunteer any additional information
- **DO NOT** argue with the inspector

- If you don't know an answer to a question you were asked, say so, write down the question and refer it to the correct person
- **The designated escort should keep an exhibit log that includes a list of ALL questions asked by the inspector**

5.6 Items the Inspector will review[6]

During the audit, the FDA inspector will review/confirm:

- Who performed the different aspects of the study (e.g. eligibility review, obtaining consent)
- How authority has been delegated
- Whether or not specific aspects of the investigation were performed
- How and where data has been recorded
- How and where study staff have been oriented or trained about the clinical protocol and investigational agent
- Whether or not the PI has followed the study protocol as it was approved by the IRB
- Dates of IRB approvals (original, continuing review, etc.)
- Date of the first subject screening
- Date of the first subject consenting
- Date of the first administration of the investigational product
- Date of the last follow-up for any study subject
- Whether or not communication with the IRB, including the initial submission, continuing reviews, adverse event reporting, progress reports, etc. was satisfactory
- How complete accountability documentation is for the receipt, storage, administration and return of the investigational agent
- Whether or not the study team was compliant with the protocol and documentation of deviations and amendment received by the IRB and sponsor
- IRB approvals of study amendments
- The informed consent process and consent forms
- Whether or not reporting of adverse events to the IRB and sponsor was performed in a timely manner
- Whether or not record retention requirements were upheld
- Whether or not site monitoring and communication with the sponsor (monitoring reports) was satisfactory

5.7 Common indications of fraud[3]

- Lack of any errors or corrections on CRFs
- Participants who are perfectly compliant with study visits and evaluations
- 100% of all participants who were screened, enrolled and completed the study
- Study staff exhibiting lack of knowledge about the study, seeming lack of equipment or resources when compared to audited work.
- Abnormally large amount of work compared to the resources noted
- Inconsistent sources of data
- Lack of variation in handwriting, ink, or writing style
- Study staff that are guarded or suspicious

6.0 Post-Audit Activities[6]

At the conclusion of their visit, the FDA inspector will hold an exit interview to discuss findings and deficiencies. During this interview, study staff should document the interview, specifically noting observations, comments, and any commitments discussed. During this interview, the PI will be made aware of any deficiencies identified which will be noted on the Form FDA 483 (Inspectional Observations).

NOTE: It is required that a representative of the IRB be present for all FDA audit meetings. Additionally, if a SKCCC trial, a member of the CRO audit team must be present at the audit close-out meeting as per the SKCCC **"Preparing for a Regulatory or Cooperative Group Audit"** guidance.

6.1 Common deficiencies[1]

The most commonly identified deficiencies include:

- Failure to follow the investigational plan
- Protocol deviations (and failure to properly document and report deviations)
- Failure to ensure that informed consent was obtained in accordance with 21 CFR 50
- Failure to maintain accurate, complete, and current records
- Lack of appropriate accountability for investigational agent
- Failure to obtain IRB approval

6.2 Form FDA 483 responses[6, 7, 8]

While there is no regulatory requirement to respond to the 483, a response is the current expectation of the FDA. A well-thought out Form FDA 483 response will demonstrate 1) an understanding of the observations made, 2) a commitment to correct any infractions and comply with regulation, 3) establishes the investigator's credibility, and 4) may help avoid receipt of a formal warning letter.

It is suggested that Form FDA 483 responses:

- include a statement of commitment from senior leadership
- address each of the identified observations separately
- include a statement of whether or not the investigator agrees with the observation
- provide a description of the corrective actions taken or planned to address the observation;

  In doing so:
  - be specific and complete
  - make sure that you are able to deliver what you promise
  - address affected products
  - provide time frames for corrective actions

- Provide method of verification and/or monitoring for corrections
- Consider submitting documentation of corrections where reasonable & feasible

NOTE: Before drafting a 483 response, see **Best Practices: Responding to FDA Form 483's**, **FDA Inspections: How to Survive an FDA Inspection**, and **Writing an Effective 483 Response** for more information about structure and content.

NOTE: It is required that the team's formal response to the audit be reviewed and approved by the IRB and, if a SKCCC trial, the CRO prior to submission to the sponsor.

6.3 Form FDA 483 response timing[8]

The PI may respond to the 483 verbally during the exit interview and/or may respond in writing. **If the PI elects to respond in writing, the response should be directed to the FDA District Office listed in the upper left corner of the 483. Form FDA483 responses should be received within 15 business days so that they may be formally reviewed before any letter/ Establishment Inspection Report (EIR) is issued. If the responses received to the 483 issues are reviewed and thought to adequately address the issue, they may be removed from the Form 483 and will not be addressed in the EIR.**

NOTE: See the Review of Post-Inspection Responses [Federal Register Volume 74, Number 153 (Tuesday, August 11, 2009)]

6.4 Establishment Inspection Report (EIR) [6]

Following the inspection, the FDA inspector will prepare a written Establishment Inspection Report (EIR). The EIR, Form FDA 483 (if one is issued), copies of any materials collected during the inspection, and any clinical investigator response that has been received by the District Office are forwarded to the appropriate FDA Center for further evaluation and final classification of the inspection outcome.

6.5 Classification of outcomes[6]

At the appropriate FDA Center, the EIR will undergo supervisory review and classification will be assigned as one of the following:

- **No action indicated (NAI):** No objectionable conditions or practices were found during the inspection, or the significance of the objectionable conditions does not justify further FDA action

- **Voluntary Action Indicated (VAI):** Objectionable conditions were found and documented, but the FDA is not prepared to take or recommend further regulatory action because the objectionable conditions are few and do not seriously impact subject safety or data integrity

- **Official Action Indicated (OAI):** Regulatory violations uncovered during the inspection are repeated or deliberate and/or involve submission of false information to FDA or to the sponsor. If OAI, the inspection report is sent to the district Compliance Branch for further review.

6.7 FDA letters to the investigator[1]

Per the FDA "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors FDA Inspections of Clinical Investigators," after supervisory review and classification one of the audit findings, one of the following types of letters is usually sent to the clinical investigator:

(1) A letter that generally states that FDA observed basic compliance with pertinent regulations.

Note: A letter is not always sent when FDA observes no significant deviations.

(2) An *Informational or Untitled Letter* that identifies deviations from statutes and regulations that do not meet the threshold of regulatory significance for a Warning Letter. Generally, such letters may request a written response from the clinical investigator.

Note: See FDA's procedures regarding initiation of Untitled Letter procedures, found in the Regulatory Procedures Manual (RPM) in Chapter 4-2.10

(3) A *Warning Letter* that identifies serious deviations from applicable statutes and regulations. A Warning Letter is issued for violations of regulatory significance and may lead to enforcement action if not promptly and adequately corrected. Warning Letters are issued to achieve voluntary compliance, and include a request for correction and a written response to the agency.

Note: See FDA's procedures regarding initiation of disqualification proceedings, found in the Regulatory Procedures Manual (RPM) Chapter 4-1

(4) Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)

An NIDPOE is issued when the PI has repeatedly or deliberately failed to comply with the requirements for conducting clinical trials and/or has repeatedly or deliberately submitted false information to FDA or to the sponsor. The FDA may initiate a process to disqualify the clinical investigator from receiving investigational new drugs and/or biologics.

Note: See FDA's procedures regarding initiation of disqualification proceedings, found in the FDA Regulatory Procedures Manual (RPM) Chapter 5-9.13

Additional Cited Resources

1- **FDA: Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: FDA Inspections of Clinical Investigators**
2- **FDA: Compliance Program Guidance Manual (CPGM)** *(Chapter 48)*
3- **Preparing for an FDA Audit** *(Jean Connor. Heidi Moses. Eunice Yim Newbert, Children's Hospital, Boston)*
4- **Site_FDA_Inspection_Preparation_Checklist_v1[1].0_22Nov10.doc** *(Microbicide Trials Network)*
5- **FDA Inspections - Johns Hopkins Bloomberg School of Public Health** *(JHBSPH)*
6- **FDA Inspections: How to Survive an FDA Inspection** *(Cynthia Monahan, QI Specialist, Partners HRQI Program)*
7- **Writing an Effective 483 Response** *(Anita Richardson, FDA, Office of Compliance & Biologics Quality)*
8- **Best Practices: Responding to FDA Form 483's** *(John R Godshalk, Biologics Consulting Group)*