ASCO® Research Community Forum

TOOLKIT OF RESOURCES

FDA Audit Readiness

ASCO® CENTRA
Center for Research & Analytics

TABLE OF CONTENTS

OVERVIEW

This Toolkit was developed as part of an initiative led by the American Society of Clinical Oncology's Research Community Forum (ASCO RCF), which provides tools and resources to assist oncology research programs with conducting and managing clinical trials. It contains links to helpful references as well as templates, checklists, and forms related to FDA audits and audit readiness. This Toolkit was initially prepared for a workshop at the 2019 ASCO Research Community Forum Annual Meeting, *When FDA Calls: Introduction to FDA Audit Readiness*.

The references and resources are not exhaustive and decisions to include resources were based on the contributors' own go-to resources, consultation with colleagues, and an environmental scan of available resources. Resources from commercial entities, or that are made available for profit, are generally excluded. The references are not necessarily endorsed by ASCO; they are listed based on the discretion and expertise of the contributors noted in the acknowledgements. If you have suggestions for additional resources for inclusion, please email them to researchcommunityforum@asco.org.

ACKNOWLEDGEMENTS

There are several important contributors to this Toolkit, including: Andrea Buchmeier, MHA, CCRC, LSSGB from Sarah Cannon; Katie Goodman, RN, CCRC and James Reeves, MD from Florida Cancer Specialists; Susan Modugno, BSN, OCN, CCRC from Sarah Cannon Research Institute; Leslie Byatt, CPhT, CCRC from New Mexico Cancer Care Alliance; and Aisha Peterson Johnson, MD, MPH, MBA from the US Food and Drug Administration. Some of the resources are adapted, with permission, from materials they or their colleagues at their affiliate organizations have developed to assist them with audit readiness.

Patricia Hurley, MSc and Courtney Davis from ASCO's Center for Research and Analytics and the ASCO RCF also assisted with developing the toolkit.

Disclaimer: This Toolkit contains templates and resources that are provided as examples only for research programs to consider as they formulate their own resources. ASCO makes no warranties, expressed or implied, as to results obtained by individuals using the information and is not responsible for any action taken in reliance on the information contained herein.

When citing this Toolkit, or any of its components, please include the following content in the citation:

American Society of Clinical Oncology Research Community Forum Toolkit: FDA Audit Readiness. Alexandria, VA; American Society of Clinical Oncology; 2019.

For more information contact researchcommunityforum@asco.org.

FDA Inspections of Clinical Trials

ASCO Research Community Forum

FDA INSPECTIONS OF CLINICAL TRIALS

– AT A GLANCE –

BOTTOM LINE

Conduct every study as if it will be inspected.

KEEP CALM
Do not panic!
Know the right questions to ask.

Have an audit plan and checklist ready.

Communicate with your team, study sponsor, FDA.

KEY CONSIDERATIONS, TIPS, AND BEST PRACTICES

A successful FDA inspection will lead to improved processes, improved communication, better training, and overall a higher quality research program. The following provides some suggested best practices for research sites to ensure FDA audit readiness. A toolkit is also available asco.org/research-community-forum.

Reasons for FDA Audits

Top Reasons for an FDA inspection[1]

- Risk based ranking of site
- Sites with a high number of enrollments
- Sites with known issues from previous inspections
- Concern with scientific misconduct, outliers, and protocol violations
- A complaint about the PI or the site

Common Deficiencies[1]

- Failure to conduct an investigation in accordance with signed investigator statement or agreement/investigational plan/applicable regulations
- Inadequate or inaccurate case histories
- inadequate investigator subject records
- Inadequate drug/device disposition records
- Failure to obtain informed consent in accordance with Part 50

When the FDA Calls…

Critical Questions to ask the FDA

- ❑ Which study is under review?
- ❑ What type of audit is it?
- ❑ What is the inspector's name?
- ❑ When would they like to visit?
- ❑ What is anticipated length of inspection?
- ❑ Who will be coming with inspector?
- ❑ What records will they review?

What to Expect – Day of Inspection

The Inspector will…

- ❑ Introduce themselves and show credentials
- ❑ Review FDA form 482, notice of inspection, and give the investigator the original form
- ❑ Review why the study is being inspected
- ❑ Review the inspection process and what to expect during the audit
- ❑ Provide a projected timeline for the audit
- ❑ Start the inspection by reviewing the regulatory binder, then move to informed consent and patient charts
- ❑ Conduct interviews with the investigator and select members of research team

Key Steps to Prepare for an FDA Inspection

- ❑ Complete inspection preparation checklist
- ❑ Notify all key study staff, sponsor, and institutional official
- ❑ Pull all original research records
- ❑ Review the protocol under inspection
- ❑ Review all reported serious adverse events
- ❑ Review all participants' consent forms
- ❑ Review and organize all regulatory documents
- ❑ Identify a quiet conference room for interview

The Interview Dos and Don'ts

- ❑ Be calm - Don't be defensive or get emotional
- ❑ Listen carefully and repeat the question - Ask for the question to be repeated or for clarification
- ❑ Answer questions directly, completely, and honestly. It is fine to say "I do not know."
  - Do not guess or make up the answer
  - Do not provide your opinion, only the facts
  - Do not volunteer more information than necessary
  - Do not answer for someone else
- ❑ Ensure someone takes detailed notes of the questions asked
- ❑ Leave as soon as the interview is over

After Inspection Follow-Up

- ❑ Conduct a team meeting to review what went well and opportunities for improvement.
- ❑ Share learnings widely with your research team, IRB, sponsor, and other colleagues; what you have learned is valuable to others.
- ❑ If you received an FDA Form 483, prepare a detailed response to each finding and submit the response to FDA within 15 business days.[2]
- ❑ The FDA inspector will write an establishment inspection report (EIR) and send to FDA regional office for review and classification. The principal investigator will receive a copy of the EIR in a few months.
- ❑ The inspection will be classified in one of three ways: no action indicated, voluntary action indicated, official action indicated.[2]

FDA Form 483 Responses – Dos and Don'ts

Do…

- ❑ Send a response to the FDA within 15 days set a timeline with your team to prepare and finalize your response
- ❑ Determine the root cause of each observation
- ❑ Anticipate potential questions
- ❑ Support all claims and actions with facts. Include documents that address actions (training logs, process revisions, meeting sign in sheets, etc.)
- ❑ Ensure your responses includes clear and compelling corrective action plans; include a Corrective and Preventive Actions (CAPA) owner
- ❑ Double check your response for quality and thoroughness
- ❑ Make certain that your changes are realistic and sustainable
- ❑ Consider sending follow correspondence to the FDA regarding progress (this is dependent on severity of observation)
- ❑ Prepare for a re-audit

Do Not…

- ❑ Give vague or broad plans of actions
- ❑ Respond quickly to significant issues
- ❑ Include irrelevant data and comments
- ❑ Exaggerate the potential outcome the findings could have on the business
- ❑ Respond defensively or rationalize the findings

REFERENCES

1. Bioresearch Monitoring (BIMO) Fiscal Year 2018 Metrics. (2019). Retrieved from https://www.fda.gov/media/127110/download.
2. Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors. FDA Inspections of Clinical Investigators (2010). Retrieved from https://www.fda.gov/media/75185/download.

OTHER RESOURCES

- ASCO Research Community Forum Toolkit: FDA Audit Readiness. 2019.
- Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBS. Frequently Asked Questions-Statement of Investigator (Form 1572): https://www.fda.gov/media/78830/download
- Clinical Investigator Responsibilities at CFR: https://www.ecfr.gov/cgi-bin/text-idx?SID=85342f2ba76551ed53ba168bb4d10b8d&mc=true&node=sp21.5.312.d&rgn=div6
- FDA Form 482c. (2019): https://www.fda.gov/media/75425/download
- Inspections Database Frequently Asked Questions (2019): https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspections-database-frequently-asked-question
- Walters, J.P. (2004). Guidance on Responding to the FDA Warning Letter and Possible Enforcement Consequences for Clinical Investigators and Sponsors. Retrieved from https://onlinelibrary.wiley.com/doi/pdf/10.1002/qai.296
- Clinical Investigator Responsibilities at CFR: https://www.ecfr.gov/cgi-bin/text-idx?SID=85342f2ba76551ed53ba168bb4d10b8d&mc=true&node=sp21.5.312.d&rgn=div6
- Guidance on Investigator Responsibilities: https://www.fda.gov/media/77765/download
- Guidance on Financial Disclosure: https://www.fda.gov/media/85293/download
- Signatures in Clinical Investigations: https://www.fda.gov/media/105557/download
- Use of Electronic Records and Electronic Signatures in Clinical Investigations: https://www.fda.gov/media/105557/download
- FDA Good Clinical Practice Contacts: CDER-OSI-GCPReferrals@fda.hhs.gov

Email researchcommunityforum@asco.org with ideas and suggestions for content revisions, and/or recommendations for new topic summaries.

Visit asco.org/research-community-forum to learn more about the ASCO Research Community Forum initiatives and to access resources and tools for oncology research sites.

ACKNOWLEDGEMENTS

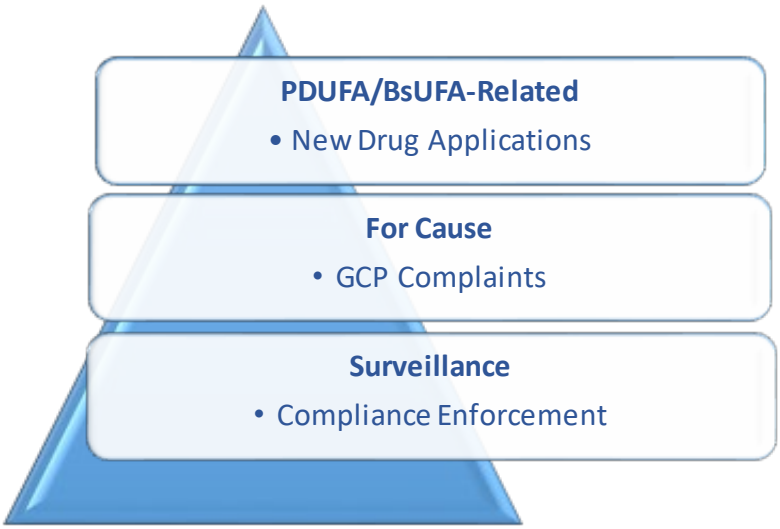
This document was developed in conjunction with content for an ASCO Research Community Forum Annual Meeting workshop on FDA Audit Readiness. Content was developed by Andrea Buchmeier, MHA, CCRC, LSSGB; Aisha Peterson Johnson, MD, MPH, MBA; James A. Reeves, MD; Katie Goodman, RN, BSN, CCRP; Leslie Byatt, CPhT, CCRC; and ASCO staff leads, Patricia Hurley MSc and Courtney Davis.

Curious about how others address issues related to FDA audits for clinical trials?

Join the ASCO Research Community Forum Online Forum to discuss challenges and share best practices with colleagues. Visit myconnection.asco.org/rcf.

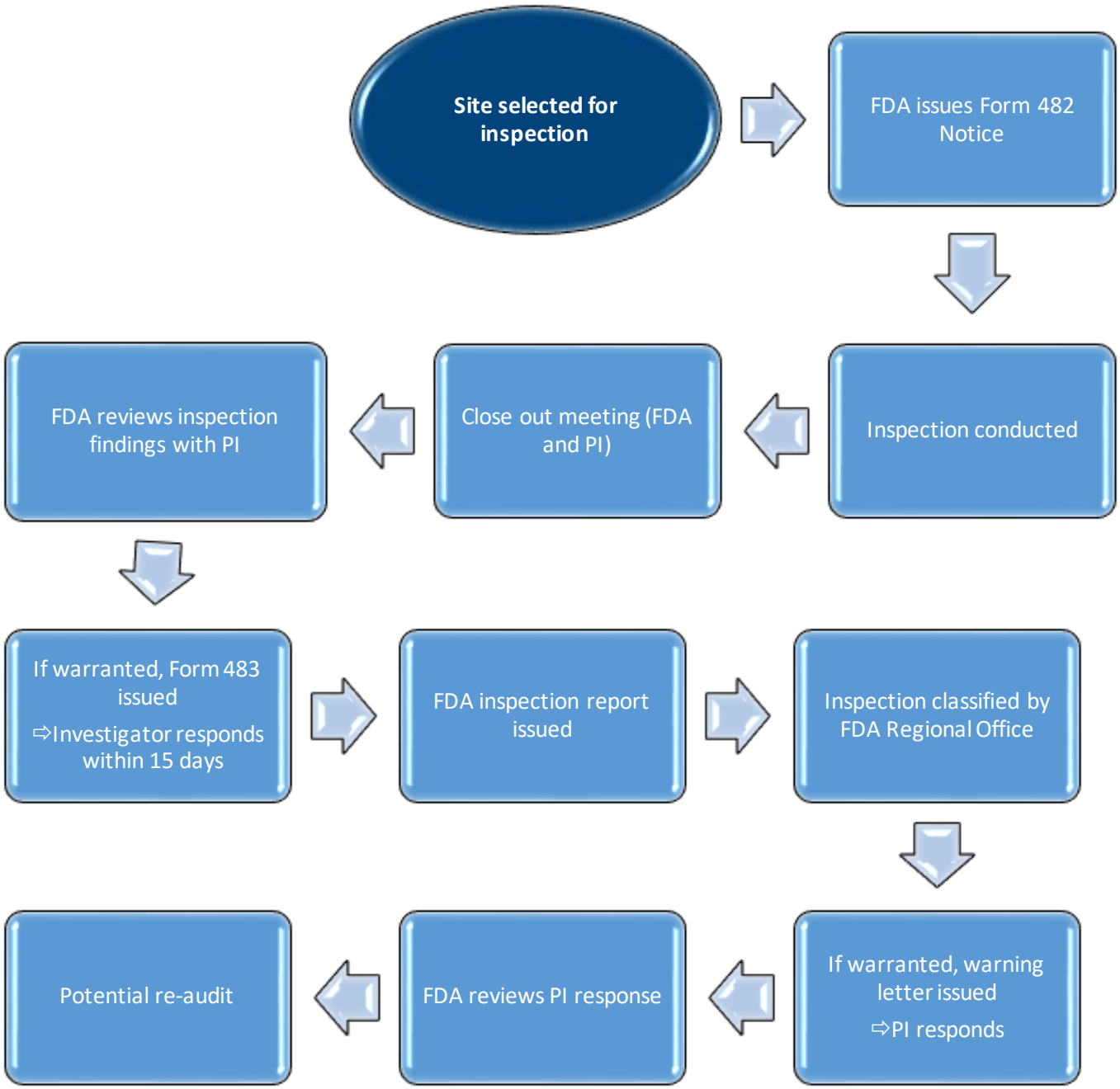
TYPES OF FDA INSPECTIONS

There are three types of FDA audits: Prescription Drug User Fee Act (PDUFA) or Biosimilar User Fee Amendment (BsUFA) Related; 2) For Cause; and 3) Surveillance.



FDA Audit Process

There are several elements within the FDA audit process for which the investigator and research site will need to prepare and act upon before the audit, during the audit, and after the audit.



QUESTIONS TO ASK FDA

- ❑ Which study is under review?
- ❑ What type of audit is it?
- ❑ What is the inspector's name?
- ❑ When would they like to visit?
- ❑ What is anticipated length of inspection?
- ❑ Who will be coming with inspector?
- ❑ What records will they review?

FDA FORM 482 - SAMPLE

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	1. DISTRICT OFFICE ADDRESS & PHONE NO.

TO	2. NAME AND TITLE OF INDIVIDUAL		3. DATE
	4. FIRM NAME	5. HOUR	a.m.
	6. NUMBER AND STREET		p.m.
	7. CITY AND STATE & ZIP CODE		8. PHONE # & AREA CODE

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)(1)][1]. Written request is hereby given to access and/or copy the records described below, pursuant to the Federal Food, Drug and Cosmetic Act, Section 414(a) [21 U.S.C. 350c][2] and Title 21 Code of Federal Regulations, Section 1.361[3].

9. SIGNATURE *(Food and Drug Administration Employee(s))*	10. TYPE OR PRINT NAME AND TITLE *(FDA Employee(s))*

Applicable portions of Sections 704 and 414 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 374 and 350c) and Title 21 of the Code of Federal Regulations, are quoted below:

[1]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, 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, 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, when the standard for records inspection under paragraph (1) or (2) of section 414(a) applies, subject to the limitations established in section 414(d). In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, or restricted devices are manufactured, processed, packed, or held, the 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, or restricted devices 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 (3) 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 Act), and research data (other than data, relating to new drugs, antibiotic drugs and devices and, subject to reporting and inspection under regulations lawfully issued pursuant to section 505(i) or (k), section 519, or 520(g), and data relating to other drugs or devices which in the case of a new drug would be subject to reporting or inspection under lawful regulations issued pursuant to section 505(j). A separate notice shall be given for each such inspection, but a notice shall not be required for each entry made during the period covered by the inspection. Each such inspection shall be commenced and completed with reasonable promptness.

[2]Sec. 414(a) RECORDS INSPECTION. - (1) ADULTERATED FOOD. - If the Secretary has a reasonable belief that an article of food, and any other article of food that the Secretary reasonably believes is likely to be affected in a similar manner, is adulterated and presents a threat of serious adverse health consequences or death to humans or animals, each person (excluding farms and restaurants) who manufactures, processes, packs, distributes, receives, holds, or imports such article shall, at the request of an officer or employee duly designated by the Secretary, permit such officer or employee, upon presentation of appropriate credentials and a written notice to such person, at reasonable times and within reasonable limits and in a reasonable manner, to have access to and copy all records relating to such article, and to any other article of food that the Secretary reasonably believes is likely to be affected in a similar manner, that are needed to assist the Secretary in determining whether the food is adulterated and presents a threat of serious adverse health consequences or death to humans or animals. (2) Use of or exposure to food of concern. --If the Secretary believes that there is a reasonable probability that the use of or exposure to an article of food, and any other article of food that the Secretary reasonably believes is likely to be affected in a similar manner, will cause serious adverse health consequences or death to humans or animals, each person (excluding farms and restaurants) who manufactures, processes, packs, distributes, receives, holds, or imports such article shall, at the request of an officer or employee duly designated by the Secretary, permit such officer or employee, upon presentation of appropriate credentials and a written notice to such person, at reasonable times and within reasonable limits and in a reasonable manner, to have access to and copy all records relating to such article and to any other article of food that the Secretary reasonably believes is likely to be affected in a similar manner, that are needed to assist the Secretary in determining whether there is a reasonable probability that the use of or exposure to the food will cause serious adverse health consequences or death to humans or animals. (3) Application.--The requirement under paragraphs (1) and (2) applies to all records relating to the manufacture, processing, packing, distribution, receipt, holding, or importation of such article maintained by or on behalf of such person in any format (including paper and electronic formats) and at any location.

[3]321 CF CFR 1.361 What are the record availability requirements? When FDA has a reasonable belief that an article of food is adulterated and presents a threat of serious adverse health consequences or death to humans or animals, any records and other information accessible to FDA under section 414 or 704(a) of the act (21 U.S.C. 350c and 374(a)) must be made readily available for inspection and photocopying or other means of reproduction. Such records and other information must be made available as soon as possible, not to exceed 24 hours from the time of receipt of the official request, from an officer or employee duly designated by the Secretary of Health and Human services who presents appropriate credentials and a written notice.

FORM FDA 482c (4/12) **NOTICE OF INSPECTION - REQUEST FOR RECORDS**

POTENTIAL AUDIT QUESTIONS FOR PRINCIPAL INVESTIGATORS

Provided by Susan Modugno from Sarah Cannon Research Institute.

This section provides examples of audit questions that a Principal Investigator may be asked. It is the Principal Investigator's responsibility to be prepared to respond appropriately when an auditor asks such questions.

Question: How many studies do you currently have open?

This information should be provided to you prior to the audit via e-mail. If not known, staff can provide that info prior to the end of the audit. The info typically includes # of studies currently Principal Investigator (PI) for that are open to enrollment and closed to enrollment. It does not include the # of studies that have been closed with the IRB and archived, though that information can be provided.

Question: What types of studies do you typically conduct?

Answer: Phase II-IV Oncology Trials

Question: What responsibilities do you delegate to your coordinators?

Answer:

- Screening
- Consent
- Subject management
- Study drug dispensing and accountability
- CRF completion
- Source documentation
- Protocol deviation process
- Data and lab collection and submission

Question: What methods of recruiting does your site use?

Answer: Screening of subjects through the EMR and per Investigator referral

Question: What are your responsibilities as a PI? How do you demonstrate PI oversight?

Answer:

- Oversight of all aspects of the trial
- Conducting the trial according to the protocol
- Supervision of Sub-Is and research staff
- Ensuring patient rights and safety are protected via maintaining informed consent and IRB review
- Working with sponsors and CROs to maintain accurate and updated study documents
- Monitoring and reporting adverse experiences/SAEs to the sponsor
- Review and assessment of deviations on a regular basis with submission to IRB as indicated.
- Review of INDSRs
- E-mail blasts are sent to research staff at specified time points: enrollment, at study discontinuation, at time a SAE occurs to disseminate information in real time
- Site Management Plan and SOP procedures

Question: Where is the investigational drug stored?

Answer:

- Main Pharmacies at regional headquarters sites
- Shipped to clinic sites prior to planned study visits

Question: Are your studies monitored on a frequent basis? Do you meet with the monitors? How much time do you spend with them?

Answer:

- Monitored via the sponsor monitoring plan but usually every 4-6 weeks
- Meet with monitors via telecons or in-person and spend 15-30 meetings depending on discussion items or needs

Question: How do you assess adverse events, labs, and procedures?

Answer:

- Sub-Is are delegated assessment of AEs
- AE logs are created with AE name, grade, relationship to IP or other drugs for review
- Labs are reviewed and signed off on in EMR. Clinically significant labs are documented in the MD note

Question: Do you seek IRB approval for your advertising?

Answer: Yes, if utilized

Question: Do you review all recorded data (CRFs / eCRFs)?

Answer: Review and sign off on eCRFs as needed

Question: Where are your old study files archived?

Answer: Long term storage facility in xxx

Question: Are you located in this office?

Answer: Located in ____ office in _____Region

Question: How often do you come to this office?

Answer: As needed

Question: Who typically conducts the informed consent process?

Answer: PI and delegated to Sub-Investigators and/or Research Coordinators

Question: Please explain the consent process?

Answer:

- Current consent is printed from the portal and presented to patient in quiet area and discussed
- Patient given opportunity to ask questions and take home if needed
- Re-consent is completed per IRB Certificate of Approval (COA) instructions

Question: What is the reporting process for SAEs?

Answer:

- Report SAE within 24 hours of site awareness
- Current process is to escalate SAE information to the study team (PI, Sub-Is, Research Coordinators, Managers, and data) via e-mail communications or 'blasts'
- E-mail, phone and text are most common forms of communication

Question: Do you review the SAE data?

Answer:

- Yes, via the SAE notifications (via e-mail). This is real-time PI oversight of the event
- Reports are scanned into the EMR where subject information is available 24 hours/day as needed

Question: Any atypical occurrences or SAEs that have happened on your recent studies?

Answer:

- SAE logs are kept in order to determine number, frequency, trends if identified
- SAE logs are reviewed and signed yearly and at end of study
- Atypical occurrences would be identified on a per study basis

Question: What type of training is required for the site staff?

Answer:

- GCP training for all research staff every 2 years
- Study specific training is required for research staff and enrolling Sub-Is
- Updated amendment training is required of the same staff
- Protocol training is completed via the SIV and/or electronic review of version controlled protocol specific slide decks on intranet
- Training logs are kept for tracking of training

Question: Do you complete and Good Clinical Practice (GCP) Training?

Answer: All research staff are required to complete GCP training at hire and every 2 years

Question: Do you have Standard Operating Procedures?

Answer: Yes. Current version approved MMM/YYYY

Question: Are you or your coordinators accessible after business hours? What is the process for this?

Answer:

- MDs are on-call after hours
- PI is always accessible
- EMR is web-based for easy access for subject review 24/7

FDA INSPECTION PREPARATION CHECKLIST

Provided by Susan Modugno from Sarah Cannon Research Institute.

ADMINISTRATIVE ACTIVITIES			
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			
	Clinical trial(s) selected:	Details:	
	Principal Investigator:	Details:	
	Routine (e.g., IND):	Details:	
	Directed (e.g., for cause):	Details:	

HAS FDA REQUESTED THAT SPECIFIC PERSONNEL BE AVAILABLE? IF YES, PLEASE LIST.	
Who has been requested?	When must they be available?
HAS FDA REQUESTED THAT SPECIFIC DOCUMENTS BE AVAILABLE? IF YES, PLEASE LIST.	
Documents requested:	Check if requested prior to inspection:
	Date:
	Date:
	Date:

AFTER RECEIVING A CALL FROM ANY GOVERNMENTAL AGENCY, NOTIFY THE APPROPRIATE PARTIES:			
	Notified/ Available	**Not notified/ Unavailable**	**Comments or check N/A if not applicable**
Principal Investigator			
Clinical Operations			
Clinical Quality Assurance			
Sponsor / CRO of selected trial(s) – Clinical Quality Assurance will assist			
Sub-Investigator(s)			
Research Staff / Study Coordinator(s)			
Investigational Pharmacy			☐ N/A
Regulatory Affairs Department			
Clinical Laboratory(ies)			☐ N/A
Other Sponsors as determined by contract review			

DESIGNATE AN INSPECTION PREPARATION AND SUPPORT TEAM.			
Identify and assign staff in preparation efforts (see below for further details of the review): • Regulatory files • Subject records • Pharmacy • Laboratory • Staff Overview on FDA Inspections **Identify and assign staff for support during the Inspection:** • Two inside inspection room (facilitator of EMR/records, note taker, liaison to facilitate interviews, etc.) • Two outside of inspection room (photo-copier, document reviewer and tracker, preparing end of day communications, etc.) Any other site staff that would be needed.			

	Notified/ Available	Not notified/ Unavailable	Comments or check N/A if not applicable
Ensure the following are available for the PI: • Preparation Report to include the following: – Subject List – Study List (all open to enrollment and closed to enrollment still open at the IRB) – SAEs – Deviations • Sample FDA Questions • Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors *FDA Inspections of Clinical Investigators* June 2010 **Other Preparations:** • Prepare a Study List and Subject List to be provided to the inspector upon arrival (see details later in checklist) • Administrative needs (see details below)			

DESIGNATE AN AREA OR ROOM FOR THE INSPECTION AND OUTSIDE WORK AREA.	
Conference Room with EMR availability	Room #: COMMENTS:
Outside Work Area	Room # or description:
CONFIRM THAT A COPY MACHINE WILL BE AVAILABLE FOR USE DURING THE INSPECTION.	
Copier location:	
***NOTE*: 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**. *This ensures a copy for future reference when responding to the inspection findings.*	
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 from Iron Mountain confirm that delivery will occur prior to audit date	
Confirm ready access to all study related materials that are maintained electronically	
Confirm ready access to all records for SAEs during the trial	
Have available all records related to drug accountability	
Have available all laboratory records and manuals	

REGULATORY DOCUMENTATION				
	Regulatory Reference	**Completed/ Available**	**Incomplete/ Unavailable**	**Comments or check N/A if not applicable**
List of Principal Investigator's studies (all active and closed to enrollment with subjects in follow up)	BIMO Compliance Program Guidance Manual, Chapter 48[-2]			
Have available copies of any signed agreement between involved parties (E.g. investigator and sponsor, investigator and CRO, Sponsor and CRO, etc.)	ICH GCP 8.2.6			☐ N/A
PROTOCOL				
All versions of the clinical protocol with Protocol Signature pages completed	21CFR§312.30 ICH GCP 8.2.2, ICH GCP 8.3.2			
All protocol amendments and clarification memorandums	21CFR§312.30 ICH GCP 8.2.2, ICH GCP 8.3.2			
INVESTIGATOR'S BROCHURE				
All versions of the Investigator's Brochure(s) and/or Package Insert(s) (if applicable) to include signature of receipt by the investigator	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				
All IND Safety Reports provided by the sponsor are uploaded to the portal and acknowledged by the PI	21 CFR 312.50 21 CFR 312.32 (c)(1)(i) ICH GCP 8.3.18			☐ N/A
All Investigator Safety Letters are on file and actions taken are documented	21 CFR 312.50 21 CFR 312.32 (c)(1)(i) ICH GCP 8.3.18			☐ N/A
All Continuing Review Reports are completed, submitted to the IRB and filed in the site binder	21 CFR.109(f) ICH GCP 8.3.19			☐ N/A
CONSENTS				
IRB approved Informed Consent Forms (all versions including screening consent forms and any translated versions as well)	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.			☐ N/A

	Regulatory Reference	Completed/ Available	Incomplete/ Unavailable (Provide comment)	Comments or check N/A if not applicable
IRB APPROVAL				
Initial IRB submission and Certificate of Approval	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 a local IRB involved, have available appropriate documentation of the IRB's requirements _____ Specify name of IRB:	21 CFR 56.103(a), 21 CFR 56.109(e), ICH GCP 8.2.7 ICH GCP 8.3.3			☐ N/A
All IRB protocol amendment(s) submissions and Certificates of Approval	21 CFR 56.103(a) 21 CFR 56.109(e), ICH GCP 8.2.7 ICH GCP 8.3.3			☐ N/A
All IRB continuing review approvals	21 CFR 6.103(a), 21 CFR 56.109(e), ICH GCP 8.2.7 ICH GCP 8.3.3			☐ N/A
IRB submissions for all revised Informed Consent Forms and Certificates of Approval including those translated from English to another language	21 CFR § 312.60 ICH GCP 8.2.3 ICH GCP 8.3.2			☐ N/A

	Regulatory Reference	Completed/ Available	Incomplete/ Unavailable (Provide comment)	Comments or check N/A if not applicable
IRB APPROVAL				
IRB submissions and Certificates of Approval for subject recruitment materials as needed (advertisements, videos, handouts to participants, etc.)	21 CFR § 56.109(a), FDA Information Sheet, "Recruiting Study Subjects," December 1999; ICH GCP 8.2.3			☐ N/A
CORRESPONDENCE FROM INVESTIGATOR TO SPONSOR/SPONSOR-INVESTIGATOR				
All correspondence between the investigator and the sponsor (and CRO, if applicable), 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				
IRB acknowledgement letters for receipt of SAE submissions to the IR.	21 CFR 312.64(b) ICH GCP 8.3.11 ICH GCP 8.3.16			☐ N/A
IRB acknowledgement letters for the major protocol deviations submitted to the IRB	21 CFR 312.64(b) ICH GCP 8.3.11 ICH GCP 8.3.16			☐ N/A
IRB acknowledgments letters for site serious adverse events, and any other adverse event information submitted to the IRB, as well as annual reports, periodic reports if applicable, and the final report	ICH GCP 8.3.17	☐	☐	☐ N/A
LOGS				
Completed subject screening/ enrollment log	ICH GCP 8.3.20 ICH GCP 8.3.22			☐ N/A
Completed and up to date Delegation of Authority Log				☐ 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				
Copy of all versions of Form FDA 1572 signed and dated by the principal investigator	21 CFR 312.53(c)(1)			☐ N/A
All financial disclosure documentation for the principal investigator and all sub-investigators as listed on Form FDA 1572	21 CFR 54.1(b) 21 CFR 54.4(3)(b) 21 CFR 12.53(c)(4) ICH GCP 8.2.4			☐ N/A
Signed and dated Curriculum Vitae for the principal investigator and each sub-investigator listed on Form FDA 1572 evidencing their qualifications. Also for all research staff associated with the conduct of the trial.	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				
GCP training documentation for individuals listed on the Form FDA 1572 and clinical research site personnel involved with the conduct of the research.	ICH GCP 8.2.10 21 CFR 312.53			☐ 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				
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 un-blind 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				
	Regulatory Reference	**Completed/ Available**	**Incomplete/ Unavailable**	**Comments or check N/A if not applicable**
STUDY TEAM				
CV of pharmacist(s) and other 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/PHARMACY RECORDS				
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
Most recent version of Investigator's Brochure(s) or Package Insert(s)	21CFR 312.55; ICH GCP 8.2.1			☐ N/A

LABORATORY				
	Regulatory Reference	**Completed/ Available**	**Incomplete/ Unavailable**	**Comments or check N/A if not applicable**
LABORATORY DOCUMENTATION				
Documentation of CAP, CLIA, or State laboratory certification for the entire period of the trial for each lab used	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 and dated lab normal ranges for all lab tests done and all lab facilities used by the site for the trial	ICH E6 8.2.11			☐ 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
Temperature logs for applicable clinic equipment are complete and current (E.g. storage cabinets, refrigerators, freezers, etc.)	21 CFR 58.63			☐ N/A
Equipment maintenance & calibration records are current (E.g. electronic scales, electronic blood pressure cuff, etc.)	21 CFR 58.63			☐ N/A
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

LOCATE, COMPILE, ORGANIZE, AND REVIEW DOCUMENTS FOR ACCURACY AND COMPLETENESS			
	Completed/ Available	**Incomplete/ Unavailable (Provide comment)**	**Comments or check N/A if not applicable**
Site Standard Operating Procedures and SSO Standard Operating Procedures			☐ N/A
Source documents and medical records for each study subject (Review for ALCOA: Ensure that all data is *Attributable, Legible, Contemporaneous, Original, Accurate*)			☐ N/A
Case Report Forms (CRFs) available for each study subject.			☐ N/A
Inclusion/exclusion criteria for each study subject have been met and documented			☐ N/A
All signed and dated Informed Consent Forms on file for each study subject			☐ N/A
All visits conducted within protocol windows			☐ 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 assessed/signed appropriately by the PI or treating investigator for clinical significance			☐ 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**
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 violations/ deviations have been identified and documented appropriately			☐ 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 if applicable			☐ N/A

FDA GUIDANCE INFORMATION

Below are links to FDA guidance documents that may be useful with regards 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:	Form 483 Frequently Asked Questions
FDA Information Sheet:	Guidance for IRBs, Clinical Investigators, and Sponsors: FDA Inspections of Clinical Investigators
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:	Regulatory Procedures Manual (RPM)

FDA Inspection Site Summary

Provided by Katie Goodman, Florida Cancer Specialists.

The following lists items to consider for a site summary for an FDA inspection.
There is an Excel template file available upon request from reaserchcommunityforum@asco.org.

PI List of Active Research

- Protocol Title
- Study ID #
- IND # or PMD #
- Sponsor
- Sponsor Address
- Site Start Date
- Site End Date
- IRB Name
- IRB Address
- IRB Chair
- Study Status

Patient Summary

- Internal MR#
- Patient Name
- DOB
- Screening #
- Enrollment #
- Enrolling Physician
- Office
- Sex
- Race
- Initial ICF Date
- Enroll Date
- End Date
- Expire Date
- SAE Summary (include relationship to IP)
- Deviation Summary
- Clinical Notes

Protocol Amendment Summary

- Protocol Version
- IRB Approval Date
- Changes to ICF(s)
- IRB directive on reconsent

Deviation Log

- Patient Initials
- Patient Number
- Deviation Type
- Date of Deviation
- Location and Clinic
- Principal Investigator
- Treating Investigator
- Cycle & Day Number
- Corrective Action Plan
- Classification (Major/Minor)
- IRB Submissions Date

SITE SUMMARY OF INSPECTION

Provided by Katie Goodman, Florida Cancer Specialists.

Site Summary of FDA Inspection Day Click or tap here to enter text.

PI: Click or tap here to enter text.

Date: Click or tap here to enter text.

Attendees: Click or tap here to enter text.

Investigator: Click or tap here to enter text.

Site Attendees: Click or tap here to enter text.

Questions/discussion during the entrance meeting: Click or tap here to enter text.

Requests and questions from Inspector review throughout the day: Click or tap here to enter text.

End of Day Summary: Click or tap here to enter text.

End of Inspection Summary: Click or tap here to enter text.

If 483 issued, when is our response due to the FDA: Click or tap here to enter text.

Who and where do we send the 483 response: Click or tap here to enter text.

If no 483 issued, when will the site receive the final FDA report of inspection: Click or tap here to enter text.

FDA Form 483

FORM 483 DOS AND DON'TS

Do:

1. Send a response to the FDA within 15 days set a timeline with your team to prepare and finalize your response
2. Determine the root cause of each observation
3. Anticipate potential questions
4. Support all claims and actions with facts. Include documents that address actions (training logs, process revisions, meeting sign in sheets, etc.)
5. Ensure your responses includes clear and compelling corrective action plans; include a Corrective and Preventive Actions (CAPA) owner
6. Double check your response for quality and thoroughness
7. Make certain that your changes are realistic and sustainable
8. Consider sending follow correspondence to the FDA regarding progress (this is dependent on severity of observation)
9. Prepare for a re-audit

Don't:

1. Give vague or broad plans of actions
2. Respond quickly to significant issues
3. Include irrelevant data and comments
4. Exaggerate the potential outcome the findings could have on the business
5. Respond defensively or rationalize the findings

FDA FORM 483 – SAMPLE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
	FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

FIRM NAME	STREET ADDRESS
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

OBSERVATION 1

OBSERVATION 2

OBSERVATION 3

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED

FORM FDA 483 (09/08) PREVIOUS EDITION OBSOLETE **INSPECTIONAL OBSERVATIONS** PAGE 1 of 5 PAGES

SAMPLE RESPONSES TO FDA FORM 483

This section is intended to provide examples of how a site might respond to particular types of observations in an FDA 483. It is important to note that a real response to FDA would be much longer. ASCO makes no warranties, expressed or implied, as to results obtained by individuals using the information and is not responsible for any action taken in reliance on the information contained herein.

OBSERVATION 1

Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others 21 CFR § 312.64(b)
Specifically,

Subject D01-002 was hospitalized with pneumonia on 07/05/2016 and was never reported as an SAE.

Subject D01-007 was hospitalized with myocardial infarction on 08/10/16 as documented on 08/16/16 and not reported until 08/21/16.

SITE RESPONSE:

We understand the importance of SAE reporting and have reviewed each of the observations and believe that the deficient SAE reporting was a result of clinical staff failing to alert the research staff of the SAE. As a result, we have reviewed with our research coordinators, research staff, and all physicians that participate in our research program the importance of prompt reporting of any hospitalizations, serious adverse events, and deaths. We have reviewed this with our hospitalists and mid-levels on the inpatient service as well.

We are engaging with our education department to prepare an instructional slide deck that must be completed to maintain research and hospital privileges. Additionally, we are modifying our electronic medical record to clearly indicate when a patient is enrolled on a clinical trial this EMR is viewed by any providers that interact with the patient to ensure it is clear that additional reporting is required. Each of these actions will be completed by November 1, 2019. Lastly, we will perform a process audit of our own SAE reporting processes in 6 months to ensure this change has ensured ongoing compliance.

In this example the site:
Documented assessment of finding and actions taken to avoid in the future.
The site also implemented an internal review to assess the action taken.

OBSERVATION 2

An investigation was not concluded in accordance with the signed statement of investigational plan. CFR21§312.60
Specifically,

Subject D01-007 received C2D28 scans on 07/15/2016 which is 10 days out of window

Subject D01-009 started investigational product on 07/15/16. CT scans performed on 10/6/16 which documented progression of disease however, was continued on study therapy for 6 months

Subject D01-005 had dose reduction at C3D1, dose increases at C5D1 and C6D1 without documentation of protocol rationale.

SITE RESPONSE:

We understand the importance of following the protocol and strive for compliance at all times. There are different reason why each of the observations above occurred, each is noted below.

Subject D01-007: Since the time that this study was conducted, we implemented a centralized scheduling process for all radiology exams. These schedulers receive special training on the importance of adhering to ordered scan schedules of research patients. This process is outlined in attachment A.

Subject D01-009: We have conducted retraining with all research coordinators, research staff, and physicians that patients on a research trial who meet criteria for disease progression must cease taking study drug. The patient must be listed as progressing on the study and end-of-study procedures must be initiated.

Subject D01-005: We have also conducted retraining on the importance of adherence to dosing and dose modification tables must be followed as per protocol. Physicians are not to make arbitrary dosing decision in patients on research protocols.

To ensure ongoing communication, we are instituting a weekly mandatory research meeting for all physicians, mid-levels, and coordinators in our research program. At this meeting each currently active patient will be reviewed and any communication between the study PI and sub-I's and/or coordinators will be documented. At these meetings important protocol changes, amendments, etc. will be reviewed and documented. The minutes of our weekly meeting is attached as attachment B.

In this example the site:
Documented their assessment of finding and actions taken to avoid in the future. Created new site process, trained staff on process, and provided the FDA with the written processes.

OBSERVATION 3

Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to drug administration
Specifically,

Subject D01-009 restarted on study drug on 10/15/16 prior to being consented with Liver Toxicity Consent Form which was signed on 11/12/16.

SITE RESPONSE:

We understand the importance of ongoing consent and overlooked the timely reconsent of this subject. Since the inspection we have reviewed our process of obtaining re-consents and have implemented at the above mentioned weekly mandatory research meeting a standing agenda item where all in attendance will review all amendments and revised consents. This will ensure that any patients with appointments the following week will have the reconsent processes completed. The minutes of our weekly meeting is attached as attachment B.

In this example the site:
Documented their assessment of finding and actions taken to avoid in the future. Created new site process and provided the FDA with the minutes of a meeting as an example of the process in action at the site.

OBSERVATION 4

Investigational drug disposition records are not adequate with respect to dates, quantity, and use by subjects.
Specifically,

Three vials of study drug (101598, 101601, 101602) are not accounted for in the study accountability log.

SITE RESPONSE:

Since the inspection we reviewed our records in greater detail and medication administration records have been identified and attached (attachment C) which document the administration of vials 101598, 101602, and 101602. Late entries have been added to the accountability log (attachment D).

Additionally, we will implement a process where each drug accountability log will undergo review on a quarterly basis to ensure complete documentation.

In this example the site:
Shared their assessment of the finding and was able to correct the error. The site provided the FDA copies of the corrections and furthermore implemented a process to identify and correct future error.

KEY RESOURCES

- Clinical Investigator Responsibilities at Code of Federal Regulations
- 21CFR: 312.68 Part 312 -- Investigational New Drug Application/Inspection of investigator's records and reports
- FDA Inspections Database Frequently Asked Questions
- Walters, J.P. (2004). Guidance on Responding to the FDA Warning Letter and Possible Enforcement Consequences for Clinical Investigators and Sponsors
- FDA: Bioresearch Monitoring - Clinical Investigators and Sponsor - Investigators' Guidance for FDA staff
- FDA: Bioresearch Monitoring Information Page
- FDA: Bioresearch Monitoring Field Guide for the Inspector
- FDA: Compliance Program Guidance Manual (CPGM) *(Chapter 48)*
- FDA Guidance: Computerized Systems Used in Clinical Investigations
- FDA Guidance: FDA Inspections of Clinical Investigators
- FDA: Form 483 Frequently Asked Questions
- FDA Information Sheet - FDA Inspections of Clinical Investigators: Guidance for IRBs, Clinical Investigators, and Sponsors
- FDA: Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBS. Frequently Asked Questions-Statement of Investigator (Form 1572)
- 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: Regulatory Procedures Manual (RPM)
- FDA: Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations
- FDA: 5-10 Form 482c Notice of Inspection - Request for Records (2019)
- FDA Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects
- FDA Guidance: Clinical Investigators, Industry, and Staff - Financial Disclosure by Clinical Investigators
- FDA Guidance for Industry: Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers
- FDA Good Clinical Practice Contacts: CDER-OSI-GCP Referrals@fda.hhs.gov