ARE YOU PREPARED?

Site Responsibilities

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Preparing for Regulatory Inspections:
FDA, EMA and the MCC
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Preparing for Regulatory Inspections

Overview

- **Purpose of a regulatory inspection**

- **Preparing for an inspection by the Food and Drug Administration (FDA), European Medicines Agency (EMA) and Medicines Control Council (MCC)**

- **The inspectional process (Before and During the Inspection)**
  - **- What Inspectors Review**
  - **- Focus of the Regulators and what is considered significant**
  - **- Triggers which result in regulator questions**
  - **- Process used by Inspectors during the inspection: Interviews, Observations/Demos and Data Reviews**

- **Helpful Tips: Best Practices for Communication and Documentation**

- **Dialoging with Regulators: Dos and Don'ts**

- **Differences in approaches between EMA and FDA**

Purpose of a Regulatory Inspection

The purpose of any regulatory inspection is human subject protection (HSP) which is universally accepted by all agencies and is achieved through the following harmonized approaches by regulators which include:

- Focus on Good Clinical Practices (GCP) and Data Integrity

- Sharing of information between regulatory agencies

- Providing advance notice of an inspection, shared open and closing meetings

- Regulators will compare what is submitted in the application against the regulations and processes followed at the site through review of your regulatory binder, source data, subject charts and interviews

- Regulators when reviewing data from your site must consider all of the information provided which includes the processes followed by your site, the protocol, information provided in interviews, information contained in emails and other correspondence

- Regulators have more similarities than differences. EMA and FDA are making efforts to harmonize inspection processes.

- The 3 entities sites will most likely be inspected by are as follows: MCC, FDA and EMA

Preparing for an Inspection: Pre-Inspection: Site Focus

4 key areas of focus for review of documentation

- Regulatory

  - Includes investigator sites files and the site regulatory binder (IEC submission/approval documents, training logs, delegation of authority logs, EAE submissions)

- Clinical (case report forms and source docs)

  - Informed consent form – correct Informed Consent for correct subject, all versions present for correct date/time, correct study and correct IEC approval(s), documentation of process

  - Evidence of documented eligibility at screening and enrollment

  - Source documents and medical records are available for each participant (Review for ALCOA Attributable, Legible, Contemporaneous, Original, and Accurate)

  - Information flows in logical order; data entries make sense and are authorized per delegation log

Preparing for an Inspection: Pre-Inspection: Site Focus

- Laboratory

  - Logs for eligibility and protocol endpoints are adequately documented and present
  - Reference ranges are present
  - Labs are graded and signed
  - Chain of custody documented

- Pharmacy

  - All records are present: for the right subject including all pharmacy receipts, storage, dispensing and return/destruction records
  - All records are well organized so that inspectors can readily find documents that they have requested
  - Controlled access to pharmacy is important!

Remember, first impressions are important. If the inspectors does not find anything upon first review, they move onto the next area! Remember – Perfection is not the key. Things are not expected to be perfect! What is important to the inspector is that you can address things in a consistent and reasonable manner (**Storyboarding – Tell the story**).
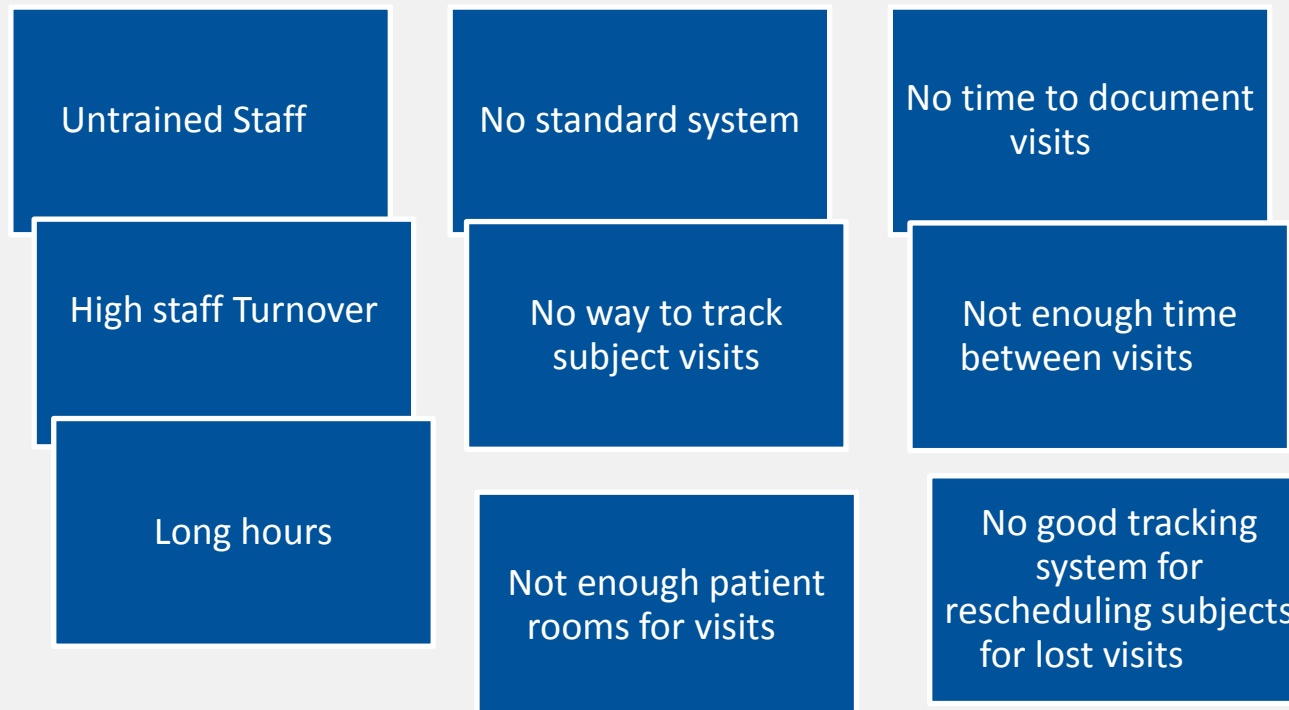
*Note this is not an exhaustive list. Refer to the "Site Inspection Preparation Checklist" for a comprehensive list of items to review.

Creating a Storyboard when you uncover issues

What do you do when you discover a problem: Your Dilemma: The database is locked

Storyboards are used to create a visual representation. The site and your key team are the actors in the script.

Write your problem statement: Subjects are missing too many study procedures to identify the solution (story).

Untrained Staff	No standard system	No time to document visits
High staff Turnover	No way to track subject visits	Not enough time between visits
Long hours	Not enough patient rooms for visits	No good tracking system for rescheduling subjects for lost visits

During the Inspection: Types of Sources Reviewed

Clinical

- Informed consents
- Medical history
- Nurses/clinician notes (missed visits)
- Contraceptive and risk reduction counseling notes
- Behavioral assessments
- Intercurrent illlness
- Concomitant medications
- Staff and subject handwriting
- Radiological reports, etc.
- Pelvic exams
- Physical exams
- Site SOPs

Regulatory

- IEC submission/approval documents
- Training logs
- Delegation of authority logs
- Signature logs
- Recruitment materials
- Reference ranges for lab

Pharmacy and Lab

- Dispensing records
- Vaginal ring return/destruction records
- Protocol required test results (e.g., urine, blood, pelvic)
- HIV rapid testing logs
- Pregnancy testing logs

During the Inspection: Inspector's Expectations for Medical Records

- Study eligibility criteria were met

- Documentation that subjects existed and came to appointments

- Monitor evaluations

- Missing information (dates, signatures, lab results, etc.)

- Whether the investigational plan/protocol/agreement was followed

- Any deviations from the protocol were properly assessed and reported to the IEC and Sponsor

- Frequency of protocol deviations and whether they resulted in an amendment to the protocol

- Informed Consents properly administered prior to performance of any screening test. All versions of the ICF approved by the Sponsor and the IEC

- The subject received any potentially interfering medication prohibited by the protocol

- There was proper follow-up as outlined in the protocol

- The clinical investigator submitted all reportable adverse events (including all clinical signs and symptoms)

During the Inspection: Inspector's Expectations for Regulatory Binder

- Access to all hospital inpatient charts for all SAEs involving hospitalization during the trial.

- Complete list of IND Safety Reports

- Have a system to be able to readily retrieve all trial records and source documents from storage

  *Inspectors can cross over into other studies that have been conducted that may not be stored on site.

- All versions of protocol, protocol amendments, Investigator Brochures or Package Inserts

- All documentation with the IEC and DSMB

- Documentation of any subject payments (if authorized per ICF)

- All correspondence (e.g., between the site and the IEC, Sponsor, CRO)

- All monitoring confirmation letters, signed/dated monitoring visit log, trial initiation visit, follow-up letters

- Case Report Form Guidelines

- Subject Screening/Enrollment Log (including list of all screen failures)

- Delegation of Authority Log

Refer to the "Site Inspection Preparation Checklist" for a comprehensive list of items to review.

During the Inspection: Inspector's Expectations for Laboratory

Laboratory Documents that should be present

- CV and Licenses for Laboratory Director(s), Central Lab, Local Lab and key laboratory personnel

- Laboratory certifications for the entire period of the trial for each lab used

- Laboratory normal ranges for all labs used during the trial, including updates to normal ranges and medical laboratory/technical procedures or tests included in the clinical protocol

- Updates of medical/laboratory/technical procedures/tests (e.g., laboratory certifications, accreditations established quality control and/or external quality assessments)

- Specimen logs for recording tests performed (traceability)

- Chain of Custody process/SOP for sample integrity (e.g., transporting of samples)

- Temperature logs (e.g., storage cabinets, refrigerators, freezers)

- Equipment maintenance and calibration records (e.g., patient scales, blood pressure cuffs)

- Laboratory reports display correct identifiers

- Laboratory report reviews showing signed/dated report by investigator, including out-of-range values graded appropriately

During the Inspection: Inspector's Expectations for Pharmacy

Pharmacy Documents that should be present

- Signed CV of pharmacist(s) and key personnel

- Current licenses of pharmacy personnel for period of the trial

- Sample label(s) attached to investigational product container(s), per protocol

- Signature list and/or Delegation log covering period of the trial

- Investigational agent accountability logs showing all logs present and all discrepancies verified

- Current and all IRB-approved versions of the protocol

- All records of study product dispensation to appropriate staff member

- All shipping records and records for investigational product(s) and trial-related materials

- Temperature logs for all protocol-required equipment (refrigerator, freezers, storage cabinets)

- Calibration and maintenance records for all equipment used for the trial

- Most recent version of Investigator's Brochure(s) or Package Insert(s)

- All certificates of analysis of investigational product shipped, including new batches

During the Inspection: Common Signals that tip off Inspectors that data collected may need to be investigated

- Handwriting Differences
- Ink/signature discrepancies
- Inconsistencies in data
- Inconsistencies in explanations by PI and staff regarding data discrepancies
- Backdating dates next to signatures or adding signatures to already dated tasks
- Pre-dating or pre-signing forms, templates, progress notes
- Progress notes out of order, or entries squeezed in, or cut-and-paste entries

- Frequent change in study personnel
- Missing/sketchy progress notes
- Missing visits, tests, exams when monitoring is on site
- Unusually high or low number of AEs, SAEs
- Obstruction of corrections where original entry is obscured
- Failure to address monitor findings
- Significant data missing from study records without adequate explanation

During the Inspection: Lab Inspectional Triggers for Any Inspection

- Inconsistencies between the numbers of samples collected, analyzed and reported
- Insufficient information to confirm the integrity of the samples (e.g. regarding storage, shipment and stability)
- Lab samples not being repeated when required (subject safety)
- Missing samples not adequately followed up/described
- Delays in collection or analysis of the samples
- Large number of samples re-assay
- Chain of custody not apparent and or documented
- Issues with sample collection (e.g., sample hemolyzed or not stored at the correct temperature)
- Issue with sample shipment (e.g., sample shipment did not occur on time, resulting in unusable sample)
- Lab results identified with wrong participant identifier

*Note this is not an exhaustive list. Refer to the "Site Inspection Preparation Checklist" for a comprehensive list of items to review

During the Inspection: Pharmacy Inspectional Triggers for any inspection

- Incomplete training records for Pharmacists and Pharmacy Technicians

- Inadequate security measures (e.g., cameras, alarms, card key access)

- Proper computer security measures not in place

- Incomplete information required to be present on prescriptions and study product

- Missing information to confirm inspection and integrity of the study product

- Process errors documented that relate back to failure to follow pharmacy process for receipt, storage, return, study product accountability discrepancies and destruction of study product

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The Inspectional Process: Common Inspector Findings regarding Investigator Oversight

Inspector Evidence leading to findings	Inspector Findings
Allowing untrained and/or undelegated staff to conduct duties on clinical trial	Poor supervision and training of study staff
No documentation that investigator was reviewing subject safety in a timely manner. • Not reviewing inclusion/exclusion criteria • Late review of laboratory results	Insufficient investigator involvement in study conduct
Site staff are performing duties in which they are not approved. • Delegation Log did not list individual performing tasks • Person performing tasks was unqualified	Inappropriate delegation of study tasks to unqualified persons (non-medical staff performing medical exams)
A pattern of missed safety assessments putting subjects at risk (e.g., missed physical exams, lab tests, follow up visits)	Failure to adequately protect study subjects

The Inspectional Process: Common Inspector Findings regarding Investigator Oversight (continued)

Inspector evidence leading to findings	Inspector Findings
High number of unresolved queries, protocol deviations and unreported adverse events, late sign-off/review of lab reports	Overworked investigator and study staff (e.g., too many subjects, complex study with large data collection, too many concurrent studies)
Late or no reporting of Adverse Events (AEs), Study Coordinator performing causality assessment of AE; late reporting of AEs	Improper AE review and reporting
Investigator not present during monitoring visits, not responding to monitoring findings in a timely manner, or allowing enrollment of ineligible subjects	Absent Investigator (late sign-off of lab reports, late reporting of AEs, ineligible subjects enrolled, missing subject visits/tests, untrained or inappropriate delegation
No documented follow-up with IECs for when annual approvals are due or when there are conflicting IEC deadlines which may result in a gap in IEC approval	Lapse in IEC approval
Obvious gaps in medical history that are unexplained	Gaps in medical history for a subject screened and/or enrolled in the trial

Interacting with Regulators

RECOMMENDATIONS

BEST PRACTICES

Inspector: Hello, Dr. Jao, this is Inspector Al with the U.S. Food and Drug Administration. It's my understanding that you're a clinical investigator with XYZ trials?

Dr. Jao: Yes, I am.

Inspector: I'd like to make arrangements to visit with you and your staff in 2 months to conduct a clinical investigator inspection for the study.

Dr. Jao: I think I can arrange that. Will you be the only one coming?

Inspector: Yes, Dr. Jao, I'll be the only FDA employee conducting the inspection. I can be available, say around 9 a.m. Will that be good for you?

Dr. Jao. Yes, that is fine.

Inspector: Dr. Jao, in preparation for the inspection, I'd like to request that all study records are accessible, available and organized.

Dr. Jao: I can arrange that. Would you need anything else?

Inspector: Yes, I'll need access to a photo copier to make copies of any study-related documents.

Dr. Jao: Is there a timeframe for the inspection?

Inspector: Timeframe? Given the number of study subjects you have enrolled in this study, I suspect that my visit to your site will take approximately 3 to 5 days.

Dr. Jao: In that case, I'll have my study coordinator also assist you during your visit.

Inspector: Wonderful. Thank you, Dr. Jao, for making yourself and your staff available. I look forward to seeing you on Monday morning. Have a good day.

Dr. Jao: Thank you, Inspector Al. We look forward to meeting with you as well.

Best Practices for Interacting with Regulators

- Provide documents/interviews upon request

- Maintain a log to record the order in which the documents were requested

- Take notes of key discussions and follow-up items

- Have end-of-day meetings with staff for preparation for preparing for next day. Limit staff to those who are critical and involved in inspection

- Explain deficiencies detected and corrective and preventative action planned/implemented

- Discuss any misinterpretations of information provided but do not argue with the inspector

- Provide objective evidence to support explanations

- Consult with subject matter when required (Sponsor, CRO)

- Refer to regulations and formal processes/procedures

- Leave no question unanswered

List of Dos and Don'ts

DO	DO NOT
• Assign a workroom for the inspectors	• Answer questions if you do not know the answer or in which you do not have direct responsibility
• Take notes – summarize findings each day	• Leave the Inspector alone in the room
• Dress professional	• Volunteer information that is not requested
• Provide introduction	• Lie, guess, estimate, provide misleading information
• Project confidence	• Argue with the Inspector(s)
• Provide a complete answer	• Do not volunteer extra information
• Provide clarification to inspector	• Don't blame others when errors are found
• Ask for restatement of question if question is not clear	• Fall for Inspector traps to uncover information. For example, so tell me about some problems that you have had on the study. Did you have any problems that you want to tell me about? Did you feel you were adequately trained to perform your duties for this study? (This could occur before or after they look at your documentation)
• Take notes for follow-up on what the inspector is requesting and the inspector's findings	
• Be honest	
• Answer the question asked	
• Ask for more time to research the question	
• Keep a record of questions the Inspector asks	
• Escort the Inspector	
• Refer the question to the appropriate person	

Additional Tips for Successful Outcomes

Do not provide/perform the following during an inspection:

- Offer to buy the inspector's meal or provide gifts

- Sign or make corrections to Affidavits (written statements)

- Attempt to alter or create documents to replace missing documents requested by inspectors

- Attempt to delay providing records to inspectors without a reasonable excuse (data stored off-site or massive requests)

- Bring someone into talk to inspectors without prior notice of topic/preparation

- Create records for the inspectors (unless part of a corrective action)

Differences in Regulators – FDA and EMA

- FDA Inspectors is more focused on document review; EMA inspectors more focused on process review (SOPs and interviews)

- FDA follows FDA regulations (21 Code of Federal Regulations)

  - Part 50, Informed Consent

  - Part 54, Financial Disclosure

  - Part 56, Institutional Review Board

  - Part 312, Investigational New Drug Application

- EMA follows ICH-GCP

- FDA issues written observations at the end of the inspection to the Principal Investigator for significant findings (FDA-483); EMA issues findings after the inspection has ended to the Principal Investigator and after the report is issued

In Summary

Preparation is everything.
Remember, you are the subject matter expert!

STAY TUNED - AFTERNOON INTERACTIVE SESSION

References:

- FDA COMPLIANCE PROGRAM 7348.811, CHAPTER 48- BIORESEARCH MONITORING, CLINICAL INVESTIGATORS AND SPONSOR-INVESTIGATORS, December 8, 2008, Guidance for FDA Staff

- SADC Pharmaceutical Programme, South African GCP Guidelines, MCC Guidelines for Preparation of the Site Master File, MEDICINES AND RELATED SUBSTANCES ACT 1965 (ACT NO. 101 OF 1965) and amended 22 July 2011

- Annex I EMA GUIDANCE FOR THE CONDUCT OF GOOD CLINICAL PRACTICE INSPECTIONS Investigator site 28 May 2008

- http://www.fda.gov/downloads/Training/CDRHLearn/UCM293102.pdf

Thank you for you time! sherri.hubby@premier-research.com