Preparing for Regulatory Inspections

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Presentation Outline

- Definitions
- QA Audits of MTN-020
- All About Inspections
- Preparing for an Inspection
- Conduct during an Inspection
Definitions

• “Audit” -- a systematic examination of records by personnel independent of the operation of the system being examined

• “Inspection” -- an audit conducted by a representative of a regulatory authority

• “Observation” -- a detailed description of a set of circumstances that appears to represent a departure from established standards
Ratings of Observations

• Critical – where evidence exists that a significant or unjustified departure from (standards) has occurred with evidence that:
  o The safety, well-being or confidentiality of clinical trial participants has been jeopardized
  o Serious doubt exists relating to accuracy or credibility of data
  o There are a large number of major observations
  o Previous major observations were not corrected appropriately

• Major – a non-critical observation where evidence exists that a significant or unjustified departure from standards has occurred and/or a number of departures indicating a systematic failure

• Other – departure from standards that is not major or critical
IPM QA Audits of MTN-020

• 12 clinical research site (CRS) audits were conducted from December 2012 to January 2014
  o 0 critical observations (congratulations are in order!)
  o 7 major observations
  o 39 other observations

• Remember that we’re only sampling during QA audits
Responses to MTN-020 Audits

- Comprehensive and thorough
- All clinical research sites were considered in response to individual site observations
- All audits are closed except where responses are not yet due
All About Inspections
Inspection Experience

• Primary sponsor host for:
  o four FDA GLP inspections
  o five FDA GCP/PV inspections (PV=pharmacovigilance)
  o one FDA QSR inspection (medical devices)
  o one EMA GCP inspection

• Sponsor representative at:
  o two foreign FDA GCP inspections (Bulgaria, Romania)
  o five foreign EMA GCP inspections (Russia, Bulgaria, Romania)
  o one foreign EMA CRO inspection (Poland)
  o two MHRA PV inspections (United Kingdom)
  o one foreign HPB GCP inspection (Canada)

• Facilitated many inspections while not on site
Inspection Experiences

• Low points:
  o six FDA inspectors arrive unannounced for a “for cause” inspection, which lasts for six weeks
  o poor inspection outcome triggered further inspections and delayed approval for two years

• High points:
  o managed QA program for 5 approved NDAs
What triggers inspections?

• Submission for approval
  o Pre-approval inspection of manufacturing
  o Several clinical investigators
  o Sometimes a sponsor inspection

• Complaints or allegations made to regulatory authority by
  o Clinical trial participants or consumers
  o Disgruntled ex-employees
  o Activists
Why are inspections a good thing?

• It means we have positive results from clinical trials
• It means we have submitted a complete application
• It means the regulatory agencies are taking our application seriously
FDA Inspections in the USA

• Usually unannounced*
• Begin with issuance of Form FDA-482 “Notice of Inspection” to highest level employee present
  o Anything you say can and will be used against you in court (if it comes to that)
  o You do not have the right to remain silent
  o Making a knowingly false statement is a crime
  o You are not guaranteed the right to a lawyer
Foreign Inspections (FDA, EMA)

• There will be plenty of advance notice
• Sponsor usually makes travel arrangements and accompanies inspector
• FDA notifies local regulatory agency and invites them to join inspection
Foreign FDA Inspections

• FDA cannot prosecute foreign clinical investigators (they don’t issue Form FDA-482)

• But they can issue Warning Letters, which become publicly available on FDA website and newsletters

• And, of course, they can reject the data and application
GCP Inspections by MCC

• Arranged in advance, unless there is suspicion of serious issues
• Clinical investigator is contacted by phone to make arrangements and written confirmation
• Medical Director of sponsor is also notified
  o Monitor of site is expected to be present
• Delays in conduct of inspection need to be investigated
Preparing for Inspections
Pre-inspection Visits

- You can’t “fix” poor study conduct at this point
- These are not monitoring visits or audits
  - do not verify CRFs vs. source
  - do not sign monitoring log
- Conducted by combined Clinical & QA personnel
- Timing is an important consideration
  - Begin during NDA filing period in US
Pre-inspection Visits

• Inventory of the study documents and data
  o Work with Clinical Operations to create a list of documents and data that should be at the CRS

• Training session with staff
  o Regulatory timeline
  o Preparing for an inspection
  o Conduct during an inspection
Follow-up to Pre-inspection Visits

- Replace documents that were misplaced or lost during or after the trial
- Do not file documents at the clinical site that were never provided during the trial
Before the Inspection

• Develop an SOP and a policy for inspections
• Educate your staff on the process
• Assign responsibilities in advance, e.g. host, scribes, document reviewers, photocopier, answering questions
• Determine where to put inspector during inspection
• Have a mock inspection or conduct mock interviews
Before the Inspection (2)

- Read the SOPs and Guidance Manual
  - FDA Compliance Program Guidance Manual for Clinical Investigators (7348.811)
  - SOP for EMA GCP inspections
Conduct during an Inspection

• DO the following:
  o Be polite, courteous and professional
  o Establish the scope of the inspection
  o Fully understand questions before answering (ask questions to clarify)
  o Answer questions truthfully and directly
  o Pursue clarification of any possible misunderstandings
Conduct during an Inspection (2)

• DO the following:
  o Make duplicate copies of any documents copied for the inspector
  o Remember that everything you say is “on the record”
  o Follow your SOP and policy
  o Ask for a summary of observations at the end of every day
Conduct during an Inspection (3)

• DO NOT do the following:
  o Guess, lie or deny the obvious
  o Volunteer additional information, unless clearly in your best interests
  o Answer hypothetical questions
  o Answer questions outside of your knowledge or expertise (find the right person)
Conduct during an Inspection (4)

• DO NOT do the following:
  o Engage in arguments
  o Make all-encompassing statements, like those using “always” or “never” or “impossible”
  o Allow inspectors to wander unescorted or have unrestricted access to files
  o Sign anything (e.g., affidavits, written statements)
  o Make promises without due consideration
Conduct during an Inspection (5)

• DO NOT do the following:
  o Attempt to mislead the inspector
  o Try to be funny
  o Become openly defensive or fearful (genuine concern may sometimes be appropriate)
  o Comment on the quality of the inspection
The Exit Meeting

• FDA issues Form FDA-483 to summarize any significant observations—review it carefully and propose corrections when applicable
  o Respond in writing in agreed-upon timeframe

• EMA and MCC provide oral summary of observations and send written report to sponsor and investigator for a collaborative response
Questions?