INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

Preparing for Regulatory Inspections

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Developing HIV Prevention Products for Women worldwide

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:
  - The safety, well-being or confidentiality of clinical trial participants has been jeopardized
  - Serious doubt exists relating to accuracy or credibility of data
  - There are a large number of major observations
  - 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
  - 0 critical observations (congratulations are in order!)
  - 7 major observations
  - 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:
  - four FDA GLP inspections
  - five FDA GCP/PV inspections (PV=pharmacovigilance)
  - one FDA QSR inspection (medical devices)
  - one EMA GCP inspection
- Sponsor representative at:
  - two foreign FDA GCP inspections (Bulgaria, Romania)
  - five foreign EMA GCP inspections (Russia, Bulgaria, Romania)
  - one foreign EMA CRO inspection (Poland)
  - two MHRA PV inspections (United Kingdom)
  - one foreign HPB GCP inspection (Canada)
- Facilitated many inspections while not on site

Inspection Experiences

- Low points:
  - six FDA inspectors arrive unannounced for a “for cause” inspection, which lasts for six weeks
  - poor inspection outcome triggered further inspections and delayed approval for two years
- High points:
  - managed QA program for 5 approved NDAs

What triggers inspections?

- Submission for approval
  - Pre-approval inspection of manufacturing
  - Several clinical investigators
  - Sometimes a sponsor inspection
- Complaints or allegations made to regulatory authority by
  - Clinical trial participants or consumers
  - Disgruntled ex-employees
  - 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
  - Anything you say can and will be used against you in court (if it comes to that)
  - You do not have the right to remain silent
  - Making a knowingly false statement is a crime
  - 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
  - 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
  - o do not verify CRFs vs. source
  - o do not sign monitoring log
- Conducted by combined Clinical & QA personnel
- Timing is an important consideration
  - o Begin during NDA filing period in US

Pre-inspection Visits

- Inventory of the study documents and data
  - Work with Clinical Operations to create a list of documents and data that should be at the CRS
- Training session with staff
  - Regulatory timeline
  - Preparing for an inspection
  - 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 http://www.ema.europa.eu/ema/index

Conduct during an Inspection

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

Conduct during an Inspection (2)

- DO the following:
  - Make duplicate copies of any documents copied for the inspector
  - Remember that everything you say is “on the record”
  - Follow your SOP and policy
  - Ask for a summary of observations at the end of every day

Conduct during an Inspection (3)

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

Conduct during an Inspection (4)

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

Conduct during an Inspection (5)

- DO NOT do the following:
  - Attempt to mislead the inspector
  - Try to be funny
  - Become openly defensive or fearful (genuine concern may sometimes be appropriate)
  - 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
  - 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?