FDLI Enforcement Conference

How to Respond to a BIMO Inspection: During & After

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FDA's Bioresearch Monitoring (BIMO) Program

- **Protecting the rights, safety and welfare of research subjects**
  - Begins with the development of the trial concept
  - Is incorporated into all stages of a clinical trial
- **Compliance with FDA regulations**
  - Protection of human subjects is integral to FDA's mission, statutes and regulations
  - FDA and other regulators cannot ensure HSP by themselves
  - HSP is a collaborative effort
  - Familiarize yourself with applicable FDA regulations, guidances, and BIMO Compliance Programs
- **Quality and integrity of data**
  - Data integrity is dependent on careful planning and execution throughout every phase of clinical trial

What are the BIMO inspectors looking for?

- In short, they are **assessing compliance**
- Violations can be found in your:
  - Case report forms
    - Are there protocol violations?
    - Are the dates / signatures correct?
  - Copies of signed informed consent documents
    - Was informed consent documented properly?
    - Was the version used correct?
  - Drug disposition records
  - IRB study files
  - IRB meeting minutes
  - Your written policies and procedures

Common mistakes researchers make…

- **The most common violations in 2016 for investigators were:**
  - (1) failure to follow the investigational plan and/or regulation;
  - (2) protocol deviations;
  - (3) inadequate recordkeeping;
  - (4) inadequate accountability for the investigational product;
  - (5) inadequate communication with the IRB;
  - (6) inadequate subject protection – failure to report adverse events and informed consent issues; and
  - (7) investigational product represented as safe and effective.

Common mistakes IRBs make…

- **The most common IRB deficiencies in 2016 included:**
  - (1) inadequate initial and/or continuing review;
  - (2) inadequate written procedures;
  - (3) inadequate meeting minutes, membership rosters;
  - (4) quorum issues;
  - (5) prompt reporting of noncompliance, suspension/termination;
  - (6) Subpart D issues; and
  - (7) lack of or incorrect SR or NSR determination.

What happens if you have regulatory violations? This is serious business.

- **FDA's administrative actions and enforcement tools**
  - **To investigators and/or sponsors:**
    - Place study on clinical hold or stop study—see 21 CFR 312.42 and 21 CFR 812.30
    - Warning or Untitled letter
    - Investigator Disqualification—see 21 CFR 312.70 and 21 CFR 812.119
      - Occurs when FDA has information indicating that an investigator has repeatedly or deliberately failed to comply with 21 CFR Parts 50, 56, or 312/812, or has repeatedly or deliberately submitted to FDA or the sponsor false information in any required report
    - Investigator Debarment (criminal violations)
  - **To IRBs:**
    - Lesser administrative actions, usually in the form of a noncompliance letter—see 21 CFR 56.120
    - IRB disqualification—see 21 CFR 56.121

What should you do (and how should you behave) when the government shows up…

- whether it's:
  - FDA, OHRP, ORI, DOJ…

- whether it's:
  - for cause, unannounced, routine…

…try to set yourselves up for the best possible outcome.

Your goals…

- To get through the inspection without any findings of violations; or
- To get through the inspection with minimal findings that will not generate an enforcement action; or
- To get through the inspection with findings that you can develop a plan to address that will be acceptable to the government; and
- To stay out of the news.

If you have advance notice (or even if you don't, when you get a chance):

- Prep your people
  - Appropriate behavior
    - Be polite
    - Be respectful
    - Take the inspection seriously
  - Tell them to be sure that they:
    - Understand questions; don't speculate
    - Answer what asked only; don't offer additional information
    - Are truthful
    - Don't admit wrongdoing; you'll have time to acknowledge shortcomings later in a well thought-out response
  - Let them know you support them
- Discuss with your legal department

During the inspection…

- **Set the right tone**
  - **Do not be:**
    - Defensive
    - Secretive
    - Pointing fingers
  - **Do be:**
    - Respectful
    - Helpful
    - Open to critique
    - Open to suggestion
    - Open to improving your research program

During the inspection…

- **Get the right team together**
  - Figure out key personnel who should be involved
  - Have a specific person(s) assigned to meet with the inspectors, answer questions, provide documents
  - Have a separate note taker (for each inspector) to transcribe comments, observations, etc.
- **Have additional members of the team working on:**
  - Locating documents
  - Keeping binders and a log of all documents and materials provided
  - Finding answers to questions
  - Attempting to predict outcome
  - Preparing for ultimate response

During the inspection…

- **At the end of each day of the inspection**
  - Meet with team to debrief
  - Continue to locate any needed documents
  - Find answers to unanswered questions
  - If violations are being found:
    - Think about your response
      - Are they mistaken? Do you have an explanation or justification?
      - How could you change your program to avoid these problems in the future?
        - Better institutional support? Training? Monitoring/oversight? Organization?
  - Have good communication with your people and the inspectors

At the closeout and just after…

- As the inspectors finish up:
  - Stay calm
  - Accept the oral findings (usually written findings arrive a few days later)
  - Understand their timeline/process
- After they leave:
  - This is your small window to change the outcome of any written findings of violations
    - Are there additional documents that would support your cause?
    - Are there additional explanations that would support your cause?

Responding to a 483…

- You still have an opportunity to avoid being the subject of an enforcement action
  - Submit any additional information
- Develop a clear, point by point response to the 483
- Think about the components of a comprehensive action plan
  - Training of staff
  - Better oversight
  - Being responsible for less studies
  - Put mentors in place
- What will your follow up reporting plan look like?

Responding to a 483…

- Start preparing for drafting the response letter while the inspection team is still on site
  - Try to anticipate what the 483 will state **before** you receive it
  - Gather key documents
  - Determine who will write the first draft of the response letter
    - Compliance personnel
    - Investigators and staff
    - General counsel's office/outside counsel

Responding to a 483…

- Plan for the logistics
  - Determine the signatory(ies) of the response letter
  - Calculate the due date
  - Know the recipient of the response
  - Determine how you will transmit the response
  - Keep all information where team members can find it easily

Responding to a 483…

- Set the Tone
  - Show that the agency's findings have been taken seriously
  - Avoid defensive statements and/or trying to place blame on third parties
  - If the 483 included a factual statement that is incorrect AND you have solid evidence to prove the mistake, correct the error in a respectful manner
  - Avoid discussing the strength of your existing policies and procedures

Responding to a 483…

- Not the time for creative writing
  - Respond in a point-by-point manner to all agency findings
  - Respond completely
  - Create a cross-walk of the findings letter and your response
  - Make sure that your narrative makes logical sense and is backed by evidence
- Goal is to avoid receiving a request for additional information

Developing a Corrective Action Plan

- Do you understand fully the problems that led to the regulatory findings?
  - If not, organize an internal investigation to determine the **root cause**
  - In your response letter:
    - Describe the nature of the investigation
    - Explain your plan for reporting the findings of the investigation to the agency

Developing a Corrective Action Plan

- Determine what needs to be changed
  - Driven by what the inspection team found
  - Were policies and procedures deficient, or did investigators and staff fail to follow the policies and procedures in place?
    - In the former situation, policies and procedures may need to be revised
    - In the latter, re-training of staff and investigators may be needed
  - Determine a plan for ongoing monitoring and follow-up reporting (if appropriate)

Developing a Corrective Action Plan

- Create a timeline for your action plan
  - Describe in the response letter a target date by which certain activities will be completed, *e.g.*, completion of staff re-training
  - Make the target date achievable—the agency may ask you in a follow-up letter for proof that certain activities were completed timely
  - Offer to provide some of the materials in a follow-up letter

Developing a Corrective Action Plan

- Work does not end just because response letter has been submitted
  - Create a tracking mechanism to monitor completion of all promises made in the response letter
  - Document all steps taken
    - Revised drafts of policies
    - Training materials
    - Records of attendance at training sessions
    - Evaluation materials used during training

Developing a Corrective Action Plan

- What did agency miss that might come up next time?
  - Use the momentum for change to revise other practices that may be deficient
  - Do not mention these additional findings in your response letter to the agency, *i.e.*, avoid temptation to “overshare”

Role of Counsel

- Counsel can provide an outside, objective perspective during response process
  - Counsel can take a lead role in organizing documents and interviewing personnel
  - Use of counsel can maintain internal investigation under privilege
  - Counsel can take lead in drafting response letter and incorporating comments from key stakeholders
- Counsel can help manage corrective actions
  - Manage the timeline to ensure tasks are completed on time
  - Convene meetings to discuss policies that need to be reviewed
  - Redraft policies that need modifications

Any questions?

Just ask!

Thank you!

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