AN OVERVIEW OF CBER BIORESEARCH MONITORING PROGRAM AND SUGGESTIONS FOR SUCCESSFUL CLINICAL RESEARCH

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IVD Workshop
July 15-16, 2019
Agenda

- CBER’s Biores research Monitoring (BIMO) Program
- Types of BIMO inspections and when they are conducted
- Profile of CBER INDs and IDEs
- Responsibilities of sponsor, clinical investigator, and sponsor-investigator roles
- Common Violations
- Suggestions for successful clinical research
- FDA resources

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CBER’s BIMO Program

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CBER’s BIMO Branch

• Issue inspection assignments
• Investigate complaints
• Answer questions about Good Clinical Practice
• Evaluate concerns about data integrity
• Participate in inter and intra center working groups for developing policies and guidance documents
• Conduct internal and external educational and outreach activities to stakeholders

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What is the inspection review function of BIMO branch?

• Detect errors or misconduct in a clinical study that might impact subject protection, data integrity, or decision making

• Evaluate data quality/integrity
Types of BIMO inspections and when they are conducted

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CBER’s BIMO Program Inspects

• Clinical Investigators (CIs)
• Sponsors/Monitors/Contract Research Organizations (CROs)
• Institutional Review Boards (IRBs)
• Nonclinical Laboratories (Good Laboratory Practice)

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When are BIMO inspections conducted?

- Submission of BLA/NDA/PMA
- Referrals from Center staff
- Referrals from other parts of FDA
- Complaints from sponsors, IRBs, and consumers
- Initiated by Office of Regulatory Affairs (ORA): advertisements, news reports
- “Real time” Surveillance of ongoing studies

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Profile of CBER INDs and IDEs

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### CBER Active IND/IDE By Sponsor Type
As of 9 April 2019 from CBER submission database

<table>
<thead>
<tr>
<th>Sponsor Type</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>2756</td>
<td></td>
</tr>
<tr>
<td>Commercial</td>
<td>1214</td>
<td>44</td>
</tr>
<tr>
<td>Individual</td>
<td>810</td>
<td>29</td>
</tr>
<tr>
<td>Government (NIH, CDC, …)</td>
<td>251</td>
<td>9</td>
</tr>
<tr>
<td>Hospital/Medical center/University</td>
<td>354</td>
<td>13</td>
</tr>
<tr>
<td>Zoo</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Military</td>
<td>48</td>
<td>Less than 5</td>
</tr>
<tr>
<td>Other (COGS, nonprofits)</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Excludes emergency and single patient exceptions. About 8% are on complete or partial clinical hold.

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### CBER Active IND/IDE by Product Category
**As of 9 April 2019 from CBER submission database**

<table>
<thead>
<tr>
<th>Product Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2756</td>
</tr>
<tr>
<td>Cell and Gene Therapies</td>
<td>1479</td>
</tr>
<tr>
<td>Vaccines</td>
<td>704</td>
</tr>
<tr>
<td>Hematologics</td>
<td>316</td>
</tr>
<tr>
<td>Devices</td>
<td>173</td>
</tr>
<tr>
<td>Allergenics</td>
<td>66</td>
</tr>
<tr>
<td>Blood Bank/Source Plasma</td>
<td>13</td>
</tr>
<tr>
<td>Live Biotherapeutics</td>
<td>5</td>
</tr>
</tbody>
</table>

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Sponsor and CI

Sponsor

An individual or entity who takes responsibility for and initiates a clinical investigation. May be an individual, a pharmaceutical company, government agency, academic institution, or other organization.

CI

An individual who conducts a clinical investigation under whose immediate supervision the investigational drug/device is administered.
Sponsor-Investigator

- An **individual** who both initiates and conducts a clinical investigation under whose immediate supervision the investigational drug/device is administered.

  Individual is Sponsor and Investigator

  Sponsor-Investigator research does not involve other sites

- The individual must comply with the requirements of both an investigator and a sponsor

  with one exception—there is no need for sponsor-investigators to submit an investigator brochure
Responsibilities of sponsor, clinical investigator, and sponsor-investigator roles
Responsibilities of IND Sponsors

21 CFR §§ 312.50 – 312.59

• Select qualified investigators
• Provide all investigators with sufficient information to conduct the investigation including all standard operating procedures (SOPs)
• Train the investigators on sample collection and testing as per protocol
• Control the investigational drug/testing kit
• Prepare and maintain records
• Inform FDA & investigators of Serious Adverse Events or newly identified risks to subjects.
• Monitor the ongoing investigations
• Obtain signed investigator statement (Form FDA 1572)
Responsibilities of CIs

21 CFR §§ 312.60 – 312.64

- Follow the investigator statement (Form FDA 1572), the investigational plan, and applicable regulations
- Protect the rights, safety, and welfare of subjects
- Obtain informed consent/assent
- Obtain IRB approval
- Supervise all subordinates
- Follow the investigational plan and protocol provided by the sponsor
  - submit the deviations and incidents report as per protocol
- Prepare and maintain adequate and accurate records
- Maintain drug/testing kit accountability records

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Common Violations
Significant Sponsor Violations

- Failed to monitor the investigation/collect information from investigators
- Did not provide adequate information to the investigators to conduct the study
- Did not send the deviation reports to the sites to be retained in the study binder
- Did not update all participating sites of significant safety signals at one site, and of resulting amendments to the protocol.

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Most Common CI Violations

- Failed to follow protocol requirements
- Failed to perform laboratory testing or confirmatory testing as per protocol
- Failed to maintain adequate study records such as deviation reports
- Incorrect donor samples used for testing
- Inadequate case histories

*If it is not documented, it did not happen!*
Most Common CI Violations

- Discrepancies between source records and case report forms
- Failure to notify the IRB or sponsor of adverse events
- Failure to list all sub investigators on Form FDA 1572
- Inadequate informed consent form
- Inadequate drug/device accountability records
Significance of Violations

- Do the violations
  - affect rights, safety, and welfare of the subjects?
  - directly impact integrity of data set?
  - indicate systemic problems within the study?
    - are they sponsor problems?
      - did the sponsor report the problems to FDA?
  - Indicate that other studies at that site might be impacted?
Suggestions for successful clinical research

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Suggestions for Sponsors - BEFORE

- Understand what you are responsible for... and obtain training as needed.

- Request a pre-IND meeting with FDA, and listen to the advice.
  

  [https://www.fda.gov/drugs/developmentapprovalprocess/smallbusinessassistance/ucm069906.htm](https://www.fda.gov/drugs/developmentapprovalprocess/smallbusinessassistance/ucm069906.htm)

- Seek advice for maintaining your IND. Ask for help and ask questions.

- Document duties delegated to contractors.

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Suggestions for Sponsors - BEFORE

• Prepare a **detailed** protocol including all testing procedures and SOPs.

• Develop plans for monitoring. What are the critical activities? Is it protocol specific? How often? Which activities? Who will monitor? Did you collect all deviation reports?

• Develop plan for data collection. How will you collect the data from the sites? How often? Are the monitors adequately trained in various data collection?

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Suggestions for Sponsors - BEFORE

• Develop protocol specific case report forms or checklists
• Don’t overextend; too many concurrent projects
• Train study staff before the study starts....and train replacements when staff leave.
• Develop plan for organizing records.
• If electronic record keeping is planned make sure there is
  – adequate access control
  – adequate data archival and retrieval procedures are in place

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Suggestions for Sponsors - DURING

• Contact the respective FDA product office as needed to consult about trial or product issues.
  Were all the procedures followed in the preparation and testing of the investigational product?

• Perform monitoring during critical activities. Make sure replacement staff at sites are trained.

• Amend the protocol when needed – and submit to your IRB, the CIs, and FDA.

• Verify that delegated duties are performed.

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Suggestions for Sponsors - DURING

• Keep up with data as the trial progresses
• Track dates when your IND annual reports are due
• Correct small problems before they grow
• Train your replacement staff
• Report adverse events to the IND/IDE

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Suggestions for Sponsors - AFTER

Organize the study records ---

• To ensure non-study staff can find them
  – Document the archived storage of records
  – Create an index of records stored (helpful if data loss occurs)

• To fulfill record retention requirements 21 CFR 312.57(c)
  – For IND/IDE studies-retain records for at least 2 years after the marketing application approval or until 2 years after the study drug shipment and delivery is discontinued

• For possible FDA inspection

  Keep track of the location of study records for possible FDA Inspection of the study sites

  Notify FDA of status changes (withdraw, inactivate) so your IND/IDE is current.

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FDA resources
FDA Resources

How to Find Investigator Inspection History

CDER
http://www.accessdata.fda.gov/scripts/cder/CLIIL/index.cfm

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CDRH
Submit request under Freedom of Information Act

ALL FDA Inspections (Transparency Initiatives)
http://www.fda.gov/ICECI/EnforcementActions/ucm222557.htm

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FDA’s Electronic Reading Room

Warning letters
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

CIs
http://www.fda.gov/ICECI/EnforcementActions/ucm321308.htm

Disqualified and restricted CIs
Presiding officer decisions

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Compliance References-1

http://www.fda.gov/ICECI/default.htm
Regulatory Procedures Manual
  warning letters, untitled letters, judicial actions
Application Integrity Policy
Debarment list
BIMO compliance programs

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Good Clinical Practice References
http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm

Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring-August 2013

Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs - Frequently Asked Questions-Form FDA 1572-May 2010

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Contact

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