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 Bioresearch 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

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

CBER's BIMO Branch-contd-2

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)

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

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

	#	%
Total	2756	
Commercial	1214	44
Individual	810	29
Government (NIH, CDC, …)	251	9
Hospital/Medical center /University	354	13
Zoo	69	Less than 5
Military	48	
Other (COGS, nonprofits)	10	

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

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

Total	**2756**
Cell and Gene Therapies	1479
Vaccines	704
Hematologics	316
Devices	173
Allergenics	66
Blood Bank/Source Plasma	13
Live Biotherapeutics	5

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

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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

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.

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

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.

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070568.pdf

  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.

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?

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

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.

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

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.

FDA resources

FDA Resources

How to Find Investigator Inspection History

CDER

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

CBER

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/ucm165743.htm

CDRH

Submit request under Freedom of Information Act

ALL FDA Inspections (Transparency Initiatives)

http://www.fda.gov/ICECI/EnforcementActions/ucm222557.htm

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

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

Compliance References-2

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

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf

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

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf

CBER's BIMO Branch

Contact

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Questions

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