INSPECTION OF INSTITUTIONAL REVIEW BOARDS (IRBs)

NANCY A. BELLAMY
Bioresearch Specialist/ BIMO Monitor
US Food & Drug Administration
Office of Regulatory Affairs
Detroit District Office
May 2, 2013

1

Objectives

- **Explain process of an IRB inspection**
- **Identify documents inspected**
- **Describe the inspectional guidelines in the IRB compliance program**
- **Common IRB deficiencies**

2

Institutional Review Boards

- **IRB – "any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects"-21 CFR 56.102(d)**

IRB Priority:

Protect rights and welfare of research subjects

3

INSPECTION ASSIGNMENTS ARE ISSUED BY 3 FDA CENTERS

- **CDER- Center for Drug Evaluation & Research**
- **CDRH- Center for Devices and Radiological Health**
- **CBER- Center for Biologics Evaluation and Research**

4

Types of Inspection Assignments

- Types of Inspections
  - Routine / Surveillance
    - IRBs inspected every 5 years
  - Directed / For Cause
    - Specific Studies
      Complaint follow-up
    - Compliance follow-up of previous inspection

5

Compliance Program 7348.809 (Institutional Review Boards)

- Objective
  - **To improve IRB performance by providing information to IRBs and by applying administrative sanctions when an IRB is out of compliance**
    http://www.fda.gov/downloads/iCECI/EnforcementActions/BioresearchMonitoring/UCM133768.pdf
  - (Issued 11/28/11)

6

Preparing for an IRB Inspection

- Have records accessible –files, protocols/ Investigator Brochures, Informed Consents,
- Correspondence with CI and sponsor
- IRB Meeting minutes have details of controverted discussions
- CVs for all IRB members/ Alternates
- List of Studies – Open or closed for 3 years

7

Pre-inspection

- Update written procedures as needed
- Review IRB references (Compliance Program, regulations, guidance documents)
- Review any previous Establishment Inspection Report (EIR), FDA-483 and FDA correspondence

8

FDA Pre-announce

- Phone call to set time for initial meeting and will ask for copies
  - Written procedures for previous 3 years
  - Membership rosters for previous 3 years
  - Chairperson(s) CV(s)
  - List of FDA regulated studies (including status –open/closed) reviewed in previous 3 years

9

Opening Meeting Questions

- Organizational structure (Org chart)
- Chairperson's, members', and staff responsibilities
  - Who attends meetings
  - Who performs expedited reviews
  - Who corresponds with investigators
  - Who is responsible for written procedures
  - Who takes meeting minutes

10

Opening Meeting

- Membership
  - How are members selected
  - Who selects/approves members
  - Length of membership terms; renewable
  - How is conflict of interest handled
  - Use of alternate members

11

Opening Meeting

- What do members receive for each study (online or paper copies/summaries)
- What are members responsible for reviewing
- Primary/secondary reviewers
- Who presents studies at IRB meetings – principal investigator or primary reviewer

12

Opening Meeting

- Expedited review process (21 CFR 56.110)
  - What is reviewed by expedited review
  - Who performs expedited review
  - How often is it performed
  - How are decisions reported to the full board

13

Opening Meeting

- Adverse event (AE) review process
  - Who reviews
  - Are SAEs reported to the full board
- Reviewed any protocols for waiver of informed consent (Emergency Research)
- Any emergency use, treatment use, or HUD

14

Opening Meeting

- Any instances of investigator non-compliance or study termination?
- How are Recruitment Ads reviewed
- Records: how long maintained
  - Where
  - Paper or electronic

15

Inspectional Process- Overview

1. Written Procedures - 21CFR 56.108
2. Membership Lists - 21CFR 56.115(a)(5)
3. Meeting Minutes - 21CFR115 (a)(2)
- and…

16

Inspectional Process- Overview

4. IRB Files
   - Select 3 studies plus specialty areas
   - Expedited review - 21CFR 56.110
   - Emergency use - 21CFR 56.102(d)
   - Treatment IND - 21CFR 312.34
   - Pediatric Studies -21CFR 50 Subpart D
   - Central IRB reviews -21CFR 56.114

17

Required Written Procedures: 21 CFR 56.108 (a) and (b)

1. Conducting initial and continuing review and reporting actions/findings to investigator and institution
   - Significant and non-significant risk devices http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf
2. Determination of which projects require review more often than annually and which require verification of no changes since previous IRB review

18

Required Written Procedures: 21 CFR 56.108 (a) and (b)

3. For ensuring prompt reporting to IRB of changes in research activity

4. For ensuring that changes are not initiated without IRB review and approval

19

Required Written Procedures: 21 CFR 56.108 (a) and (b)

5. For ensuring prompt reporting to IRB, institutional officials, and FDA of
   - -unanticipated problems involving risk
   - -serious or continuing noncompliance
   - -suspension/termination of IRB approval

20

IRB Membership Lists- 21 CFR 56.115(a)(5)

- Identified by name/Earned degree Representative capacity/Indication of experience (Licenses, certifications)
- Relationship to institution
- Alternate Members/who they represent

21

IRB Meeting Minutes 21 CFR 56.115(a)(2)

- Attendance
  - Compare with membership list
    - Count Quorum
    - Member/Alternate can't vote together
    - Non-scientist must be present
    - Vote numbers-For/Against/Abstain
    - Summary of controverted discussions

22

IRB Files- How to Select Studies for Review

- Must be FDA regulated studies
- Follow assignment instructions from the Centers
  - May direct review of specific study
  - May direct review of several studies covered by one center
- Study identified in IRB minutes with compliance issues or sponsor suspension/termination

23

Inspection of IRB Files

- IRB records (21 CFR 56.115)
  - IRB shall prepare and maintain
    - Copies of research proposals
      - Protocols with amendments
      - Consent forms (different versions - not originals signed by subject)
      - Progress reports
      - Injury reports

24

Expedited Review- 21 CFR 56.110

- IRB may use the expedited review procedure to review either or both of the following:
  - Found by the IRB to involve no more than minimal risk, or on the list provided by FDA-including:
  - #8 Continuing Review of prev. approved research; closed to enrollment, with long term follow-up only.
  - Minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized.

25

IRB Review of Adverse Events

- Review IRB's AE reporting requirements (type and time frames)
- Verify investigators are reporting AEs as required by IRB
- Review IRB's process for reviewing AEs
  - 1/09 AE guidance document listed on
  - http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf

26

8 Basic Elements of Consent (21 CFR 50.25a&b)

- Statement that the study involves research, purpose of study, expected duration, procedures used
- Risks or discomforts
- Benefits
- Alternate treatments
- Confidentiality

27

8 Basic Elements of Consent 21 CFR 50.25(a)(b)

- Compensation for injury/further information
- Who to contact for injury and subject rights
- Participation is voluntary/no retribution
- (b) Additional elements when appropriate
- New statement required to reference the ClinicalTrials.gov website. 21CFR50.25(c).

28

Closing Meeting

- Issue FDA-483 to IRB chair or top mgmnt.
- Review Discussion Items
- Remind IRB of regulatory responsibilities
- Get response/commitment
  - Inform of written response needed within 15 business days for Center's review

29

Potential Actions by FDA

- Reinspection within a shorter period
- Withhold approval of new studies
- Terminate ongoing studies
- Regulatory meeting
- Rejection of data
- Untitled Letter
- Warning Letter
- Disqualification
- Injunction/prosecution

30

Common IRB Deficiencies

21 CFR 56.108(a)(1)- The IRB [has no] [did not follow its] written procedure for conducting its [initial] [continuing] review of research. Specifically, ***

--IRB contingencies not completed and study was initiated

-- no HUD procedures

31

Common IRB Deficiencies

21 CFR 56.108(c)- For other than expedited reviews, the IRB does not always review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. Specifically, ***

(Quorum and Non-scientist at each meeting)

32

Examples of IRB 483 Observation

- Continuing review [21 CFR 56.109(f)]

  The IRB does not conduct continuing review of research at intervals of not less than once per year. Specifically, *** IRB approval for study number *** expired on July 17, 2012***The study was not reapproved until September 5, 2012.

33

Examples of IRB 483 Observations

- Expedited Review (21 CFR 56.110(b)(2)

  "The IRB used an expedited review procedure to review supposedly minor changes to previously-approved research, but the changes were not minor in nature. Specifically, the IRB approved the re-opening of a closed study via expedited review (study ***)."

34

Examples of IRB 483 Observations

- Membership [21 CFR 56.115(a)(5)]

  "A list of IRB members has not been prepared, identifying members by name, earned degrees, representative capacity, indications of experience sufficient to describe each member's chief anticipated contribution to IRB deliberations, and any employment or other relationship between each member and the institution. Specifically,

  a) The IRB maintains the following membership rosters with conflicting membership information:***

  b) Dr. S.M. is listed as a voting member at seven out of eight IRB meetings held between***Dr. S.M. is not listed on the roster for the corresponding time period, dated***."

35

Examples of IRB 483 Observations

- Meeting minutes - 21 CFR 56.115(a)(2)

  Minutes of IRB meetings have not been prepared in sufficient detail to show the vote on actions, including the number of members voting for, against and abstaining and a written summary of the discussion of controverted issues and their resolution. Specifically,

  a) Eight (8) out of ten (10) sets of meeting minutes reviewed, dated between January 10, 2009 and May 13, 2012 do not contain any discussion of studies which were reviewed and approved.

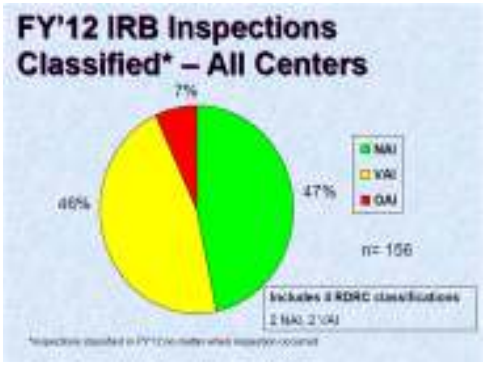
  b) Eight (8) out of ten (10) sets of meeting minutes reviewed, dated between January 10, 2009 and May 13, 2012 do not contain voting counts.

36

Examples of IRB 483 Observations

- Record Maintenance [21 CFR 56.115(b)
  - "Records required by 21 CFR 56 have not been maintained for three years following completion of the research. Specifically, the IRB is unable to locate meeting minutes for the period of***."

37



38

Resources

- **Guidance Documents**
  1. IRB Information Sheets
  http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm
  - **"Frequently Asked Questions"**
  - **"Cooperative Research"**
  - **"Recruiting Study Subjects"**
  - **"Continuing Review After Study Approval"**
  - **"Screening Tests Prior to Study Enrollment"**
  - **"Emergency Use of an Investigational Drug or Biologic"**
  - **"Frequently Asked Questions about IRB Review of Medical Devices"**

39

Humanitarian Use Device

Requires initial and continuing IRB review

- Does not require review for each use of device
- http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf (07/10)
- http://www.fda.gov/downloads/ForIndustry/DevelopingProductsforRareDiseasesConditions/DesignatingHumanitarianUseDevicesHUDS/LegislationRelatingtoHUDsHDEs/UCM336515.pdf (01/13)

40

Guidance for IRBs- Registration

- July 2009 – Guidance for complying with the requirement for IRB Registration under amendment to 21 CFR 56.106
- http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM171256.pdf
- Modified the requirement from OHRP for IRBs under institutions with Federalwide Assurances (FWA) for NIH-funded studies, to include all IRBs of regulated products

41

Emergency Use of Test Articles

- Emergency Use – defined 21CFR102(d)
- Exempt from prior IRB review if reported in 5 days. Any subsequent use needs IRB review. 21CFR56.104(c)
- Informed consent from patient or LAR is still required unless an uninvolved physician writes a letter to the IRB agreeing with the emergency nature and lack of time for informed consent. 21CFR50.23(a)

42

Treatment IND 21CFR 312.34

- FDA may approve if
  - there is evidence of drug efficacy and
  - drug is intended to treat a serious or life-threatening disease or if there is no comparable alternative drug or therapy available to treat that stage of the disease in the intended patient population.

43

Questions

44