

Conducting a Basic Audit of an IRB

David Vulcano, LCSW, MBA, CIP, RAC
Prepared for: Research Compliance Conference
Health Care Compliance Association
Minneapolis, MN
October 18, 2009

Session Objectives

- Learn identifiable danger signs that an IRB is potentially negligent.
- Create an audit tool to identify sentinel signs that an IRB is on the right or wrong track.
- Learn ways of off-site review to decrease travel.

Most Cited CFR in FDA Warning Letters

56.115	27.6%	IRB records
56.108	25.7%	IRB functions and operations.
56.109	19.1%	IRB review of research
56.107	8.6%	IRB membership
56.111	3.9%	Criteria for IRB approval of research
56.110	3.9%	Expedited review
812.66	2.7%	Significant risk device determinations
50.25	2.3%	Elements of informed consent

Observations on Key Points

Membership/Roster
Informed Consent
Meetings/Quorum
Policy Manuals
Minutes

Membership/Roster

Membership/Roster

- Inadequate Membership
- Problems with the Roster Itself
 - Upkeep
 - Representative Capacity Details
 - Handling Alternate Members
- Other Issues

OHRP and FDA Law Are Almost Identical

OHRP (45CFR46.107)	FDA (21CFR56.107)
<p>at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution</p> <p>The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.</p>	<p>at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.</p> <p>The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.</p>
<p>In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.</p>	<p>In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice. In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice.</p>
<p>The IRB shall therefore include persons knowledgeable in these areas.</p>	<p>The IRB shall therefore include persons knowledgeable in these areas.</p>
<p>If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects</p>	<p>If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.</p>

OHRP and FDA Law Are Almost Identical

OHRP (45CFR46.107)	FDA (21CFR56.107)
<p>Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.</p>	<p>Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.</p>
<p>Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.</p>	<p>Each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas.</p>
<p>Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.</p>	<p>Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.</p>
<p>No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.</p>	<p>No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.</p>
<p>An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.</p>	<p>An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.</p>

*From OHRP Guidance on Written IRB
Procedures (January 15, 2007)*

- Institutions may wish to consider including additional pertinent information in their written IRB procedures, such as the following
 - procedures for selecting and appointing the IRB chairperson and members in order to satisfy the requirements of HHS regulations at 45 CFR 46.107
 - procedures for training and educating IRB members and staff and investigators

Minimum Requirements, In Summary

- At Least Five Members
- Varying Backgrounds/Gender
- At Least 1 Scientific Member
- At Least 1 Non-Scientific Member
- At Least 1 Unaffiliated Member

- Yes, a member may serve in more than one capacity
 - Except cannot be both scientific AND non-scientific

Scientific/Non-Scientific

- OHRP “Members whose training, background, and occupation would incline them to view scientific activities from the standpoint of someone within a behavioral or biomedical research discipline should be considered a scientist.”
- FDA: “...nurses, pharmacists and other biomedical health professionals should not be regarded to have ‘primary concerns in the non-scientific area’.”
- FDA: “Some members have training in both scientific and non-scientific disciplines, such as a J.D., R.N. While such members are of great value to an IRB, other members who are unambiguously non-scientific should be appointed to satisfy the non-scientist requirement.”
- PHRP: “The ‘unscientific’ determination must meet the criteria of ‘unambiguously unscientific’- *i.e.*, a physician does not lose their scientific representation upon retirement.”

“Affiliated/Unaffiliated”: OHRP Criteria

- Affiliated members include, but are not limited to individuals who are:
 - Full Or Part-time Employees;
 - Current Students;
 - Members Of Any Governing Panel Or Board Of The Institution;
 - Paid Or Unpaid Consultants;
 - Healthcare Providers Holding Credentials To Practice At The Institution;
 - Volunteers Working At The Institution On Business Unrelated To The IRB/IEC.
- Unaffiliated members may include people whose only association with the institution is that of a
 - Patient,
 - Subject,
 - Former Student At That Institution.
- Paying an unaffiliated member a reasonable market value for their services would not make the member “otherwise affiliated” as stated in the regulations or cause the member to have a conflicting interest.

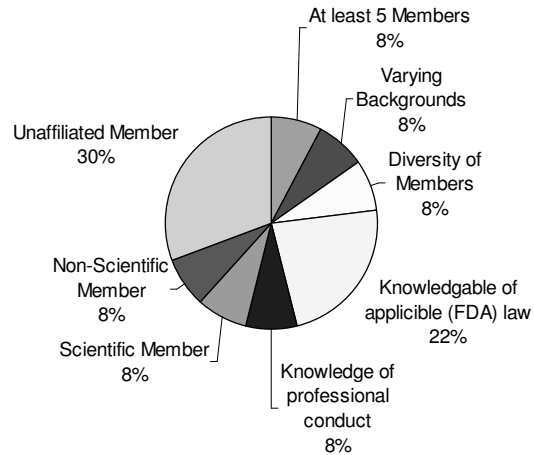
“Affiliated/Unaffiliated”: Examples of Members Erroneously Classified as “Unaffiliated” per FDA Warning Letters

- “_____ is the spouse of _____ a scientific member of the IRB.”
- “_____ is employed by _____, who is a scientific member of the IRB.”
- “_____ is employed by _____ M.D., who is a scientific member of the IRB.”
- “_____’s employer is a laboratory contracted to perform laboratory analyses for at least one study approved by the Hospital.”

“Alternate”: OHRP Guidance

- Each alternate IRB member has [the] experience, expertise, background, professional competence, and knowledge comparable to that of the primary IRB member whom the alternate would replace.
- If both a primary IRB member and his or her alternate(s) attend the same IRB meeting, OHRP assumes that the primary member is acting as the official voting member of the IRB for review of research protocols, unless the minutes clearly indicate otherwise.
- The minutes of an IRB meeting should document the attendance of all primary and alternate IRB members who attended any part of the IRB meeting.
 - A designated alternate IRB member for a primary IRB member may substitute for the primary IRB member for an entire meeting or at any time during a meeting.
 - Substitution during a meeting commonly occurs when the primary member is
 - (a) absent from the room for part of the meeting, or
 - (b) recused from review of certain research protocols because the primary IRB member has a conflicting interest with respect to a specific research protocol.
 - Whenever this occurs, the minutes of the IRB meeting should indicate clearly that the alternate IRB member has replaced the designated primary IRB member.
- OHRP recommends that the reason for the substitution of the alternate IRB member also be documented in the minutes.

Most Common Missing Membership Requirement



Roster: FDA and OHRP Regulations Are The Same

OHRP - 45CFR46.103(b)(3)	FDA - 21CFR56.115(a)(5)
Name	Name
Earned Degrees	Earned Degrees
Representative Capacity	Representative Capacity
indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations	indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations
any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant	any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.

IRB Registration

- Long Time Mandatory for OHRP Governed Studies
- Required for FDA Governed Studies As Of September 14, 2009
- List is publically available
 - <http://ohrp.cit.nih.gov/search/>
- Three Classifications
 - OHRP Only
 - FDA Only
 - OHRP/FDA

Required Fields for IRB Registration

Item	FDA	OHRP
Institution Operating the IRB (name, mailing address and street address if different from mailing address)	✓	✓
Senior Officer over IRB (name, mailing address, phone number, facsimile number, email)	✓	✓
IRB (name, mailing address, street address if different from mailing address, phone number, facsimile number, email)	✓	✓
IRB Chair (name, phone number, email)	✓	✓
Person registering a.k.a. Contact Person (name, mailing address, phone, fax, email)	✓	✓
Approximate Total Number of Protocols		✓
Approximate Number of HHS Conducted/Supported protocols		✓
Approximate Number of Active Protocols of FDA-Regulated Products	✓	
Description of types of FDA Regulated Products (i.e. human drugs, medical devices, biological products, food/color additives or other) involved in the protocols that the IRB reviews	✓	
Number of FTEs dedicated to IRB 's administrative activities		✓
IRB Roster (including but not limited to each member's name, gender, earned degrees, scientific status, affiliation status and any designated (i.e. Prisoner representative) or alternate status).		✓

FDA Warning Letter Quotes on Problems with Upkeep of Rosters

- “There were no IRB membership rosters available for this time period”.
- “It is unclear which membership list is current. Specifically, the list in your Guidelines shows fifteen members; the Cooperative Project Assurance list [during the same month] identifies sixteen members.”
- “The IRB did not date the membership rosters.”
- “We suggest that the IRB update the membership roster each time there is a change to reflect the actual membership. The IRB’s practice of preparing a roster for a calendar year is not adequate to document that the membership requirements are met at any given time.”
- “The most recent IRB membership roster obtained during the inspection is dated September 30, 1998. FDA is in possession of a more recent roster dated July 28, 1999, that was submitted to FDA by the sponsor of a study reviewed and approved by the IRB.”

FDA Warning Letter Quotes on Specific Education

- “The IRB appears to lack personnel who are knowledgeable about FDA requirements, and who can distinguish when proposed research must be performed under an IND or IDE.”
- “Moreover, there was no IRB member familiar with applicable FDA regulations.”
- Records of Training
 - “Four of [redacted] regular members and [redacted] of three alternate members did not have CVs/resumes on file.”
 - “Also, training records of members are not available.”

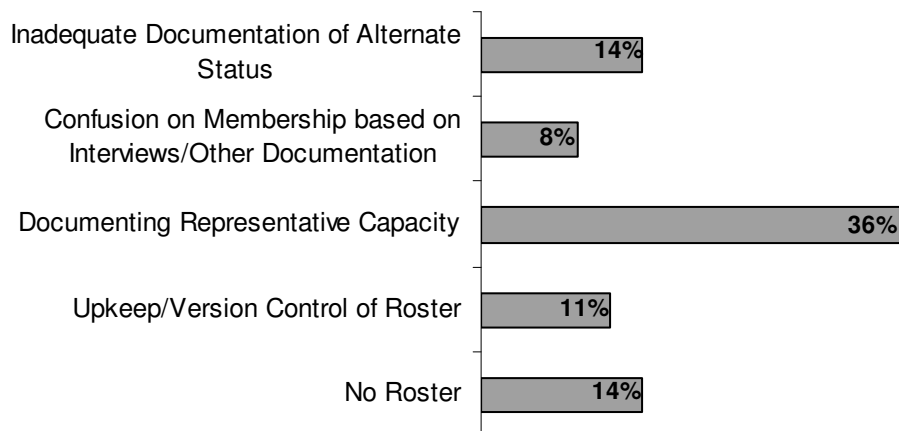
FDA Warning Letter Quotes on Representative Capacity

- “The current listing of IRB members does not objectively describe members’ affiliations to the institution”
- “[IRB] membership listings from July 01, 2000 to June 30, 2004, do not identify an affiliation with the hospital for most members, and none of the members had CVs/resumes on file.”
- “The current membership list does not identify any community representative and does not designate the voting and non-voting members.”
- “In addition, the membership list fails to identify each member’s earned degrees, representative capacity, indications of experience, or other criteria sufficient to describe the member’s anticipated contributions to the IRB deliberations.”
- “The IRB membership list from 1998-2003 failed to show each member’s earned degree, representative capacity, indications of experience such as board certifications and licenses, etc.”
- “You should specify which member(s) meet the nonscientist requirement”
- “Documentation of the [IRB] membership and its roster is inadequate in that it does not identify those who are knowledgeable in regulations, institutional commitments, applicable law, and standards.”
- “The current IRB membership roster as of May 15, 2002 does not list the Chair, the Secretary, or the non-scientific member.”
- “For example, the list of IRB committee members, or roster, dated June 8, 1999, does not accurately reflect membership. This roster does not contain any identification of the nonscientific and non-affiliated members. In fact, the represent or incomplete for 18 of the 19 members listed. One member [redacted] is listed as ‘Community representation’. The meeting minutes make no further clarification.”
- “Regarding the IRB membership, please define the role of the single nonvoting member listed on the IRB membership roster. The role of guests should also be addressed if specific individuals regularly attend IRB meetings.”
- “The IRB membership list for 2003 failed to include two members’ earned degrees, representative capacity, experience, and employment or relationship between the members and the institution.”

FDA Warning Letter Quotes on Alternates

- “In addition, we recommend that the membership list also identify the alternates representation.”
- “The IRB membership roster does not identify regular members for whom each alternate member may substitute”

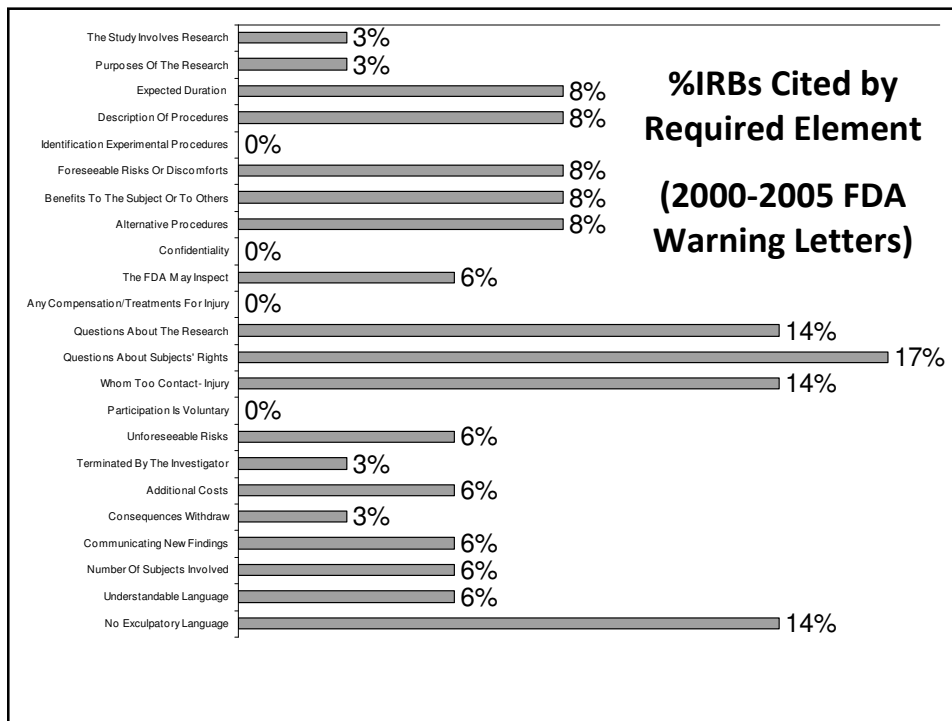
Problems with the IRB Roster



Informed Consent

Informed Consent

- Failure to use a checklist of Required Elements
- Failure to Proof Read
- Failure to Assure One is in Place
- Failure to Revise in Presence of New Information



Examples of Overly Reassuring Language

- *“...to confirm a very exciting and promising treatment,”*
- *“...hopefully cure my cancer.”*
- *“The new liquid formulation of the [...] vaccine has been shown to be safe.”*
- *“[the FDA] may inspect all records from this study due to their interest in and support of this vaccine.”*
- “It is not reasonable that prospective subjects would understand what is required by law.”
- “Use of the wording ‘You understand,..’ is inappropriate”.
- “Subjects should not be required to certify such understanding or completeness of disclosure.”

Failure to Proof Read

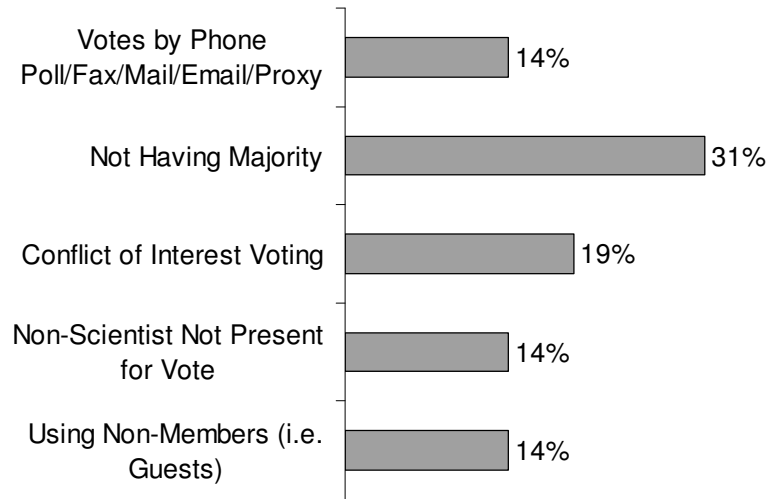
- “Easily To Spot” Examples
 - Approved ICD contained blanks to be filled in for investigators name and contact numbers
 - The name of the clinical investigator is indicated only by “XXXXXX.”
 - The paragraphs are not sequentially numbered
 - Some items are repeated.
 - The consent form is written in the form of a protocol and does not directly address the perspective of a potential study subject.
- Harder to Spot Examples
 - Number on who to call for questions about the study was a disconnected number and no new number was ever given to subjects.
 - The consent states “I understand ... that I may have a copy of this document.” 21 CFR 50.27(a) requires that a copy shall be given to the person signing the form.

Processing of Consent Documents

- “The IRB failed to review the informed consent documents for the study”
- “The IRB conditionally approved [but] did not follow up to ensure that [the Investigator] submitted and received IRB approval of informed consent documents before ... the study.”
- “[in the presence of new information] however, the IRB did not require the informed consent document to be revised.”
- “IRB approval date” on consent forms ...is considered to be a good practice.”

Meetings/Quorums

Problems with Voting (FDA Warning Letters)



WHAT IS A QUORUM?

1. Majority of Members

- >50% of Voting Members on Current Roster
- Not Equal to 50%
 - 6 of 11 = Quorum
 - 6 of 12 has been documented as NOT being a quorum

2. Presence of a Non-Scientific Member

Additional Notes on Defining a Quorum

- If policies state a higher %, FDA will hold you to that.
- Use of Sub-Groups (i.e. for “quicker review”) must meet the majority requirements of the whole IRB.

Most Common Dangers in Obtaining Quorums

- Not enough reliable Non-Scientific members
 - Can't Show Up
 - Must Arrive Late/Leave Early
- Not enough members to cover for members with conflicts of interest
- Too many members of sporadic attendance
 - Inability to get >50%
- Chair as “non-voting in case of a tie”
 - Considered nonvoting, then not counted
 - Example 3 + “non-voting” chair on a roster of 7 is NOT a majority
- Ad Hoc Additions Without
 - Proper Training
 - Opportunity To Review Materials
- Overpolicied
 - i.e. making it 2/3rds instead of >50%
 - i.e. stating “in no event less than ___ must be present”

Common Issues with Conflict of Interest (COI) Voting

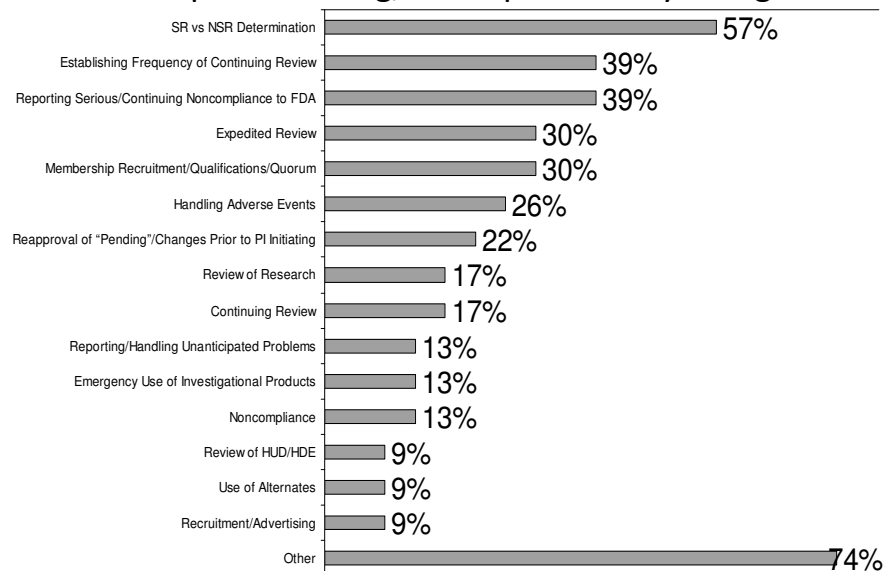
- Investigators/Sub-Investigators/Subcontractors
 - Being counted in determination of quorum status
 - Not leaving room during deliberations and voting
 - Having their votes count/Failing to Abstain
- Defining COI
 - “current **or former** employment by the clinical investigator”
 - “Employed by the subcontracting laboratory”
- Not cited but FDA expressed concern over...
 - “...clinical investigator personally recruited several of the IRB members with whom he had a personal or professional relationship...”
 - “Most IRB meetings took place in the clinical investigator’s office...”

Policy Manual

Common Issues with Procedure Manuals

- Under-Policed
 - Missing Policies Altogether (19%!)
 - Missing Key Items
- Doesn't describe "HOW" the IRB will...
 - "Simply restating or rewording the federal regulations does not meet the requirement for written procedures." (2000)

Most Frequent Missing/Inadequate Policy Categories



Common Issues with Procedure Manuals (continued)

- Not following them
 - Interesting Observation: In 2004-2005, <50% letters cited inadequate manuals as opposed to nearly 100% in previous years.
 - May be “Over-Policied” (34%!)
- Technical Issues
 - Policies unintentionally limited to Drug or Device
 - Policies unintentionally limited to (or conflict with) FDA vs OHRP

Common Issues with Procedure Manuals (continued again)

- Outdated
- Citations are incorrect
 - FDA vs OHRP
 - Refers to Documents that do not/no longer exist

Creating a Checklist for Policy Manual Review

- **OHRP Guidance on Written IRB Procedures**
 - January 15, 2007
 - <http://www.hhs.gov/ohrp/humansubjects/guidance/irbgd107.htm>
- No “comprehensive” FDA guidance
 - Review FDA CFR
 - Review FDA Information Sheets
 - Review FDA Warning Letters

Meetings & Minutes

OHRP and FDA Law Are Identical

OHRP (45CFR46.115(a)(2))	FDA (21CFR56.115(a)(2))
“Minutes of IRB meetings which shall be in sufficient detail to	“Minutes of IRB meetings which shall be in sufficient detail to
attendance at the meetings;	attendance at the meetings;
actions taken by the IRB;	actions taken by the IRB;
the vote on these actions including the number of members voting for, against, and abstaining;	the vote on these actions including the number of members voting for, against, and abstaining;
the basis for requiring changes in or disapproving research; and	the basis for requiring changes in or disapproving research; and
a written summary of the discussion of controverted issues and their resolution.”	a written summary of the discussion of controverted issues and their resolution.”

OHRP Guidance on Written IRB Procedures Revised: January 15, 2007

- “The minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.”
- “OHRP recommends that except when requested by the IRB to be present to provide information, IRB members absent themselves from the meeting room when the IRB reviews research in which they have a conflicting interest, and such should be noted in the IRB meeting minutes.”

OHRP Guidance [continued]

- **“Minutes of IRB Meetings.** The minutes of IRB meetings must include all the information stipulated by HHS regulations at 45 CFR 46.115(a)(2). The minutes of IRB meetings should document, among other things:
 - (a) Separate deliberations, actions, and votes for each protocol undergoing initial or continuing review by the convened IRB.
 - (b) The vote on all IRB actions including the number of members voting for, against, and abstaining. In order to document the continued existence of a quorum, OHRP recommends that votes be recorded in the minutes using the following format: Total = 15; Vote: For-14, Opposed-0, Abstained-1.”

OHRP Guidance [continued]

- “OHRP recommends that when approving such a waiver [of consent] for research reviewed by the convened IRB, these findings be documented in the minutes of the IRB meeting, including protocol-specific information justifying each IRB finding.”
- “Similarly, where HHS regulations require specific findings on the part of the IRB, such as...
 - (a) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)];
 - (b) approving research involving pregnant women, human fetuses, or neonates (see 45 CFR 46.204-207);
 - (c) approving research involving prisoners (see 45 CFR 46.305-306);or
 - (d) approving research involving children (see 45 CFR 46.404-407),
- ...the IRB should document such findings.

OHRP Guidance [continued]

- OHRP recommends that for research approved by the convened IRB, all required findings be fully documented in the minutes of the IRB meeting, including *protocol-specific* information justifying each IRB finding.”
- IRBs must determine which protocols require continuing review more often than annually, as appropriate to the degree of risk [see 45 CFR 46.103(b)(4) and 46.109(e)]. OHRP recommends that the minutes of IRB meetings clearly reflect these determinations regarding risk and approval period (review interval).

FDA Information Sheets 1998

- A hospital IRB may review outside studies on an individual basis when the minutes clearly show the members are aware of where the study is to be conducted and when the IRB possesses appropriate knowledge about the study site(s).
 - Note: this is not necessarily HCA’s policy.
- The IRB minutes should document when an alternate member replaces a primary member.

Major Sections Explained

- Attendance
- Preliminary/Informational Matters
 - Approval of Prior Meeting Minutes
 - Conflict of Interest Declaration
 - Expedited Reviews/Emergency Use
 - Announcements
- Continuing Reviews
- Initial Reviews
- Amendments
- Adverse Event Review
- Other Items

Attendance

- Identify Members Present
 - Potential Problem: Not clearly identifying who is Present and who is Absent
 - FDA does not like “Tick Marks”
 - Potential Problem: Sign-In Sheets to not match minutes
 - Potential Problem: Non-Scientific individual not clearly identified. This can be accomplished in the attendance or a statement in the preamble like “Jane Doe was a non-scientific member that was present during the entire meeting”
- Note who Chaired the meeting
 - If the Chair is present, they chair the meeting
- Note if an Alternate is Being Used and Who They Are Alternating For
 - Can only alternate for “like” individuals i.e. nonscientific for nonscientific

Attendance [Continued]

- Differentiate Between Non-Members and Non-Voting Members
 - Non-Voting Members
 - Guests
 - Students
 - Observers
- Auditors will count the number of Voting Members present and total each vote to see if they match
 - Match them to the roster in effect on that date
 - Always note when people leave the room and when they came in.
 - Especially if a conflict of interest was the reason they left the room.
 - Especially if a vote took place

Other Preliminary/Informational Matters

- Approval of Previous Minutes
 - BEST PRACTICE: Have meeting minutes QA'd prior to going to the next meeting to be ratified.
 - If a member wasn't at the previous meeting, they should abstain.
- Conflicts of Interest with Members
 - BEST PRACTICE: (Assuming this was done) document the Chair's solicitation for conflict of interest regarding upcoming protocols and if there were any.
- Announcements (Can Be Done At End Of Meeting)
 - Exempt and Expedited Reviews
 - Protocol Identifiers
 - Name of Reviewer
 - Classification justifying Exempt/Expedited Status
 - BEST PRACTICE: Standing agenda items and putting "None" if none.
 - Emergency Use
 - Investigational Product
 - Treating Physician
 - BEST PRACTICE: Standing agenda items and putting "None" if none.
 - Other operational Issues
 - Change of Policies
 - Change of meeting time/place

Protocol Reviews (Continuing Review/Initial Review and Amendments)

- What Are You Discussing?
- What Did You Discuss?
- What Was The Outcome?

- Note: Identify any Primary or Secondary Reviewers by Name
 - FDA Warning Letter: “The meeting minutes for the period of July 1998 through January 2002, and the current list of "IRC Open Study Protocols" do not identify the primary and secondary reviewers assigned to review new studies as required by the IRB’s written procedures. It is important to include this information in the meeting minutes to document that the IRB reviewers do not have a conflict of interest.”

What Are You Discussing? Protocol Identification

- **Each protocol reviewed separately**
- **Uniquely Identify Each Study By Protocol Number**
 - FDA Warning Letter: “Meeting minutes do not always identify the identification/tracking number of the study which was discussed and voted on during a meeting. In many cases a protocol number is included in the meeting minutes, but the practice is not routine. The meeting minutes should identify each study for which continuing review was conducted.”
 - FDA Warning Letter: “Meeting minutes do not always identify the title of the study which was discussed and voted on during a meeting. Many studies are referred to by acronyms, such as _____ or by the last name of the clinical investigator.”
 - FDA Warning Letter: “In many instances the IRB did not document the name of the clinical investigator and/or the title of the clinical trial under discussion.”
 - FDA Warning Letter: “The IRB meeting minutes do not identify the title of the study, version of the study protocol or version of the consent forms that the IRB discussed and/or approved during the meetings. For example, the meeting minutes for 3/9/05, 6/1/05, and 9/28/05 do not specify the study title that the IRB renewed for another year. Without a means of clearly identifying which study is being discussed, the IRB may not be able to track the actions required by the IRB and assess the subjects' safety in the studies. ”

What Are You Discussing? Details and Version Control

- Protocol Version Number/Date
- Informed Consent Version Number/Date
- List out all other documents received. For example:
 - Application
 - Advertisement
 - Recruitment script
 - Investigator's Brochure

What Did You Discuss?

- "Discussion" is not a re-summarization of the protocol!
- Documentation of risk evaluation:
 - Risks of the research
 - Physical
 - Social
 - Economic
 - Impact of study design on risk
 - Provisions for safety monitoring
 - Risks have been minimized to the extent possible
 - The determination of the level of risk
 - Risk level of investigational device, if any.
- Documentation of benefit evaluation
 - To subjects
 - To society
- Documentation of Equitable Selection
- Documentation of Additional Protections for Vulnerable Populations

What Are You Discussing?: Continuing Review

- **Identify New Information Obtained Since Last Meeting**
 - Continuing Review Reports
 - SAE Reports
 - Expedited Reviews
 - Protocol/Consent Amendments
 - Other Items Received

- dv2 – FDA Warning Letter: “Meeting minutes do not identify which periodic reports have been received since the previous meeting.”
- FDA Warning Letter: “Elsewhere in the minutes, adverse events are listed by product and often lack the protocol identifier. There is no documentation that the adverse events are linked to a specific protocol and are discussed by the IRB.”

Criteria For Approval: OHRP and FDA Law Are Near Identical

OHRP (45CFR46.111)	FDA (21CFR56.111)
(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:	(a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:
(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.	(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

Slide 57

dv2

Verify this

David Vulcano, 9/2/2008

Criteria For Approval: OHRP and FDA Law Are Near Identical

OHRP (45CFR46.111)	FDA (21CFR56.111)
<p>(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.</p>	<p>(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.</p>

Criteria For Approval: OHRP and FDA Law Are Near Identical

OHRP (45CFR46.111)	FDA (21CFR56.111)
<p>(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.</p>	<p>(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.</p>

Criteria For Approval: OHRP and FDA Law Are Near Identical

OHRP (45CFR46.111)	FDA (21CFR56.111)
(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.	(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by part 50.
(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.	(5) Informed consent will be appropriately documented, in accordance with and to the extent required by Sec. 50.27.
(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.	(6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

Criteria For Approval: OHRP and FDA Law Are Near Identical

OHRP (45CFR46.111)	FDA (21CFR56.111)
(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.	(7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.	(b) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Justifying Criteria

- Again, “discussion of controverted issues” is NOT a resummation of the protocol.
- Discussions should be mapped to approval criteria
- Special circumstances must be documented to show certain criteria was met. For Example:
 - Alteration/Waiver of Informed Consent
 - Waiver of Documentation of Informed Consent
 - Alteration/Waiver of HIPAA Authorization
 - Devices
 - Vulnerable Population
 - Conflict of Interests
 - Suspending/Terminating a Study
 - Adverse Events

Did You Alter or Waive Informed Consent?

- NOTE: THERE IS NO PROVISION OF WAIVER OF CONSENT FOR FDA GOVERNED STUDIES
- Document how it met the criteria at 45CFR46.116(c) or (d)
 - (c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:
 - (1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and
 - (2) The research could not practicably be carried out without the waiver or alteration.
 - (d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
 - (1) The research involves no more than minimal risk to the subjects;
 - (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
 - (3) The research could not practicably be carried out without the waiver or alteration; and
 - (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Did You Waive Documentation of Informed Consent?

- NOTE: THERE IS NO PROVISION OF WAIVER OF DOCUMENTATION OF CONSENT FOR FDA GOVERNED STUDIES
- Document how it met the criteria at 45CFR46.117(c)
 - (c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:
 - (1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
 - (2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

Did You Waive or Alter HIPAA Authorization Language?

- Document how it met the criteria at 45CFR164.512(i)(2)(ii)
 - (A) The use or disclosure of the PHI involves no more than minimal risk to the privacy of individuals based on, at least, the presence of the following elements:
 - (1) An adequate plan to protect health information identifiers from improper use and disclosure.
 - (2) An adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so).
 - (3) Adequate written assurances that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.
 - (B) The research could not practicably be conducted without the waiver or alteration.
 - (C) The research could not practicably be conducted without access to and use of the PHI.

Did You Review a Device?

- Have You Documented its SR/NSR Status?
 - A Significant Risk (SR) device study is defined [21 CFR 812.3(m)] as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and
 - (1) is intended as an implant; or
 - (2) is used in supporting or sustaining human life; or
 - (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
 - (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
 - An Non-Significant Risk (NSR) device investigation is one that does not meet the definition for a significant risk study.
- Have you Documented that It Has Or Otherwise Does Not Need an IDE from the FDA?
 - Testing an unapproved Significant Risk (SR) device or a legally marketed device for a new indication requires IDE
 - IDE exemption criteria is statutory under 21CFR812.2 or via subsequent written opinion
- If it was a Humanitarian Use Device (HUD)/Humanitarian Device Exemption (HDE), was the initial approval done by a convened meeting (i.e. NOT via expedited review)?

Did You Review A Study Involving A Vulnerable Population?

- Statutory Vulnerable Populations Are
 - Pregnant Women, Human Fetuses and Neonates
 - Prisoners (note requires a Prisoner or Prisoner Representative as voting member of IRB)
 - Children
- Other Populations You May Consider Vulnerable By Policy
 - Decisionally Impaired
- Have you documented what additional protections are required, or the reason for the absence of any?
 - Note, if a statutorily defined vulnerable population, did you document the required elements by their respective subparts?
 - **45CFR46 Subpart B for Pregnant Women, Human Fetuses and Neonates Involved in Research**
 - **45CFR46 Subpart C for Prisoners**
 - **45CFR46 Subpart D and 21CFR 56 Subpart D for Children**

Did You Review A Study Involving Children?

- Did you document your categorization of the study into one of the four categories as required in 45CFR46 Subpart D and 21CFR50 Subpart D?
 - Research not involving greater than minimal risk; OR
 - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects; OR
 - Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition; OR
 - Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (thus needing approval from the FDA or OHRP Secretary).
- Have you documented your determination as to if the study requires one or both (when available) parent's consent?
- Have you documented if assent is needed from the child? (NOTE: ASSENT IS REQUIRED IN FDA STUDIES EXCEPT IN CERTAIN CRITERIA)
 - If so, have you documented your determination if assent needs to be in writing?

Did You Review A Study With A Conflict of Interest?

- Have you documented what that COI is?
- Have you documented that the COI is either:
 - Eliminated; or
 - Minimized/Managed through additional protections (and what they are); or
 - Unmanageable, thus the study cannot continue.
- Have you documented that the individual(s) with the conflict of interests were not in the room during deliberations or voting on the protocol?
 - If the person with a COI was an IRB member, did you not count them towards a voting quorum?

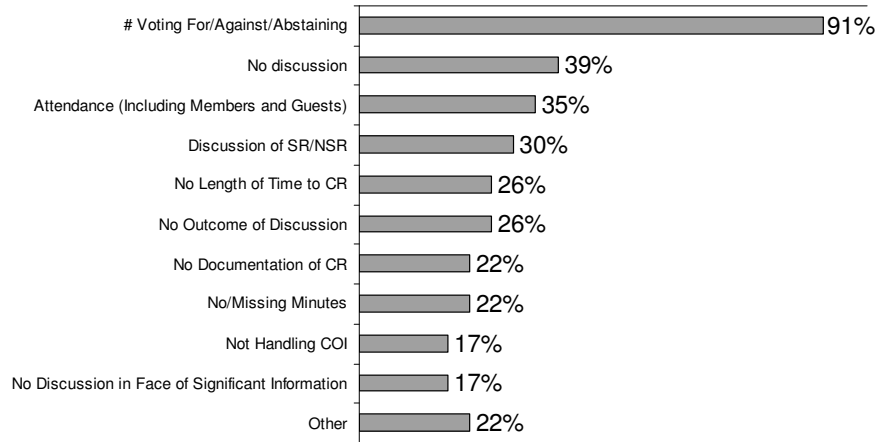
Did you Suspending or Terminate a Study?

- Did you document the reason for suspension/termination
 - I.e. Passed continuing review date
- Did you determine that the reason was for Serious or Continuing non-compliance (thus requiring notification to FDA and/or OHRP)?
- Did you specify if current subjects were allowed to continue receiving any investigational therapies? And if so, for how long and under what circumstance?

Minutes

- No/Missing Minutes (22% in FDA Warning Letters)
- Missing Basic Items
 - Attendance
 - Record of Voting
- No Record of Discussions
 - No Discussion
 - No Outcome/Follow-Through on Discussion
 - Discussions Contrary to What Is In File

Problems with Minutes



Number Voting

- Looking for the actual number voting For, Against and Abstaining
- “‘unanimous’ [is] unclear how many members and/or alternates had voted”
- Those abstaining from voting were not identified

Summary of Discussions

- Selection of subjects is equitable
- Adequate provision for monitoring the data collected to ensure safety
- Protection of privacy
- Additional protections for vulnerable populations
- Local community attitudes

Attendance

- Clearly distinguish between "members present" and "member absent."
 - Unclear if “non-scientific” member was present
 - Inconsistencies in voting numbers, sign-in sheets etc
 - Discourages use of “tick marks”
- Not Identifying Non-Members present

Documenting Votes

- MUST contain the # For, # Against and # Abstaining
 - Abstaining means that they were eligible to vote but chose not to (i.e. those with a conflict are not eligible to vote thus not counted)
 - Number of votes must total to the number of eligible members to vote
 - Account for any missing votes that differ from the attendance call (i.e. ____ left early, ____ stepped out to make a phone call etc).
- The following are not acceptable and have been cited as such
 - “Unanimous vote”
 - “All voted in to approve”
- Document names of those with a Conflict of Interest (COI) and that they were not in the room during deliberations and voting
 - NOTE: Those with a COI are not counted as “abstained” as they are not eligible to vote.

Others Comments on Minutes

- No Length of Time to CR documented
- “ ...do not always identify the identification/tracking number of the study”
- fail to document that this study was either suspended or terminated
- COIs leave the room for deliberation and viting
 - IRB Members
 - Research Team
 - PI
 - Subcontractors (Lab)
 - Former Employer of PI

Other Comments on Minutes (Continued)

- Retroactive approvals of studies
- How “Contingent” Approvals are verified prior to research starting
- Wet Ink Minutes seem to be ok

Other (Not So) Amusing Findings

- IRB Chairman stated that he did not know the other IRB members
- [Redacted] stated that he never read the protocol that he voted to approve
- 93 studies were reviewed within 55 minutes, 210 studies in 50 minutes, 200 studies in 60 minutes, 200 studies in 55 minutes
- [IRB Members] do not receive any study materials for review [only an agenda]

Sample FDA Warning Letter Quotes on “Dirt Dumb” Issues

- “There is currently no IRB Chair.”
- “The membership list for your IRB does not include [redacted], although he participated in the Board’s review of and voting for the study.”
- “The IRB 2002 membership roster also listed an individual as a voting member, even though [redacted] stated during the inspection that this individual was not an IRB member or alternate, and participated only as an ad hoc substitute in the September 18, 2002 and December 9, 2002 IRB meetings”
- “Members identified as primary reviewers were neither identified as IRB members nor present for meetings when the protocols were discussed.”
- “For example, the FDA Field Investigator interviewed [redacted], IRB Chairman. [redacted] stated that he did not know the other IRB members and that he believed Dr. [redacted] to be the person most responsible for the IRB’s functions.”

Questions/Comments