Interpreting and Learning From OHRP Determinations

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Presentation Overview

- Background and OHRP compliance oversight procedures
- Common findings
- Corrective actions
- Case examples
- Conclusions and resources

OHRP’s Jurisdiction

- Research involving human subjects conducted or supported by HHS that is not otherwise exempt
- Non-exempt human subject research covered by Assurance of Compliance
Compliance Oversight Investigation
- Receive allegation or indication of noncompliance
- Determine OHRP jurisdiction
- Send written inquiry to appropriate institutional officials
- Review institution report and relevant IRB documents
- Communicate with institution as needed (correspondence/telephone interviews/site visit)
- Issue final determinations

May Refer Complaint
- FDA
- Other Common Rule agency
- Other HHS agency

For-Cause vs. Not-For-Cause
- For-Cause: Responds to substantive allegations or indications of noncompliance in HHS-supported research or under an applicable assurance; usually through correspondence (>90%)
- Not-for-Cause: Assess institutional compliance with 45 CFR 46 in absence of specific allegations; can be partially “for-cause” (previous compliance problems or vague allegations); often through site visit (~50%)
Compliance Oversight Investigation Possible Determinations/Outcomes (1)

- Protections under an institution’s Assurance are in compliance
- Protections under an institution’s Assurance are in compliance, but recommended improvements have been identified
- Noncompliance identified, corrective actions required
- Noncompliance identified, Assurance restricted/suspended pending required corrective actions

Compliance Oversight Investigation Possible Determinations/Outcomes (2)

- Noncompliance identified, OHRP approval of Assurance withdrawn
- OHRP may recommend to appropriate HHS officials or PHS agency heads that
  - an institution or investigator be temporarily suspended or permanently removed from participation in specific project
  - peer review groups be notified of an institution’s or an investigator’s past noncompliance prior to review of new projects

Compliance Oversight Investigation Possible Determinations/Outcomes (3)

- OHRP may recommend that institutions or investigators be declared ineligible to participate in HHS-supported research (debarment). Debarment initiated in accordance with procedures specified at 45 CFR Part 76.
Common Findings

- Determination letters:
- Significant findings:
  [http://www.hhs.gov/ohrp/compliance/findings.pdf](http://www.hhs.gov/ohrp/compliance/findings.pdf)

Most Common Findings (1)

- ICDs deficient with respect to basic elements [§46.116(a)]
- Inadequate written procedures [§46.103(a) and 46.103(b)(4)(5)]
- Research conducted without IRB approval [§46.103(b) and 46.109(a)]
- Insufficient info to make determinations required for approval [§46.111]
- Failure to document informed consent [§46.117(a)]
Most Common Findings (2)

- Protocol changes without IRB review ([§46.103(b)(4)(iii)])
- Failure to conduct continuing review at least annually ([§46.109(e)])
- Inappropriate application of exempt categories of research ([§46.101(b)])
- Failure to obtain legally effective informed consent ([§46.116])
- Enrollment procedures didn’t minimize possibility of coercion or undue influence ([§46.116])

Most Common Findings (3)

- Failure of IRB to Determine That Criteria for IRB Approval Are Satisfied ([§46.111])
- Failure of IRB to Document Consideration of Additional Safeguards for Vulnerable Subjects
- Failure of IRB to Make Required Findings When Reviewing Research Involving Prisoners ([§46.305])
- Inadequate IRB meeting minutes and retention of IRB records ([§46.115(a)])
- IRB meeting convened without quorum (lack of a majority) ([§46.108])

Consent Document Deficient with Respect to Risks and Discomfort

- §46.116(a)(2) states that in seeking informed consent the following information shall be provided to each subject … A description of any reasonably foreseeable risks or discomforts to the subject
Risks and discomforts- Need to be in Informed Consent Document?

POLL
1. Risks associated with add’l PET scans
2. Risks of standard care if dictated by protocol
3. New findings of risks in a study arm
4. Risks of violation of confidentiality - could damage a subject’s reputation
5. None of the above

Inadequate Written Procedures

§46.103(a)&(b)(4) & (5) requires that institutions have written procedures that the IRB will follow:
- Initial and continuing review
- Reporting findings
- Which projects need verification of no changes
- Prompt reporting to the IRB of proposed changes
- Reporting of:
  - Unanticipated problems
  - Suspension/termination of IRB approval
  - Serious or continuing noncompliance

Do the Regulations Require the following Written Procedures?

POLL
1. The procedures for determining when to audit research.
2. Procedures for determining exemptions.
3. Procedures for reporting suspension by DSMB.
4. Procedures for approving research involving prisoners.
5. None of the above.
Research Conducted Without IRB Approval - Examples

- A randomized, controlled trial of teaching vascular surgery skill to interns
- Studies of whole body vibration, in which the athletes stand on a machine with a vibrating platform.

Insufficient Information to Make Determinations

- §46.111 In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:
  - Risks to subjects are minimized and reasonable in relation to anticipated benefits
  - Selection of subjects is equitable
  - Informed consent will be sought and documented
  - Study has adequate provisions for monitoring
  - Study has adequate provisions to protect privacy
  - Study has additional appropriate safeguards for vulnerable subjects

The IRB May Approve Research with the Following Questions/Conditions without Re-review by Convened IRB

**POLL**

1. Concern about supervisors encouraging their employees to participate in research.
2. Info on where biopsies were taken from.
3. Precise language changes to protocol or ICDs.
4. Substantive changes with clearly stated parameters that the changes must satisfy.
Protocol Changes without IRB Review

§46.103(b)(4) requires that IRBs ensure prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

The Regs require IRB review of which of the following protocol changes?

Poll
1. Enrolling ineligible subjects.
2. Added lab to test for emergent risk.
3. Increase enrollment limits.
4. New recruitment ads.
5. None of the above.

Which of the Following Need to be Reported to OHRP?

Poll
1. Subjects’ confidential contact information was used inappropriately by study staff.
2. Non-exempt human subjects research conducted without IRB review/approval.
3. Suspension/Terminations of sponsor approval.
4. Study drug dosing errors.
5. None of the above.
Consent documentation needed?
- Medical records chart review of hospital records.
- Survey on quality of life after kidney transplant
- Survey on illicit drug use and drug-seeking behavior
  - If no identifiers collected
  - If identifiers collected
- Parental permission "opt out"

Coercion or undue influence-
Example
- Student athletes underwent testing of various physical performance characteristics by researchers who are team coaches, so some of the student athletes might believe that if they do not agree to have the test results used for research purposes, they will not be able to play and will lose their athletic scholarships, or will receive a lower grade.

CORRECTIVE ACTIONS
OHRP evaluates corrective actions

- OHRP will look for two types of corrective action plans:
  - Addressing the systemic issue, in hopes of preventing similar types of noncompliance in future
  - Addressing the specific noncompliance cited

General Categories of Corrective Actions

- Revision of IRB application forms
- Modify IRB/Institutional structure
- Addition or revision of policies and procedures
- Education/Training
- Protocol/case-specific changes

Corrective Actions in Compliance Cases 2008-2014

- SOPs 36%
- Educ 24%
- Case specif 15%
- IRB structur 4%
- App forms 5%
- other 12%
Examples of Modification of IRB/Institutional Structure

- Restructure IRB
- Additional staff/change staff
- Additional IRB(s)
- Change signatory official
- Change IRB reporting lines
- Add research compliance officer/office

Examples of Addition or Revision of Policies and Procedures

- Add or Revise IRB procedures
- Implement or revise IRB reviewer checklists
- Revise documentation of IRB findings/actions
- Electronic tracking of protocols/Development of electronic IRB record
- Implement auditing program(s)
- Develop/Revise procedures for conducting investigations
- Add/Revise research SOPs

Examples of Revision of IRB Application Forms

- Solicit information on 111 criteria
- Solicit information on informed consent process
- Solicit information on subpart D, other subparts
- Solicit information on other vulnerable populations
Examples of Education/Training
- IRB members/staff
- Investigators/Research staff
- Institutional Officials
- All investigators at institution

Examples of Protocol/Case-Specific Changes
- Suspension of PI
- Termination of PI or other research staff
- Replace PI
- Monitoring/Auditing of PI
- Require PI to submit amendment
- Require PI to revise consent forms for specific studies
- PI to obtain additional research staff
- Termination of protocol
- Suspend/Revoke PI’s privileges to conduct HSR
- Use of data disallowed or conditions attached
- Reconsent subjects

Case Example
Case Involving Hip Pads

- Large, multicenter, randomized controlled clinical trial to study the effect of hip protection underwear on preventing hip fractures.
- Use of a type of underwear containing a single pocket and a hip pad covering either the left or right hip of enrolled nursing home residents.
- Each subject could serve as their own control: they would each have a "protected" and an "unprotected" hip.

Unexpected Development

- During the conduct of the study there was growing evidence that, for unclear reasons, subjects appeared to be falling more often to the "protected hip" side.
- This was a risk that was new, and had not been described in the initial consent form for the study.
- The subjects in the study were never informed about that new risk.

Institution Response to Development

- Efforts were made to either "slant," or completely fail to report (e.g., the data relating to the pilot study) information to the groups (the DSMB and the IRBs reviewing the study) that might have found this information highly relevant in their deliberations.
Determinations Regarding this Study

- When obtaining informed consent from subjects after the research team became sufficiently aware of the risk of increased falling on the protected side, the research team failed to disclose to subjects or their legally authorized representatives a description of reasonably foreseeable risks to the subjects.

Determinations Regarding this Study (cont’d)

- Investigators failed to report unanticipated problems, i.e., increased falling to the pocketed side and the associated risk of possible fractures, to their respective IRBs, institutional officials, the funding agency and OHRP.

Required Action

- Develop a plan for contacting research subjects (or LARS) and informing them of the risk of increased falls and hip fractures on the padded side and that the investigators should have provided them with this undisclosed risk information.
Follow-up

- Journal of the American Medical Association published their first-ever "Expression of Concern" related to OHRP’s findings that the researchers failed to notify the institutional review board and human subjects of newly identified risks of the pads.

Conclusions and Resources

Solutions to Correct/Prevent Noncompliance

- Education
- Adequate IRB staff and resources
- Adequate number of IRBs
- Adequate IRB documentation (in particular, adequate minutes of IRB meetings)
- Periodic self-assessment of institutional system for protecting human subjects
- Adequate written procedures
- Utilize the flexibility in the regulations
OHRP Education Resources

- Research Community Forums
- Speaking invitations
- OHRP website -- http://www.hhs.gov/ohrp/
- OHRP Email Box -- ohrp@hhs.gov
- Quality Assessment Program
- Training materials -- http://www.hhs.gov/ohrp/education/training/index.html

OHRP Quality Improvement (QI) Resources

- QI Consultation
- QI/Standard Operating procedures workshops

OHRP Contact Information

- OHRP website: http://www.hhs.gov/ohrp/
- OHRP telephone: 1-866-447-4777
- OHRP e-mail: ohrp@hhs.gov