Anatomy of a Site Visit: An Encounter with OHRP’s Compliance Oversight Process

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HHS protection of human subjects regulations

- 45 CFR part 46 – HHS Protection of Human Research Subjects
    - Applies to 17 other Federal Departments and Agencies
  - Subparts B (pregnant women, fetuses and neonates), C (prisoners), D (children), E (IRB registration)
Scope of OHRP jurisdiction

- HHS-conducted or -supported human subjects research

- Human subjects research covered by an applicable assurance of compliance (FWA)
  - If research institution chooses to extend FWA to all research regardless of funding source, includes privately funded research
### OHRP compliance oversight investigations – for cause

- **For-cause compliance oversight evaluations**
  - Specific written allegations/indications of noncompliance with 45 CFR part 46
  - Purpose: determine whether allegations or indications are substantiated; assess institutional compliance
  - Conducted by written evaluation or site visit

  300 since January 2000; 13 site visits; 7 suspensions/restrictions of FWA

### OHRP compliance oversight investigations – not for cause

- **Not-for-cause compliance oversight evaluations**
  - No specific allegations/indications of noncompliance
  - Purpose: assess institutional compliance
  - Conducted through written evaluation or site visit

  28 since January 2000; 15 site visits; 3 suspensions/restrictions of FWA
Factors influencing selection of institutions for not-for-cause evaluations

- Geographic location
- Large volume of HHS-funded research
- Lack of accreditation
- Institution not submitting incident reports to OHRP
- Disturbing nonspecific complaints ("This IRB is in meltdown")

Factors influencing methods of compliance oversight evaluation

- Site visit
  - Allegations or indications of systemic noncompliance
  - Nature/severity of allegations or indications
  - Inadequate corrective actions
  - Need to interview staff
- Written evaluation
  - Absence of site visit triggers
FC and NFC Site visits compared

For-Cause:
- Site visit team includes OHRP legal counsel, 2-5 OHRP staff, 2-3 outside consultants

Not-For-Cause:
- Site visit team consists of 1-2 OHRP compliance staff plus 1-2 outside consultants

Record reviews

- Prior to site visit, OHRP selects between 30 and 75 active protocols for review of entire IRB record on-site
- Records institution must have available:
  - Last 25 protocols and amendments approved by IRB under expedited review procedures
  - Protocols determined to be exempt during the past 6 months
  - Minutes for all IRB meetings for last 4 years
Site Visit Schedule

- Usually 3 days
- Can be extended if necessary
- Site visit team on a tight schedule

First day of site visit

- OHRP meets with signatory official on assurance
- OHRP conducts record review
- On-site lunch facility or delivery
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<th>Institutional/IRB preparation for OHRP site visit</th>
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<tr>
<td>– space issues</td>
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<tr>
<td>■ Ensure that there is adequate space for OHRP site visit team to conduct record review</td>
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<tr>
<td>■ Requested files should be easily accessible to OHRP team</td>
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<td>□ In room where record review happening, or</td>
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<td>□ Transportable via cart between rooms</td>
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<td>■ Make available IRB staff to retrieve additional requested items</td>
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<tr>
<td>– records/files</td>
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<tr>
<td>■ Are files in order? Easy to follow chronologically?</td>
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<td>■ Access to electronic files? Easy to follow interface between electronic files and paper files?</td>
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<td>■ Are excerpts from minutes in each IRB file? If not, are minutes available?</td>
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Day #2 of OHRP Site Visit

- Record review
- Interviews with:
  - IRB Chair
  - IRB Members
  - IRB administrative staff
  - Investigators
  - Others, as appropriate
- Tour of IRB Office space

Institutional/IRB preparation for OHRP site visit
- interviews
  - Confirm that parties to be interviewed by OHRP will be available at the specified times
    - Allow adequate time to contact investigators prior to site visit
    - Variety of investigators
  - If IRB members or investigators will be teleconferencing, ensure technological facilities/capabilities
Day #3 of OHRP Site Visit

- Exit interview with signatory official and others
  - Presentation of preliminary findings

After site visit

- OHRP will send a letter with official findings (of noncompliance) and additional questions/concerns within a few weeks
- Institution will be asked to respond with corrective action plans within about 6 weeks
- OHRP will evaluate adequacy of corrective action plans
Focus of compliance site visit

Retrospective:
- (If for-cause) review of the complaint and alleged noncompliance
- Review past identification of problems by institution/IRB and how problems were addressed

Prospective:
- Identification of problems/issues by OHRP
- Assessment of systemic protections to address future problems
- Review of institution’s policies and procedures

Most common determinations of noncompliance

- Review of OHRP determination letters 8/02-8/07
  - 235 letters to 146 institutions; 762 citations of noncompliance/concerns over deficiencies
  - Update to previous review: 10/98-6/02
Key findings -- institutions

- 91% of institutions received at least 1 citation
- Percentage of institutions cited – top 5:
  - IRB initial review (56%)
  - Informed consent documents/process (51%)
  - Continuing review (22% -- down from 45%)
  - Written IRB policies/procedures (20% -- down from 55%)
  - IRB records/minutes (16% -- down from 37%)

Key findings – categories of noncompliance/deficiencies

- Most common categories:
  - Informed consent documents/process (34%, up from 27%)
  - Initial IRB review (20% -- down from 25%)
  - Written IRB policies/procedures (15% -- up from 8%)

- Most serious noncompliance
  - Research conducted without IRB review or informed consent – 5% (43 citations at multiple institutions)
Key findings – Initial review citations

■ Criteria for IRB approval – 45 CFR 46.111 (61%, up from 32%)
■ Subpart D required findings (18%)

Key findings – Informed consent citations

■ Description of purpose, procedures, duration of research (23%)
■ Description of risks and discomforts (23%)
■ Complex language (16%)
■ Alternatives (13%)
Level of noncompliance

- Investigator
- IRB
- Senior institutional officials

OHRP compliance outcomes

- No determinations of noncompliance
- Recommendations for improvement
- Determinations of regulatory noncompliance and request for corrective action
- Restrict or condition FWA
- Suspend FWA
OHRP compliance outcomes (2)

- Recommendations to HHS officials
  - Suspension/removal of institution or investigator from specific project
  - Notification to HHS scientific peer review groups of past noncompliance prior to review of new projects
- Recommendation of debarment of institution or investigator

Case Study – UC Berkeley’s Not-for-cause site visit

- Formal Notification to IO – 5/6/2010
- Draft Agenda of visit enclosed with a Request for materials by 5/24/2010
- Date of Visit – 6/15-17/2010
- 4 OHRP staff & 2 consultants
- Note – academic semester ended 5/14/2010
Materials Requested

- Organizational Chart of Institution
- Current IRB Membership Roster
- IRB Agenda & Minutes for last 6 months
- List of all IRB Administrative staff (*name, title, duties*)
- List of active IRB approved protocols*
- IRB Policies and Procedures
- Guidelines for Investigators
- IRB Application Materials

UCB Historical Context

- UCB unchecked “the box” on FWA around 2004
- 8/2006 – UCB notified of the first of three whistle-blower complaints to OHRP
- OHRP initiated a written evaluation and investigation of UCB (*see determination letters online at OHRP website*)
Context Continued

- April 2008 – OHRP stated that UCB was compliant but to expect a site visit in the future

- As of 2/4/2010 – electronic IRB protocol submission software fully implemented for review & approval processes

- Very little DHHS funded clinical research, more public health and basic sciences

Administrative Logistics

- Preparation of initial material request
  - Print hard copies of materials on website
  - Arbitrary date when materials were “finished”
  - *Accuracy of Protocol List – reconciliation of IRB records and Sponsored Projects Office (C & G)
    - Title
    - PI Name
    - Type of IRB Review (expedited or full committee)
    - Funding Source
    - Initial IRB Approval Date
    - Date of most recent CR & approval
Second Round of Material Preparation

notified on June 1, 2010

- Additional minutes from 6/2008 – 10/2009
- Last 25 expedited amendments
- Copies of all DHHS funded protocols determined to be exempt in past 6 months
- Complete* IRB files of:
  - All Full Committee reviewed protocols - 18
  - Expedited reviewed protocols as identified – 36

Complete IRB File

label and include the following:

- Initial IRB application & any federal grant applications
- CR progress reports
- UP/AE reports
- All amendments
- All correspondence between PI & IRB
- All forms submitted to DHHS
- Any other pertinent documents
Key Code for Files

- Each section organized in specific sequence
- Color coded each section to correspond to type of document
- Huge staff undertaking to accomplish
- OPHS staff = 9 FTE at the time

Of note -

- All materials must be in hard copy
- Meeting space and availability of IRB staff for assistance
- Recruitment of PIs and IRB members for group interview sessions
- Meet and brief “new” IO about prior investigation and program improvements
Reflections

- There were errors and omissions found in files – but they were noted for OHRP
- Documents were presented “as is”
- No advance prep done with any group (PIs, IRB members or IRB Staff)
- PIs didn’t know about prior investigation but some IRB members did
- Participation was based on availability
- Presentation and discussions were candid and open

Reflections continued…

- Schedule visit during academic semester
- Request OHRP review documents electronically rather than print out everything
- Double and triple-check that all documents are ready
- Staff auditing of meetings – very helpful to identify areas for program improvement and PI education.
General Questions for PI’s

- Impression of IRB?
- Of IRB Staff?
- What type of things to report between initial & CR?
- What does IRB do with report?
- Do you report subject complaints?

PI Questions continued…

- Meaning of protocol deviations and how soon do you report them?
- Subject withdrawal classification and reporting?
- Role as faculty mentor to students?
- Are students vulnerable by nature of their role?
Questions for IRB Staff

- Workload distribution?
- Training opportunities?
- Unfortunate run-ins with PIs – how are they handed?
- Do you do outreach education?

IRB Staff questions continued…

- If you’ve worked at another IRB, what would you import here?
- PIs with terribly prepared protocols – what do you do?
- Tools or worksheets for exempt/expedited and vulnerable subject?
- Do you have enough tools at your disposal?
IRB Director’s Questions

- Institutional support & resources?
- Level of involvement of IO?
- General questions about managing UCB’s HRPP; and,
- Lots of others I don’t remember! 😊

IRB Chair Questions

- Duration of IRB service as member and Chair?
- Use of consultants in meeting?
- How do you handle the workload & responsibility?
- Describe a typical IRB meeting.
Chair Questions continued…

- What difference has electronic system made?

- Controverted issues management in meetings? And, recording such in minutes.

- Utilization of nonscientists and/or nonaffiliated?

- Training opportunities for the Chairs?

Chair Questions continued…

- IRB role in monitoring ongoing projects?

- SAE & noncompliance management and reporting?

- PI awareness of reporting UP/SAE’s or noncompliance requirements?
Exit Meeting With IO

- Other UCB Attendees
- Summary of Site Visit
  - Lingering questions asked regarding P&P’s implementation and understanding by parties.
  - Acknowledgement of great improvement in UCB’s HRPP since 2006.

Follow-up…

- UCB received written report – July 15, 2010
- Response to questions posed – due August 13
- Final, closure letter of site visit – October 12, 2010
Outcome

“As a result, our evaluation of the University of California, Berkeley (UCB) human subject protection program has been completed. We appreciate your institution’s continued commitment to the protection of human research subjects.”

No citations or determinations of noncompliance!

No specific recommendations for improvement!
Thank you for listening!

Questions?