

ORI and OHRP Compliance Oversight: Jurisdiction, Recent Cases and Initiatives

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Topics

- ORI regulatory authority and compliance oversight process
- OHRP regulatory authority and compliance oversight process
- Comparison of ORI and OHRP jurisdiction
- Lessons learned from recent ORI cases
- New OHRP compliance-related initiatives

Overview of ORI's regulation and compliance oversight process

PHS Research Misconduct Regulation

- Public Health Service Policies on Research Misconduct
 - 42 C.F.R. Part 93, effective June 16, 2005
- Purpose of the regulation is to protect the public health and safety, to protect the integrity of scientific research, and to conserve public funds.

Protecting PHS funds

- General policy states that grantee institutions have affirmative duty to protect PHS funds from misuse by ensuring the integrity of PHS-supported research.
 - Each grantee institution must submit an assurance to ORI that it will comply with the research misconduct regulation.

Definition of Research Misconduct

- Research misconduct is defined as “fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.”
 - Research misconduct does not include honest error or differences of opinion.

Institutional Responsibilities

- Institutions retain responsibility for:
 - Responding to allegations
 - Conducting an inquiry
 - Conducting an investigation and reporting it to ORI
 - Institutional appeal (if institution's procedures provide for one)

ORI's Responsibilities

- After ORI receives the final investigation report, it conducts an oversight review of the institutional findings.
- ORI may make findings of research misconduct and propose corresponding administrative actions, *e.g.*
 - Debarment (Debarring Official must concur)
 - Supervision/certification
 - Retraction/correction

OGC's Role in ORI Research Misconduct Cases

- Draft charging documents and other legal memoranda.
- Negotiate settlements
- Represent ORI in HHS administrative hearings

Respondent's Choices

- If ORI makes findings and proposes administrative actions, Respondent
 - May agree to settle the case
 - May contest the findings by requesting an administrative hearing before an administrative law judge (ALJ) within HHS Departmental Appeals Board (DAB).

HHS Administrative Hearing

- Regulation outlines the process of the administrative litigation. 42 C.F.R. Part 93, Subpart E.
- At the conclusion of the hearing process, ALJ issues a written decision.
- The ALJ sends a copy of the ruling to parties and the Assistant Secretary for Health

ASH's Decision

- ALJ's ruling is a recommended decision to the ASH.
- Within 30 days of service of the ALJ's recommended ruling, ASH must notify parties of **whether or not he intends** to review.
 - If ASH does not provide notification of review, ALJ's recommended decision becomes final HHS action, unless debarment/suspension is involved.

ASH's Decision (2)

- If ASH decides to review the ALJ's recommended decision, ASH may
 - Accept the ALJ's recommended decision
 - Modify it or reject it in whole or in part
 - after determining that the modified or rejected part is arbitrary and capricious or clearly erroneous.
- ASH's acceptance, modification or rejection becomes final HHS action, unless debarment/suspension is involved.

Final HHS action

- If the ALJ or ASH decision recommends debarment/suspension, ASH serves copy of decision to debarring official.
 - Debarring official accepts decision as findings of fact
 - Debarring official's decision is the final HHS action re: administrative actions **against the Respondent.**

Overview of OHRP authority and compliance oversight process

HHS protection of human subjects regulations

- 45 CFR part 46 – HHS Protection of Human Research Subjects
 - Subpart A is the Federal Policy for the Protection of Human Subjects – “Common Rule” (1991)
 - Applies to 16 Federal Departments and Agencies
 - Subparts B (pregnant women, fetuses and neonates), C (prisoners), D (children)

Regulatory requirements

- 3 basic requirements:
 - Assurance of compliance
 - Federalwide Assurance (FWA)
 - 45 CFR 46.103(e): OHRP may “condition or restrict approval” of assurance
 - Institutional review board (IRB) review of research
 - Informed consent

OHRP compliance oversight authority

- “The Secretary shall establish a process for the prompt and appropriate response to information provided to [OHRP] respecting incidences of violations of the rights of human subjects of research for which funds have been made available under this chapter. The process shall include procedures for the receiving of reports of such information from recipients of funds under this chapter and taking appropriate action with respect to such violations.”
42 U.S.C. 289

Scope of OHRP compliance oversight jurisdiction

- HHS-conducted or -supported human subjects research
 - Conducted, funded, or otherwise ‘supported’
- 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 sites 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

OHRP compliance oversight process

- Receipt of written allegations or indications of noncompliance; or decision to conduct not for cause evaluation
- Determine jurisdiction
- Review institution's report/documents
- Site visit?
- Determination letter

New! Revised OHRP compliance oversight procedures!

- **“OHRP’s Compliance Oversight Procedures For Evaluating Institutions.”**

<http://www.hhs.gov/ohrp/compliance/ohrpcomp.pdf>

- Supersedes October 19, 2005 version
- New clarifications:
 - OHRP’s discretion to initiate compliance evaluations
 - OHRP will coordinate with other HHS agency if shared jurisdiction

Revised OHRP compliance oversight procedures (2)

- More new clarifications:
 - The use of external expert consultants for assistance in compliance evaluations
 - OHRP will assist institutions in developing a corrective action plan
 - Complainants, as well as institutions, may request reconsideration of determinations
 - Institutions are free to implement (or not) OHRP recommendations

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

Comparison of ORI and OHRP jurisdiction

Jurisdiction

- ORI and OHRP exert jurisdiction differently:
 - ORI:
 - Jurisdiction over investigators
 - Institution conducts compliance investigation
 - OHRP:
 - Jurisdiction over institutions
 - OHRP conducts compliance investigation

Concurrent ORI and OHRP jurisdiction

- ORI and OHRP can exert concurrent jurisdiction over same set of circumstances
 - Reciprocal referral of allegations
 - Rare; when this occurs, institution typically submits reports to each, ccing the other office

ORI	OHRP
Examples of Research Misconduct Allegations	Examples of OHRP Issues
Backdating enrollment form to make patient eligible	Enrolling patient outside of time window stated in protocol, but recording true date
Fabricating a lab report required for admission to clinical trial	Failure to order lab test required to confirm patient eligibility
Intentionally reversing end point results between treatment and control patients to improve the statistics	Accidentally reversing [Ca ⁺⁺] and [K ⁺] values in report to DSMB

ORI Issues that are **NOT** OHRP Issues

Examples

- Investigator falsely reports results of patient record in a publication, but patient treatment during clinical trial is not affected.
- Investigator falsely reports the number of patients in a study, but actual patients all signed informed consent documents.

OHRP issues that are not research misconduct (if no falsification or fabrication)

- Failure to report adverse event to IRB
- Protocol deviations
- Forging physician's signature on research records
- Failing to obtain or properly document informed consent
- Breaching confidentiality of subject data

Lessons learned from recent ORI cases

Examples of falsified clinical data: ORI 2007-2009

- Substituting one subject's record for another
- Altering dates and results for required eligibility tests
- Backdating patient records to fit study protocol
- Falsifying patient's test results
- Selective suppression of results or reporting data from a sub-set of patients only

Examples of falsified clinical data: ORI 2007-2009

- Falsely reporting a larger “n” or number of subjects or falsifying outcome of statistical tests
- Selective “omitting” of data
- Using the bloods/tissues from one subject to represent two or more additional subjects
- Falsifying interview results (interviews were not conducted)

Examples of falsified clinical data: ORI 2007-2009

- Falsifying breath analyzer results (recording “0.00” when test was not conducted)
- Representing animal data as if it were from humans
- Falsifying images in presentations and published reports

Lessons Learned from ORI

Clinical Cases

- Any person involved in clinical research may be responsible for research misconduct, regardless of rank or duties on the project
- The majority of respondents in ORI clinical cases are in technical positions (not doctoral degree holders)
- Respondents may have had excessive work loads or time pressure - or pressured to increase enrollment

Lessons from ORI Clinical Cases (2)

- There are many different motivations for research misconduct:
 - financial (enrollment or accrual bonuses)
 - professional advancement (papers, grants,
 - tenure, job promotion/change)
 - personal
 - misguided altruism

Uncovering Misconduct

- Misconduct commonly discovered by:
 - Routine data audit
 - Whistleblower
 - Staff member

Cases for Discussion

- Jennifer N. Arriaga
- Judith Thomas, Ph.D.
- Juan Luis Contreras, M.D.
- Robert Fogel, M.D.

New OHRP initiatives

IRB accountability

- ANPRM on holding IRBs directly accountable (March 5, 2009)
- Issue: whether OHRP should revise 45 CFR part 46 to enable HHS to hold IRBs and IRB organizations (IORGs) directly accountable for compliance

Current Regulatory Flexibility (2)

- Designating IRBs on an FWA:
 - Internal IRB
 - External IRB
 - IRB of another institution
 - Independent or commercial IRB
 - Internal and external IRB
 - IRB composed of members from both inside and outside of the institution

Current Regulatory Flexibility

- Cooperative review arrangements for multi-site research (45 CFR 46.114):
 - Joint IRB review
 - Facilitated IRB review
 - Reliance on external IRB

Background for ANPRM on IRB accountability

- OHRP-sponsored meetings on alternative IRB models (November 2005 and November 2006)
- Conclusion: Despite existing regulatory flexibilities, some institutions remain reluctant to designate external IRBs and rely on cooperative review arrangements.

Why this conclusion?

- A key factor: OHRP currently holds institution engaged in human subjects research study accountable for noncompliance on the part of the external IRB designated on FWA to review the research

Comments Received on ANPRM

- 30 comments
- 13 comments were “joint” (e.g., Consortium of Independent Review Boards, PRIM&R, AAMC, COGR, PhRMA)
- Other entities: universities, IRBs, investigators, NGOs, private sector, individuals

Key Question Asked

Should HHS pursue regulatory change to hold IRBs directly accountable for compliance with certain requirements of 45 CFR part 46?

YES	NO	?
21	6	3

If regulatory change...

- Process:
 - Notice of proposed rulemaking seeking notice and public comment
 - OHRP review of comments
 - Final rule
- Result: New exertion of compliance oversight jurisdiction by OHRP directly over IRBs

Related Information

- **Reports from 2005 and 2006 meetings on alternative IRB models**
 - <http://www.dhhs.gov/ohrp/sachrp/documents/AltModIRB.pdf>
 - <http://www.aamc.org/research/irbreview/irbcconf06rpt.pdf>
- **March 5, 2009**
ANPRM<http://edocket.access.gpo.gov/2009/pdf/E9-4628.pdf>

Questions?