

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

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## Topics

- ORI regulatory authority and oversight review process
- OHRP regulatory authority and compliance oversight process
- Comparison of ORI and OHRP jurisdiction
- Lessons learned from recent ORI cases
- Discussion of recent OHRP publication

## **Overview of ORI's regulation and oversight review 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

- 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
    - Standard: 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.
  - ALJ's decision considered as findings of fact
  - Debarring official's decision =
    - final HHS action re: debarment 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), E (IRB registration)

## Scope of regulations

- 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

## Regulatory requirements

- 3 basic requirements:
  - Assurance of compliance
    - Federalwide Assurance (FWA)
  - 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.... The process shall include procedures for the receiving of reports of such information ... and taking appropriate action with respect to such violations.” 42 U.S.C. 289
- 45 CFR 46.103(e): OHRP may “condition or restrict approval” of assurance

## 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

307 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
- 30 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
- Inquiry letter
- Review institution's report/documents
- Site visit?
- Determination letter – on OHRP website

OHRP compliance oversight  
procedures – October 2009 revision

■ **“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

- ORI and OHRP exert jurisdiction differently:
  - ORI:
    - Jurisdiction generally exerted over investigators
      - But can take compliance action against institution
    - Institution conducts compliance investigation
  - OHRP:
    - Jurisdiction generally exerted over institutions
    - OHRP conducts compliance investigation

## Jurisdiction (2)

- OHRP: human subjects research
- ORI: broader scope of research
  
- OHRP: research conducted, funded or “supported” by HHS
- ORI: PHS-funded research

## 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

<b>ORI</b>	<b>OHRP</b>
Examples of Research Misconduct Allegations	Examples of Human Subject Protection Issues
Backdating enrollment form to make subject eligible	Enrolling subject outside of time window stated in protocol
Fabricating a lab report required for admission to clinical trial	Failure to order lab test required to confirm subject eligibility
Intentionally reversing end point results between treatment and control subjects to improve the statistics	Deliberately unblinding treatment and control subjects, contrary to the protocol, to reverse end point results

## ORI Issues that are **NOT** OHRP Issues

### Examples

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

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

- Failure to report unanticipated problem
- Protocol deviations
- Failing to obtain or properly document informed consent
- Breaching confidentiality of subject data
- Falsifying informed consent signature

Departmental Appeals Board Hearing

- ORI regulation includes process for DAB hearing
- OHRP has no formal appeals process
  - May submit request to Director for reconsideration

## **Lessons learned from recent ORI cases**

### Examples of falsified clinical data:

- Substituting one subject's record for another
- Altering dates and results for required eligibility test
  - 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
  - Selective "omitting" of data

## Examples of falsified clinical data:

- Falsely reporting a larger “n” or number of subjects or falsifying outcome of statistical tests
- Falsifying interview results (interviews were not conducted)
- Representing animal data as if it were from humans
- Falsifying images in presentations and published reports

## Lessons Learned from ORI Clinical Cases

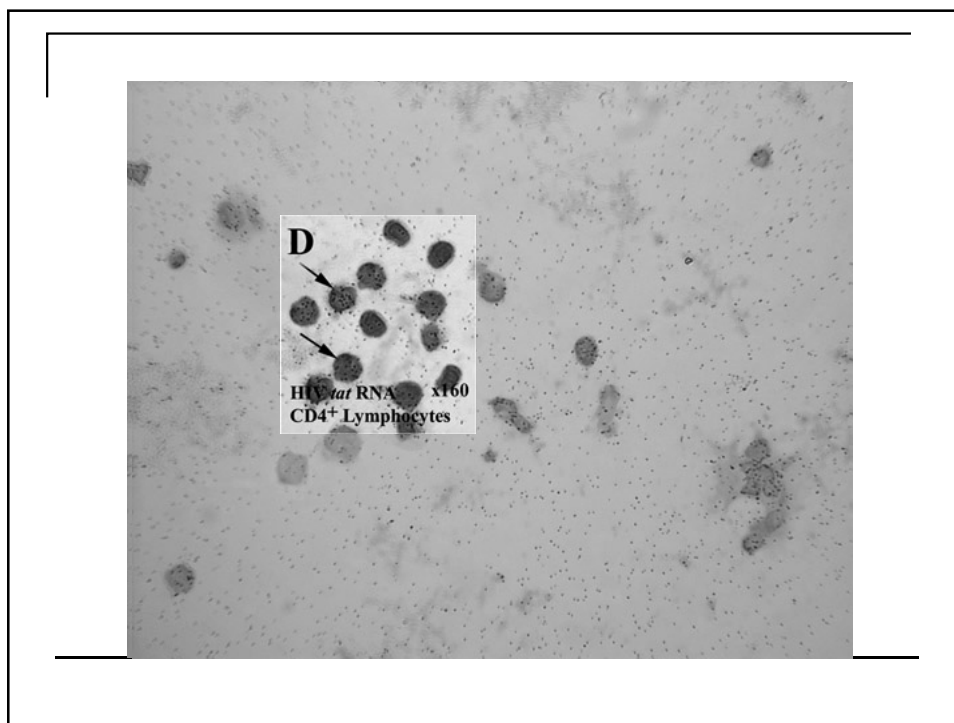
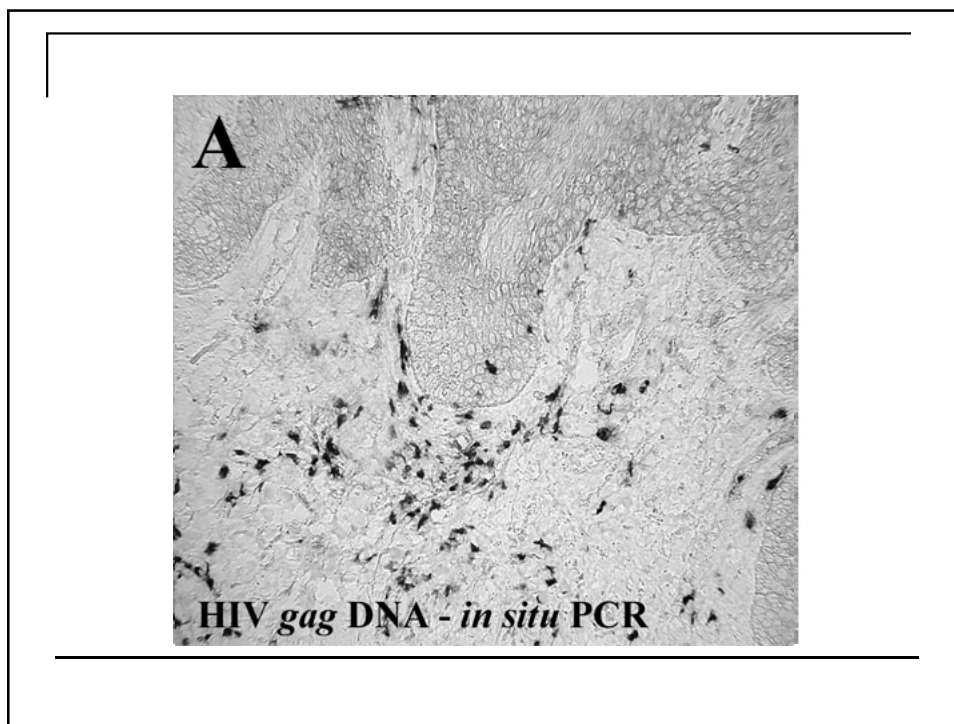
- Any person involved in clinical research may be responsible for research misconduct, regardless of rank or duties on the project

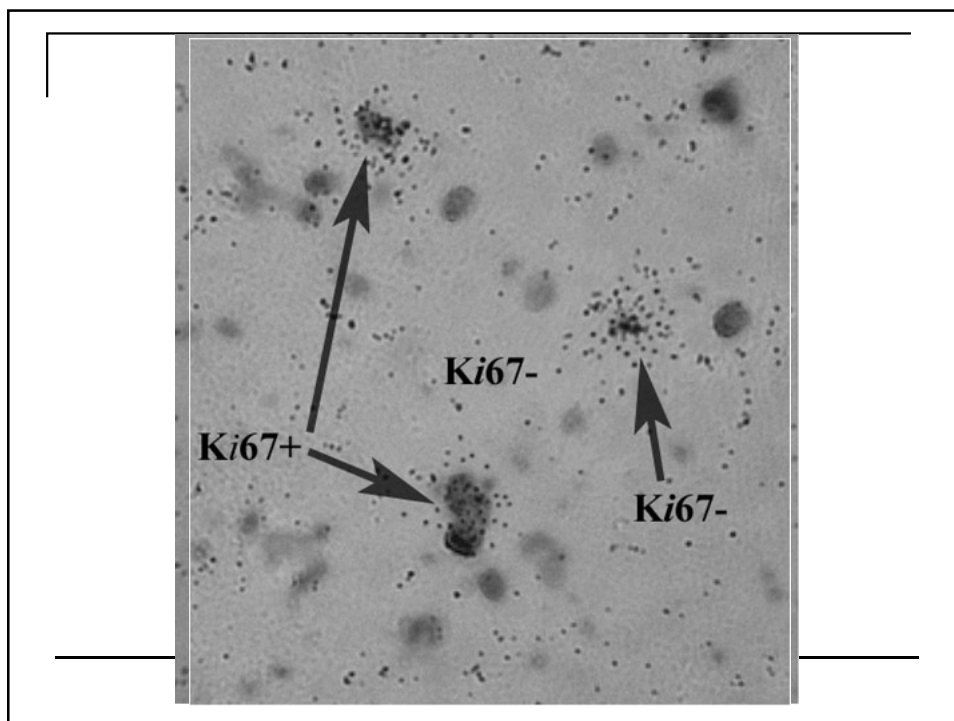
## Lessons from ORI Clinical Cases (2)

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

## Discussion of Recent ORI Case--- Falsification or Simple “Beautification”

- The next few slides show that adding or removing important elements of a figure can often be considered evidence of research misconduct.





**Recent OHRP publication**

## “OHRP Compliance Oversight Letters: An Update”

- *IRB: Ethics & Human Research* 32, no. 2 (2010):1-6
- Review of OHRP determination letters August 1, 2002 – August 31, 2007
  - 235 letters to 146 institutions; 762 citations of noncompliance/concerns over deficiencies
- Update to previous review: October 1, 1998 – June 20, 2002
  - 269 letters to 155 institutions; 1120 citations/concerns

## 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%)

## Underlying causes of noncompliance

- Inadequate education of IRB members, IRB staff, and investigators
  - Conduct of research not under IRB's control
  - Changes in research without IRB review/approval often investigator noncompliance
- Inadequate staff and resources for the IRB
- Overburdened IRBs

## Correcting/preventing noncompliance

- Education
- Adequate IRB staff/resources
- Adequate number of IRBs
- Adequate IRB documentation (in particular, IRB meeting minutes)
- Improving communication between investigators and IRB
- Periodic self-assessment of institutional system for protecting human subjects

Questions?