



# Office for Human Research Protections

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## Guidance on Reporting Incidents to OHRP

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## Overview

- Regulatory Background
- What needs to be reported?
- Corrective actions
- Time frame
- Common noncompliance reported
- OHRP processing of reports
- Institutional considerations
- Future of reporting

## Regulatory Background

IRBs are required to have and follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, OHRP, and the Department or Agency head of any unanticipated problems involving risks to subjects or others, any serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB, and any suspension or termination of IRB approval.

*45 CFR 46 103(a), 46.103(b)(5) and 46.108(a)*

## Applicability of Reporting Requirements

- Reporting of these events is required for all nonexempt human subjects research that is:
  - conducted or supported by HHS
  - conducted or supported by other federal dept/agency that has adopted the Common Rule, AND covered by an FWA determined by that agency to be appropriate for such research, or
  - covered by an FWA, regardless of funding source

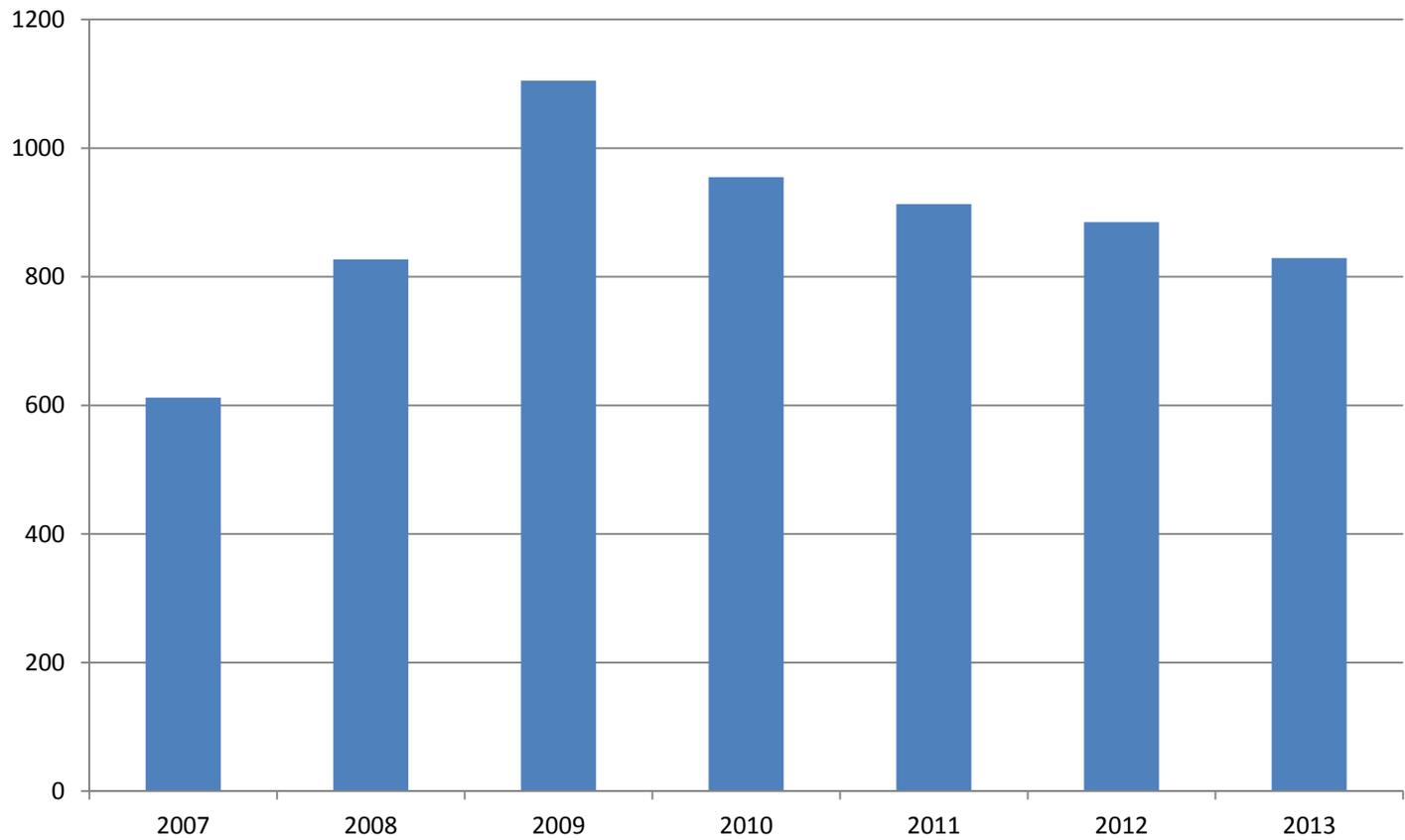


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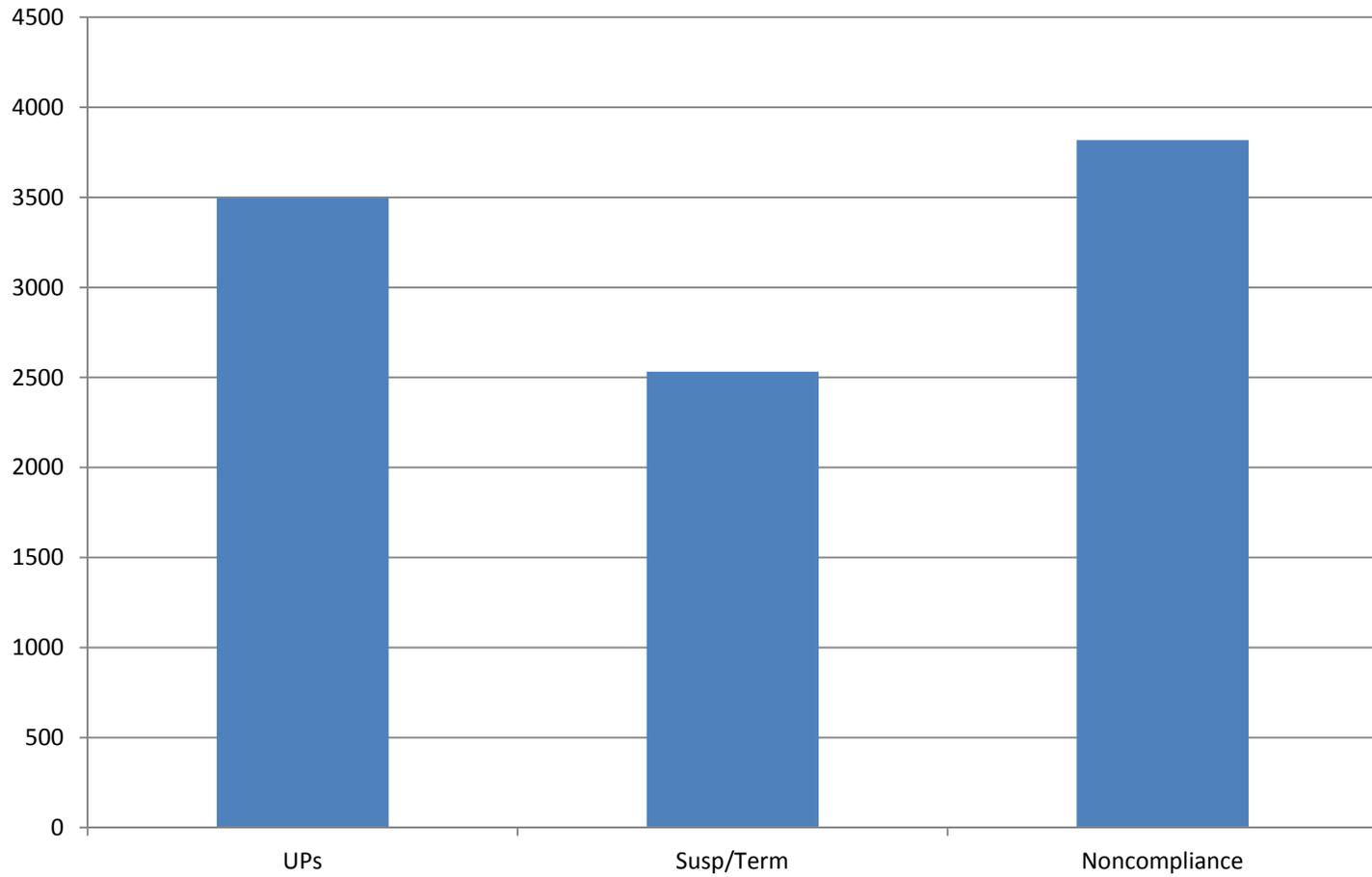
## Reporting Requirements

	IRB	IO	Funding Agency	OHRP
Unanticipated Problems	✓	✓	✓	✓
Non-compliance	✓	✓	✓	✓
Suspension/ Termination	✓	✓	✓	✓

**Total Incident Reports to OHRP per Year**



Events by Type- 2007-2013



## Noncompliance

- Any failure to follow 45 CFR part 46 (including any applicable subparts), the requirements or determinations of the IRB or the provisions of the IRB-approved research study.
- Can occur as a result of performing an act(s) that violate(s) requirements.
- Can also occur as a result of failing to act when required.

## What is Serious Non-Compliance?

- Regulations do not define “serious”
- Non-exempt human subjects research conducted without IRB review and approval or without appropriate informed consent is always serious, particularly if its greater than minimal risk
- Significant modifications to IRB-approved research without IRB approval is always serious
- Other instances determined by IRB

## What is Continuing Non-Compliance?

- Regulations do not define “continuing”
- PI or IRB makes same mistake repeatedly, particularly after IRB has informed PI of problems
- PI or IRB has multiple problems with non-compliance over a long period
- PI or IRB has problems with multiple projects
- Anything the IRB considers to be “continuing”



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# SUSPENSIONS AND TERMINATIONS OF IRB APPROVAL



## Does expiration of IRB approval need to be reported to OHRP?

- When continuing review does not occur prior to the end of the approval period, IRB approval expires automatically.
- OHRP does not consider such an expiration of IRB approval to be a suspension or termination of IRB approval and such expirations do not need to be reported to OHRP as suspensions or terminations of IRB approval
- However, if the IRB notes a pattern of non-compliance with the requirements for continuing review, that may represent serious or continuing noncompliance that needs to be reported.

## What suspensions or terminations do NOT need to be reported?

- Decision by an investigator to suspend or terminate some or all activities being conducted under an IRB-approved research protocol.
- Directives by non-IRB entities (IO, institutional internal review committees, sponsors, cooperative groups, DSMBs, or funding agencies) to suspend or terminate some or all activities being conducted under an IRB-approved research protocol.



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## UNANTICIPATED PROBLEMS

# What are Unanticipated Problem (UPs)?

- Unexpected
- Related or possibly related
- Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

Reviewing and Reporting Unanticipated Problems And Adverse Events:

<http://www.hhs.gov/ohrp/policy/advevntguid.html>

## What is “Unexpected?”

The nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of events associated with the procedures involved in the research; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) and the subject’s predisposing risk factor profile.

## What Does “Possibly Related” Mean?

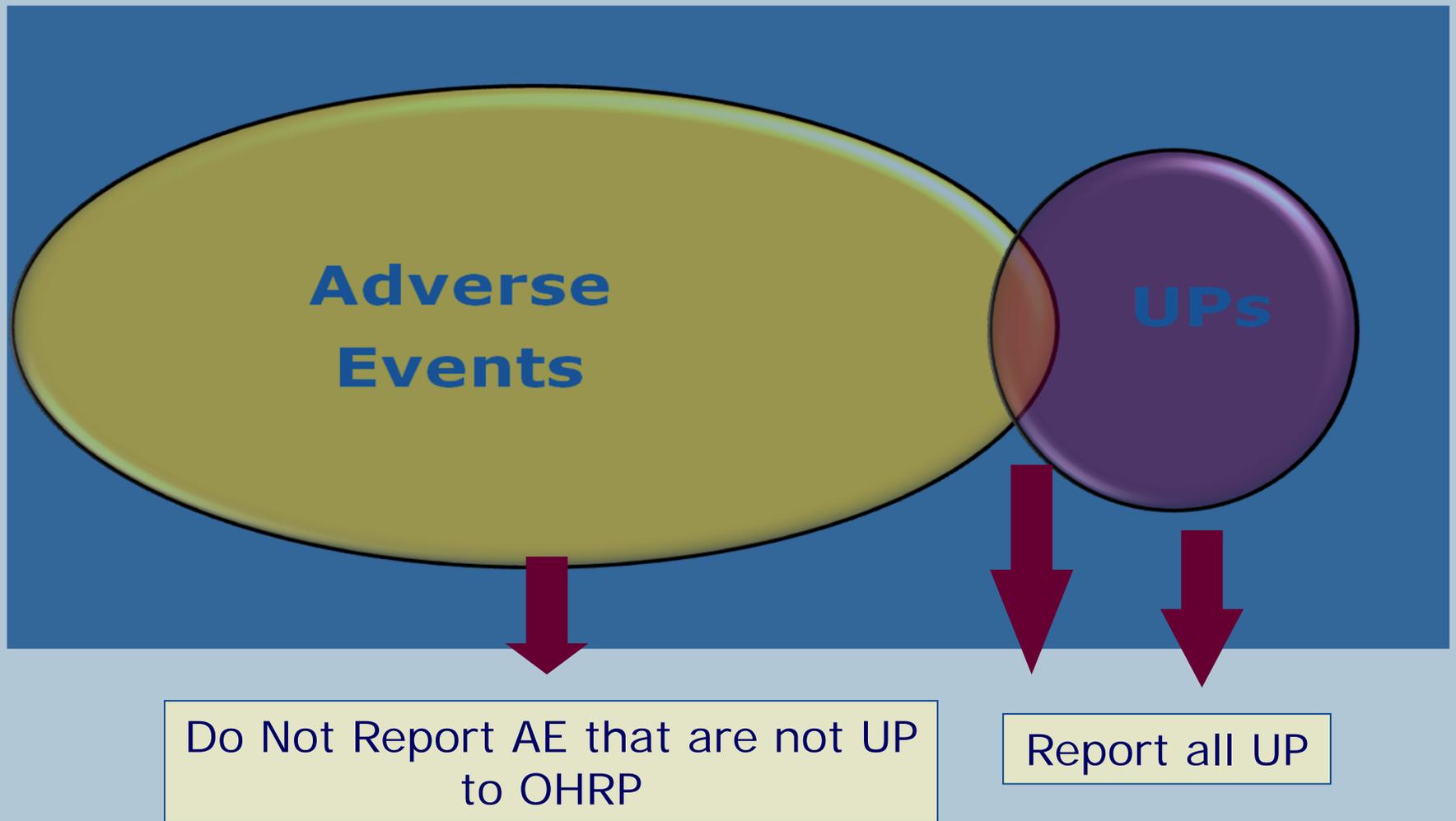
- *Possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by participation in the research.



## Does Event suggest that the research places subjects or others at greater risk?

- Is the event *serious*?
- Or does event suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized? Such events routinely warrant consideration of changes in the research protocol or informed consent process/document or other corrective actions

# Most Adverse Events are not Unanticipated Problems





## How do you determine which AEs are UPs?

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- The vast majority of AEs occurring in human subjects are not UPs.
- A small proportion of AEs are Ups: those that are unexpected, related or possibly related, & suggests greater risk of harm.
- UPs include other incidents, experiences, and outcomes that are not AEs.

## Example of UPs That Are Not AEs

- Stolen unencrypted laptop computer with individually identifiable sensitive information about illicit drug use by surveying college students.
- Large drug dosing error in which no harm came to the subjects.
- Investigational biologic administered to subjects was obtained from donors who were not appropriately screened and tested HIV or hepatitis B virus.

## Internal vs. External UPs

- For multicenter research projects, only the institution at which the subject(s) experienced an unanticipated problem must report the event to OHRP.
- Alternatively, the central monitoring entity may be designated to submit reports of unanticipated problems to OHRP.



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## **REPORT CONTENT**



## For unanticipated problems involving risks to subjects or others:

- Name of the institution conducting the research;
- Title of the research project and/or grant proposal in which the problem occurred;
- Name of the PI on the protocol;
- Number of the research project assigned by the IRB and the number of any applicable federal award(s);
- A detailed description of the problem; and
- Actions the institution is taking or plans to take to address the problem.

## For serious or continuing noncompliance:

- Name of the institution conducting the research;
- Title of the research project in which the NC occurred, or, for IRB or institutional NC, the IRB or institution;
- Name of the PI, if applicable;
- Number of the research project, if applicable;
- A detailed description of the noncompliance;
- Actions the institution is taking or plans to take to address the noncompliance.

## For suspension or termination of IRB approval:

- Name of the institution conducting the research;
- Title of the research that was susp/term;
- Name of the PI on the protocol;
- Number of the research project that was susp/term;
- A detailed description of the reason for the susp/term; and
- The actions the institution is taking or plans to take to address the susp/term.



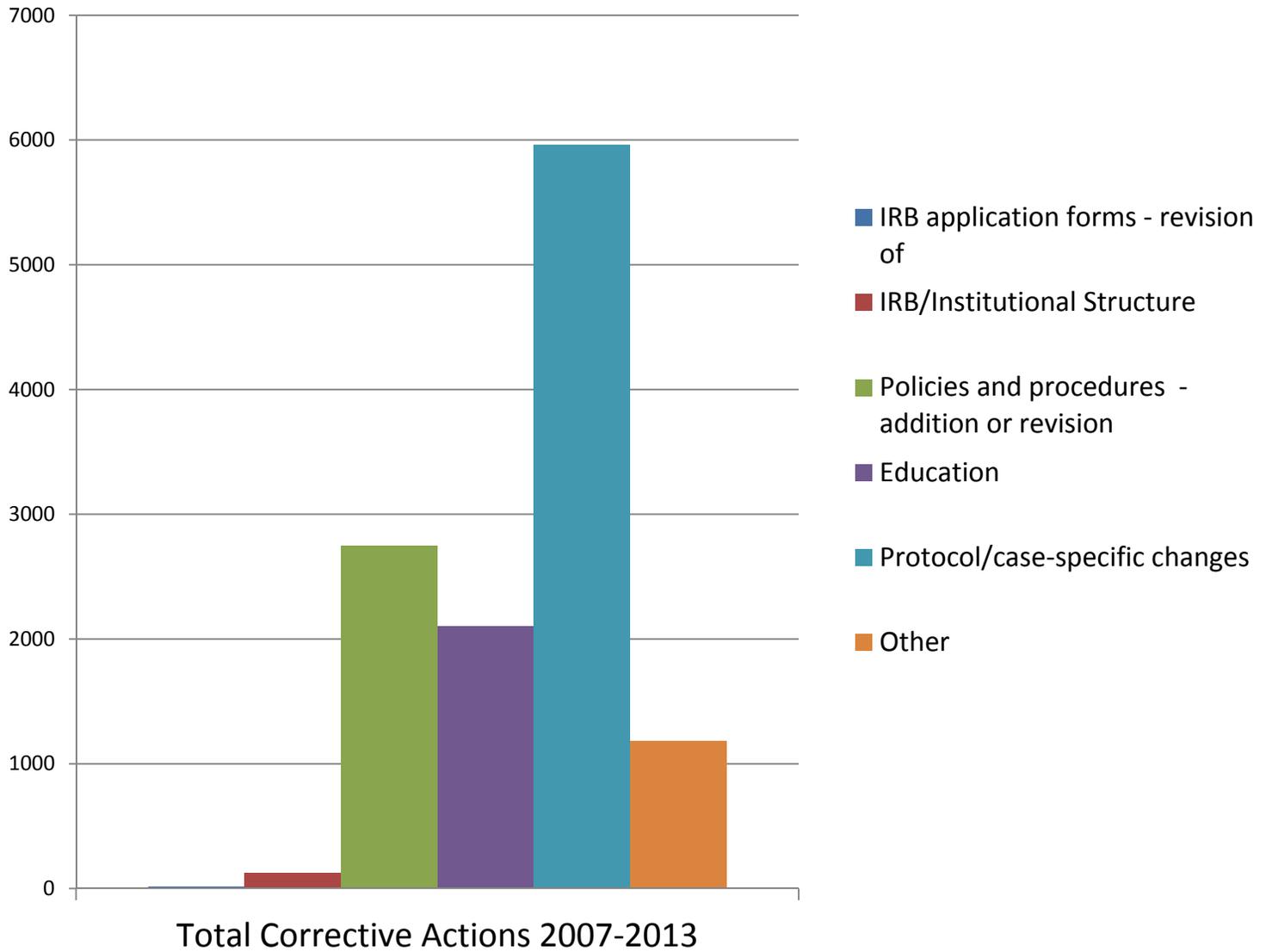
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# CORRECTIVE ACTIONS



## 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





# 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

## Example of Addition or Revision of research SOPs

- For ordering radiation doses for research DXA scans
- Only record assessments on encrypted tablets, password protected and cleaned remotely if ever lost/stolen.
- For obtaining consent from subjects, answering subject questions, and managing refusals
- Checklist of excluded medications to be reviewed at screening and study entry<sub>32</sub>

## 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 or notify subjects

## Other Corrective Actions

- Mentor/supervise researcher
- Remove subject from study
- Document event in subject's medical record
- Report event to FDA
- Send failed device back to the sponsor for evaluation
- Educate subjects about research procedures



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# TIME FRAME FOR REPORTING INCIDENTS TO OHRP



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## Time frame for reporting incidents to OHRP

Immediate

Never

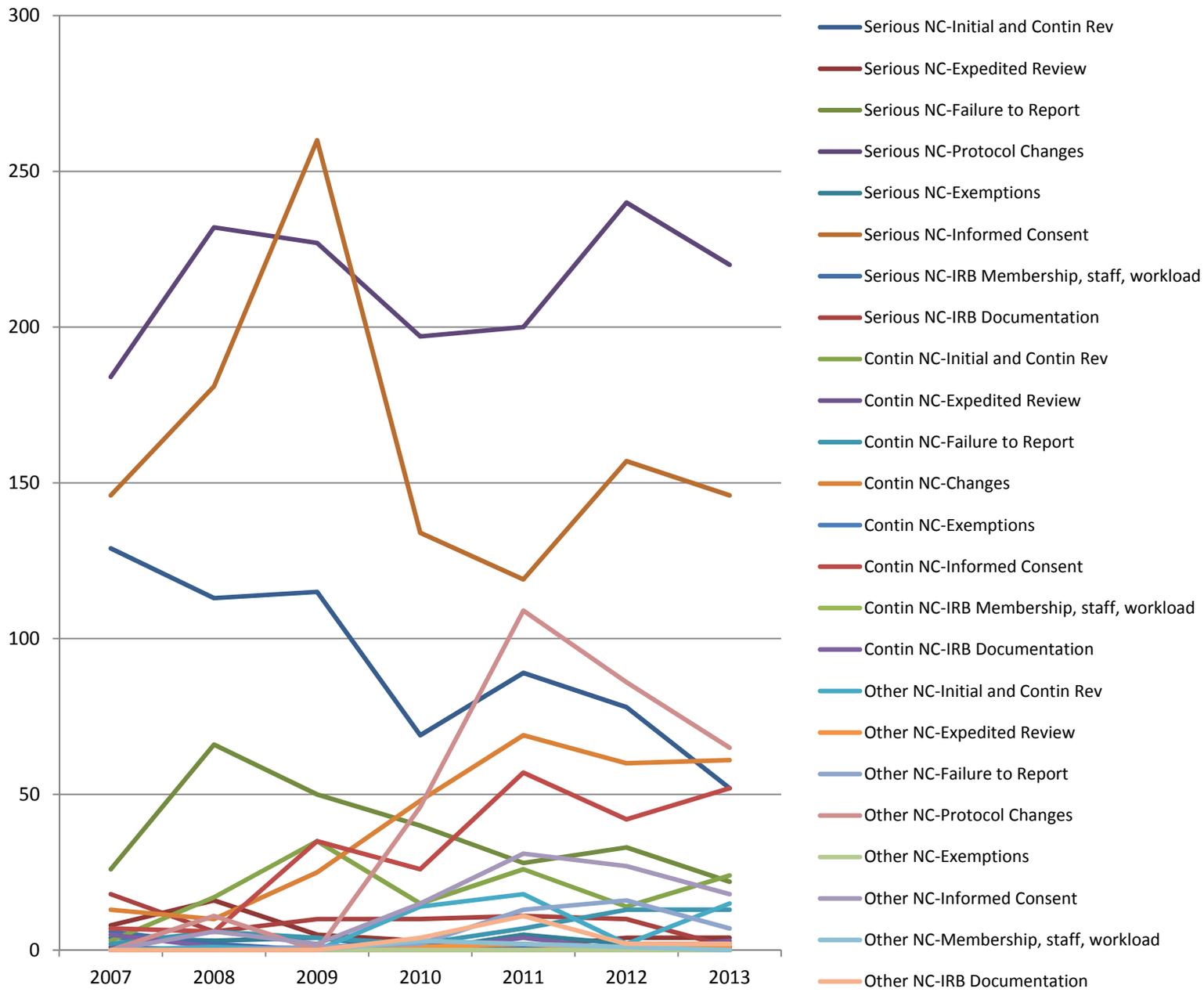


## Time frame for reporting incidents to OHRP

- The regulations at 45 CFR 46.103(a) and (b)(5) don't specify a time frame for reporting, just "promptly."
- Serious incident--report to OHRP within days.
- Less serious incident-- a few weeks
- It may be appropriate to send an initial report, with follow-up or final report by:
  - a specific date; or
  - when an investigation has been completed or a corrective action plan has been implemented.

## Common Areas of Noncompliance Reported to OHRP

- No prior review by IRB of protocol changes
- Consent process/document
- Continuing review
- Failure to report susp/term/UPs/NC
- Research conducted w/o prior IRB review
- IRB records, minutes
- Expedited review



## What Does OHRP do with Incident Reports?

- Reviews for adequacy of information and corrective actions
- Responds stating that the report was adequate, or requesting additional information
- In rare circumstances, opens a compliance oversight evaluation
- Incident reports sent to OHRP are available to the public through FOIA

## Adequacy of Corrective Actions

- OHRP looks closely at corrective actions and assesses whether or not they will help ensure that the incident will not happen again (a) with the investigator/protocol in question, and (b) with any investigator or protocol.
- Thus, OHRP recommends that corrective actions be systemic in nature

## When do incident reports result in an oversight investigation?

- Seldom
- Institution's response was grossly inadequate
- Serious problem (e.g. Death of a healthy subject)
- Previous complaint re: same incident

## Where to send incident reports

- Please send reports (PDF or Word documents preferred) to the following email address:

**[IRPT.OS@hhs.gov](mailto:IRPT.OS@hhs.gov)**

## Institutional Considerations

- Incident reports are general IRB records that need to be maintained in accordance with **§46.115**
- The IRB or signatory official is generally the agent/office that reports incidents to OHRP, but institutions are free to task others (needs to be described in written SOPs)
- The IRB is generally the agent/office that determines when an incident needs to be reported to OHRP, but institutions are free to task others



## Future of Reporting

- Encouraging all reports to be sent by email
- Possibility of a web-based system for reporting
- ANPRM calls for a standardized, streamlined set of data elements flexible enough to enable customized safety reporting and compliance with agency reporting requirements
- Prototype of Web-based, Federal-wide portal--BAER



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**for protecting  
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