Research Compliance Year In Review: 2015
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Agenda
A Year in Review and Special Topics: What Should You Know?
- FY 2015 OIG Work Plan
- Human Research Subjects Protections
- Quality vs. Research
- OMB Uniform Guidance
- NSF – OMB Uniform Guidance Implementation
- DOJ/HHS OIG Actions
- Research Misconduct
- Clinical Research Billing
- Energy & Commerce Committee Legislation
- WHO Guidance/Publications

OIG Work Plan
FY2015
OIG 2015 Work Plan Overview

• The Work Plan highlighted the priorities that the OIG’s more than 1,700 employees will have as they:
  1. Conduct audits, evaluations, investigations;
  2. Provide guidance; and
  3. Impose civil monetary penalties, assessment and administrative sanctions.

• Familiarity with the focus of the OIG is crucial. The OIG reported FY 2014:
  1. Exclusions of 4,017 individuals and entities;
  2. 975 criminal actions; and
  3. 533 civil actions.

• For FY 2014, the OIG:
  • Reported expected recoveries of over $4.9B, consisting of nearly $834.7M in audit receivables and about $4.1B in investigative receivables;
  • Identified about $15.7B in savings estimated on the basis of prior period actions supported by OIG recommendations.

OIG 2015 Work Plan

Hospitals

• Medicare costs associated with defective medical devices:
  • The OIG will review claims to identify costs resulting from additional utilization of medical services associated with defective medical devices and determine the impact of the cost on the Medicare Trust Fund.

The Food and Drug Administration

1. Inspections of generic drug manufacturers: The FDA typically inspects drug manufacturing facilities prior to generic drug approval and also conducts routine inspections of both foreign and domestic manufacturers to monitor compliance with current good manufacturing practices.

  • The OIG will describe the extent to which FDA conducts inspections of generic drug manufacturers as well as the results of such inspections and the enforcement actions taken by FDA in response to deficiencies.
2. Oversight of post marketing studies of approved drugs.
FDA has the authority to require a new drug applicant to conduct postmarketing studies of a newly approved prescription drug or biological product, at the time of approval or after approval, if FDA becomes aware of new safety information or an unexpected serious risk associated with the use of the drug.

• OIG will determine the extent to which FDA requires postmarketing studies and clinical trials of new drug applications. OIG will also assess how FDA monitors postmarketing studies and takes enforcement action against applicants that do not comply with them.

3. Drug sponsors’ compliance with clinical trial reporting requirements.
In 2007, Congress passed the FDAAA which mandated that certain clinical trials be registered and their results be reported in the clinical trial registry and reporting data bank known as ClinicalTrials.gov.

• OIG will determine the extent to which clinical trials comply with the reporting requirements set forth by the FDAAA and the way in which FDA is ensuring that these requirements are met.

1. Extramural Construction Grants:
OIG will perform reviews at facilities that received extramural construction grants to determine whether the funds were spent in accordance with Federal requirements. OIG will also determine whether appropriate bidding procedures were followed and whether expenditures were allowable under the terms of the grants and applicable Federal requirements.

• Extramural construction grants are awarded to build, renovate, or repair non-Federal biomedical and behavioral research facilities.
OIG 2015 Work Plan

Colleges' and Universities’ Compliance With Cost Principles

- **Grantee Compliance**: OIG will assess colleges’ and universities’ compliance with selected cost principles issued by OMB Uniform Guidance (previously Circular A-21, Cost Principles for Educational Institutions).

- OIG will specifically conduct reviews at selected colleges and universities on the basis of dollar value of Federal grants received and on input from HHS operating divisions.

OIG 2015 Work Plan

NIH (cont.)

2. Grants Management: NIH issues grants administration policy to the ICs and oversees ICs’ compliance with Federal regulations and HHS guidance. Each IC maintains a Grants Administration Office that implements its own procedures. Federal regulations establish uniform administrative requirements governing HHS grants.

- OIG will examine the NIH’s oversight of postaward grants administration among the 24 institutes and centers (ICs) that award extramural grants.

- OIG will also examine NIH’s oversight of each IC’s compliance with regulations, department directives, and agency policies.

OIG 2015 Work Plan

Public Health Legal Activities

Violations of select agent requirements.

HHS issued a regulation on possession, use, and transfer of select (biological) agents and toxins that applies to academic institutions; commercial manufacturing facilities; and Federal, State, and local laboratories. The rule authorizes OIG to conduct investigations and to impose civil monetary penalties against individuals or entities for violations of these requirements.

- OIG is coordinating efforts with CDC, the Federal Bureau of Investigation, and the Department of Agriculture to investigate violations of Federal requirements for the registration, storage, and transfer of select agents and toxins.
OIG 2015 Work Plan

Other HHS-Related Issues

1. HHS Efforts to Address Grantee Risks: The OIG will determine how HHS awarding agencies mitigate grantee risks and whether HHS awarding agencies receive and/or share information on grantees for which they have concerns regarding performance expectations and/or accountability requirements.

2. Prevent grant awards to individuals and entities who were suspended and/or debarred (new). To protect the Government’s interests, Federal agencies are required to make awards only to responsible sources. One way to protect the Government’s interests is through suspensions and debarments.

   • OIG will determine whether HHS operating divisions are taking adequate precautions to ensure that individuals and entities suspended or debarred are not awarded Federal grants or contracts.

Protecting Human Subjects Participating in Research

OHRP
Human Research Protections Modernizing the "Common Rule" (45 CFR 46) - What is the hold up?

• Seems to have stalled.
• Some blame the current political climate and the often divergent interests of the seventeen agencies that adhere to the rule.
• Many share a view that modernization of the Common Rule is desperately needed.
• Regulatory requirements have become so complicated that most researchers cannot fully understand or remember them, and thus cannot draw the connections between many of those requirements and the goal of protecting subjects.
• Stay tuned! But, meaningful systemic modernization of the Common Rule is not likely to occur any time soon.


Human Research Protections Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care (SOC)

• Draft issued 10/24/14; Initial comment period end date 12/23/14; extended to 1/22/15.
• Explains how to apply 45 CFR Part 46 to studies evaluating one or more SOC.
• Discusses whether risks are risks of research when one of the purposes of research is evaluation/comparison of risks associated with SOC.
• Discusses disclosing certain reasonably foreseeable risks to prospective subjects when seeking informed consent.
• Explains OHRP’s position that in general reasonably foreseeable risks of research include already identified risks of the SOC being evaluated as a purpose of the research when the risks being evaluated are different from the risks some of the subjects would be exposed to outside of the study.
• Reasonably foreseeable risks must be described to subjects when seeking informed consent in accordance with 45 CFR 46.116(a)(2).

Human Research Protections
OHRP Determination Letters

<table>
<thead>
<tr>
<th>Date</th>
<th>Institution</th>
<th>Issue(s) Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/25/14</td>
<td>Eastern Tennessee State</td>
<td>For cause investigation; research conducted without prior IRB review and approval; parental permission was either not appropriately obtained or documented for some subjects.</td>
</tr>
<tr>
<td>11/17/14</td>
<td>State University of New Jersey (Rutgers)</td>
<td>Not for cause investigation; no findings of noncompliance.</td>
</tr>
<tr>
<td>11/17/14</td>
<td>University of South Alabama</td>
<td>For cause investigation; IRB did not document waiver of IC appropriately.</td>
</tr>
<tr>
<td>12/11/14</td>
<td>University of Illinois at Chicago</td>
<td>For cause investigation; IRBs lacked sufficient information to make IRB approval determinations.</td>
</tr>
</tbody>
</table>
Human Research Protections
OHRP Investigations

Findings in recent determination letters:

• Research conducted without IRB review and/or approval
• Failure of IRB to review HHS grant applications
• Lacking sufficient information to make determinations required for approval
• Inadequate review at convened meetings
• IRB members lacking expertise to make thoughtful determinations required for approval
• Approval of research not approved by the IRB
• Contingent approval of research with substantive changes expected, yet no additional review by convened IRB

Ongoing priorities for the OHRP’s Division of Compliance Oversight

• Meetings convened without quorum (i.e., not enough members present, no non-scientist present, etc.)
• Meetings convened by IRB members with a COI
• Inadequate continuing review
• Failure to conduct continuing review at least once a year
• Inappropriate use of expedited review procedures
• Failure to advise IRB members of expedited approvals
• Expedited review conducted by someone other than an IRB member

Failure to report unanticipated problems, noncompliance, suspensions, terminations, etc. to IRB, IO, or OHRP
• Changed to researcher initiated without IRB review and approval
• Inappropriate application of exempt categories of research
• Failure of Investigator to obtain legally effective and/or to document Informed Consent or of the IRB to waive requirements
• Failure to provide a copy of the signed ICF to the subject (or their representative)
• Inadequate ICF (e.g., lacks key elements, language too complex, exculpatory language, etc.)

• IRB membership is not aligned with standards/rules/guidance
• Poor documentation (minutes, records, files, retention of information)
• Lack of appropriate written policies and SOPs
• Lack of OHRP-approved FWA
• IRB failure to determine that criteria for IRB approval are satisfied
• Failure of IRB to make required findings when reviewing research involving children or prisoners.
• Failure to notify Investigator / Institution of IRB actions
• Failure of signatory official to fulfill obligations

NIH
Human Research Protections
NIH Draft Policy – Promote Use of a Single IRB of Record for Domestic Sites of Multi-Site Studies funded by NIH

- Release date 12/3/14; Comment period end date 1/29/15.
- Purpose: Increase use of single IRB review for multisite studies funded by NIH
- Goal: Enhance & streamline IRB review process reduce inefficiencies
- Expectation: NIH funded institutions will use a single IRB of record for domestic sites of multi-site studies unless:
  - Designated single IRB can not meet the needs of specific populations; or
  - Local IRB review required by federal, tribal or state laws/regulations.
- The funding NIH Institute or Center will have final authority for approving the selected single IRB
- Use of the designated single IRB will be a term and condition of award.
- If the agreed-upon single IRB is a fee-based IRB, costs included in Notice of Award as a direct cost.

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FDA

New Draft guidance on informed consent form

- July 2014 – FDA released draft guidance on informed consent, potentially replacing its 17-year old guidance
- New guidance reflects an emphasis on the informed consent process, rather than just the consent document
- "FDA believes that obtaining a subject’s oral or written informed consent is only part of the consent process. Informed consent involves providing a potential subject with adequate information to allow for an informed decision about participation in the clinical investigation, facilitating the potential subject’s comprehension of the information, providing adequate opportunity for the potential subject to ask questions and to consider whether to participate, obtaining the potential subject’s voluntary agreement to participate, and continuing to provide information as the clinical investigation progresses or as the subject or situation requires. To be effective, the process must provide sufficient opportunity for the subject to consider."
Human Research Protections
New Draft guidance on informed consent form

• Emphasized topics:
  • Discussion about non-English speakers in research - the prior guidance required that translations be ‘understandable.’ The FDA emphasizes that understandable means the language and its reading level should be appropriate for a non-English speaker.
  • Complexity of consent form –
    • “Consent forms that are long, complex, legalistic, and have a high reading level may overwhelm potential subjects and may inhibit reading of the full document and understanding of the relevant information.”
  • The IRB should ensure that technical and scientific concepts and terms are explained so that the anticipated subject population can understand all provided information.

New topics introduced:
• Financial Relationships and Interests
  • Consider including information about the source of funding and funding arrangements for the conduct and review of the clinical investigation
  • Avoid having individuals present during the consent process when a potential or actual conflict of interest could influence the tone, presentation, or type of information presented during the consent process

• Recruitment of Study Subjects
  • IRB must review all recruitment material (including advertisements), as this is part of consent process

• Alternative Methods of obtaining Informed Consent
  • Discusses newer technologies and the potential to use them in the consent process. The guidance provides examples of when the consenting process could include something other than an in-person interview

New topics (continued)
• Impaired Consent Capacity
  • IRBs and investigators should carefully consider whether the inclusion in research of individuals who lack consent capacity is ethically appropriate and scientifically necessary
  • New guidance on assessing consent capacity

• Sponsor’s Role in Multisite Studies
  • Updated guidance discusses what a research sponsor’s role in the consent process can be

• Assent in Children
  • New guidance to present the agency’s concerns over the complex and sensitive task of ensuring a child’s assent and parents’ consent when children are involved in clinical research
### Human Research Protections
#### FDA Warning Letters - Clinical Investigators

<table>
<thead>
<tr>
<th>Date</th>
<th>Investigator</th>
<th>Summary Summary</th>
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<tbody>
<tr>
<td>07/14/14</td>
<td>Weiner</td>
<td>• Investigation not conducted according to investigation plan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Failed to maintain adequate and accurate case histories</td>
</tr>
<tr>
<td>07/17/14</td>
<td>Alshahi</td>
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<td></td>
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<td>• Failed to maintain adequate and accurate case histories</td>
</tr>
<tr>
<td>08/12/14</td>
<td>Wise</td>
<td>• Failed to maintain records for requisite period of time</td>
</tr>
<tr>
<td>09/02/14</td>
<td>Asa</td>
<td>• Investigation not conducted according to investigation plan</td>
</tr>
<tr>
<td>09/25/14</td>
<td>Calenoff</td>
<td>• Failed to retain records for requisite period of time</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>10/09/14</td>
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</table>

### Quality vs. Research

- Activities that do vs. do not meet the regulatory definition of research involving human subjects or a clinical investigation involving human subjects
  - Activities not meeting these definitions do not require submission to the IRB
  - Activities meeting these definitions do require submission to the IRB
  - Failure to obtain IRB approval of applicable research is a violation of federal regulation, HIPAA regulation, and most likely the policies of your institution.

### Overview
HHS & FDA

Regulations are not harmonized

HHS
Research
Human Subject

FDA
Clinical Investigation
Human Subject

HHS Definition of Research

Research is a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge

45 CFR 46.102(d)

When evaluating a project it is useful to think of the research definition as a requirement for two key elements:

1. The project involves a systematic investigation

2. The design—meaning goal, purpose, or intent—of the investigation is to develop or contribute to generalizable knowledge
Systematic Investigation

- Most often characteristic of both research and non-research projects
  - Public health practice, QI, QA are examples of non-research activities that may utilize statistical analysis and other scientific methods to collect and analyze data

Contribution to Generalizable Knowledge

Generalizable knowledge: knowledge related to health that can be applied to populations outside of the population that is being studied.

- Participants in the research may or may not benefit directly from the study, but a larger group is expected to gain from the knowledge obtained in the study

Generalizable Knowledge

- Is the project DESIGNED to contribute to generalizable knowledge?
  - What is the intent?
**Human Subject - DHHS**

*Human Subject* means a living individual about whom an investigator conducting research obtains:

1. Data through intervention or interaction with the individual, or
2. Identifiable private information

45 CFR 46.102(f)

**Intervention & Interaction**

*Intervention* includes both physical procedures by which data are gathered and manipulations of the subject or the subject's environment that are performed for research purposes

*Interaction* includes communication or interpersonal contact between the investigator and the subject

**Private Information**

*Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes. Private information must be individually identifiable
**FDA - Clinical Investigation**

*Clinical Investigation:* Any experiment that involves a test article and one or more human subjects that either is subject to requirements for prior submission to the FDA, or is not subject to the requirements for prior submission to the FDA but the results of which are intended to be submitted to, or held for inspection, by the FDA as part of an application for a research or marketing permit.

**Human Subject - FDA**

*Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

21 CFR 56.102(e)

**QI Under HIPAA**

HIPAA Section 164.501 Defines Quality Improvement:

“Conducting quality assessment and improvement activities, including outcomes evaluation and development of clinical guidelines, provided that the obtaining of generalizable knowledge is not the primary purpose of any studies resulting from such activities: population-based activities relating to improving health or reducing health care costs; protocol development, case management and care coordination, contacting of health care providers and patients with information about treatment alternatives; and related functions that do not include treatment.”
Quality Improvement

- When an activity is specifically initiated with the goal of improving the performance of institutional practice in relationship to an established standard, the activity is called QI.
- If the intent of the project is to promote “betterment” of a process of care, clinical outcome, etc., then it may be considered QI.
- If an investigator wishes to expand the findings of a QI project into a research study, IRB review will be required.

Publications related to QI activities must clearly describe the activates as such.

- Journal editors will require evidence of “IRB exemption.”
- Publications related to QI activities must clearly describe the activities as such.
- What they are really asking for is evidence that the IRB has made a non-human research determination.

Quality Improvement

<table>
<thead>
<tr>
<th>Quality Improvement</th>
<th>Human Subject Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent</td>
<td>contribute knowledge to “generalizable” knowledge</td>
</tr>
<tr>
<td>Design</td>
<td>studies to determine whether or not the knowledge, skills, and behaviors of individuals, may result in change in institutional practice, may include comparisons of interventions in program, may involve comparisons of interventions in program</td>
</tr>
<tr>
<td>Phase of Study</td>
<td>not the specific intent that findings or the activities not intended as a part of program, however, they may influence future practice</td>
</tr>
<tr>
<td>Population</td>
<td>protects against a breach of confidentiality, reduces the probability of sample selection and ensures that sample size is not less than the population</td>
</tr>
<tr>
<td>Benefits</td>
<td>participants are required to benefit directly from the study</td>
</tr>
<tr>
<td>Dissemination of Data</td>
<td>results are reported to benefit directly benefits, if any, to individuals traditionally disadvantaged</td>
</tr>
</tbody>
</table>

QI – HSR attributes compared

- Results of non research activities may be published; publication does not automatically define generalizable knowledge.
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Human Subject Research Determination
Flow Chart

Authority to determine HSR

OHRP recommends:

- Institutions have policies that designate the individual or entity authorized to determine whether human subjects are involved in research.
- The person(s) authorized to make determination should be knowledgeable about the human subject regulations.
- The institution should ensure appropriate communication of such a policy to all investigators.
- Investigators should not be given authority to make an independent determination.

OHRP Guidance on Research Involving Coded Private Information or Biological Specimens, 2008

HSR determinations at the local level

At the local level:
- Investigators should know where they can obtain a HSR determination and when a HSR determination might be required.
- Institutions should create a systematic and transparent process to provide HSR determinations.
- Providing HSR determinations is not necessarily a function of the IRB committee.
- The person(s) authorized to make HSR determinations must be knowledgeable and provide consistent and timely determinations.
- Institutions should create a process to distribute information related to HSR determinations to the IRB, HIMs, medical records department, HIPAA privacy officer, compliance department, quality department, or other departments as they deem necessary.
OMB Uniform Guidance: Cost Principles, Audit, and Administrative Requirements for Federal Awards

OMB Uniform Guidance
BACKGROUND & CONTEXT OF NEW GUIDANCE

The OMB issued the proposed guidance in 2013 to consolidate eight separate OMB circulars, each with its own unique rules and requirements, into a single regulation governing federal grants to IHEs, non-profits, and tribes.

Reforms to Audit Requirements

Reforms to Cost Principles

Reforms to Administrative Requirements
- Updates OMB Circulars A-110, A-133, and A-89

According to the OMB, “the guidance is aimed at eliminating duplicative…language in order to clarify where policy is substantively different across types of entities, and where it is not.”

OMB Uniform Guidance
CHANGES TO EXISTING REGULATIONS

- The Uniform Guidance, which went into effect at the end of 2014 includes a combination:
  - Current Language from Existing Circulars
  - Revised Language Clarifying and Updating Current Requirements
  - New Language Adding New Requirements

- The Uniform Guidance places greater emphasis and provides a specific framework for necessary, effective institutional internal controls.

In many respects the core of federal regulations remains unchanged. However, the change itself should lead institutions to conduct an enhanced review of existing institutional policies and procedures as a result of a renewed awareness of regulations.
### Summary of New Guidance

**HIGHLIGHTS & INSTITUTIONAL IMPACT**

The updated OMB Uniform Guidance is organized into 6 subparts and touch on key research topic areas

<table>
<thead>
<tr>
<th>Functional Area</th>
<th>Final OMB Uniform Guidance</th>
<th>Institutional Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subrecipient</td>
<td>• Pass Through Entities must pass on either a negotiated or minimum 10% of MTDC indirect cost rate to subrecipients.</td>
<td>• Promote 10% MTDC minimum rate facilitates collaboration with subrecipients</td>
</tr>
<tr>
<td></td>
<td>• Clarification made limiting the review of performance and financial reports to what the pass-through entity has decided to require to meet their own requirements under the federal award.</td>
<td>• Prime awardees institutions decide what responsibilities for monitoring subrecipients, including the review of financial and programmatic reports, to meet their own requirements under federal awards.</td>
</tr>
<tr>
<td></td>
<td>• Only when findings pertain to Federal award funds does the pass-through entity have to follow up and ensure corrective action on weaknesses found.</td>
<td>• Only when findings pertain to federal funds provided to subrecipients must the pass-through entity manage corrective actions.</td>
</tr>
<tr>
<td>Direct Charging</td>
<td>• Explicit language was added to clarify that for these costs to be allowable, they must have the prior approval of the Federal awarding agency.</td>
<td>• Institutions may charge administrative and clerical salaries directly to federal awards when it is appropriate, allocable, and meets the conditions outlined in the federal guidance. The burden for justifying direct costs as allocable to an award remains with the institution.</td>
</tr>
<tr>
<td>(Admin/Clerical Salaries)</td>
<td>• Additional language was added to allow for this approval after the initial budget approval in order to allow for flexibility in implementation.</td>
<td></td>
</tr>
<tr>
<td>Direct Charging</td>
<td>• Computing devices are subject to the less burdensome administrative requirements of supplies (as opposed to equipment) if the acquisition cost is less than the lower of the capitalization level established by the non-Federal entity for financial statement purposes or $5,000, regardless of the length of its useful life.</td>
<td>• Computing devices not considered a depreciable asset by an institution’s capitalization policy may be charged and treated as supplies. However, institutions must follow the same practices for determining and documenting allocability (direct versus indirect use) when charging computing devices to sponsored awards.</td>
</tr>
<tr>
<td>(Computing Devices)</td>
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NSF PAPPG

- NSF's implementation of OMB's Uniform Guidance;
- Effective for proposals submitted or due on or after 12/26/14;
- Some Significant Changes/Clarifications to PAPPG Part I Resulting from Uniform Guidance
  - Chapter II.C.2.g.(i)(b), Administrative and Clerical Salaries & Wages Policy - Revised to reflect the conditions under which inclusion of administrative and clerical staff salaries may be appropriate on a proposal budget.
  - Chapter II.C.2.g.(ii), Fringe Benefits - Clarifies when inclusion of fringe benefits on a proposal budget are allowed.
  - Chapter II.C.2.g.(iv), Travel - Revised to state that all travel (both domestic and foreign) must now be justified. Revised definition of what constitutes domestic travel.

Some More Significant Changes/Clarifications to PAPPG Part I Resulting from Uniform Guidance

- Chapter II.C.2.g.(v), Participant Support - Clarified to reflect that any additional categories of participant support costs other than those described in 2 CFR § 200.75 must be justified in the budget justification, and such costs will be closely scrutinized by NSF.
- Chapter II.C.2.g.(vi)(a), Materials and Supplies - Includes coverage on costs of computing devices.
- Chapter II.C.2.g.(vi)(c), Consultant Services - Clarifies that costs of professional and consultant services are allowable when certain criteria are met.
NSF PAPPG

Some More Significant Changes/Clarifications to PAPPG Part I Resulting from Uniform Guidance

- Chapter II.C.2.g.(vi)(e), Subawards – Requires organizations to make a case-by-case determination regarding role of a subrecipient vs. contractor for each agreement. Also clarifies NSF's expectations regarding indirect cost rate recovery under subawards.
- Chapter II.C.2.g.(viii), Indirect Costs - Provides updated guidance on NSF's expectations regarding indirect cost rate recovery.
- Chapter III.F, NSF's Risk Management Framework and Decision to Award or Decline Proposals - Describes the NSF framework for evaluating the risks posed by proposers prior to issuance of an NSF award. Also, outlines the appeal process that a proposer may utilize if NSF declined their proposal for financial or administrative reasons.

NSF PAPPG

Some Significant Changes/Clarifications to PAPPG Part II Resulting from Uniform Guidance

- Chapter II.A.2, Grantee Notifications to NSF and Requests for NSF Approval and Exhibit II-1.
- Consolidated Listing of Program- and Cost-Related Grantee Notifications to, and Requests for
- Approval from, the National Science Foundation - Has been revised for consistency with the Uniform Guidance. There are three new requests that require NSF approval, including salaries of administrative or clerical staff, travel costs for dependents, and additional categories of participant support costs other than those described in 2 CFR § 200.75.
- Chapter II.B.2, Changes in PI/PD, co-PI/co-PD, or Person-Months Devoted to the Project - Has been revised to remove the requirement to notify NSF of the short-term absence of the PI/PD or co-PI/co-PD. Requirement has been eliminated as it goes beyond what is stipulated in the Uniform Guidance, which addresses PI disengagements of 90 days or longer.

NSF PAPPG

Some More Significant Changes/Clarifications to PAPPG Part II Resulting from Uniform Guidance

- Chapter II.B.3, Subawarding, Transferring or Contracting Out Part of an NSF Award (Subaward) – Has been modified for consistency with the Uniform Guidance terminology and guidance. If it becomes necessary to subaward, transfer or contract out part of an NSF award after a grant has been made, the grantee shall submit the documentation outlined in this section.
- Chapter II.C, Cost Sharing - Requires that awards with any mandatory cost sharing must document such cost sharing (on an annual and final basis), the Authorized Organizational Representative must certify that the amount is correct, and the cost sharing must be reported to NSF via use of NSF's electronic systems.
Some More Significant Changes/Clarifications to PAPPG Part II Resulting from Uniform Guidance

- Chapter II.D, Technical Reporting Requirements - Reflects that the "where practicable" requirement specified in 2 CFR § 200.301 is not required because the Research Performance Progress Report (RPPR) does not relate financial information to performance data.

- Chapter III.D.4, Program Income – Clarifies that registration fees collected under NSF-supported conferences are considered program income. Grantees have no obligation to NSF with respect to program income earned from license fees and royalties for copyrighted material, patents, patent applications, trademarks, and inventions produced under an award.

DOJ/HHS OIG Actions

Former Northwestern Physician To Pay $475,000 To Settle Cancer Research Grant Fraud Claims

10/30/14: A former cancer research physician at Northwestern University’s Robert H. Lurie Comprehensive Center for Cancer in Chicago pays United States $475,000 to settle claims of federal research grant fraud.

- The government contended that Dr. Bennett submitted false claims under research grants from NIH.
- The settlement covers improper claims that Dr. Bennett submitted for reimbursement from the federal grants for professional and consulting services, food, hotels, travel, conference registration fees, and other expenses that benefited Dr. Bennett, his friends, and family from Jan. 1, 2003, through Aug. 31, 2010.
Columbia University to Pay $9M to Resolve False Claims Case on AIDS Research Grants

10/28/14: Columbia University has agreed to pay $9 million to settle a civil fraud case alleging that one of its affiliated public health programs submitted false claims to the government under federal AIDS research grants.

- Columbia failed to use suitable means of verifying whether salary and wage charges for employees of its International Center for AIDS Care and Treatment Programs (ICAP) were based on actual effort under specific federal grants.
  - As a result, ICAP filed inaccurate effort reports for the grants and, for several years, mischarged for work that was not allocable to those grant agreements.
  - The principal investigators under the grants would certify the reports as correct in large batches, without inquiring about their accuracy, according to the charges.

Drug Company to Pay $2.1 Million To Resolve NIH Contract Allegations

1/7/15: Biopharmaceutical company Ansun BioPharma Inc. agreed to pay about $2 million to settle criminal and civil matters brought against it for allegedly submitting false claims on grants and a $50 million influenza contract with the National Institutes of Health.

- Ansun allegedly maximized reimbursements from the NIH by over-reporting time spent on the development of influenza drug Fludase as part of a $50 million contract.
  - Ansun also falsely reported time spent on projects covered under other NIH-funded research grants, according to the U.S. attorney’s office for the Southern District of California.
  - As part of its settlement, Ansun has agreed to pay the NIH $1.65 million. Separately, the company entered into a settlement agreement to resolve civil allegations that it violated the False Claims Act and will pay $495,000.

Federal court allows claims against Gilead to proceed

Plaintiff sued Gilead Sciences in the U.S. District Court for the Southern District of Texas, asserting that he sustained permanent heart damage as a result of participating in a clinical trial for treating hepatitis C with the pharmaceutical combination of sofosbuvir and ledipasvir.

- January 16, 2015: federal district court allowed the participant’s claims to go forward
  - Court could not determine whether plaintiff's physician was a “learned intermediary” considered responsible for conveying drug warning information in the context of a clinical trial or whether the Food and Drug Administration had “approved” the study drug combination as required by statute.
- Defense is arguing FDA approval of these warning signs protects Gilead
  - Patient must prove a safer alternative design in order to prove that the study design was unreasonably dangerous.
Recent ORI Administrative Actions

Bin Kang, Ph.D., Oklahoma Medical Research Foundation: ORI found that Dr. Kang, Postdoctoral Fellow, Immunobiology and Cancer Research Program, engaged in research misconduct (RM) by reporting falsified and/or fabricated data (Western blot gel images) in:

- Two manuscripts (an original and a revised); and
- Two grant applications submitted to NCI (an original and revised).

Dr. Kang has agreed for 3 years to:

- Have his research supervised if employed by an institution that receives or applies for U.S. Public Health Service (PHS) funding;
- Have any institution that employs Dr. Kang submit to ORI a certification that data provided by Dr. Kang is based on actual experiments and accurately reported; and
- Exclude himself from providing advisory services to PHS.

Recent ORI Administrative Actions

Dong Xiao, Ph.D., University of Pittsburgh: ORI found that Dr. Xiao, former Research Assistant Professor, Department of Urology, UP, engaged in RM in research supported by National Cancer Institute (NCI), National Institutes of Health (NIH), grant R01 CA157477. In particular, ORI found that Dr. Xiao reported falsified figures that appeared in an online paper.

Dr. Xiao has agreed for 3 years to:

- Have his research supervised if employed by an institution that receives or applies for U.S. Public Health Service (PHS) funding;
- Have any institution that employs Dr. Xiao submit to ORI a certification that data provided by Dr. Xiao is based on actual experiments and accurately reported; and
- Exclude himself from providing advisory services to PHS.
Recent ORI Administrative Actions

Bijan Ahvazi, Ph.D., National Institutes of Health:
ORI found that Dr. Bijan Ahvazi, former Director of the Laboratory of X-ray Crystallography, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIH, engaged in research misconduct in research supported by the Intramural Program at NIAMS, NIH. In particular, ORI found that Dr. Ahvazi engaged in RM by falsifying data related to or in three published papers.

- Dr. Ahvazi has agreed for 2 years to:
  - Have his PHS research supervised and notify any employer(s)/institution(s) at which he may participate in PHS-funded projects of terms of his supervision;
  - Have any institution that employs Dr. Ahvazi submit to ORI a certification that data provided by Dr. Ahvazi is based on actual experiments and accurately reported; and
  - Exclude himself from providing advisory services to PHS.

Recent ORI Administrative Actions

Kaushik Deb, Ph.D., University of Missouri-Columbia:
ORI found that Dr. Deb, former Postdoctoral Fellow, Life Sciences Center, UM, engaged in misconduct in science in research that was supported by National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), and National Center for Research Resources (NCRR). In specific, ORI found that Dr. Deb intentionally, knowingly, and recklessly fabricated and falsified panels of data/figures reported in published papers.

- ORI implemented the following administrative actions for a period of three years:
  - Dr. Deb is debarred from any contracting or subcontracting with any agency of the United States Government and from eligibility for, or involvement in, non-procurement programs of the United States Government; and
  - Dr. Deb and is prohibited from providing advisory services to PHS.

Recent ORI Administrative Actions

Dr. Igor Dzhura, Vanderbilt University:
ORI found that Dr. Dzhura, former Senior Research Associate, Department of Biomedical Engineering, VU, engaged in RM in research supported by PHS funds. Specifically, ORI found that Dr. Dzhura: (a) provided falsified and/or fabricated data to his supervisor and colleagues; (b) falsified and/or fabricated the research record of patch-clamp data; and (c) submitted and published multiple falsified and/or fabricated action potential traces and summary data in at least sixty-nine (69) images in twelve (12) different figures across seven (7) publications and three (3) grant applications by duplication and relabeling of traces, resizing, modifying, and splicing different traces; and modifying and/or duplicating bar graphs.

- Dr. Dzhura has agreed for 3 years to:
  - Exclude himself from any contracting or subcontracting with any agency of the United States Government and from eligibility or involvement in nonprocurement programs of the United States Government;
  - Exclude himself from providing advisory services to PHS; and
  - Retract or correct the affected publications.
**Recent ORI Administrative Actions**

**Jun Fu, Ph.D., University of Texas MD Anderson Cancer Center:**
ORI found that Dr. Fu, former Postdoctoral Fellow, Department of Neuro-Oncology, MDACC, engaged in RM in research supported by National Cancer Institute (NCI), National Institutes of Health (NIH), grants. Dr. Fu admitted to knowingly and intentionally falsifying a figure that appeared in a publication.

Dr. Fu has agreed for 2 years to:
- Have his research supervised if employed by an institution that receives or applies for U.S. Public Health Service (PHS) funding;
- Have any institution that employs Dr. Fu submit to ORI a certification that data provided by Dr. Fu is based on actual experiments and accurately reported; and
- Exclude himself from providing advisory services to PHS.

**Makoto Suzuki, M.D., University of Texas Southwestern Medical Center:**
ORI found that Dr. Suzuki, currently a Professor in the Department of Thoracic Surgery, Kumamoto University Hospital, Kumamoto, Japan, and formerly a Visiting Scientist in the Hamon Center for Therapeutic Oncology Research, UT Southwestern, engaged in RM in research supported by NCI. Specifically, ORI found that Dr. Suzuki knowingly, intentionally, and recklessly falsified data reported in six (6) publications relating to glyceraldehyde 3-phosphate dehydrogenase (GAPDH) loading controls and methylated/unmethylated polymerase chain reaction (PCR) in reverse transcription-PCR (RT-PCR) gel panels.

Dr. Suzuki agreed for 3 years to:
- Have his research supervised if employed by an institution that receives or applies for U.S. Public Health Service (PHS) funding;
- Have any institution that employs Dr. Suzuki submit to ORI a certification that data provided by Dr. Suzuki is based on actual experiments and accurately reported; and
- Exclude himself from providing advisory services to PHS.

**Takao Takahashi, M.D., Ph.D., University of Texas Southwestern Medical Center:**
ORI found that Dr. Takahashi, currently a faculty member in the Department of Surgical Oncology, Gifu University, Graduate School of Medicine, Gifu, Japan, and formerly a Visiting Scientist in the Hamon Center for Therapeutic Oncology Research, UT Southwestern, engaged in RM in research supported by NCI. Specifically, ORI found that Dr. Takahashi knowingly, intentionally, and recklessly falsified data reported in four (4) publications relating to glyceraldehyde 3-phosphate dehydrogenase (GAPDH) loading controls and methylated/unmethylated polymerase chain reaction (PCR) in reverse transcription-PCR (RT-PCR) gel panels.

Dr. Takahashi agreed for 3 years to:
- Have his research supervised if employed by an institution that receives or applies for U.S. Public Health Service (PHS) funding;
- Have any institution that employs Dr. Takahashi submit to ORI a certification that data provided by Dr. Takahashi is based on actual experiments and accurately reported; and
- Exclude himself from providing advisory services to PHS.
Recent ORI Administrative Actions

James P. Warne, Ph.D., University of California San Francisco:
ORI found that Dr. Warne, former Senior Scientist, Diabetes Center, UCSF School of Medicine, engaged in RM in research supported by NIDDK. ORI found that Dr. Warne engaged in RM by falsifying data that were included in two (2) publications and two (2) grant applications. Specifically, ORI found that Dr. Warne falsified data and related text by altering the experimental data to support the experimental hypothesis.

Dr. Warne agreed for 3 years to:
• Have his research supervised if employed by an institution that receives or applies for U.S. Public Health Service (PHS) funding;
• Have any institution that employs Dr. Warne submit to ORI a certification that data provided by Dr. Warne is based on actual experiments and accurately reported;
• Exclude himself from providing advisory services to PHS; and
• Request retraction or correction of papers affected by the misconduct.

Recent ORI Administrative Actions

H. Rosie Xing, Ph.D., University of Chicago:
ORI found that Dr. Xing, former Assistant Professor, UC, engaged in RM in research supported by NCI. Specifically, ORI found that Dr. Xing engaged in RM by using images that had been among a set of manipulated images produced while at another institution, which had been found to be false by that institution. ORI found that Dr. Xing falsely reported these images in a publication.

Dr. Xing has agreed for 3 years to:
• Have her research supervised if employed by an institution that receives or applies for U.S. Public Health Service (PHS) funding;
• Have any institution that employs Dr. Xing submit to ORI a certification that data provided by Dr. Xing is based on actual experiments and accurately reported; and
• Exclude herself from providing advisory services to PHS.

Recent ORI Administrative Actions

Zhihua Zou, Ph.D., Harvard Medical School and Fred Hutchinson Cancer Research Center: ORI found that Dr. Zou, former Postdoctoral Fellow, Department of Neurobiology, HMS, and former Staff Scientist, Division of Basic Sciences, FHCRC, engaged in RM in research supported by NIDCD. ORI found that Dr. Zou engaged in RM by falsifying data that were included in two publications.

Dr. Zou has agreed for 3 years:
• Have his research supervised if employed by an institution that receives or applies for PHS funding;
• Have any institution that employs Dr. Zou submit to ORI a certification that data provided by Dr. Zou is based on actual experiments and accurately reported; and
• Exclude himself from providing advisory services to PHS.
RESEARCH MISCONDUCT

RESOURCES

- ORI website: http://ori.hhs.gov/
- Statutes and Regulations
  - ORI Statutory Authority – 42 U.S.C. § 289b
  - OIG Doxument Regulations - 45 CFR Part 76
- ORI Sample Policy and Procedures for Responding to Research Misconduct Allegations
- ORI Guidelines for Institutions and Whistleblowers: Responding to Possible Retaliation Against Whistleblowers in Extramural Research
- ORI Handbook for Institutional Research Integrity Officers

Clinical Research Billing

Clinical Trial Number (August 9, 2013)

August 9, 2013 CMS Transmittal (Change Request 8401):

- Changes to Claims Processing Manual, Chapter 32
- Effective for claims with dates of service on or after January 1, 2014, it is mandatory to report a clinical trial number on claims for items/services provided in clinical trials/studies registries, or under CED* (emphasis in original)
**Clinical Trial Number (January 6, 2014)**

January 6, 2014 MLN SE1344:

- Since the release of CR 8401, the Centers for Medicare & Medicaid Services (CMS) has learned that some physicians, providers, and suppliers do not have the capability at this time to submit the clinical trial identifier number associated with trial-related claims. This article presents those physicians, providers, and suppliers with an alternative means of satisfying the CR 8401 requirements until January 1, 2015. At that time, such providers must fully comply with CR 8401.

- Beginning January 1, 2014, and continuing no later than through December 31, 2014, those above-mentioned physicians, providers, and suppliers may instead report an 8-digit, generic number of 99999999 using the instructions in CR 8401. This will allow trial-related claims to process appropriately if they are prepared according to instructions in CR 8401. (emphasis added)

- Keep in mind that trial-related claims will be returned if they do not contain either the actual clinical trial identifier number or the 8-digit generic number 99999999 - you may not leave those indicated fields blank. (emphasis added)

- Beginning January 1, 2015, without further notice, CR 8401 shall be fully implemented.
BUILDING A 21ST CENTURY CLINICAL DATA SHARING SYSTEM

SUBTITLE G—UTILIZING REAL-WORLD EVIDENCE

This provision (Section 2101) would authorize FDA to utilize real world evidence and require FDA to issue guidance on collecting such evidence.

Source: 21ST CENTURY CURES DISCUSSION DOCUMENT SUMMARY – JANUARY 27, 2015; energycommerce.house.gov

SECTION 2101. UTILIZING REAL-WORLD EVIDENCE

Chapter V of the Federal Food, Drug, and Cosmetic Act, as amended by section 1261, is further amended by:

• Establishing a program under which a sponsor may submit real-world evidence for purposes including—
  (1) to support the approval of the use of a drug for a new indication; and
  (2) to support or satisfy post-approval study requirements

REAL-WORLD EVIDENCE DEFINED:

Data about the usage, benefits, or risks of a drug derived from sources other than randomized clinical trials, including from observational studies and registries, used to establish safety or effectiveness under section 505(d)
SECTION 2101.
UTILIZING REAL-WORLD EVIDENCE

Implementation of the Real-World Evidence Program

The reports will be submitted to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate.

Secretary Reports:
Real-World Evidence Program

1. How the program under this section has been utilized by sponsors of drugs.
2. How the program under this section has impacted regulatory decision making, including "substantial evidence" determinations under section 19 505(d).
3. How the program under this section could be expanded for the use of real-world evidence for additional purposes.

SEC 2121. COVERAGE WITH EVIDENCE DEVELOPMENT FOR MEDICAL DEVICES

The provision (Section 2121), would address the long and sometimes costly process that new technology developers must go through to secure CMS coverage, while reducing seniors medical costs by allowing for Medicare beneficiaries to secure coverage from the program for products that are the subject of the clinical trial in which they participate.

Source: 21ST CENTURY CURES DISCUSSION DOCUMENT SUMMARY – JANUARY 27, 2015; energycommerce.house.gov
CED Item or Service

- Exception to the "Reasonable and Necessary Requirement"
  - New amendment would allow for coverage of medical devices that meet the definition of CED item or service
- Item or service is for coverage with evidence development if:
  (A) the item or service is furnished to individuals as part of a clinical study performed to determine whether the furnishing of such item or service improves the health outcomes of such individuals, as determined under paragraph (3); and
  (B) the furnishing of the item or service to the individual is determined by the Secretary to be reasonable and necessary to the carrying out of such clinical study.

World Health Organization (WHO) Guidance/publications

Call for Public Consultation: WHO Statement on Public Disclosure of Clinical Trial Results

October 2014: WHO asked for comment on its draft statement regarding public disclosure of clinical trial results

Draft statement summary:

- Before any clinical trial (CT) is initiated, its details are to be registered in a publicly available, free to access, searchable CT registry. The CT registry entry should be made before the first subject receives the first medical intervention in the trial.
- All CT registry sites are to be updated as necessary to include final enrollment numbers achieved, and the date of actual study completion.
Call for Public Consultation: WHO Statement on Public Disclosure of Clinical Trial Results

Draft statement summary:

- CT results are to be reported within 30 months of the study completion date. Reporting is to occur in BOTH of the following two modalities.
  - The main findings of CTs are to be submitted for publication in a peer reviewed journal within 18 months of study completion;
  - The main findings of CTs are to be published through an open access mechanism unless there is a specific reason why open access cannot be used, or otherwise made available publicly at most within 30 months of study completion.

Key outcomes are to be made publicly available by posting to the results section of the primary CT registry. Where a registry is used without a results section, the results should be posted on a free, publicly available, searchable website of the Regulatory Sponsor, Funder or Principal Investigator.

- The Trial ID or registry identifier code/number is to be included in all publications of CTs, and should be provided as part of the abstract to PubMed and other bibliographic search databases for easy linking of trial reports with CT registry site records.

Questions?
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Critical Thinking at the Critical Time ™