Advanced Research Compliance

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Research Compliance and Clinical Research

What is Compliance?

Compliance is a comprehensive program that helps institutions and their employees conduct operations and activities ethically; with the highest level of integrity, and meet legal and regulatory requirements.

Research Compliance Motivators

- Research volume and complexity are increasing
- The number of research constituents is increasing
- Broader, multiple and nontraditional collaborations
- Shift from "traditional" funding to alternate funding sources and sponsors
- Numerous areas exist for potential non-compliance
- Increasing focus on requirements/enforcement
- The risks associated with non-compliance are high
- Changes in healthcare regulation/system
- Increasing external access to information

Research Compliance Environment

Fiscal

- Award monitoring
- Cost sharing
- Cost transfers
- Direct charging practices
- Effort reporting
- Pre-authorized spending authority
- Program income
- Service and recharge centers
- Sub awardee management
- Other support

Research Conduct

- Animal subject protections
- Human subject protections
- Conflicts of interest
- Biosafety & select agents
- Environmental health & safety
- Laboratory safety
- Invention licensing, disclosure & reporting
- Scientific misconduct & research integrity
- Data and information security

Case for a Research Compliance Program

- Good business practice
- Expected as part of a comprehensive compliance program
- Enhances public trust
- Meets expectations of internal and external constituents
- Establishes institutional expectations and accountability
- Provides real time insight into current issues which facilitates identification and prevention of significant compliance issues
- Reduces negative impact of having non-compliance identified by external regulators or agencies
- Reduces/prevents civil/criminal enforcement by regulatory agencies
- Provides structure for continuous quality improvement
- Promote 'engagement' between research administration office and research community
- Helps ensure research integrity and high quality data

Characteristics of an Effective System for Research Oversight

- Proactive
- Objective
- Consistent
- Authoritative
- Autonomous
- Transparent
- Accountable

Common Contributors to Compliance Problems

- Inadequate resources
- Lack of understanding of roles and responsibilities
- Inadequate training and education
- Outdated or nonexistent policies and procedures
- Inadequate management systems (e.g., effort reporting, financial management)
- Perception that internal control systems are not necessary
- Poor communications between components

The Challenge

Develop a research compliance program that:

- Establishes a culture of conscious
- Promotes ethical conduct
- Ensures regulatory requirements are met
- Make operational sense
- Is achieved with the least burden possible

Critical Program Elements

- Leadership
- Organizational Compliance Structure
- Written Policies and Procedures
- Effective Training and Education
- Effective Lines of Communication
- Evaluation Process
- Responding to Detected Offenses
- Established Disciplinary Guidelines

OIG Work Plan FY 2016

OIG Work Plan FY2016 Overview

- The Work Plan highlights the priorities that the OIG's more than 1,700 employees will have as they:
  - Conduct audits, evaluations, investigations;
  - Provide guidance; and
  - Impose civil monetary penalties, assessment and administrative sanctions.
- Familiarity with the focus of the OIG work plan is crucial. For FY 2015, the OIG reported
  - 4,112 exclusions (individuals and entities);
  - 925 criminal actions; and
  - 682 civil actions.
- For FY 2015, the OIG
  - Reported expected recoveries of over $3B, consisting of nearly $1.13B in audit receivables and about $2.22B in investigative receivables; and
  - Identified about $20.6B in savings estimated on the basis of prior period actions supported by OIG recommendations.

OIG Work Plan FY2016

Hospitals

- Medical device credits for replaced medical devices (New)

  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.

OIG Work Plan FY2016

Prescription Drugs

- Covered uses for Medicare Part B drugs (Revised)

  OIG will review the oversight actions that CMS and its claims processing contractors take to ensure that payments for Part B drugs meet the appropriate coverage criteria. OIG will also identify challenges contractors face when making coverage decisions for drugs.

- Medicare Part D beneficiaries' exposure to inappropriate drug pairs (New)

  OIG will determine whether Medicare Part D beneficiaries are being prescribed drugs that should not be prescribed in combination with other drugs.

OIG Work Plan FY2016

Prescription Drugs

- Specialty drug pricing and reimbursement in Medicaid (New)

  OIG will determine how State Medicaid agencies (States) define specialty drugs, how much States pay for specialty drugs, how States determine payment methodologies for specialty drugs, and the differences in reimbursement amounts for these drugs among the States. Specialty pharmacies dispense prescription drugs that often require special handling or administration. These specialty drugs are often expensive and are used to treat rare conditions, such as Hepatitis C, HIV, and certain cancers. States use CMS's national average drug acquisition cost to set Medicaid pharmacy reimbursement amounts. However, this average does not include the cost of drugs sold at specialty pharmacies.

OIG Work Plan FY2016

- The Food and Drug Administration
  - Controls over networked medical devices at hospitals (New)

OIG will examine whether FDA's oversight of hospitals' networked medical devices is sufficient to effectively protect associated electronic protected health information (ePHI) and ensure beneficiary safety. Computerized medical devices, such as dialysis machines, radiology systems, and medication dispensing systems that are integrated with electronic medical records (EMRs) and the larger health network, pose a growing threat to the security and privacy of personal (or protected) health information.

OIG Work Plan FY2016

- Colleges and Universities with National Institutes of Health Grants
  - Controls Over Subcontracting of NIH Grant and Contract Work (New)

OIG will assess colleges' and universities' controls over the subcontracting of NIH grant and contract work. Specifically, OIG will determine whether colleges and universities effectively monitor the services subcontracted to other organizations and ensure that Federal funds are spent on allowable goods and services in compliance with selected cost principles and the terms and conditions of the grants and subcontracts. Cost principles for Educational Institutions at 2 CFR 220, are used in determining the allowable costs of work performed by colleges and universities under sponsored agreements.

OIG Work Plan FY2016

Public Health-Related Reviews

- Controls over the preparation and receipt of select agent shipments (New)

OIG will review controls in place at NIH and FDA that are designed to ensure shipments are made and received in accordance with regulations and related supporting laboratory guidance or instruction.

Federal regulations at *42 Code of Federal Regulations (CFR) §73.16* regulate the transfer of select agents.

OIG Work Plan FY2016

Public Health-Related Reviews

- Review of Office for Human Research Protections (OHRP) compliance evaluations to ensure human subject protection (New)

  Section 492 of the Public Health Service Act authorizes OHRP to establish a compliance oversight process to review violations of HHS regulations protecting human research subjects.

  OIG will describe the extent and scope of OHRPs' compliance evaluations from 2000 to 2014.

  OIG will explain the process of how OHRP works with relevant government entities and IRB's during its compliance evaluations, and how working with these entities enhances or constrains its capacity to conduct compliance evaluations.

OIG Work Plan FY2016

Other HHS-Related Issues

- Office for Civil Rights' oversight of the security of electronic protected health information (New)

  OIG will assess the adequacy of the Office for Civil Rights (OCR) oversight over the security of electronic protected health information (ePHI).

  Prior OIG audits reported that OCR had not assessed the risks, established priorities, or implemented controls for its HITECH Act requirement to provide for periodic audits of covered entities and business associates to ensure compliance with HITECH Act and HIPAA Rule requirements and, therefore, had limited assurance that covered entities and business associates adequately protected ePHI.

  Prior OIG audits have also summarized numerous vulnerabilities in the systems and controls to protect ePHI at selected covered entities.

Common Rule Notice of Proposed Rulemaking (NPRM)

Why Change?

- Research enterprise has changed dramatically since promulgation of Common Rule

THEN	NOW
Single Site Studies	Multi Site Studies
No internet/data	Internet/data
No Genome Sequencing	Whole Genome Sequencing

- Modernize, strengthen & make more effective the Common Rule

8 Major Changes

- Informed Consent
- Secondary Research Involving Biospecimens
- Single IRB Review
- Continuing Review
- Scope of Common Rule
- New Excluded Research Categories
- Revised Exempt Research Categories
- New Privacy Standards

Informed Consent

- Informed Consent Overview
  - Revise content and organization to facilitate better understanding;
  - Use reasonable person standard;
  - Present core information first in “core consent form” followed by less crucial information included in appendices;
  - Mandate sufficient detail in ICF;
  - Upload IRB approved clinical trial ICF on government website 60 days after recruitment closes;

Informed Consent (cont'd)

- Introduce new informed consent elements:
  - 116(a)(9): Possible future use of data stripped of identifiers;
  - 116(b)(7): Possible commercial profit;
  - 116(b)(8): Whether clinically relevant research results will be given to subjects; and
  - 116(b)(9): Option to allow re-contact.

Informed Consent (cont'd)

- Introduce new waiver of documentation requirements

Can waive obtaining subject's signature if:

- Subjects are members of a distinct community in which signing forms is not the norm;
- Research involves no more than minimal risk; and
- Alternative mechanisms for documenting consent is obtained.

Informed Consent (cont'd)

- Eliminate need for recruitment waiver
  - IRB no longer needs to waive informed consent prior to gathering information for recruitment purposes so long as data will be protected
  - Harmonized with FDA rules

Secondary Research Involving Bio-specimens

- Currently: Secondary research involving de-identified bio-specimens does not require IRB review or informed consent because not “human subjects research”
- Human subjects research – research involving living individuals about whom the investigator obtains:
  - » Data through intervention or interaction with the individual or
  - » Identifiable private information.

Secondary Research Involving Bio-specimens (cont’d)

- NPRM: Modifies definition of human subject to include all uses of bio-specimens by an investigator.
- As a result, secondary research involving bio-specimens, regardless of identifiability, requires limited IRB review and informed consent (with one exception) because now considered to be human subjects research.
  - » Exception: Secondary research use involves non-identifiable bio-specimens designed to generate information about a subject that is already known.

Secondary Research Involving Bio-specimens (cont’d)

- With this change, how obtain informed consent?
  - Currently: Include secondary research use involving bio-specimens in main study informed consent form;
  - NPRM: Stand alone government developed new broad consent form that would allow bio-specimens to be stored and used for unspecified future research
- Broad consent will cover bio-specimens acquired via:
  - Non-research activities; and
  - Research activities other than proposed study.

Secondary Research Involving Bio-specimens (cont'd)

- If broad consent is signed, both storage and use of bio-specimens (and identifiable private information) is exempt from IRB review if meets new privacy standards
  - One exception: IRB would be expected to review an institution's protocol outlining the procedures its researchers must follow to obtain broad consent

Secondary Research Involving Bio-specimens (cont'd)

- Waiver of informed consent for secondary research involving bio-specimens - more stringent;
  - Research has a compelling scientific purpose;
  - Research can not be conducted with other bio-specimens in which informed consent was/could be obtained; &
  - Individuals were not previously asked to provide consent and declined

Do New Bio-specimen Rules Affect Secondary Research Using Data?

- No. New bio-specimen rules do not apply to secondary research involving data
  - If research involves de-identified data, then not human subjects research
  - However, new rule increases ability to conduct research with identifiable data without consent assuming appropriate new privacy protections are met and notice was provided.

Conducting Secondary Research Using Data

- Currently, researchers could:
  - » Strip data of identifiers;
  - » Keep one way link to identifiers; or
  - » Waive informed consent for use of identifiable data
- NPRM, researchers can:
  - » Use the new broad consent for bio-specimen research; and
  - » If used, exempt as long as meet new privacy standards.

Single IRB Review

- Require U.S. institutions engaged in cooperative research to rely on a single IRB for research taking place in the U.S. unless:
  - » Contrary to law, e.g., FDA regulated devices; or
  - » Funding department says and documents single IRB not appropriate.
    - Funding department is responsible for choosing the IRB of record and for studies with no funding agency, the lead institution conducting the research is responsible
    - Does not take away an institution's decision to still conduct its own ethics review

Continuing Review Eliminated

- Continuing Review is eliminated for:
  - Certain exempted secondary research using information or bio-specimens;
  - Minimal risk research that qualified for expedited review; and
  - Research approved under convened board review, but at time of continuing review only involves:
    - Analyzing data (even identifiable private data) or
    - Accessing follow-up clinical data from standard of care procedures.

Continuing Review Eliminated (cont'd)

- Such research must still undergo IRB review before any proposed changes are implemented, unless meets the exception;
- Requires annual certification to IRB that research is still ongoing; and
- If IRB decides to conduct continuing review when not required under regulations, rationale must be documented.

Expand Scope of Common Rule

- Currently, the Common Rule only applies to research that is funded or conducted by one of the Common Rule agencies or to all research, regardless of funding source, if institution elects this option.
- Under the NPRM proposal, the Common Rule will apply to all clinical trials, regardless of funding source, conducted at an institution that receives federal support for non-excluded, non-exempt human subjects research.

New Excluded Research Categories

- Clarifies which activities fall within the Common Rule vs. outside the Common Rule
- Excluded categories:

Do Not Meet Research Definition	Have Non-Research Purposes	Low Risk Activities with Other Controls
Program Improvement	QA/QI	Old Exempt Category 2
Oral History, Journalism, Biography	Public Health Surveillance	Research involving collection or study of information that has or will be collected
Criminal Justice	Intelligence Surveillance	Research conducted by government agency using government-generated or government-collected data
		HIPPA regulated activities

Revised Exempt Research Categories

– Revised exempt research categories consist of:

- Existing exempt categories (unrevised), e.g., exempt category 6;
- Revised existing exempt categories, e.g., exempt category 1 & 5; and
- New categories.

Revised Exempt Research Categories (cont'd)

New exempt categories

– Certain research involving benign interventions with adults;

– Old exempt category 2 when sensitive information is collected, provided that data security and information privacy protections are followed;

– Secondary research use of identifiable private information originally collected as part of a non-research activity, where notice of possible use was given;

– Storing & maintaining bio-specimens & identifiable private information for future unspecified secondary research studies, or conducting such studies, when:
  – A soon to be developed broad consent template is used;
  – Privacy safeguards are followed; and
  – Limited IRB approval of the consent process is obtained.

Revised Exempt Research Categories (cont'd)

– Two new procedural requirements for exempt categories:

» Determinations must take place a certain way; and

» Determinations must be documented a certain way.

- A soon to be developed government created web based decision tool will assist individuals with these new procedural requirements.

New Privacy Standards

- Apply to non-exempt human subjects research & some exempt research;
- With new privacy safeguards, IRBs need not review safeguards for every protocol, unless safeguards are deemed insufficient.
- Standards can come from:
  - » New privacy standards developed by HHS;
  - » HIPAA; or
  - » New rules for research conducted by federal government.

What is Next?

- Receive and analyze comments submitted in response to the NPRM;
- Issue a final rule; and
- Implement the final rule by:
  - » 3 years following publication of final rule for single IRB of record & bio-specimen research changes; and
  - » No later than 1 year following publication of final rule for all other changes.

ICH GCP Proposed Changes

Why Change?

- Amendments were needed to:
  - Encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and data integrity; and
  - Update electronic records and essential documents standards intended to increase clinical trial quality and efficiency.

Major Changes

- ALCOA"C" source document requirements
- Sponsor focused risk-based trial quality management guidance, including risk based monitoring (RBM)
- Investigator oversight responsibilities
- Sponsor oversight responsibilities regarding vendors
- Sponsor responsibilities regarding serious breaches
- Computer validation, electronic record and essential document standards

Source: http://www.therqa.com/assets/js/tiny_mce/plugins/filemanager/files/Publications/Online_Articles/ICH_E6_rewritten_to_reflect_recent_GCP_findings.pdf

Human Research Subjects Protections Enforcement Actions

FDA and OHRP Enforcement Actions

Type of Action	FDA	OHRP
Inspections ■Conducted by FDA in FY2015 ■Opened by OHRP in FY2015	Awaiting FY 2015 BIMO Stats	8
Noncompliance Letters Issued ■FDA Warning Letters (OAIs) ■OHRP Determination Letters (Noting Noncompliance)	CI – 4 IRB – 0	FWA Holding Institution - 3
CI Disqualifications	4	0
Debarments (CIs/IRBs/Sponsors)	0	0
IRB Restrictions or Suspensions	1	0

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FDA Common Findings - CIs

- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping, e.g., case histories, CFRs, etc.
- Inadequate accountability for investigational product
- Inadequate communication with IRB
- Inadequate subject protection – failure to report AEs and informed consent issues

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FDA Common Findings – IRBs

- Inadequate initial and/or continuing review
- Inadequate SOPs
- Inadequate membership rosters
- Inadequate IRB meeting minutes
- Quorum issues
- Subpart D issues
- Inadequate communication with CI/institution
- For device studies – lack of or incorrect SR/NSR determinations

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OHRP

OHRP Announcements

November 25, 2015 - 30-Day Extension of the Comment Period on Proposal to Improve Rules Protecting Human Research Subjects

- NPRM requests comment on proposed revisions to modernize, strengthen, and make more effective the Federal Policy for the Protection of Human Subjects that was promulgated as a Common Rule in 1991. Since the NPRM was published on September 8, 2015 (80 FR 53933) with a public comment end date of December 7, 2015, participating federal departments and agencies have received requests to extend the comment period to allow sufficient time for a full review of the NPRM. The new comment period deadline is January 6, 2016.

Source: http://www.hhs.gov/ohrp/newsroom/announcements/2015.html

OHRP Announcements

November 5, 2015 - OHRP and FDA Announce the Availability of a Draft Guidance Document on IRB Meeting Minutes

- OHRP and FDA have issued draft guidance titled, “Minutes of Institutional Review Board (IRB) Meetings: Guidance for Institutions and IRBs.” This draft guidance was prepared jointly by OHRP and FDA and is intended for institutions and IRBs responsible for oversight of human subject research under HHS and FDA regulations.

Source: http://www.hhs.gov/ohrp/newsroom/announcements/2015.html

Human Research Protections
OHRP Determination Letters

Date	Institution	Issue(s) Summary
10/13/15 (FY2016)	San Diego State University	▪ Investigator used an informed consent document from another study that did not adequately address the elements of informed consent required by HHS regulations. ▪ Investigator implemented changes to the research screening tool and screening script without prior IRB review and approval, in contravention of HHS regulations at 45 CFR 46.103(b)(4)(iii).
5/7/15	Howard University	▪ When reviewing chart review studies, IRB lacked sufficient information to make the determinations required for approval of research. ▪ When reviewing research involving children, IRB did not always make the required findings at 45 CFR §§ 46.404-409. ▪ IRB failed to meet the quorum requirement for certain IRB meetings; ▪ IRB meeting minutes were lacking in sufficient detail; ▪ Institution failed to report unanticipated problems involving risks to subjects or others, and suspensions or terminations of IRB approval. ▪ Institution applied an exemption to research activities that were non-exempt human subjects research. ▪ IRB approvals lapsed before continuing review took place in several research studies.

Human Research Protections
OHRP Determination Letters

Date	Institution	Issue(s) Summary
12/01/14	University of Illinois at Chicago	▪ The institutional review boards (IRBs) sometimes lacked sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. ▪ Research had been approved upon initial review by expedited review under category 9, even though that category is only applicable for continuing review of research.
11/07/14	University of South Alabama	▪ IRB failed to appropriately document its decision to waive consent in compliance with the provisions specified under Health and Human Services (HHS) regulations at 45 CFR Part 46.

Human Research Protections
OHRP Investigations

Ongoing priorities for the OHRP's Division of Compliance Oversight

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
- Meetings convened without quorum (i.e., not enough members present, no non-scientist present, etc.)
- Meeting 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

Human Research Protections
OHRP Investigations

Ongoing priorities for the OHRP's Division of Compliance Oversight

Findings in determination letters (cont.)

- 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

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FDA

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Human Research Protections
FDA Warning Letters – Clinical Investigators

Date	Investigator	Issues(s) Summary
7/13/15	Bernard A. Michlin, M.D.	▪ Investigator failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. ➢ Failed to perform screening safety laboratory tests and urine drug screens according to the protocol.
6/29/15	Howard M. Gross, M.D.	▪ Investigator failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. ➢ Enrollment of subjects who did not meet eligibility criteria; ➢ Failure to adhere to protocol requirements for study drug administration; ➢ Failure to perform protocol-required laboratory tests. ▪ Failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)]. ➢ Failed to maintain adequate and accurate case histories with respect to study records containing an adverse event requiring inpatient hospitalization.

Human Research Protections
FDA Warning Letters – Clinical Investigators

Date	Investigator	Issues(s) Summary
5/4/15	Binh Bui Nguyen, M.D.	▪ Investigator failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. ➢ Failed to perform protocol-required assessments; ➢ Failed to adhere to treatment modification rules for renal disorders; ➢ Failed to report SAEs to the sponsor within protocol-specified time frames.
10/9/14	Louise A. Taber, M.D.	▪ Investigator failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. ▪ Investigator failed to maintain adequate and accurate case histories

DOJ/HHS OIG Actions

University of Florida Agrees to Pay $19.875 Million to Settle False Claims Act Allegations

- 11/20/15: The University of Florida (UF) agreed to pay the United States $19.875 million to settle allegations that the university improperly charged HHS for salary and administrative costs on hundreds of federal grants.
  - The settlement resolves the alleged misuse of grant funds awarded by HHS to UF between 2005 and December 2010. It was alleged that the university overcharged hundreds of grants for the salary costs of its employees, where it did not have documentation to support the level of effort claimed on the grants for those employees.
  - U.S. also contended that UF charged some grants for administrative costs for equipment and supplies when those items should not have been directly charged to the grants under federal regulations.
  - Lastly, UF allegedly inflated costs charged to HHS grants awarded at its Jacksonville campus for services performed by an affiliated entity, Jacksonville Healthcare Inc.

Source: http://www.justice.gov/opa/pr

$390 Million Civil Fraud Settlement Against Novartis Pharmaceuticals For Kickback Scheme

- 11/20/15: FBI and HHS OIG announced a $390M settlement against Novartis in a civil fraud lawsuit based on claims that Novartis gave kickbacks to specialty pharmacies in return for recommending two of its drugs, Exjade and Myfortic.
  - Government alleged that Novartis gave kickbacks in the form of patient referrals and rebates to induce pharmacies to recommend Exjade refills, while also giving rebate contracts to specialty pharmacies to induce the pharmacies to recommend to doctors that they switch patients to Myfortic from competitor drugs.
  - Novartis agreed to:
    - (i) pay $370M to resolve federal and state false claims act claims,
    - (ii) forfeit $20 million as proceeds from the scheme under the federal civil forfeiture statute,
    - (iii) make extensive admissions concerning its relationship with specialty pharmacies, and
    - (iv) amend its corporate integrity agreement with HHS OIG to subject Novartis's specialty pharmacy relationships to independent review and extend the term of that agreement by five years.

Source: http://oig.hhs.gov/fraud/enforcement/criminal/index.asp

Cancer Treatment And Research Clinic Pleads Guilty To Misdemeanor Information

- 4/7/15: Cache Valley Cancer Treatment and Research Clinic, a cancer treatment clinic located in Logan, UT, pled guilty in U.S. District Court to receipt of misbranded drugs and delivery for sale.
  - Over a two year period, the Clinic received "misbranded" prescription oncology drugs from Quality Specialty Products (QSP) in Canada, a foreign drug establishment. The drugs were not listed annually with the FDA as being manufactured for commercial distribution in the United States.
  - Approximately one-half of these prescription drugs were reimbursed by federal government programs, including Medicare, Tricare, and the Federal Employees Health Benefits Program. The Clinic resolved a civil claim with the Department of Justice brought on behalf of the FDA and federal government programs.
  - U.S. Magistrate Judge imposed a six-month term of probation, and the Clinic must also must pay a fine of $175,000 and a forfeiture money judgment of $775,000.

Source: http://oig.hhs.gov/fraud/enforcement/criminal/index.asp

Medtronic Inc. to Pay $2.8 Million to Resolve False Claims Act Allegations

- 2/6/15: Medical device manufacturer Medtronic Inc. agreed to pay the United States $2.8M to resolve allegations under the False Claims Act that Medtronic caused certain physicians to submit false claims to federal health care programs for a medical procedure known as "SubQ stimulation".
  - It was alleged that from 2007 through 2011, Medtronic knowingly caused dozens of physicians located throughout more than 20 states to submit claims to Medicare and Tricare for investigational medical procedures known as SubQ stimulation that were not reimbursable.
  - The safety and efficacy of SubQ stimulation had not been established as required by the FDA, however the company promoted this procedure by arranging Medtronic-sponsored "on-site training programs" regarding the use of Medtronic spinal cord stimulation devices for SubQ stimulation.
  - The civil settlement resolves a lawsuit filed under the whistleblower provision of the False Claims Act, which permits private parties to file suit on behalf of the United States for false claims and obtain a portion of the government's recovery. The lawsuit was filed by Jason Nickell, who formerly worked as a Medtronic sales representative. Nickell will receive $602,000.

Source: http://oig.hhs.gov/fraud/enforcement/criminal/index.asp

Ansun Biopharma to Pay More Than $2 Million for Overbilling the U.S.

- 1/7/15: Ansun Biopharma entered into criminal and civil settlements with the Department of Justice that will require it to make approximately $2M in payments to the United States. These settlements resolve a criminal and related civil investigation against Ansun for submitting false and fraudulent claims on grants and a contract with NIH.
  - According to the settlements, Ansun's former CEO directed its then- Vice President of Finance and Administration to fabricate timesheets for company employees to maximize billing on NIH grants and their Fludase Contract, regardless of the actual number of employee hours spent on the contract or the other NIH-funded grants.
  - Ansun was charged with a violation of Title 18, United States Code, Section 1031, executing a scheme to defraud the United States in a contract valued more than $1 million. As part of its settlement, Ansun agreed to pay the NIH $1,654,600.00.
  - Separately, Ansun entered into a settlement to resolve civil allegations that it violated the False Claims Act by submitting invoices that falsely stated the number and category of hours worked by employees in connection with several research grants and a contract funded by NIH. Ansun agreed to settle the civil matter with a payment of $495,000 to the United States.

Source: http://oig.hhs.gov/fraud/enforcement/criminal/index.asp

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Research Misconduct

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Recent ORI Administrative Actions

- **David Anderson, University of Oregon, Eugene:** ORI found that Mr. Anderson engaged in RM in research supported by National Institute of Mental Health (NIMH), NIH, grants R01 MH087214 and R01 MH077105 by falsifying and/or fabricating data in four (4) publications and knowingly falsifying data by removing outlier values or replacing outliers with mean values to produce results that conform to predictions.

- **Mr. Anderson has agreed for 3 years to:**
  - Have his research supervised, and shall not participate in any PHS-supported research until such a supervision plan is submitted to and approved by ORI;
  - Any institution employing him shall submit to ORI a certification that data provided by Mr. Anderson is based on actual experiments and accurately reported;
  - Excluded from providing advisory services to PHS;
  - Assist UOE in advising publishers of the need to retract or correct.

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Recent ORI Administrative Actions

- **Julia Bitzegeio, Ph.D., Aaron Diamond AIDS Research Center:** ORI found that Dr. Julia Bitzegeio, former Postdoctoral Fellow, ADARC, engaged in RM in research supported by National Institute of Allergy and Infectious Diseases (NIAID), NIH, grants R01 AI078788, R21 AI093255, and R37 AI064003 by falsifying and/or fabricating data that were included in one (1) publication, two (2) unfunded grant applications, and one (1) unpublished manuscript.

- **Dr. Bitzegeio has agreed for 3 years to:**
  - Have her research supervised, and shall not participate in any PHS-supported research until such a supervision plan is submitted to and approved by ORI;
  - Any institution employing her shall submit to ORI a certification that data provided by Dr. Bitzegeio is based on actual experiments and accurately reported;
  - Excluded from providing advisory services to PHS;

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Recent ORI Administrative Actions

- **Brandi Blaylock, Wake Forest School of Medicine:** ORI found that Ms. Brandi Blaylock, former Graduate Student, WFSOM, engaged in RM in research supported by National Institute of Drug Abuse (NIDA), NIH, grant R01 DA012460 and Ruth L. Kirschstein National Research Service Award (NRSA) K31 DA033106 by falsifying and/or fabricating data reported in two poster presentations, several laboratory meetings, and progress reports.

- **Ms. Blaylock has agreed for 3 years to:**
  - Have her research supervised, and shall not participate in any PHS-supported research until such a supervision plan is submitted to and approved by ORI;
  - Any institution employing her shall submit to ORI a certification that data provided by Ms. Blaylock is based on actual experiments and accurately reported;
  - Excluded from providing advisory services to PHS

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Recent ORI Administrative Actions

- **Ryousuke Fujita, Ph.D., Columbia University:** ORI found that Dr. Ryousuke Fujita, former Postdoctoral Scientist, Taub Institute for the Aging Brain, Departments of Pathology and Cell Biology and Neurology, CU Medical Center, engaged in RM in research supported by National Institute of Neurological Disorders and Stroke (NINDS), NIH, grant R01 NS064433 and National Institute of Aging (NIA), NIH, grant R01 AG042317 by inflating sample numbers and data, fabricating numbers for data sets, manipulating analysis, mislabeling images, and manipulating and reusing Western blot images.

- **Dr. Fujita has agreed for 3 years to:**
  - Excluded 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;
  - Excluded from providing advisory services to PHS.

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Recent ORI Administrative Actions

- **Anil Potti, M.D., Duke University School of Medicine:** ORI found that Dr. Anil Potti, former Associate Professor of Medicine, Duke, engaged in RM in research supported by National Heart, Lung, and Blood Institute (NHLBI), NIH, grant R01 HL072208 and NCI, NIH, grants R01 CA136530, R01 CA131049, K12 CA100639, R01 CA106520, and U54 CA112952 by including false research data in published papers, a submitted manuscript, a grant application, and the research record.
- **Dr. Potti has agreed for 5 years to:**
  - Have his research supervised, and shall not participate in any PHS-supported research until such a supervision plan is submitted to and approved by ORI;
  - Any institution employing him shall submit to ORI a certification that data provided by Dr. Potti is based on actual experiments and accurately reported;
  - Excluded from providing advisory services to PHS.

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Recent ORI Administrative Actions

- **Venkata J. Reddy, University of Minnesota:** ORI found that Mr. Venkata J. Reddy, former Graduate Student, Department of Chemistry, UMN, engaged in RM in research that was included in grant application R01 GM095559-01A1, submitted to the National Institute of General Medical Sciences (NIGMS), NIH. In specific, ORI found:
  - Respondent intentionally and knowingly engaged in research misconduct by falsifying and/or fabricating data that was provided to his mentor to include in grant application.
- **Dr. Reddy has agreed for 5 years to:**
  - Dr. Reddy has been debarred by the Federal agency with joint jurisdiction;
  - Excluded from providing advisory services to PHS.

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Research Misconduct Resources

- **ORI website: http://ori.hhs.gov/**
- **Statutes and Regulations**
  - ORI Statutory Authority - 42 U.S.C. § 289b
  - Public Health Service (PHS) Policies on Research Misconduct – 42 CFR Part 93 – June 2005
  - HHS Debarment Regulations - 45 CFR Part 76
  - Federal Whistleblower Protection Act of 1989 - 5 U.S.C. § 1201
  - Freedom of Information Regulation - 45 CFR Part 5
  - Public Health Service Records Related to Inquiries and Investigations of Scientific Misconduct, HHS/OASH/ORI. 74 Fed. Reg. 44847 (2009)
- **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**

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Energy & Commerce Committee Legislation

To accelerate the discovery, development, and delivery of 21st century cures

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21ST CENTURY CURES ACT

- **Removes barriers to increase research collaboration**

  Breaks down existing barriers to sharing and analyzing the growing amount of health data generated in research and clinical settings, while protecting patient privacy

- **Incorporates patient perspectives into the drug development and regulatory review process**

  Strengthens FDA's ability to take into account the direct experiences of patients with particular diseases and conditions and the effect of their current therapies and use the data to modify and improve potential treatments

- **Measures success and identifies diseases earlier through personalized medicine**

  Advances personalized medicine by making sure patients can be treated based on their unique characteristics at the appropriate time

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21ST CENTURY CURES ACT

- **Modernizes clinical trials**

  Allows for greater use of patient generated registries to speed recruitment of study participants

  Allows researchers to screen study participants in advance to determine if genetic predisposition makes them better candidates for targeted therapies

  Clears the way to use new, creative and adaptive trial designs and modern statistical and data tools, while reducing existing, duplicative or unnecessary paperwork requirements

- **Removes regulatory uncertainty for the development of new medical applications**

  Provides more certainty for medical application developers, clarifying the regulatory path moving forward and speeding the creation and deployment of innovative health tools

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21ST CENTURY CURES ACT

- **Provides new incentives for the development of drugs for rare diseases**

Creates new economic incentives for the development of therapies for serious and life threatening conditions, including rare diseases

- **Creates a new coordinating mechanism for the biomedical ecosystem to find faster cures**

Creates an innovation infrastructure that removes obstacles that slow connections between scientific discovery, drug and device development and how such therapies are approved and made available to patients

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21ST CENTURY CURES ACT

- **Invests in 21st century science and next generation investigators**

Creates a dedicated and offset funding stream of $1.75B per year for 5 years for the NIH and $110M per year for 5 years for FDA that will allow congressional appropriators to invest additional resources without impacting current budget caps

Includes provision to invest more resources in the next generation of scientists for the next generation of drugs

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World Health Organizations (WHO) Guidance/Publications

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WHO Statement on Public Disclosure of Clinical Trial Results

- **April 14, 2015: WHO published a new statement on the public disclosure of clinical trial (CT) results that:**
  - Defines reporting timeframes;
  - Calls for results-reporting of older, but still unpublished trials; and
  - Outlines steps to improve linkages between CT registry entries and published results.

WHO Statement on Public Disclosure of Clinical Trial Results

- **Reiteration of WHO position on clinical trial registry sites**
  - Before a CT is initiated (at any phase), its details are to be registered in a publicly available, free to access, searchable CT registry.
  - Registry entry should be made before the first subject receives first CT medical intervention.
- **Updating clinical trial registry entries**
  - All CT registry sites are to be updated as necessary to include final enrollment numbers achieved and date of actual study completion.
  - If CTs are terminated, status is updated to note the termination, and to report the numbers enrolled up to the point of termination.

WHO Statement on Public Disclosure of Clinical Trial Results

- **Reporting timeframes for CTs**
  - CT results are to be reported according to the timeframes outlined below. Reporting is to occur in BOTH of the following two modalities:
  - Main findings of CTs submitted for publication in a peer reviewed journal are to be reported within 12 months of study completion and 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 24 months of study completion.
  - Key outcomes are to be made publicly available within 12 months of study completion by posting to the results section of the primary CT registry. Where a registry is used without a results database, results should be posted on a free-to-access, publicly available, searchable institutional website of the Regulatory Sponsor, Funder or Principal Investigator.

WHO Statement on Public Disclosure of Clinical Trial Results

- **Reporting of past clinical trials results**
  - Unreported CTs conducted in the past are to be disclosed in a publicly available, free to access, searchable CT registry. In addition it is desirable that unreported clinical trials are published in a peer reviewed journal.
- **Inclusion of Trial ID in clinical trial publication**
  - Trial ID or registry identifier code/number must 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. Bibliographic search databases such as PubMed are encouraged to make Trial IDs easily available by inclusion in the abstract of each clinical trial record.

SOCRA: NIH / FDA Draft Guidance Protocol Template for Phase 2 & 3 IND/IDE Applications

SOCRA: NIH / FDA Draft Guidance Protocol Template for Phase 2 & 3 IND/IDE Applications

- **March 17th, 2016: The National Institutes of Health ("NIH") and Food and Drug Administration ("FDA") issued an announcement stating**
  - Development of a template with instructional and sample text for NIH funded investigators to use in writing protocols for phase 2 or 3 clinical trials that require Investigational New Drug application (IND) or Investigational Device Exemption (IDE) applications.
  - The goal is to encourage and make it easier for investigators to prepare protocols that are consistently organized and contain all the information necessary for the clinical trial to be properly reviewed.
  - The draft template follows the International Conference on Harmonisation (ICH) E6 Good Clinical Practice.

SOCRA: NIH / FDA Draft Guidance Protocol Template for Phase 2 & 3 IND/IDE Applications

- NIH and FDA are seeking public comment on the draft template:

"We would welcome feedback from investigators, investigator-sponsors, and institutional review board members, and any other stakeholders who are involved in protocol development and review. We are particularly interested perspectives on the utility of such a template and whether the instructional and sample text is clear and readable."

- Template can be downloaded at:

http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/clinical-research-policy/clinical-trials

- Comments may be submitted at

http://grants.nih.gov/grants/rfi/rfi.cfm?ID=54

Removing Barriers to Clinical Research Act of 2016

Removing Barriers to Clinical Research Act of 2016

- **March 3rd, 2016: The House of Congress introduced a bill to amend title XVIII of the Social Security Act to ensure Medicare coverage of certain costs associated with FDA-approved clinical trials involving medical devices.**

In summary, this Bill

- Clarifies Medicare Coverage of routine services and Category B devices
- Provides the industry with welcome guidance going forward

Removing Barriers to Clinical Research Act of 2016

- **The amendment clarifies the following points:**
  - Medicare coverage for clinical trials in which a Category A or Category B medical device is involved;
  - Which "routine costs" are covered for research using either a Category A or Category B medical device;
  - Assuming there is medical necessity and the use is consistent with routine standards, Category B devices are also covered; and
  - Clinical trials automatically meet the "Category A and Category B" definitions when the trial is conducted under an Investigation Device Exemption filing.

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Clinical Research Billing (CRB)

Managing billing compliance during a research study

Rules & Operational Considerations

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CRB Risks

- Institutions must manage the following clinical research billing risks:
  - Billing for services that are already paid by the sponsor (double billing)
  - Billing for services promised free in the informed consent
  - Billing for services that are for research-purposes only
  - Billing for services that are part of a non-qualifying clinical trial

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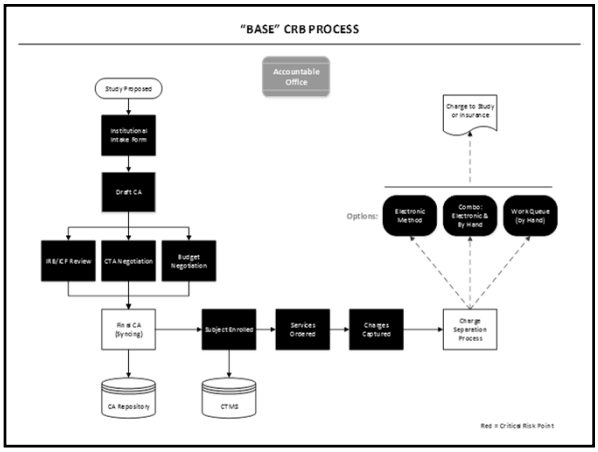
Managing Risks

- Coordination of information
- Proper hand-offs between departments
- Integration of Coverage Analyses under central office
- Decisions made about how to direct charges
- Do you know your process?



Role of Funding Documents

Parts of a Clinical Trial Agreement

- Many parts of a Clinical Trial Agreement can have impact on billing
- Possible parts of the contract:
  - Main body of contract (typical legal clauses)
  - Protocol incorporated as an exhibit
  - "Sponsorship budget" incorporated as an exhibit as details of compensation arrangement

Role of Funding Documents

Interpreting CTA Language

- Plain meaning of words used if no definitions exist
- If CTA words are ambiguous, is there any ancillary evidence of intention of parties?
- If words are clear that payment goes for clinical services, then service identified as not billable in MCA
- Difficult terms:
  - Pays for “research services”, then MCA assumes CTA not paying for medically necessary clinical care
  - Pays for “protocol services”, then MCA assumes CTA is paying for scheduled services

Role of Funding Documents

Examples of language

“[Payment is] inclusive of procedures required by the Protocol and in accordance with the Payment Schedule attached ....as Exhibit A.“

“[Payment is] inclusive of procedures, overhead and other indirect costs"

Role of Funding Documents

Examples of language

“Neither Institution nor Principal Investigator shall bill any third party for any Study Drug or other items or services furnished by [Sponsor] in connection with the Study, or any services provided to patients in connection with the Study for which payment is made as part of the Study including, but not limited to, Laboratory, ECG evaluations, CT scans, Bone Marrow Aspirate/Biopsy and MRI.”

Role of Funding Documents

Examples of language

"[Sponsor] shall also provide financial support in an amount not to exceed [$X] for the Study, which shall be provided as follows….[schedule for timing of payments]"

Role of Informed Consent Form

OHRP Rules

- 45 CFR 46.116: "The information that is given to the subject or the representative shall be in language understandable to the subject or the representative."
- Standard Practice for IRBs: Language in 6th to 8th grade reading level

Role of Informed Consent Form

Parts of ICF Affecting MCAs

- Description of potential benefits
- "Added costs" section

Role of Informed Consent Form

Interpreting the ICF

- ICF interpreted for MCA from the perspective of the patient
- Plain meaning of the words used in the informed consent
- Promises made to research patients should be kept
- If lines could contradict each other, then tried to reconcile the lines

Role of Informed Consent Form

"Added Costs" Section

- Regulation:
  - 45 CFR 46.116(b)(3): "Any additional costs to the subject that may result from participation in the research"
- If the "added costs" section of the informed consent form states that an item or service will not be charged to the patient, then the MCA identifies the service as not billable

Role of Informed Consent Form

Examples of language

"Tests and examinations done to be sure [the patient qualifies] for the study . . . . are performed at no cost to [the patient]."

"The sponsor…will provide [Study Drug] and all protocol-specified procedures associated with the study to you at no cost…You or your health insurance plan will have to pay for your continuing medical care and/or hospitalization that are considered "standard of care"".

Role of Informed Consent Form

Examples of language

"You or your health plan must provide payment for hospital, clinic, and other medical costs that are considered routine care for patients with your disease. The sponsor of the study…will provide the study drugs at no cost to you. Medical testing done for the purposes of the study will also be provided to you at no charge."

Role of Informed Consent Form

Examples of language

"You or your third party payor must provide payments for hospital, clinic or other medical costs related to this study. Third party payors may or may not cover costs related to experimental or research treatments. You will receive no payment for taking part in this study."

Questions?