Identifying and Mitigating Organizational Risks in Research Compliance: A Case Example

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1

Key Learning Objectives

1. List the key components of a research compliance program
2. Identify the warning signs of research compliance concerns
3. Discuss ways in which an organization mitigated compliance risks

2

Polling Question 1: Tell Us About You - Where Do You Work?

- Hospital/Physician Clinic/Other Healthcare Provider
- University/Academic Medical Center
- Industry (e.g., pharmaceutical company)
- Consultant
- Other

3

Polling Question 2: How Long Have You Been Working in this Industry?

- Less than 1 year
- Between 1-5 years
- Between 6-10 years
- Between 11-19 years
- More than 20 years

4

Key Components of a Research Compliance Program

5

Elements of a Compliance Program

- Development and distribution of written standards/policies and procedures
- Designating a compliance officer
- Education and training programs for all employees
- Deploying open lines of communication including a process to receive complaints

https://oig.hhs.gov/documents/compliance-guidance/795/PHS_Research_Awards_Draft_CPG.pdf

6

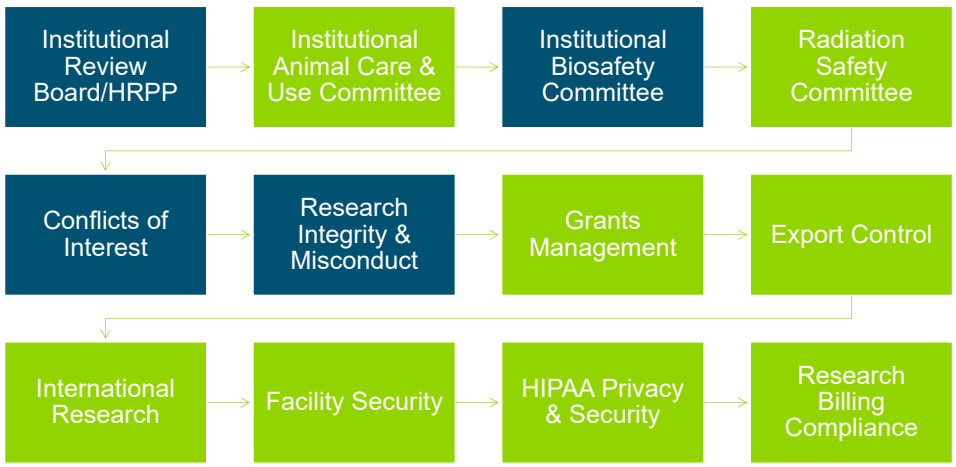
Elements of a Compliance Program

- Clearly defining roles and responsibilities and ensuring effective assignment of oversight responsibilities
- Conducting audits or other risk evaluation techniques to monitor compliance
- Enforcement of disciplinary action for violations of policies/procedures/ regulations
- Developing policies and procedures for the investigation of instances of non-compliance

https://oig.hhs.gov/documents/compliance-guidance/795/PHS_Research_Awards_Draft_CPG.pdf

7

Components of Research Compliance Programs



8

Human Subjects Research

9

Polling Question 3: How Many Clinical Trials are Currently Active at Your Institution?

- 1-50
- 51-100
- 101-200
- 201-500
- 501+
- Unknown

10

Federal Regulations

- Federal Regulations for the Protection of Human Subjects
  - » 45 CFR 46 – Common Rule
  - » Governs research sponsored or funded by any of the signatory federal agencies
- FDA Regulations
  - » 21 CFR 50 – Protection of Human Subjects
  - » 21 CFR 56 – Institutional Review Boards
  - » Governs research involving FDA regulated products (drugs, devices, biologics, foods)
- HIPAA Regulations
  - 45 CFR 160 and 164

11

HHS/Common Rule Regulations (45 CFR 46)

Research

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

Human Subject

Human subject means a **living** individual **about whom** an investigator (whether professional or student) conducting research

(1) Obtains info or specimens through intervention or interactions, and uses studies or analyzes;

(2) Obtains, uses, studies or analyzes ID info or specimens.

12

Review Categories

Not Human Subjects Research	Exempt	Expedited	Full Board
• De-identified or coded data or specimens	• Minimal risk to participants • Meets defined regulatory criteria • Contains provisions for limited IRB review	• Minimal risk to participants • Meets criteria for one of the categories • Only one reviewer (IRB member) needed; designated by the Chair	• Greater than minimal risk • Requires review by the convened committee

13

Criteria for IRB Approval of Research (111 Criteria)

Risks to subjects are minimized	**Risks to subjects are reasonable in relation to anticipated benefits**	**Selection of subjects is equitable**	**Informed consent is sought**
Informed consent is documented (or waived)	**Adequate provisions for monitoring the data**	**Provisions to protect the privacy of subjects & maintain the confidentiality of data**	**Appropriate safeguards for special populations**

14

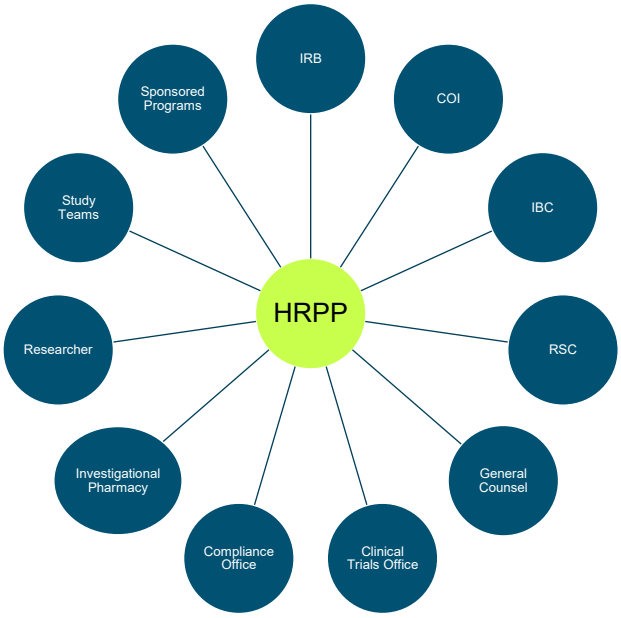
Research Involving Vulnerable Populations

Prisoners	Pregnant women	Children
Non-English-speaking subjects	Members of a group with a hierarchical structure	Patients with incurable diseases
Persons institutionalized or in nursing homes	Socio-economically disadvantaged persons	Patients in emergency situations
Ethnic minority groups	Homeless persons, nomads or refugees	Individuals incapable of giving consent
Students	Employees	

15

Human Research Protection Program

It's Not Just the IRB!



16

ClinicalTrials.gov

- Database of all applicable clinical trials (ACT) involving human participants
- The website is maintained by the National Library of Medicine at the National Institutes for Health
- Defines a clinical trial as a research study in which human volunteers are assigned to interventions (for example, a medical product, behavior, or procedure) based on a protocol (or plan) and are then evaluated for effects on **biomedical** or **health outcomes**
- Civil monetary penalties and grant funding actions for individuals who fail to comply with the requirements of the rule
- FDAAA 801 and the Final Rule

17

What Should Compliance Officers Know?

There are regulations that guide the review and conduct of research involving human participants	
The number of trials taking place at your institution	
Who are the key stakeholders at your institution	Vice President for Research Director of the Clinical Trials Office Director of the IRB/HRPP
The profile of your portfolio	What types of trials does your institution conduct: Phase 1-4 Funding source for trials

18

What Compliance Officers Should Do

- Ask to review your institutions IRB/HRPP policies and procedures
  - Ensure they are current and reflective of the regulations
- Ask to sit in on an IRB meeting
  - What is being discussed – both quality & quantity of the discussion are important
- Ensure your institution has sufficient operational policies and procedures for the conduct of research
- Assess your institution's trials on ClinicalTrials.gov
- Meet colleagues and **ask for help** when needed!

19

Common Findings

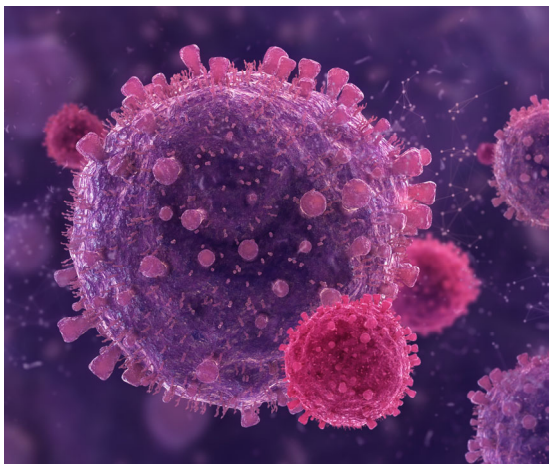
- Policies and procedures are not sufficient
- Minutes of IRB meetings are not sufficient
- IRBs are not following policies and procedures
- Administrative staff reviewing and approving items when not an IRB member and not designated to approve by expedited procedures
- Selection of the wrong review categories (exempt/expedited)
- Lack of understanding & improper processing of items by the Privacy Board (or IRB acting as Privacy Board)

20

Institutional Biosafety Committee

21

Bio – What?



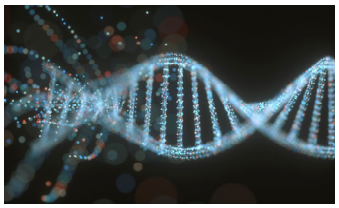
Responsible for ensuring the safety of employees when working with

- Infectious agents or toxins
- Biological toxins made for clinical research protocols
- Recombinant or synthetic nucleic acid molecules
- Genetically modified animals
- Human Gene Transfer products

22

NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

- Outlines the biosafety practices and containment principles for constructing and handling:
  - recombinant nucleic acid molecules
  - synthetic nucleic acid molecules, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, and
  - cells, organisms, and viruses containing such molecules
- Applicable to research that is conducted at or sponsored by an institution that receives any support for recombinant or synthetic nucleic acid research from NIH **AND** involves testing in humans of materials containing recombinant or synthetic nucleic acid developed with NIH funds



There are commercial IBCs so don't feel as if you have to do this alone!

https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf

23

What Should Compliance Officers Know?

- Does your institution conduct research subject to the NIH guidelines for recombinant or synthetic nucleic acid molecules?
- Who is your Biosafety Officer?
- Is your Biosafety Committee registered and following the guidelines for reporting incidents?
- If conducting human subjects research that includes a biosafety component, what are the processes for communication between the IBC and IRB?

24

What Compliance Officers Should Do

- Sit in on an Institutional Biosafety Committee (IBC) meeting if your organization has one
- Know if you are conducting research that requires oversight by an IBC
- Know the types of research your IBC is reviewing

25

Conflicts of Interest

26

Conflict of Interest

- Policies/Regulations
  - **PHS**: CFR 42 Part 50 Subpart F. Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought
    - https://grants.nih.gov/grants/compliance/42_cfr_50_subpart_f.htm
  - **FDA**: CFR 21 Part 54. Financial Disclosure by Clinical Investigators
    - https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=54
  - **NSF**: Ch. 5: Grantee Standards: 510 Conflict of Interest Policies
    - https://www.nsf.gov/pubs/manuals/gpm05_131/gpm5.jsp#510

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27

Conflict of Interest

The regulations requires Institutions to:

- Have a COI Policy
- Designate responsible official(s)
- Disclose certain financial interests of all investigators*
- Assess the disclosure to determine if a conflict exists
- If a conflict exists, development of management plan to eliminate, reduce, or manage the conflict
- Report the conflict if associated with a PHS funded research project

*specifically defined by the regulations

28

Conflict of Interest

- Purpose: Promote objectivity in research
  - Eliminate, minimize, and/or manage outside interests that could directly and significantly impact design, conduct and reporting of research
- Key Stakeholders
  - COI Officer or Committee
    - Note there is no mandate for a committee or process
  - Investigator
  - If Human Subjects Research, the IRB
  - Grants Administration

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29

Conflict of Interest

Common Elements of Management Plan

- Public disclosure of financial interests (e.g., publications, informed consent form)
- Monitoring of research by independent reviewers
- Modification of the research plan
- Disqualification from participating in all or portion of research
  - If HSR, commonly excluded from recruitment/consenting
- Divestiture

Monitor Adherence to Management Plan

- Disclosures in publications
- Confirm other elements of plan followed

30

What Should Compliance Officers Know?

- Types of conflicts overseen at your organization (e.g., personal, institutional)
- Who is responsible for reviewing conflicts and developing management plans
- What is the threshold for reporting a financial conflict
- How does your organization manage commercialization of intellectual property
- How does your institution manage international research collaborations

31

What Compliance Officers Should Do

- Attend meetings of your Conflict of Interest Committee
- Ensure you have a seat at the table for these discussions at the institutional leadership level
- Know your institutions policies around tech transfer/IP
- Be a safe space for investigators to ask questions

32

Research Misconduct

33

What Is Research Integrity?

34

Definition of Research Misconduct

Definition: Fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results

The Office of Research Integrity (ORI) oversees and directs Public Health Service (PHS) research integrity activities on behalf of the Secretary of Health and Human Services with the exception of the regulatory research integrity activities of the Food and Drug Administration

What is FFP?

- **Fabrication:** making up data or results and recording or reporting them
- **Falsification:** manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record
- **Plagiarism:** appropriating another person's ideas, process, results, or words without giving appropriate credit

What Should Compliance Officers Know?

- Does your institution have a research misconduct policy?
- Is the policy on file with the Office of Research Integrity?
- Who is your Research Integrity Officer (RIO) and what type of training do they have?
- How are allegations of RM received, assessed, investigated?
- How broad is your definition of RM?
- How many allegations, assessments, inquiries and investigations have occurred in the past year/five years?

37

The Warning Signs

38

Compliance Program

- Regulatory Knowledge
- Policies and procedures
- Conflicts of Interest
- **Auditing and monitoring**

39

Auditing v. Monitoring

Auditing

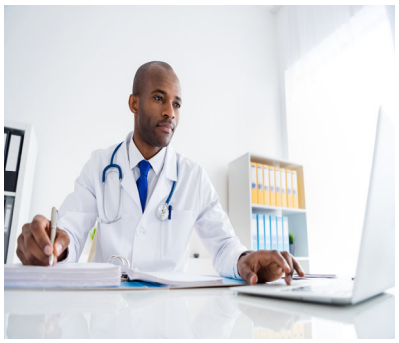
- Verification activity, such as an inspection of a process or quality system to ensure compliance with regulations
- May be seen as punitive
- Typically conducted by individuals outside your institution (i.e., independent)
- Seen with high enrolling sites, for trials submitting NDA or other high profile investigational product, etc.

Monitoring

- Verification activity to ensure compliance with regulations
- Mission: Find & Correct
  - You/your study teams want to find and identify problematic areas and correct them prior to any external agency finding them
- Collegial & Educational – typically completed by individuals internal to the organization such as the audit or compliance offices

40

Research Administration



- Ownership
- Centralized or decentralized
- Clinical Trial Management System
- Identification of active studies and study participants
- Research records
- Research education

Institutional Review Board

- Internal or External
- Knowledgeable Human Protections Administrator (HPA) & Institutional Official (IO)
- Comprehensive written policies
- Documentation of determinations
- Documentation of minutes
- Role-specific training
- Competent representation

HIPAA Privacy

- Privacy Board
- HIPAA Authorizations
- Policies and procedures
- Training

43

Good Clinical Practice

- Standard operating procedures
  - Documentation of informed consent
  - Essential documents for regulatory binders
  - Training of clinical research staff
  - Maintaining source documentation
  - Documenting protocol deviations and exceptions
  - Documenting adverse events, serious adverse events and unanticipated problems
  - Receipt, storage, shipping and disposition of investigational products
  - Managing FDA and sponsor audits
  - Internal quality assurance monitoring

44

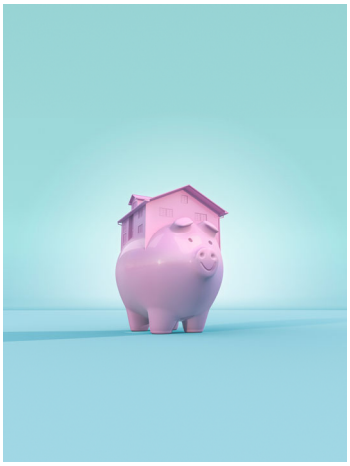
Research Business Operations

- Facility knowledge of research being conducted
- Feasibility review process
- Clinical Trial Agreement review process
- Chargemaster to identify costs for trial budgets
- Coverage analysis process

Billing Compliance

- Policies and procedures
- Coverage analysis
- Research vs. Standard of Care charges
- Claims review

Grants Administration



- Policies and procedures
- Determination of allowable costs – allocable or reasonable
- Tracking, certifying and reporting effort

47

Ways to Mitigate Risk

48

Why Have a Research Compliance Program?

BEST PRACTICE

ALLOWS YOU TO EXPAND YOUR RESEARCH PORTFOLIO

BUILDS CONFIDENCE IN YOUR RESEARCH PROGRAM

PROVIDES INSIGHTS INTO PROBLEM AREAS SO YOU CAN COURSE CORRECT

Obtain Institutional Buy-In

Critical to the success of any research compliance program

Allows you to build partnerships with key stakeholders

Where Do You Begin?

- Examine research portfolio to direct your efforts
- Assess current state of affairs
- Ensure you have the right people in place
- Don't be afraid to ask for help
- **Be a partner not the compliance police**

51

Training Your Research Workforce

- Partner with your researchers and research teams to talk about the importance of research compliance
- Ensure you have clear processes and procedures to facilitate compliance
- If you have multiple workstreams occurring, consider how you want to roll out training (step by step vs. all at once)
- Always remember training is on-going

52

Reference Material

53

Regulations/Guidance

- Food & Drug Administration (FDA) regulations at 21 CFR 50, 56, 312 and 812
- Department of Health & Human Services (HHS) regulations at 45 CFR 46 (both the pre-2018 Common Rule and the 2018 Common Rule)
- Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule Provisions at 45 CFR Parts 160 and164
- 42 CFR 50 Subpart F Promoting Objectivity in Research
- 42 CFR Part 93 Public Health Service Policies on Research Misconduct
- E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R2) Guidance for Industry (March 2018)
- 2010 amendments to the US Sentencing Guidelines (USSG)
- HHS Office of the Inspector General Recommendations

54

Grants Compliance & Oversight Regulations

- 45 CFR Part 75, Subpart C – Pre-Federal Award Requirements and Contents of Federal Awards
- 45 CFR Part 75, Subpart D – Post Federal Award Requirements
- 42 CFR Part 52 – Grants for Research projects
- 2 CFR Part 376 (2 CFR Part 180) - Debarment and Suspension
- 42 CFR Part 50, Subpart F - Financial Conflicts of Interest
- Notice of Award (NOA)

Clinical Research Billing Compliance References

- National Coverage Determination (NCD) for Routine Costs in Clinical Trials (310.1)
- Medicare Benefit Policy Manual, Chapter 14 – IDE Devices
- Medicare Coverage with Evidence Development
- Affordable Care Act (ACA) Provision Requiring Insurance Coverage for Clinical Trials
- Medicare Coverage, Clinical Trial Policies: Final National Coverage Decision
- 42 CFR 413.90
- CMS Manual – Pub 100-04 Medicare Claims Processing
- CT Number for CMS 1500 Claim Form

Questions

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