Clinical Research Integrity: A Practical Approach to Investigating and Acting Upon Alleged Improprieties

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Clinical Research Improprieties

- Ethical Breach
- Research Misconduct
- Billing & Reimbursement
- Conflicts of Interest (CoI)

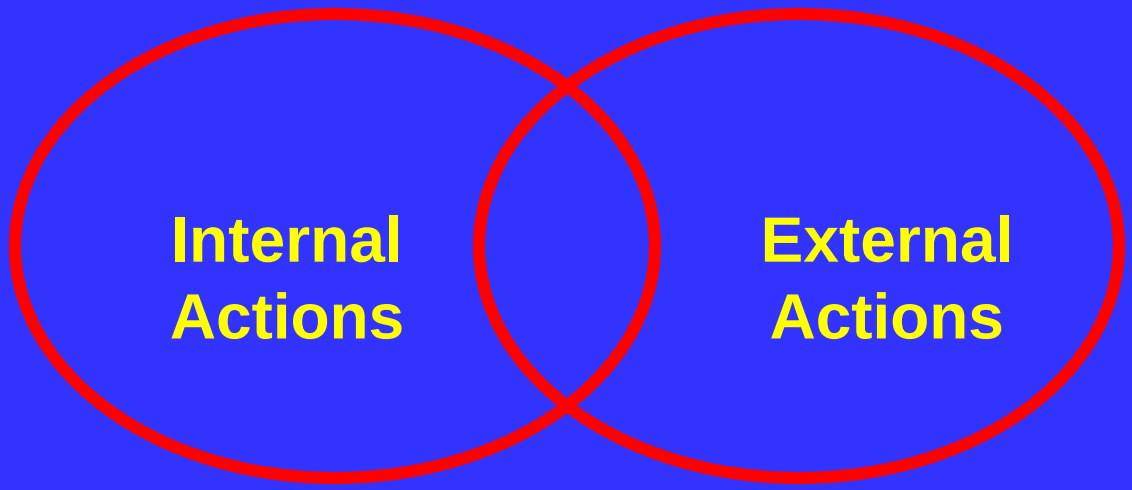
Clinical Research Improprieties

Ethics	Research Misconduct
Billing & Reimbursement	CoI

A Practical Approach to Investigating and Acting Upon Alleged Clinical Research Improprieties

Response to allegations depends on:

- Allocation of compliance responsibility
- Governing law - basic overview
- Institutional policy



Ethics Improprieties

- **Ethics 101:**
  - **Respect for Autonomy, Beneficence/Nonmaleficence, Justice**
  - **Confidentiality& privacy**
- **Ethics: The Advanced Course**
  - **Protocol Design, Inclusion/Exclusion Criteria, Vulnerable Populations, Disclosing CoIs, etc.**

Ethics Improprieties: Authorities

- The Federal Policy for the Protection of Human Subjects (the "Common Rule")
  - 45 CFR Part 46, Subpart A
  - Applies to any federally funded research; adopted by 17 federal agencies
- FDA
  - 21 CFR Parts 50, 56
  - Applies to any research involving an FDA-regulated product, *regardless* of funding source
- Confidentiality & privacy
  - State and federal (HIPAA) regulations
- Institutional policies

Research Misconduct Improprieties: Authorities

- Federal Policy on Research Misconduct (2001)
  - Fabrication, falsification, or plagiarism
  - Proposing, performing, reviewing, reporting
  - Intentionally, knowingly, recklessly
  - Applies to all federally funded research
- Office of Research Integrity (ORI)
  - Education, training, compliance (Division of Education and Integrity)
  - Prosecution (Division of Investigative Oversight)
- Institutional policies for responding to misconduct allegations
  - ORI assurance of compliance required for PHS funding

Research Misconduct Improprieties: Penalties

- Institutional sanctions (examples)
  - Letter of reprimand
  - Special monitoring of future work or probation
  - Removal from a project
  - Termination of employment
- Federal administrative actions
  - Debarment (std = 3 yrs) of supervision
  - Barred from PHS advisory committee participation
  - Certification of research legitimacy
  - Retraction/correction
- Medicare
  - Disqualification for coverage of clinical trials under NCD

Research Misconduct Improprieties: Penalties – False Claims Act*

- **Prohibits**
  - **Knowingly**
    - **actual knowledge, or**
    - **act in deliberate ignorance or reckless disregard of the truth or falsity of the information**
  - **Making a false or fraudulent claim (request or demand)**
  - **To the federal government**
  - **For payment or approval**
    - **health care (Medicare)**
    - **research funding (e.g., NIH)**
- **Qui Tam "whistleblower" suits**
  - **Relator/plaintiff can bring a civil action**

Research Misconduct Improprieties: False Claims Act Examples

- *US ex rel Yong Wu* v. *Thomas Jefferson University* (2000)
  - Falsely obtaining an NIH grant by
    - including an absentee PI (PI had resigned from TJU and was living in Italy)
    - relying on publications with falsified data
  - Relator was a former post-doctoral fellow
- *US ex rel Cantekin v. Univ. of Pittsburgh* (1999)
  - Falsely obtaining an NIH grant by not revealing funding from drug companies for same projects

Penalties – False Claims Act

- **Civil penalties**
  - **$5,000 - $10,000 *per claim* (increased by an inflation factor)**
  - **+ 3 times the amount of damages the Government sustains**
  - **+ attorneys' fees**
- **Qui tam relator/plaintiff**
  - **If government proceeds with lawsuit: 15-25% of award**
  - **If government does not pursue case: 25-30% of award**

Improprieties: Billing & Reimbursement Research Issues

- **Medicare coverage**
  - **Problem: clinical trials typically include both experimental and standard of care items/services**
  - **Medicare does *not* cover items/services:**
    - **purely experimental**
    - **paid by another payor**
    - **paid by research sponsor**
  - **Medicare coverage of clinical trials: CMS NCD (Sept. 2000)**
- **Inducements for Medicare/Medicaid referrals**
  - **Anti-kickback**
  - **Physician self-referrals (Stark)**

Billing & Reimbursement Improprieties: Clinical Trials NCD

- **Medicare covers items/services**
  - In qualifying trials
  - Routine costs (conventional care)
  - Required for the provision of the investigational item/service
  - Necessary for monitoring patient
  - Necessary to prevent, diagnose or treat complications
- **Medicare does NOT cover**
  - Investigation item/service itself (except Category B devices)
  - Items/services provided solely for data collection/analysis
  - Provided free by sponsor

Billing & Reimbursement Improprieties: Clinical Trials NCD

- Coding
  - Claims submitted with QV modifier
  - ICD-9-CM diagnosis code = V70.5 (third or subsequent diagnosis code)
- Qualifying trials
  - Deemed
    - funded by NIH, VA, DOD, AHRQ, CMS
    - IND or IND exempt
  - PI certifies to CMS that trial meets specified criteria

Billing & Reimbursement Improprieties: Clinical Trials NCD

- **Misrepresentation of qualifying status by PI**
  - **Coverage denied by CMS**
  - **Possible fraud investigations against PI and billing providers**
- **Improper billing or coding**
  - **What is covered must be determined prior to start of each clinical trial**
  - **Subject to interpretation – document determinations**
- **Double billing**
  - **Item/service paid by sponsor and billed to Medicare**
  - **Need to coordinate clinical and research billing**
- **False Claims Act & qui tam suits**

CoI Improprieties: Who?

- Investigator
- IRB Member
- Institutional

CoI Improprieties: Authorities

- FDA (21 CFR Part 54) – must disclose to FDA and manage:
  - Compensation affected by study outcome
  - *Significant* equity interest (>$50K) in sponsor
  - Proprietary interests
  - *Significant* payments (>$25K) from sponsor to PI
- DHHS 42 CFR Part 50, 45 CFR Part 94)
  - *Significant* equity interest: ≤ $10K and ≤ $5K ownership (aggregated)
  - *Significant* salary, payments, royalties: ≤ $10K (aggregated)
  - Duty to collect info, manage CoI, maintain records (3 yrs)
  - No affirmative duty to disclose to PHS unless PI fails to comply
- Institutional Policies
- Anti-kickback regulations

CoI Improprieties: Institutional Policies (Example)

- **Disclosure**
  - Annual disclosure by all clinical investigators to institution
  - Public disclosure of all significant financial interests
- **Minimizing CoI**
  - Monitoring research with independent reviewers
  - Divestiture of significant financial interest
  - Sever relationships with sponsors that create actual or potential CoI

CoI Improprieties: Anti-kickback Statue

- Generally: prohibits payment for referrals
- Specifically prohibits
  - Knowingly and willfully (= INTENT)
    - violation if even *one* purpose is to induce referrals
  - Giving (e.g. sponsors) or receiving (e.g. PIs)
  - Any remuneration (gifts, honoraria, payments, equity, travel, finders fees for subjects)
  - In exchange for referral of patients or ordering, purchasing or recommending of services
  - For which Medicare or Medicaid will pay

CoI Improprieties: Anti-kickback Research Issues

- **Payment by sponsors to PIs**
  - **If intended to induce the MD or hospital to purchase items/services paid by Medicare/Medicaid**
  - **If payments exceed the value of physician's *de minimis* "research" services (1994 OIG Fraud Alert)**
  - **Finders' fees if in excess of administrative costs and/or proportional to volume**
  - **Personal services safe harbor: compensation requirements**
  - **Agreed to in writing, in advance, for at least one year**
  - **Based on fair market value(FMV) – not referrals**
  - **Specify research services provided and document FMV**

CoI Improprieties: Penalties

- FDA
  - Data may be deemed inadequate if appropriate steps not taken to minimize bias
  - FDA may refuse to file marketing application if certification/disclosure not provided
- DHHS
  - Federal funding interrupted or rescinded
- Institutional policies
  - Disqualify any conflicted investigator from participating in sponsored research

CoI Improprieties: Anti-kickback Penalties

- $25,000 for each offense
- Jail for up to 5 years
- Exclusion from Medicare/Medicaid or other payor programs
- Civil money penalties
  - Treble damages
  - Civil fines
  - Attorneys' fees
- False claims?

Improprieties: Responding to Allegations

- Allegation & Report
- Inquiry
- Investigation
- Action (Resolution)
- Prevention

Responding to Allegations: Allegation & Report

- **Allegations**
  - **Results from any action, event, circumstance that seems suspect**
  - **May originate *within* institution (colleagues, staff, administrators)**
  - **May originate *outside* of institution (ORI, federal agency, press, family)**
- **Report: Everyone in the institution has an affirmative duty to report suspicions**

Responding to Allegations: Inquiry

- What: Information gathering and initial fact finding to determine whether an allegation or apparent instance of misconduct warrants an investigation
- Process
  - Due process (notice, neutrality & confidentiality)
  - Promptly collect and protect key evidence
  - Opportunity for input
- Inquiry findings
  - Written
  - Prompt notice to internal and external stakeholders

Responding to Allegations: Investigation

A formal hearing and evaluation of all relevant facts to determine if an instance of misconduct has taken place, the extent of the misconduct, and the adverse effects resulting from the misconduct.

If misconduct has already been confirmed, an investigation may, nevertheless, be conducted.

Improprieties: Acting Upon

- Determination: Major or minor violation?
- Process: Who are the stakeholders?
  - Institutional administration, IRB, PI's department, funding agencies and sponsors, subjects and their families, collaborators, public, journals
- Response:
  - Internal: institutional policy
  - External: governed by applicable law

Research Misconduct Improprieties: Response to Allegation

- Institution
  - Inquiry report: if investigation warranted, submit to ORI and federal funding agency
  - Investigation report: forwarded with findings and all evidence to ORI
- Office of Research Integrity (ORI)
  - Assess allegations and forward to institution
  - Monitor institutional investigation
  - Oversight review
    - evaluate evidence and issues
    - dialogue with institution, obtain additional evidence
    - issue finding on misconduct

Acting on Improprieties: Who?

Internal Response	Violations	External Response
IRB	Privacy & Confidentiality Protocols Violations Adverse Event reporting Consent issues Subject recruitment CoI	ORI
Scientific Integrity Committee	Research misconduct Grants Management Billing & Coding	ORI NIH federal funding agency
Legal	False claims (grants, billing)	CMS

Acting on Improprieties: Actions

- **Internal:**
  - **Protocol Violation Hearing**
  - **Suspension of PI**
  - **Suspension of Protocol (45CFR46.113)**
  - **Education**
  - **Tighter Continuing Review of PI's Research**
- **External:**
  - **Report to Funding Agency/Federal Agency;**
  - **Disclosures to participants, public**

Improprieties: Prevention

- **Establish Institutional Policy that Encompasses all Improprieties**
  - **Serious deviation from accepted practices such as fabrication, falsification, or plagiarism, or in carrying out research or reporting the results of research; or**
  - **Material failure to comply with federal requirements for the protection of human subjects, researchers, or the public or for insuring the welfare of laboratory animals; or**
  - **Failure to meet other material legal or institutional requirements governing research.**

Improprieties: Prevention

- Establish and Publish Clear Roles and Responsibilities
- Educate
- Organize Centrally
- Empower Locally
- Enforce
- Uniform, Clear Consequences

Useful Web Sites

- **Roles and Responsibilities in Research:**
  - www.ohsu.edu/ra/rso/rgc/randr.pdf
- **Protocol Violations:**
  - www.ohsu.edu/ra/rso/irb/protocolviol.pdf
- **Research Education:**
  - www.ohsu.edu/ra/rcr.htm
- **General:**
  - www.ohsu.edu/research