Supporting a Culture of Research Integrity

Donna Cookmeyer, Ph.D.
Research Integrity Officer; Chair, IRB
School of Medicine
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Compliance – Why So Many Rules?

- Public Trust
  - » Use of federal funds (your tax dollars) and accountability
  - » Reviews to ensure science conducted for the greater good
- Integrity of the Data – how confirmed?
  - » Peer review has limited reach and scope
  - » Independence difficult to establish within peer groups
- History
  - » Researchers blinded by science (failure to see bias, design flaws, potential for harm overlooked because research is so "important")

Cases – Research Gone Wrong

- Tuskeegee
- Nazi experiments
- Milgram
- Gelsinger
- Summerlin
- Darsee

Potential Motives for Misconduct/Non-compliance

- Financial
- Professional advancement
- Publish or perish / intense competition
- Personal/Interpersonal
- Reputation / Arrogance / Entitlement
- Misguided altruism
- Fear of loss of funding, loss of employment
- Greed
- Cultural differences

Types of Misconduct in Research

- Non-compliance
  - » With Federal regulations
  - » With Institutional policies
- Includes basic research; research with animals; research with humans
- Research Misconduct (FFP) – Federal Definition
- Significant deviations from community standards in proposing, conducting, or reporting research
  - » At Duke, a form of research misconduct

Oversight and Compliance in Animal Research

Animal Research Ethics

Ethical Foundation

- Animal models as surrogates for humans
  - » Obligation to "use" all animals humanely and as approved
  - » Not to cause unnecessary pain and suffering
  - » Not to use more animals than scientifically justified
  - » Not to duplicate work unnecessarily

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Health Research Extension Act

- Implemented through Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals
- Administered by the Office of Laboratory Animal Welfare (OLAW) under National Institutes of Health (NIH)
- Applies to all institutions that accept money from PHS for research
- Covers any **live vertebrate animal** used or intended for use in **research** and related activities
- Sets requirements for Institutional Animal Care and Use Committee (IACUC) - composition and function
- Requires animal welfare assurance agreement with OLAW

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Animal Welfare Assurance

- Commits the institution and its officials, investigators, and other agents to full compliance with the PHS Policy
- Required to receive NIH funding for activities involving animals
- Describes the institutional commitment to humane care and use of animals
- Describes the institutional lines of authority
- Describes program for Animal Care and Use
- Lists approved animal facilities
- Lists IACUC members

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Animal Welfare Act

- Administered by United States Dept. of Agriculture (USDA)
- Covers any live or dead dog, cat, non-human primate, guinea pig, hamster, rabbit, or any other warm-blooded animal which is being used or intended for use for research, teaching, experimentation, exhibition purposes, or as a pet
  - » Excludes birds, rats, and mice bred for use in research
  - » Other exclusions related to farm animals
- Specific standards for:
  - » Veterinary care and animal husbandry
  - » Handling, housing, feeding, watering, sanitation, ventilation, shelter animal transportation and other issues
  - » Use of tranquilizers, anesthetics, and analgesics to minimize pain or distress
- Sets requirements for IACUC composition and function

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What is an IACUC?

- Federally mandated committee to monitor the care and use of animals in research, teaching, and testing
- Each institution which falls under authority of the Animal Welfare Act and/or receives PHS support for research and teaching must have an IACUC
- Federal Composition Requirements:
  - » Membership appointed by the Institutional Official
  - » Minimum of 5 (PHS) or 3 (USDA) members
  - » Must include:
    - ♦ DVM with lab animal medicine training/experience and has program responsibility
    - ♦ Non-affiliated member (community representation)
    - ♦ Non-scientific member (PHS only)
    - ♦ Practicing Scientist

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IACUC – Major Functions

- Review and approve, require changes, withhold approval of all new proposed research activities using animals and all modifications to existing protocols
- Review all continuing protocols annually to ensure that no significant deviations from established and approved procedures have occurred
- Semi-annual review of institutional animal care program
- Semi-annual review of animal facilities (any area in which animal work is performed)
- Report results of reviews to Institutional Official including noted deficiencies and recommendations
- Review and investigate concerns involving care and use of animals
- Authorized to suspend activities involving animals

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IACUC – Review

- When reviewing protocols, the IACUC ensures that:
  - » Procedures avoid or minimize pain and distress
  - » Alternatives are considered to procedures that cause more than momentary pain or distress
  - » Assurance that the protocol proposed does not unnecessarily duplicate previous experiments
  - » Appropriate anesthetics and analgesics are used when necessary;
  - » Personnel are properly trained to perform the proposed procedures;
  - » Activities that involve surgery provide for appropriate pre-operative and post-operative care and that aseptic practices are followed; and
  - » Methods of euthanasia are consistent with methods set forth by the American Veterinary Medical Association's Panel on Euthanasia

Compliance Activities - IACUC

- Lab Inspections at least twice annually
- Post-approval Monitoring (not for cause)
- Investigations (for cause)
- Semi-annual Program Evaluations
- Report to OLAW and UDSA, as applicable, any serious/continuing problems in a timely fashion
- Institutional Official also reports to OLAW, USDA:
  - » Serious or continuing noncompliance
  - » Serious deviations from standards
  - » Any suspension of an activity by the IACUC

Compliance Activities - PHS

In cases of non-compliance (serious, continuing) or suspension of a research protocol:

- Review institutional program to determine if oversight is effective
- Review institution's proposed corrective actions
- OLAW provides assistance / advice

- Rare cases: if institution is unable to take corrective actions and NIH applies sanctions (withdraw or restrict funding)

Oversight and Compliance in Human Research

Human Research Ethics – The Belmont Report

- Cornerstone statement of ethical principles for human subjects research in the United States
- Distinguishes between medical treatment and research
- Established three ethical principles that should guide the resolution of ethical problems arising from research involving human subjects
  - » Respect for Persons (autonomy, voluntariness)
  - » Beneficence (maximize benefits, minimize risks)
  - » Justice (equity; equal participation)
- Requires review of proposed research by an Institutional Review Board (IRB)

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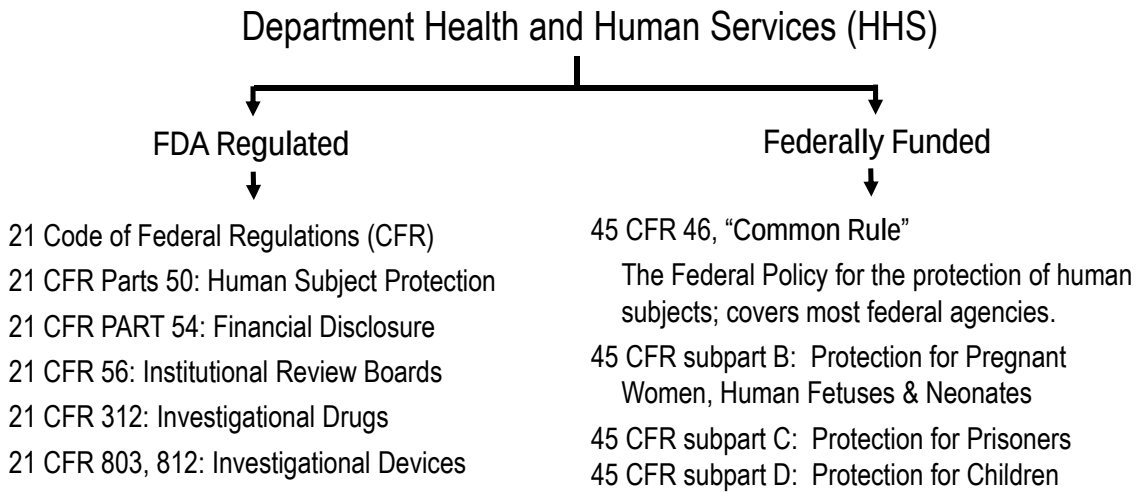
Human Research Regulations



- Health Insurance Portability and Accountability Act (HIPAA) – Office of Civil Rights

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Human Subject Research

Human Subject Definition

- OHRP: A living (with HIPAA, "or dead") individual about whom an investigator obtains data through intervention or interaction **or** obtains identifiable private information
- FDA: 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

Research Definitions

- OHRP: A systematic investigation designed to develop or contribute to generalizable knowledge
- FDA: Any experiment involving a test article and **one** or more human subjects that either is (1) subject to requirements of the FDA or (2) where the results are intended to be submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit

IRB Function and Jurisdiction

Function of the IRB

The protection of rights, welfare, and safety of human subjects through:

- Approval, requiring modifications to secure approval, or disapproval of research activities
- Suspension or termination approval of research not being conducted in accordance with the IRB's or federal requirements or if there are significant unanticipated risks to participants
- Observing, or have a third party observe, the consent process
- Conducting continuing review of research annually or more often when appropriate

Jurisdiction of the IRB

All research activities involving human subjects

*The IRB grants a **privilege** rather than restricts a right*

IRB Membership

- Five or more members with:
  - » expertise and experience
  - » more than one profession
  - » diversity including consideration to gender, ethnicity, and cultural backgrounds
  - » sensitivity to and knowledge of community attitudes
  - » members must avoid potential conflicts of interest
  - » *ad hoc* expertise as needed (non-voting)
- At least one scientist member
- At least one non-scientist member (must be present for all votes)
- At least one non-affiliated (community) member
- Knowledgeable member(s) when subjects are considered vulnerable
  - » Children
  - » Pregnant women
  - » Prisoners
  - » Individuals with limited capacity to consent

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IRB Review

To approve research the IRB must find:

- Risk to subjects are minimized
- Risks to subjects are reasonable in relation to subject benefit
- Subject selection is equitable
- Informed consent obtained and documented
- Provisions are adequate for monitoring safety
- Provisions to protect subject privacy and data confidentiality are adequate
- When subjects are likely vulnerable to coercion or undue influence there are additional safeguards to protect subject rights and welfare included

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Noncompliance - Human Research

- Failure to follow federal regulations (Common Rule, FDA regulations, HIPAA)
- Failure to follow institutional policies
- Failure to follow determinations of the IRB

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Possible Institutional Actions

- Serious/Continuing Determination
  - » Serious Noncompliance
    - ♦ Results in or poses a threat to the safety, rights or welfare of participants or
    - ♦ Effects the scientific integrity of the data
  - » Continuing Noncompliance
    - ♦ A pattern of non-compliance that if allowed to continue is likely to result in or pose a threat to the safety, rights or welfare of participants or adversely affect the scientific integrity of the study
- Potential Actions
  - » Suspension or termination of the research
  - » Notification participants (current or past)
  - » Modification of the research protocol, informed consent or other documents
  - » Modification of the information disclosed during the consent process
  - » Monitoring and/or Training

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Possible OHRP Actions

- Termination or restriction of Assurance
  - » Impacts federal funding
- Revisions or modifications to the institutional human research protection program (HRPP)
- Implementation of a corrective action plan
- Audit or inspection

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Possible FDA Actions

- Warning Letters
- Clinical hold
- Disqualification of data
- Delay approval, disapproval or withdrawal of approval of IND, IDE or BLA
- Voluntary Agreements
  - » Restriction
  - » Disqualification/total restriction
- Debarment
- Criminal investigation/prosecution

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Research Misconduct

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Definition of Research Misconduct

- Research Misconduct:
  - » 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 – appropriation of another person's ideas, processes, results or word without giving appropriate credit

Must be in the context of proposing, conducting, or reporting research

Does NOT include honest error or differences of opinion

Reporting Research Misconduct

- Reporting
  - » Department or Section Chair, Division Chief, Dean
  - » Compliance Office
  - » Research Integrity Office
  - » Research Integrity Line 1-800-826-8109
  - » Can be anonymous

- Allegation (report) must be made in Good Faith
- No Retaliation – retaliation can also be reported as above
- Confidentiality protected whenever possible; limit information to those with need to know or federal reporting requirements.

Allegation and Assessment

Once an allegation or report of potential research contact is made:

- It is submitted to the Research Integrity Officer (RIO) for assessment
- RIO may solicit assistance of
  - » Legal
  - » Other individuals
  - » Fact-finding team
- RIO assesses the allegation to determine if:
  - » There is sufficient credible evidence to proceed with an inquiry
  - » The allegation meet the definition of scientific misconduct (FFP)

- If those two conditions are met, the allegation proceeds to the inquiry phase.

Inquiry

- A preliminary evaluation of the available evidence and testimony to determine whether there is sufficient credible evidence of possible research misconduct to warrant an investigation
- Does NOT reach a final conclusion about whether misconduct occurred or responsibility
- The RIO responsibilities
  - » Clearly identifies the allegation and an related issues to be evaluated
  - » Notifies Respondent, Complainant
  - » Sequesters all relevant records and materials
- Completed within 60 calendar days from notification of the respondent unless there are extenuating circumstances
- Findings and recommendations documented in an inquiry report

Inquiry Report

- Written documentation of the Inquiry process
- Description of the evidence and process in sufficient detail to determine whether an investigation is recommended and whether any other actions should be taken if an investigation is not recommended – final determination made by Institutional Official
- Copy provided to the Respondent
  - » Any Respondent comments are made part of the report
- Final copy provided to the Institutional Official
  - » Determines whether an investigation is warranted

Investigation

- Explores in detail the allegations, to examine the evidence in depth, and to determine specifically whether misconduct has been committed, by whom, and to what extent
- Determines whether there are additional instances of possible misconduct that would justify broadening the scope beyond the initial allegations
- Begins within 30 days of the decision that investigation is warranted
- To be completed within 120 days unless there are extenuating circumstances
- Findings and recommendations documented in an investigation report

Investigation Report

- Written documentation of the investigation process
  - » Describes the policies and procedures under which the investigation was conducted
  - » Describes how and from whom information relevant to the investigation was obtained
  - » States the findings and explains the basis for the findings
- Copy provided to the Respondent for review and comment
- Summary provided to the complainant
- Report, including Respondent's comments, provided to the Institutional Official for the final determination

Action Following the Investigation

- If Institutional Official finds no misconduct:
  - » Diligent efforts will be undertaken to restore the reputation of the respondent and others whose conduct has been investigated
  - » Notification to
    - ♦ Respondent
    - ♦ Summary to Complainant
    - ♦ ORI
    - ♦ Sponsoring Agency
    - ♦ Others (law enforcement agencies; licensing boards; etc.)

Action Following the Investigation

- If Institutional Official finds that research misconduct has occurred:
  - » Notification to
    - ♦ Respondent
    - ♦ Summary to Complainant
    - ♦ ORI
    - ♦ Sponsoring Agency
    - ♦ Others (law enforcement agencies; licensing boards; etc.)
  - » Withdrawal of any resulting or pending abstracts and papers
  - » Additional sanctions related to employment, training, oversight, or academic standing

Making a Determination of Research Misconduct

A finding of research misconduct requires that:

- There were one or more acts of fabrication, falsification, or plagiarism
- There was a significant departure from accepted practices of the relevant research community; and
- The misconduct was committed intentionally, knowingly, or recklessly;

- The findings are based on a preponderance of the evidence

  - ♦ Evidence that, compared with that opposing it, leads to the conclusion that the fact at issue is more probably true than not

  - ♦ The greater weight of the evidence; superior evidentiary weight that, though not sufficient to free the mind wholly from all reasonable doubt, is still sufficient to incline a fair and impartial mind to one side of the issue rather than the other

Federal Review

- Following receipt of the final investigation report - reviews the report for timeliness, objectivity, thoroughness, and competence.
- Examines the institution's report and conclusions to determine whether the institutional findings are defensible, well supported by the evidence, and acceptable as a final resolution of the allegations.
- May review information from the investigation, reanalyze information, and request additional information.
- Prepares an oversight report that describes the rationale for determining whether the allegation was substantiated.
- Allegation not supported
  - » Copy of the report sent to the institution and requests that the institution notify the respondent and complainant of the outcome of the investigation
- Allegation supported
  - » Agreement negotiated in which the respondent accepts the imposition of administrative actions without necessarily admitting the misconduct
  - » If Agreement is not reached, agency recommends a finding of research misconduct and the imposition of administrative actions (to Deciding Official)

Consequences of a Misconduct Finding

- Administrative
- Criminal proceedings
- Civil proceedings
- Notice in Federal Register (publicity)
- Advisory Committee/supervision
- Debarment from receipt of Federal funds
- Correction of Literature
- Recovery of Federal funds

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Non-compliance and Research Misconduct

- Jurisdictions can overlap
- An act or event may represent both non-compliance and research misconduct, for example, or may involve both animals and humans, both the FDA and OHRP
- Agencies may act independently or choose a lead
- Under all non-compliance and misconduct areas, there is an urgency to act when safety of humans, animals, or the public is at risk.

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Other Areas of Research where Compliance is Needed

- Federal Grant Regulations
- Medicare Regulations
- FISMA – Electronic Security
- Export Control
- BioSafety
- Select Agents
- State law
- IRS
- HR-personnel
- Intellectual Property (copyrights, patents)

Compliance – Why So Many Rules?

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- Integrity of the Data – how confirmed?
  - » Peer review has limited reach and scope
  - » Independence difficult to establish within peer groups
- History
  - » Researchers blinded by science (failure to see bias, design flaws, potential for harm overlooked because of the "importance" of the research)

Questions?