HCCA Compliance Institute
Implementing a Clinical Research Compliance Program

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Why is there a need for a compliance program for human subject research activities at an Academic Medical Center or University?

- Federally-sponsored Research
- Relocation of OHRP to Secretary Level
  - New office of research protection
- **OIG Work plan FY 2000 and FY2001**
  - Clinical drug trial billing
  - IRB (Institutional Review Board) Reviews
  - Allegations of Medicare/Research Grant Double Billing
  - Investigations that will address bribery, grant, contract and research fraud
  - FDA - Drug and Device Regulations
- Informed consent and reporting of serious adverse events
- IRB functionality
FAILURE TO MANAGE THESE ETHICAL AND REGULATORY ISSUES HAS RESULTED IN FINANCIAL AND REPUTATIONAL DAMAGE TO SOME OF THE WORLD’S MOST RESPECTABLE INSTITUTIONS

University of Minnesota
Misuse federal grants
$32 mil

Thomas Jefferson University
Research Fraud

University of Pennsylvania
Human Gene Therapy Trials

University of Wisconsin
Madison PRISON
$10,000 Fine

Duke University
Shutdown for Clinical Trials

Public Demand for Improved Control

Report on Medical Errors

University of Oklahoma
Clinical Trial Shutdown
Consequences of Non-Compliance

- Fines and Penalties
- Shutdown of projects - Loss of research funding
- Institution considered “exceptional” by funding agency
- Loss of “expanded authorities” Federal Demonstration Partnership (“FDP”)
- Additional oversight/monitoring by the government
- Potential reduction in funding
- Professional integrity compromised
- Reputational risk
Protecting the Rights and Welfare of Human Research Subjects (Common Rule)

Compliance with federal regulations for the protection of human subjects is an obligation whenever biomedical or behavioral research is conducted or supported by any of 17 U.S. government departments or agencies, or whenever research is subject to regulation by the Food and Drug Administration (FDA).
Federal Regulations and Policy

45 CFR 46 – Basic DHHS Policy for Protection of Human Research subjects*

Additional protections for vulnerable populations in subparts B-D

*Revised June 18, 1991
Federal Regulations and Policy (continued)

Federal Regulations and Policy (continued)

- Additional Protections Included in 45 CFR 46:
- Subpart B – Additional DHHS Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant women, and Human In Vitro Fertilization
- Subpart C – DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- Subpart D – Additional DHHS Protections for Children Involved as subjects in Research
Basic Protections

- The regulations contain three basic protections for human subjects:
  - Institutional Assurances
  - IRB Review
  - Informed consent
Assurances

• “Each institution engaged in research which is covered by this policy and which is conducted or supported by a Federal Department or Agency shall provide written assurance…that it will comply with the requirements set forth in this policy.”

• Negotiated and approved by OHRP

• The institution must certify that the research has been reviewed and approved by an IRB. (45 CFR 46.103(b))

• Submitted to funding agency
Assurances

- Information to be included in the assurance:
  - Statement of principles governing the institution
  - Designation and roster(s) of the IRB(s)
  - IRB procedures for ensuring prompt reporting
Assurances

Types of assurances:

- Multiple Project Assurance (MPA)
- Single Project Assurance (SPA)
- Cooperative Project assurance (CPA)
- Federal Wide Assurance (FWA)
Office For Human Research Protections (OHRP)
(Secretary-level office that oversees Human Subject Research)

Responsibilities

- Institutional Audits of Grants
- Implementation and interpretation of federal regulations and policy
- Education programs
- Negotiation of multiple project assurances
- Evaluation of compliance
Risk Factors in Human Subject Research

- Undefined roles and responsibilities (Administrators, Principal Investigators, Clinicians)
- Decentralized Administration
- Staff allegiance to Principal Investigator rather than institution
- Faculty or administrator conflict of interest situations
- Faculty disdain for administration or for regulation
- Lack of training in proper conduct of clinical trials
Principal Investigator’s (PI) Responsibility in Conduct of Human Subjects Research

- Institution and PI ultimately responsible for conduct of grants and awards
- Insuring that there is informed consent from all research participants
- University warrants that it has proper system in place to protect human subjects
- PI acts as the agent of the grant recipient (i.e., the University)
Institutional Responsibilities

- Institutions bear full responsibility for all research involving human subjects covered under their Assurance.
- All requirements of 45 CFR 46 must be met for all federally-sponsored research.
- OHRP strongly encourages institutions to embrace the HHS regulations regardless of sponsorship, and to commit to this standard in their Assurance.
Institutional Responsibilities (continued)

- Designate one or more Institutional Review Boards (IRBs) to review and approve all nonexempt research covered by an the Assurance
- Provide sufficient space and staff to support the IRB’s review and record-keeping duties
- Ensure that appropriate Assurances and certificates of IRB review are submitted for all their federally sponsored research not only for themselves but also for cooperating performance sites
Institutional Official

- “The Buck Stops Here”
- Authorized to act for the institution
- Assumes on behalf of the institution the obligations in the Assurance – Institutional commitment to compliance
- Knowledgeable point of contact for OHRP
- Sets the “tone” for an institutional culture of compliance
- Confirms authority of and works in concert with IRB
- Responsive to IRB recommendations
- Provides IRB with necessary resources and staff
Institutional Review Board (IRB)

Membership:

- At least five members of varying backgrounds
  - Sufficiently qualified
  - Not solely of one profession
  - Gender diversity
- At least one non-scientist
- At least one non-affiliated member
- Expertise on “vulnerable populations”
- Outside consultants
What is an Institutional Review Board? (IRB)

A Committee whose primary mandate is to protect the rights and welfare of humans who are the subjects of research
Why do we have Institutional Review Boards? (IRB)

- PHILOSOPHY
- HISTORY
- REGULATIONS
Philosophical Basis for IRBs

The Belmont Report

Basic Ethical Principles:

- Respect for Persons
  - Individual autonomy
  - Protection of individuals with reduced autonomy
- Beneficence
  - Maximize benefits and minimize harms
- Justice
Historical Basis for IRBs

• NUREMBERG:

During the Nuremberg War Crimes Trials, 23 German doctors were charged with crimes against humanity for “performing medical experiments upon concentration camp inmates and other living human subjects, without their consent, in the course of which experiments the defendants committed the murders, brutalities, cruelties, tortures, atrocities, and other inhuman acts.”
Historical Basis for IRBs

• The Nuremberg Code (1947)
  As part of the verdict, the Court enumerated some rules for “Permissible Medical Experiments”, now known as the “Nuremberg Code”.

These rules include:
  – Voluntary consent
  – Benefits outweigh risks
  – Ability of the subject to terminate participation
Historical Basis for IRBs

• Tuskegee Syphilis Study:

• American medical research project conducted by the U.S. Public Health Service from 1932 to 1972, examined the natural course of untreated syphilis in black American men. The subjects, all impoverished sharecroppers from Macon county, Alabama, were unknowing participants in the study; they were not told that they had syphilis, nor were they offered effective treatment.

IRB Responsibilities

- Review and approve, require modifications, or disapprove all covered research
- Require that informed consent is in accordance with regulations
- Require documentation of informed consent or may waive documentation in accordance with regulations
- Notify investigators in writing of decisions
- Conduct continuing review of research no less than once per year
Criteria for IRB Approval

- Risks to subjects are minimized
- Risks are reasonable in relation to anticipated benefits
- Selection of subjects is equitable
- Informed consent is sought from each subject
- Informed consent is appropriately documented
Expedited Review

An IRB may use expedited review for:

- Research on list of eligible categories
- Minor changes in previously approved research
- Carried out by IRB chair or one or more experienced IRB members
- Reviewers can exercise all of the authorities of the IRB except disapproval
- All IRB members must be informed of research approved under expedited review
Purpose and Definition of Informed Consent

Informed consent is one of the primary ethical principles governing human subjects research; it assures that prospective human subjects will understand the nature of the research and can knowledgeably and voluntarily decide whether or not to participate.
Informed Consent Is...

- Risk/Benefit discussion with participants
- Voluntariness of participation
- Freedom to withdraw from study at any time
- Treatment
- Notification of serious adverse events
- Disclosure of PI’s financial interest in study (not required)
Performing a Risk Assessment For Human Subject Research Compliance

General Steps:

- Review human subject research policies and procedures or establish standard operating procedures
- Interview key administrative staff and Principal Investigators (3-5 awardees of large dollar volume research studies)
- Walk-throughs of clinical labs and administrative facilities
- Conflicts of Interest: Whose duty is it?
- Examine billing procedures/ patient tracking
• PHS has suggested nine areas for Training and Education in the Responsible Conduct of Research. They are as follows:
Data Acquisition, Management, Sharing and Ownership

- Acquiring and maintaining research data
- Record keeping, electronic data collection, storage, data privacy and confidentiality
- Ownership
Mentor/Trainee Relationships

- Responsibilities
- Conflicts
- Collaboration and competition
Publication Practices and Responsible Authorship

- Collaborative work
- Assigning appropriate credit
- Appropriate citations
- Pressure to publish
Peer Review

- Peer review in determining merit for research funding and publications
- How peer review works in the grants process
Collaborative Science

- Setting ground rules
- Authorship disputes
- Sharing of materials and information
Human Subjects

- Ethical principles
- Informed consent
- Confidentiality and privacy of data and patient records
- Preparation of a research protocol
- Institutional review boards
- Proper conduct of the study
- Special protections for targeted populations
Research Involving Animals

- Ethical principles
- Federal regulations
- Treatment of animals
Research Misconduct

- Regulations that govern PHS-funded institutions
- Institutional misconduct policies
- Procedures for reporting misconduct
- Whistleblowers
Conflict of Interest and Commitment

- Definition of conflicts
- How to manage, reduce or eliminate
- Reporting obligations for financial relationships
Routine costs of qualifying trials
Reasonable and necessary items and services used to diagnose and treat complications arising from participation in all trials
Evaluation must be of item or service that falls within a Medicare benefits category
CLINICAL TRIAL
MEDICARE COVERAGE POLICY
(cont’d.)

- CMS lists seven additional “characteristics” for qualification in Medicare Coverage Issues Manual, Section 30-1
- PI must certify that trial meets criteria when PI enrolls trial in a Medicare clinical trial registry
- “Deemed” qualifying trials include those funded by NIH, CDC, AHRQ, CMS, DOD, VA and trials conducted under IND
• Misrepresentation that trial meets qualifying criteria could result in fraud investigation

• “Covered” routine costs include items or services otherwise generally available to Medicare beneficiaries and provided in either experimental or control arm of trial including:
CLINICAL TRIAL
MEDICARE COVERAGE POLICY
(cont’d.)

– typically provided absent trial
– required to provide investigational item or service (e.g., chemotherapeutic agent)
– required to monitor effect of that item on service or to prevent complications
– required to diagnose or treat complications
CLINICAL TRIAL
MEDICARE COVERAGE POLICY
(cont’d.)

• “Routine Costs” do not include:
  – investigational item or service
  – data collection and management
  – items or services customarily provided free of charge by sponsor
  – determinations of eligibility
This policy does not affect:
- coverage under LMRP
- Category B device rule

Providers submitting claims to carriers or DMERS must identify “routine costs” with a CV modifier
CLINICAL TRIAL
MEDICARE COVERAGE POLICY
(cont’d.)

- Providers submitting claims to intermediaries will identify by ICD-9-CM code as third or subsequent diagnosis and Medicare will adjust DRG
MEDICARE BILLING FOR INVESTIGATIONAL DEVICES

- FDA IDE number obtained from sponsor
- Obtain Advance Beneficiary Notice (ABN) or waiver if you intend to bill for non-covered service
- Special CDM (Category B device with 624 revenue code)
- Make sure device is being used in FDA approved clinical trial
MEDICARE BILLING FOR EXPERIMENTAL DRUGS

• Is the drug approved by the FDA for the use?
• If not, is the drug approved by the FDA for any indication?
• Has the off-label use been approved by your carrier?