National Audio Conference

Advanced Issues in Human Research Compliance

Sponsored by

The Third Annual Medical Research Summit

Michele Russell-Einhorn, JD

Tom Puglisi, PhD

Audio Conference Topics

- Overview
  - What Constitutes Human Subject Research
  - How is Human Research Regulated
- Structural Issues in Compliance Oversight
  - HHS / Common Rule vs FDA
- HHS Approach
  - Mechanisms
  - Recent Determinations
- FDA Approach
  - Recent Determinations

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secret
Office of Public Health and Scie

FOR US POSTAL SERVICE DELIVERY:
Office for Human Research Protections
6100 Executive Boulevard, Suite 3B01
National Institutes of Health (MSC 7507)
Rockville, Maryland 20892-7507

FOR HAND DELIVERY OR EXPRESS MAIL:
Office for Human Research Protections
6100 Executive Boulevard, Suite 3B01
Rockville, Maryland 20852

Telephone: 301-402-5567
FAX: 301-402-2071
E-mail: mc2a@nih.gov

HAND-DELIVERED

July 19, 2001

Edward D. Miller, M.D.
Dean and Chief Executive Officer
Johns Hopkins Medicine
Johns Hopkins University School of Medicine
School of Medicine Administration Building
720 Rutland Avenue
Baltimore, MD 21205-2196

Chi Van Dang, M.D., Ph.D.
Vice Dean for Research
The Johns Hopkins University
School of Medicine
School of Medicine Administration Building
720 Rutland Avenue
Baltimore, MD 21205-2196

Gregory F. Schaffer, M.S.
President
The Johns Hopkins Bayview Medical Center
4940 Eastern Avenue
Baltimore, MD 21224

RE: Human Subjects Protections Under Multiple Project Assurance (MPA) M-1011

OHRP Action

In view of the above determinations and in order to ensure adequate protections for human subjects at the covered institutions, in accordance with HHS regulations at 45 CFR 46.103, OHRP hereby suspends the Multiple Project Assurance (MPA # M-1011) for the Johns Hopkins University School of Medicine, the Johns Hopkins University School of Nursing, the Johns Hopkins Hospital, the Johns Hopkins Bayview Medical Center, the Gerontology Research Center of the National Institute of Aging-Bayview Campus, the Kennedy-Krieger Institute, and the Applied Physics Laboratory.

The suspension of MPA M-1011 is effective immediately as of the date of this letter and removes the Assurance required by HHS regulations at 45 CFR 46.103(a) for all Federally supported research involving human subjects at the above MPA signatory institutions.

The suspension of MPA M-1011 is effective immediately as of the date of this letter and removes the Assurance required by HHS regulations at 45 CFR 46.103(a) for all Federally supported research involving human subjects at the above MPA signatory institutions.

As result, all Federally supported research projects at the covered institutions must be suspended. For any project affected by this suspension, enrollment of new subjects must cease immediately except in extraordinary cases approved in advance by OHRP (OHRP would expect requests for such approvals to be rare). Furthermore, research activities involving previously enrolled subjects may continue only where it is in the best interests of individual subjects. No suspended Federally supported research at these institutions may resume without OHRP reinstatement of the MPA, or approval by OHRP of an applicable Assurance.

Government Shutdowns

- Massachusetts Eye and Ear Infirmary
- UCLA
- VA Health Sys. Greater Los Angeles
- Rush Presbyterian St Luke's Med Ctr.
- University of Illinois Chicago
- Duke University Med Ctr.
- Univ. Texas Medical Branch Galveston
- University of Oklahoma Tulsa
- Johns Hopkins University

Research Involving Human Subjects

- **Human Research Halted at Major Institutions**
  - Deficient Informed Consent
  - Inadequate Initial and Continuing IRB Review
  - Multiple Areas of Concern
- **Death in Gene Transfer Research**
  - Conflicts of Interest
  - Unreported Deaths and Injuries
- **Media Attention – Congressional Hearings – Distrust**

Research Involving Human Subjects

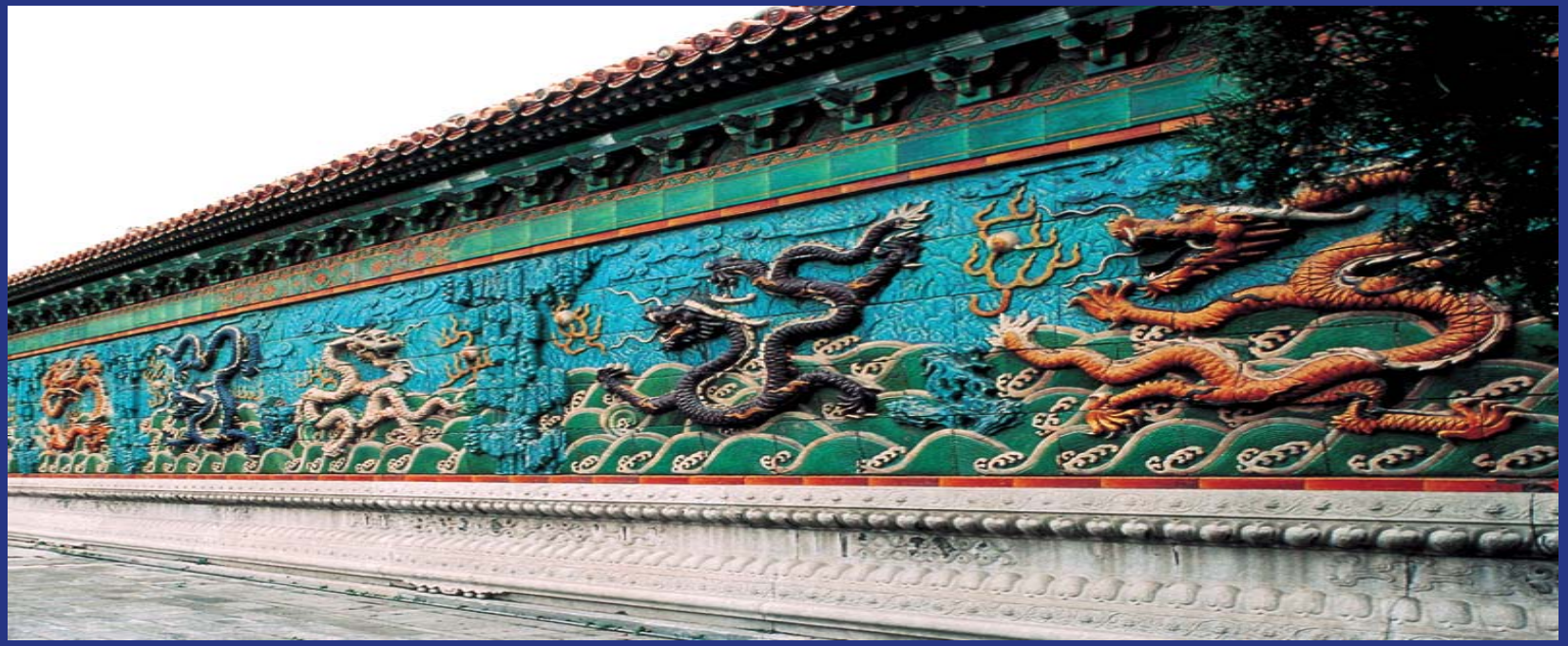
"What's at Stake is the Integrity of Research

and

Public Confidence in Research"

-- HHS Secretary, Donna Shalala, May 2000

What Constitutes Human Subject Research?



Definition of Research: 45 CFR 46.102(d)

- **Research means:**
  - a systematic investigation
  - designed to develop or contribute to generalizable knowledge
- **Research includes:**
  - research development, testing, evaluation, i.e., pilot studies

Definition of Human Subject: 45 CFR 46.102(f)

- **"Human Subject" means:**
  - a living individual
  - about whom an investigator… conducting research obtains:
    1. data through intervention or interaction with the individual, ***or***
    2. identifiable private information

Definition of Human Subject: 45 CFR 46.102(f)

- **"Private Information" means:**
  - Information about behavior in a context in which an individual can reasonably expect that no observation or recording is taking place
  - Information, provided for specific purposes, that the individual can reasonably expect will not be made public (e.g., a medical record)

Federal Oversight of Human Subject Research

- HHS Regulations
  - Revised 1981
- Federal Policy for the Protection of Human Subjects (Common Rule)
  - Adopted 1991
- FDA Regulations
  - Revised 1981

DHHS Regulations: 45 CFR Part 46

- Subpart A – **Basic Protections** ("Common Rule")
  - IRB Review
  - Informed Consent
  - Institutional "Federalwide Assurance" (FWA)
- Subpart B - Protections for **Pregnant Women, Fetuses, and Neonates**
- Subpart C - Protections for **Prisoners**
- Subpart D - Protections for **Children**

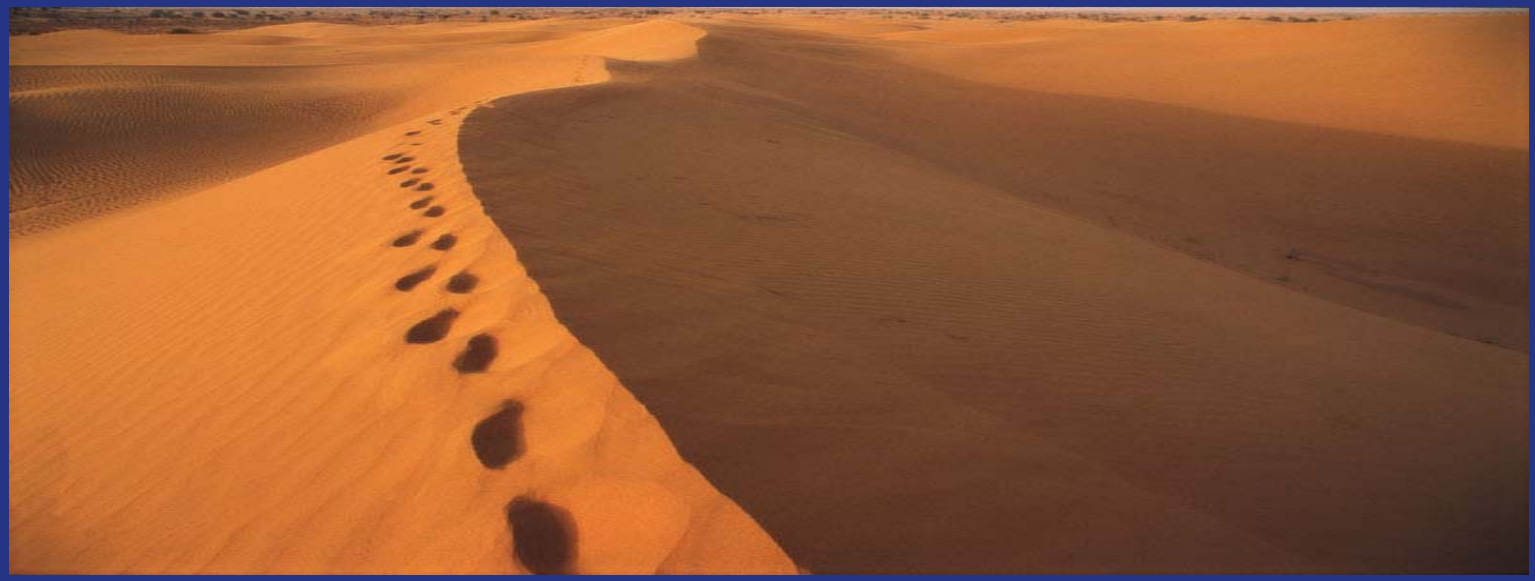
Federal Policy (Common Rule) for the Protection of Human Subjects

- **17 Federal Agencies Adopted HHS Subpart A**
- **Some Agencies Required Additional Protections**
  - VA requires compensation for research – related injuries
- **Some Agencies Never Adopted the Federal Policy**
  - Department of Labor - Miners and Coal Dust
  - Appalachian Regional Commission – Telemedicine
  - Department of Transportation - Sleepy Truck Drivers
- **No Federal Regulation for Research Not Covered Under The Common Rule or FDA Regulations**

FDA Regulations

- **Informed Consent -- 21 CFR 50**
  - Eight Required Elements
  - Written Documentation
  - Language Understandable to Subjects
  - No Coercion or Undue Influence
  - No Waiver of Subjects Rights
- **IRB Review -- 21 CFR 56**
  - Initial Review
  - Prospective Review of All Changes
  - Reporting/Review of Unanticipated Problems
  - Reporting/Review of Adverse Events
  - Continuing Review at Least Annually

Structural Issues in Enforcement of Human Subject Protections



Federal Policy (Common Rule): The Assurance Process

- Every Institution "Engaged" in Human Subject Research Supported by a Common Rule Agency Must Provide a Written "Assurance" to Comply with the Federal Policy
- Directly to the Supporting Federal Agency

or

- To the HHS Office for Human Research Protections (OHRP)

Federal Policy (Common Rule): OHRP Federalwide Assurance (FWA)

- FWA Covers All Federal Research
  - Institution Name
  - Institutional Components
  - Reference to Ethical Principles
  - Terms of Assurance from OHRP Website
  - Designation of IRBs
  - Signatures of Responsible Officials
  - Update as Changes Occur or Every 3 Years
  - Applicability (Optional Extension of HHS Regs or Common Rule to All Institutional Research)

Federalwide Assurance (FWA)

For Federally-Supported Research

- Common Rule Protections of HHS Subpart A
- IRB Review & Informed Consent

For HHS-Supported Research

- Protections of HHS Subparts A,B,C,D

FWA Institutions

- Voluntary application of Common Rule or all HHS Subparts to all research, regardless of funding source

Enforcement of DHHS Regulations: Office for Human Research Protections

- Office for Human Research Protections (OHRP)
  within Office of Public Health and Science (OPHS)
  within Office of Secretary (OS) of HHS
  - Education
  - Compliance Oversight
  - Administration of Assurances

http://ohrp.osophs.dhhs.gov/

Enforcement of DHHS Regulations: Office for Human Research Protections

- OHRP Compliance Activities
  - Compliance Oversight Procedures
  - Common Findings and Guidance
  - Determination Letters

http://ohrp.osophs.dhhs.gov/compovr.htm

Enforcement of Federal Policy

- 17 Federal Agencies Have Authority to Interpret the Federal Policy
- **Human Subjects Research Subcommittee**
  Committee on Science
  National Science and Technology Council

http:

//ohrp.osophs.dhhs.gov/references/humansubcomrost.htm

Institutional Responsibility for Protecting Human Subjects

- Institutional Commitment & Infrastructure
- Authorized Institutional Official
- IRB Chair, IRB Members, IRB Staff
- Other Institutional Committees
- Research Investigators and Co-Investigators
- Study Coordinators and Research Staff
- Everyone Else Involved in the Research Enterprise

Roles and Responsibilities: Authorized Institutional Official

- Legal Signatory for Institution (e.g. Assurance)
- Overall Organizational Responsibility
- Ensure Adequate Placement of IRB within Institutional Structure
- Ensure Adequate resources for IRB (staff, computers, office space, etc.)
- Inspire and Enforce Institutional Culture of Respect and Compliance
- eg: Oversight and Monitoring of Research

FDA Regulations

- **Informed Consent - 21 CFR 50**
- **IRB Review - 21 CFR 56**
- **Investigational Drugs - 21 CFR 31**
- **Marketing Approval - 21 CFR 314**
- **Biologics - 21 CFR 600**
- **Biologics Licensing – 21 CFR 601**
- **Investigational Devices - 21 CFR 812**
- **Pre-Market Approval – 21 CFR 814**
- **Financial Disclosure – 21 CFR 54**
- **Electronic Records – 21 CFR 11**

Definition of Human Subject: FDA Regulations

Human subject means

- An individual who is or becomes a participant in research
  - Either as a recipient of the test article or as a control
  - Either as a healthy human or a patient

-- 21 CFR 50.3(g), 56.102(e)

Definition of Human Subject: FDA Regulations

Research => clinical research => study => clinical study => clinical investigation =>

- Any investigation that involves a test article

  and

- One or more human subjects

-- 21 CFR 56.102(c)

FDA Regulations: Responsibilities of Investigators

- Ensuring Conduct of the Research per the Investigator Agreement, Investigational Plan, and All Applicable Regulations
- Protecting the Rights, Safety, and Welfare of the Research Subjects
- Controlling access to and use of the test article (drug/biologic/device)
- Monitoring and Reporting Adverse Events
- Maintaining and Retaining Accurate Records

FDA Regulations: Responsibilities of Sponsors

- Maintaining the IND
- Obtaining Qualified Investigators and Monitors
- Providing Necessary Information / Training for Investigators
- Monitoring the Investigation
- Reporting Significant Adverse Events to FDA and to Investigators
- Maintaining and Retaining Accurate Records

Clinical Trial Monitoring

Monitoring Overview

- Sponsors are required to conduct monitoring visits
- The purpose of the monitoring visits is to ensure protocol and regulatory compliance, not medical or research integrity.
- Sponsor representatives visit the site at appropriate intervals to verify that the study is being conducted properly and that the site, staffing, enrollment, record keeping, reporting, equipment and facilities remain adequate.
- **THE OVERRIDING PURPOSE OF MONITORING CINICAL TRIALS IS TO MAINTAIN THE SAFETY OF THE STUDY SUBJECTS**

Enforcement of FDA Regulations

- Good Clinical Practice Program
  - Within Office of Science Coordination & Communication
  - Within Office of Commissioner

http://www.fda.gov/oc/gcp

- Center for Drug Evaluation and Research (CDER)
- Center for Biologics Evaluation and Research (CBER)
- Center for Devices and Radiologic Health (CDRH)
- **Bioresearch Monitoring Program**
  - Within Office of Regulatory Affairs

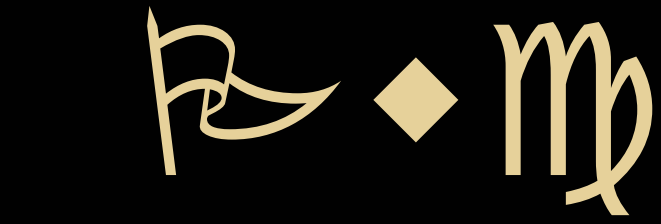
Enforcement of FDA Regulations: Bioresearch Monitoring Program

- Auditing since 1978
- On-site inspections and data audits
  - Monitor all aspects of the conduct and reporting of FDA regulated research
- Assures
  - Quality and integrity of data submitted
  - Protection of human subjects
- Implemented domestically and internationally
  - Four multi-center compliance programs
  - Over 1000 inspections annually.

Enforcement of FDA Regulations

FDA Warning Letters

www.fda.gov/foi/warning.htm



Your worlds

Our people