Protecting Human Subjects --

What Everyone Needs to Know
The Protection of Human Subjects in Research – What Everyone Needs to Know

Rutgers University

February 19, 2003

Tom Puglisi, PhD

Please note that some slides do not appear in Certification Film
HAND-DELIVERED

July 19, 2001

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

Research Project: Mechanisms of Deep Inspiration-Induced Airway Relaxation
Project Number: AAC00-07-26-02
Principal Investigator: Dr. Alkis Togias
HHS Project Number: R01 HL61277 (Principal Investigator: Dr. Solbert Permutt)
Government Shutdowns

- Massachusetts Eye and Ear Infirmary
- UCLA
- VA Health Sys. Greater Los Angeles
- 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**
“What’s at Stake is the Integrity of Research and Public Confidence in Research”

-- HHS Secretary, Donna Shalala, May 2000
Historical Overview
Historical Overview

- **Nazi Doctor Trials**
  - Nuremberg Code – 1947
  - Informed Consent

- **Declaration of Helsinki**
  - World Medical Association
  - Ethical Principles for Medical Research Involving Human Subjects 1964 (revised 2000)
Historical Overview

- Public Health Service (PHS) Policy
  - Prior Review of Research by “Institutional Associates” (PPO 129, February 8, 1966)

- United States Public Health Service
  - Syphilis Study at Tuskegee (1932 -1972)
Historical Overview

- Dr. Henry Beecher’s Review of Medical Literature
- Radiation Experiments
- Cancer Cell Injections
- “Tea Room Trade” Study
- Kansas City “Jury Deliberations” Research
- Social Psychology Research
  - Conformity / Authority
Historical Overview -- 1974

- Congressional Hearings
  - Senator Walter Mondale
  - Senator Edward Kennedy

- HHS Regulations

- National Research Act
  - National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, July 12, 1974
## Ethical Principles and Guidelines for the Protection of Human Subjects of Research

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Roles and Responsibilities

- Institutions
- Institutional Review Boards (IRBs)
- Research Investigators
- Sponsors
- Data Safety Monitoring Boards (DSMBs)
Roles and Responsibilities: Institutional Responsibility

- Institutional Commitment and 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 (e.g., Oversight and Monitoring of Research)
Roles and Responsibilities: Institutional Review Board (IRB)

- **Review and Approve Proposed Research**
  - Risks Minimized through Sound Research Design
  - Risks Reasonable Relative to Benefits
  - Subject Selection Equitable
  - Informed Consent Obtained and Documented
  - Privacy and Confidentiality Protections Adequate
  - Safety Monitoring is Adequate
  - Protections for Vulnerable Subjects are Adequate

- **Exercise Continuing Oversight of Research**
Roles and Responsibilities: Principal Investigators

General Responsibilities of Principal Investigators:

- Accept and exercise responsibility for all aspects of the research
- Ensure adequate training for entire research team
- Ensure adequate supervision of entire research team
- Know and ensure compliance with all regulatory requirements, IRB requirements, and protocol requirements
- Ensure adherence to enrollment criteria
- Monitor and report unanticipated problems and adverse events to sponsor and IRB
Federal Oversight of Human Subject Research

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

- **MPA-FWA Institutions**
  - Voluntary application of all HHS Subparts to all research, regardless of funding source
Applying the Regulations to Research Involving Human Subjects
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
“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)
Definition of Minimal Risk: 45 CFR 46.102(i)

- “Minimal Risk” means:
  - The probability and magnitude of harm or discomfort;
  - Are not greater than those ordinarily encountered in daily life; or
  - During the performance of routine physical or psychological examinations or tests.
IRB Requirements and Procedures
Institutional Review Board (IRB)

- **Mission** => To protect the rights and welfare of individuals participating in research involving human subjects

- **Duties** => To approve, disapprove, modify, suspend research as necessary to ensure protections for human subjects in research

- **Authority** => To exercise final authority within the institution for ensuring adequate protections for subjects. Officials of the institution may not approve research if it has not been approved by an IRB.
Institutional Review Board (IRB): Composition

- Minimum of 5 members
- Diverse in gender and racial background
- Sufficiently qualified in experience and expertise
- One scientific member
- Non-scientific member
- One member not otherwise affiliated with the institution
- Expertise in vulnerable populations for regular review of such research
IRB Approval Includes Findings That . . .

- Review, Approve (§46.111), Exercise Continuing Oversight:
  1. Risks are minimized through sound research design
  2. Risks are reasonable relative to anticipated benefits
  3. Selection of subjects is equitable
  4. Informed consent will be obtained
  5. Informed consent will be documented
  6. Privacy and Confidentiality provisions are adequate
  7. Data safety monitoring is adequate
  8. Appropriate safeguards are included for vulnerable subjects

PricewaterhouseCoopers
IRB Oversight Includes...

- Continued ethical evaluation of the research
- Monitoring of the research
- Monitoring of the informed consent process
- Analysis (as received) of new information, adverse events, and unanticipated problems involving risks to subjects and others
- Formal Continuing Review at intervals appropriate to the degree of risk and no less than annually
Types of IRB Review

- Verification of Exemption
- Expedited Review
- Convened (Full) Review
- Continuing Review

NOTE: Initial and Continuing Review Require Vote of the Convened IRB, Meeting All Quorum Requirements, Unless Specific Conditions for Use of Expedited Review are Satisfied
Convened (Full Board) Review

- Majority of Total Membership Must Be Present
- Non-Scientist Member Must Be Present
- Approval Requires a Majority of Those Members Present
- Vote Must Be Documented
- Same Requirements for Initial and Continuing Review
Expedited Review: Initial or Continuing Review

- Conducted by Chair or IRB member designated by Chair
- Only minimal risk research
- Must fit into a category on November 1998 list
- All other provisions and requirements apply
- Can only approve research -- Cannot disapprove
- Must be reported to full IRB
Expedited Review: Minor Changes to Approved Research

- MINOR changes in previously approved research
- During the established approval period
- Conducted by Chair or IRB member designed by Chair
- Must be reported to full IRB
Minimal Risk Research in the Following Categories:

(1) Clinical studies of drugs and medical devices where an IND (drugs) or IDE (devices) is not required.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture:
   
   (a) from healthy, non-pregnant adults weighing at least 100 lbs: 550 ml in 8-wk period, limited to 2 collections per week;

   (b) from other adults and children, not more than 50 ml or 3 ml per kg in 8-wk period, limited to 2 collections per week.
Minimal Risk Research in the Following Categories:

(3) Prospective collection of biological specimens by noninvasive means.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are no generally eligible for expedited review, including studies of cleared medical devices for new indications.)
Minimal Risk Research in the Following Categories:

(5) Research involving materials (data, documents, records, or specimens) that:
   -- have been collected
   -- will be collected for non-research purposes

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group behavior or characteristics -- cognition, motivation, identity, language, communication, cultural beliefs/practices, social behavior; survey, interview, oral history, focus group, program evaluation, human factor, quality assurance methodologies.
Minimal Risk Research in the Following Categories:

(8) Continuing review of research previously approved by the convened IRB where
   (a) the research is permanently closed to new enrollments, all subjects have completed all research-related interventions, and research remains active only for long-term follow-up of subjects; or
   (b) no subjects have been enrolled and no additional risks have been identified; or
   (c) remaining research activities are limited to data analysis.
Minimal Risk Research in the Following Categories:

(9) Continuing review of research . . . where . . . the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk, and no additional risks have been identified.
Expedited Review: Compliance Problems

- Inappropriate use of expedited review
  - greater than minimal risk
  - no appropriate category
  - failure to document category and determination

- Greater than minor changes to approved research

- Inappropriate use for Continuing Review
Continuing Review 45 CFR 46.109(e)

- Required to occur within one year (no grace period)
- IRB must review all relevant materials
- Continuing review is opportunity to see what has happened once the research started. (NOTE: At initial review the research had not yet begun)
- More than status reports should be reviewed -- review must be substantive and meaningful
IRB Meetings and Record Keeping

- All members receive complete set of materials
- Adequate time to review materials
- Minutes of meetings must be comprehensive
- Attendance and votes should be recorded
- OHRP recent approval of teleconferencing if each participating member (i) has received all pertinent material prior to the meeting; and (ii) can actively and equally participate in the discussion of all protocols
Exempt Research
Six Exemptions: 45 CFR 45.101(b)

(1) Research conducted in:
   - established or commonly accepted educational settings
   - involving normal educational practices
     e.g. instructional strategies
     effectiveness comparisons
Six Exemptions: 45 CFR 45.101(b)

(2) Research involving the use of
   – educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior
   **UNLESS**
   – information is recorded in an (directly or indirectly) identifiable manner (**NOTE**: Coded = identifiable)
   **AND**
   – disclosure would place subject at risk of criminal or civil liability or be damaging to financial standing, employability, or reputation
Six Exemptions: 45 CFR 45.101(b)

- **Survey and Interview Research**
  Involving Children **IS NOT EXEMPT**

- **Passive** Observation of Public Behavior
  Involving Children **IS Exempt**

- **Participant** Observation of Public Behavior
  Involving Children **IS NOT Exempt**
Six Exemptions: 45 CFR 45.101(b)

(3) Research involving the use of
   - educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior
   WHERE
   - subjects are elected or appointed public officials or candidates for public office
   or
   - Federal statutes require confidentiality without exception
Six Exemptions: 45 CFR 45.101(b)

(4) Research involving the collection or study of
   – existing data, documents, records, specimens
     IF
   – the sources are publicly available
     or
   – the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

   NOTE: Even brief recording of identifiers or codes disqualifies the exemption
Six Exemptions: 45 CFR 45.101(b)

(5) Research and demonstration programs designed to study, evaluate, or examine (Federal) Public Benefit or Service Programs

(6) Taste and food quality evaluation and consumer acceptance studies involving
   – wholesome foods without additives
   – additives, chemical, contaminants below safe levels determined by FDA, EPA, USDA
Verification of Exemptions

- Exemptions must be verified by a trained and qualified institutional official
- Exemptions may not be determined by the investigator
Informed Consent
Informed Consent

- Legally effective informed consent
  - Legally Authorized Representative (LAR) under State law
- No coercion or undue influence (recruitment)
- Obtained by Investigator/Staff trained and authorized by IRB
- Language understandable to the subject
- No exculpatory language
- Eight required elements
- Six additional elements
Eight Required Elements

(1) Statement that study is research and information on purposes/duration/procedures/experimental procedures

(2) Reasonably foreseeable risks or discomforts

(3) Benefits which may be reasonably expected

(4) Alternative procedures

(5) How confidentiality will be maintained
(6) For more than minimal risk, information on compensation for injuries

(7) Contact names -- at least one not associated with the research recommended

(8) Statement that participation is voluntary and the subject can withdraw at any time without penalty or loss of benefits to which the subject is otherwise entitled
Six Additional Elements

- Statement that there may be risks which are unforeseeable
- Under what circumstances investigator could terminate subject’s participation
- Additional costs to subject
- Consequences of subjects withdrawal from research
- Statement that will be told of new findings
- Approximate number of subjects in study
Informed Consent Generally

- There is no such thing as “passive consent”
  - consent is required unless formally waived
  - documentation is required unless formally waived

- There is no such thing as a “secondary subject”
  - if an investigator obtains “identifiable private information” about a living individual, the individual is a human subject, regardless of the source

- Deception Research
  - Requires a formal waiver of consent
Risks to Subjects

- A risk or problem is unanticipated if it is not in the protocol or consent document.
- Risks discussed in the protocol should usually be included in the consent document.
- Questions raised as a result of an unanticipated risk:
  - Does the informed consent form need to be amended?
  - Do previously enrolled subjects need to be re-consented?
  - Does a report need to be made to any government office?
Waiver of Informed Consent
(Not Permitted Under FDA Regulations)

- IRB must find and document that 4 criteria met:
  1. Minimal risk research
  2. Waiver or alteration will not adversely affect the rights and welfare of the subjects
  3. Research could not practicably be carried out without the waiver or alteration
  4. Subjects will be provided with additional pertinent information
Documentation of Informed Consent

- Written consent document containing all 8 elements
- In language understandable to the subject or the subject’s LAR
- Signed by subject or subject’s LAR
- Copy SHALL be given to subject
- Opportunity to read before signing
Documentation of Informed Consent

Short form written consent document requires:

(1) oral presentation

(2) witness to oral presentation

(3) an IRB approved written summary
   – given to subject
   – signed by witness
   – signed by person obtaining consent

(4) short form documenting oral presentation
   – signed by subject or LAR
   – signed by witness
The Signed Consent Document Provides the Only Link to the Subject’s Identity and Principal Risk is Breach of Confidentiality

The Research Presents No Greater Than Minimal Risk of Harm to Subjects and Involves No Procedures Requiring Consent in a Non-Research Context

IRB May Require a Subject Information Sheet