The Protection of Human Subjects in Research

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Director

Clinical Research Consulting Group

Medical Research Summit

March 2002

Compliance Issues

- Recent Compliance Cases
  - Johns Hopkins
  - The Hutch
  - NIH
  - Duke University

DEPARTMENT OF HEALTH & HUMAN SERVICES

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HAND-DELIVERED

July 19, 2001

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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)

Research Involving Human Subjects

”What’s at stake is the integrity of

research, and

public confidence in that research.”

DHHS Secretary, Donna Shalala, May 2000

Historical Overview

Historical Overview

Nuremberg Code -

Trials of War Criminals

before the Nuremberg Military Tribunals

Under Control Council Law No. 10, 1949

Historical Overview

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

- Public Health Service (PHS) Policy - Required prior review of PHS sponsored research by “Institutional Associates” (PPO 129, February 8, 1966)

- Declaration of Helsinki - Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects, World Medical Association, 1964 (revised 2000)

Historical Overview

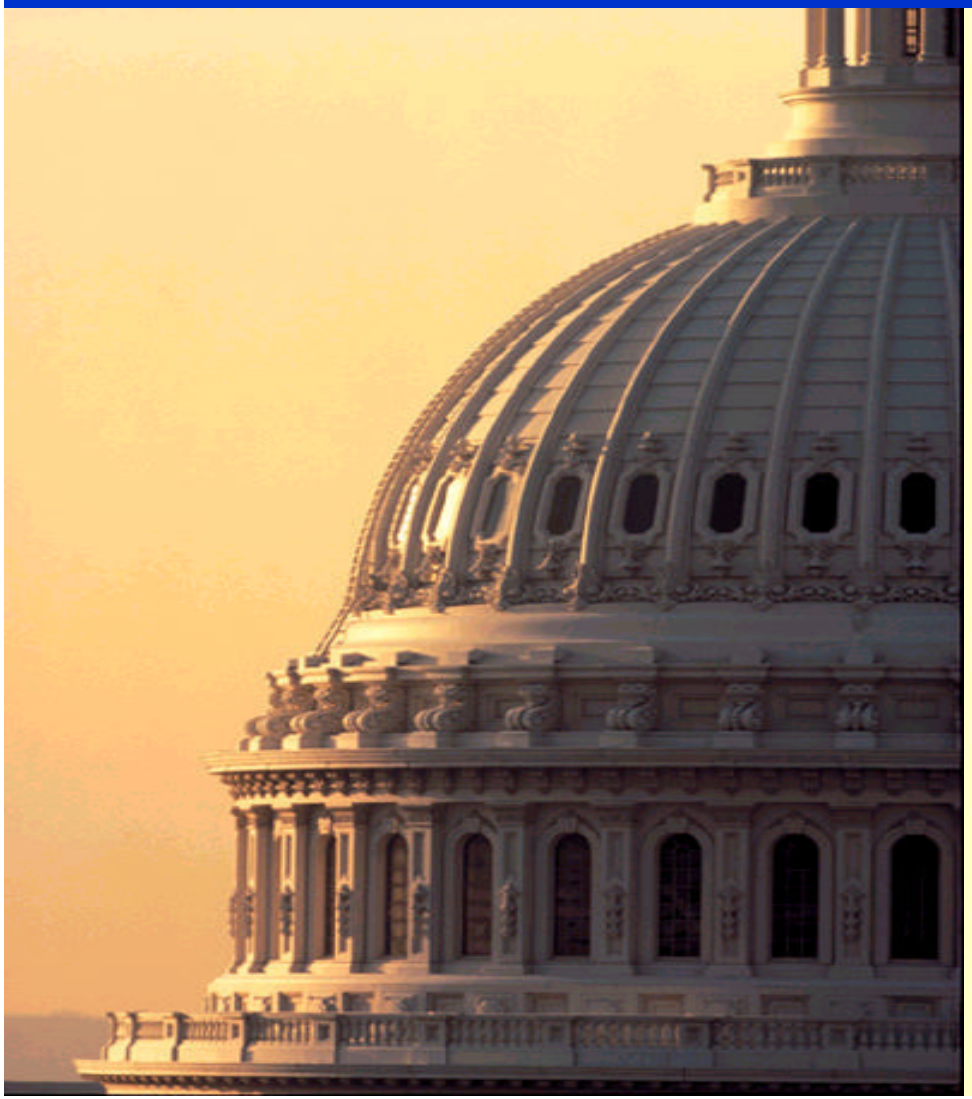
- National Research Act - Created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (July 12, 1974)
- Belmont Report - Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979

Historical Overview: Belmont Report

Ethical Principles:

- Respect for Persons => Informed Consent
- Beneficience => Do No Harm, Maximize Benefits
- Justice => Equitable Distribution of Burdens and Benefits

Federal Oversight



- DHHS - OHRP
  - 45 CFR 46
- The Common Rule
  - 17 signatory Federal Agencies
- FDA
  - 21 CFR 50 (informed consent)
  - 21 CFR 50 Subpart D (children)
  - 21 CFR 56 (IRBs)
  - 21 CFR 312 (INDs)
  - 21 CFR 812 (IDEs)

DHHS Regulations: 45 CFR Part 46

Subpart A - codification of the Common Rule

Subpart B - additional protections for pregnant women, fetuses, and human in vitro fertilization

Subpart C - additional protections for prisoners

Subpart D - additional protections for children

Additional subparts only apply to DHHS unless they have been codified by another agency.

DHHS Multiple Project Assurance (MPA) or Federalwide Assurance (FWA)

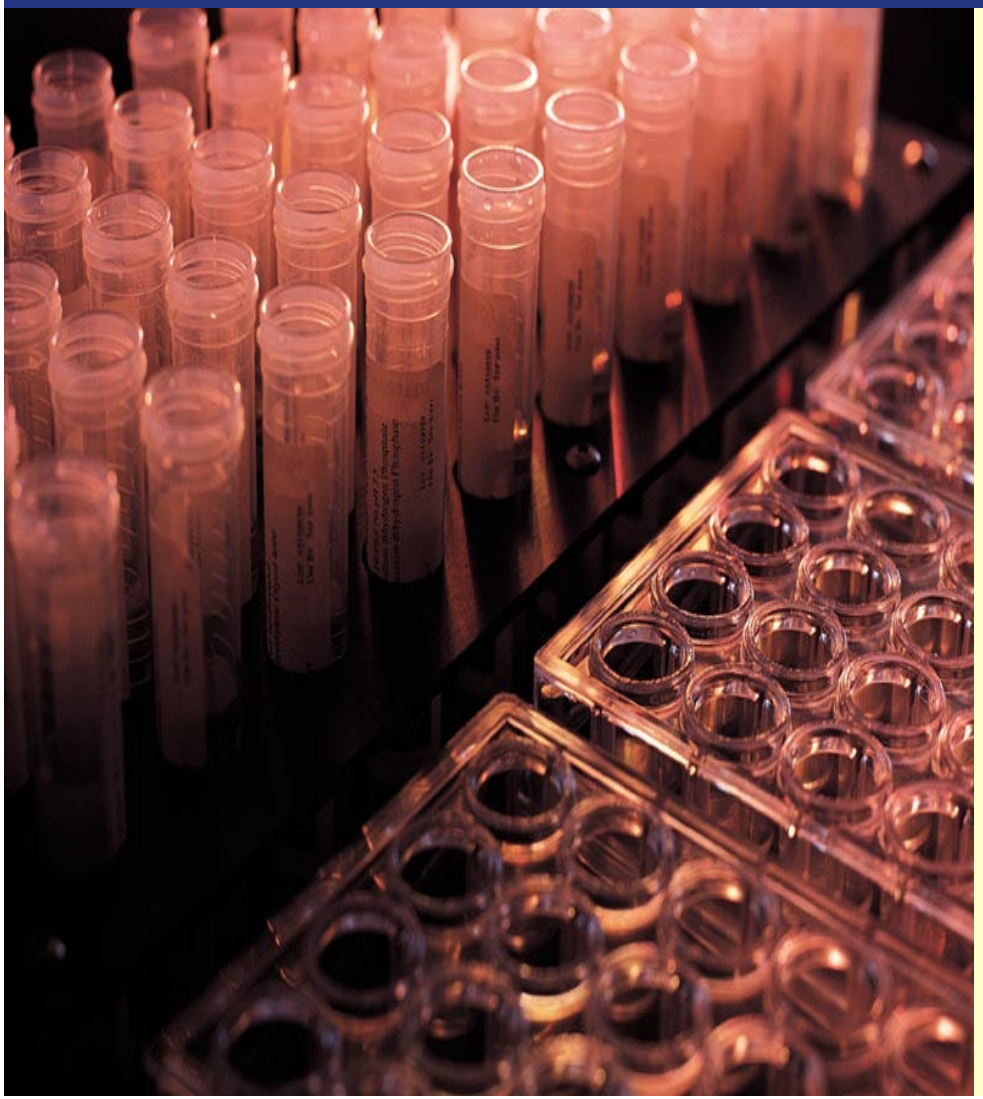
An institution with a DHHS approved MPA or FWA typically agrees to apply DHHS regulations to all research regardless of the funding source.

This means that the additional protections set forth in Subparts B, C, and D would have to be applied to any research funded by a different government agency, even if that agency does not have similar additional protections
--- unless the MPA/FWA specifies otherwise.

The Common Rule

- Federal Policy = 45 CFR 46 Subpart A
- Applies to 17 Federal agencies and offices
- Does not apply to Federal agencies that have not signed the Common Rule
  (e.g., Department of Labor)
- Cannot be changed without the agreement of all signatory agencies (classified research rule example)

FDA Regulations



- Jurisdiction
  - Drugs, biologics, devices, color additives, food additives
- FDA vs DHHS regulations
- Drugs vs Devices
- Sponsor vs Investigator responsibilities
- Reporting requirements
- Use of a test article in unplanned emergency research
- IRB Review of Clinical Investigator's Brochure

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

FDA Regulations: Emergency Use of a Test Article

- **Without Informed Consent** -- 21 CFR 50.23(a)
  - Life Threatening Situation Necessitating the Use
  - Inability to Communicate with Subject for Legal Consent
  - Insufficient Time to Obtain Consent from Legally Authorized Representative (LAR)
  - No Alternative Therapy Available
  - Certification in Writing from Investigator and an other Nonparticipating Physician of the Above
  - Report to IRB Within 5 Working Days
- **IRB Review** -- 21 CFR 56.104 (c)
  - Life Threatening Situation Necessitating the Use
  - Report to IRB Within 5 Working Days
  - Subsequent Use Requires IRB Review

FDA Regulations: 21 CFR 312 Investigational New Drug Application (IND)

Adverse Event Reporting

- **Investigator** must report **promptly** (immediately if alarming) to the **Sponsor any adverse effect** that may reasonably be regarded as caused by the drug (Sec 312.64)
- **Sponsor** must notify **FDA** of any adverse experience associated with the drug that is both serious and unexpected
  - Serious Adverse Drug Experience = death, life-threatening, hospitalization, persistent/significant disability/incapacity, congenital anomaly / birth defect (Sec 312.32)
  - Unexpected Drug Experience = any adverse drug experience, the specificity or severity of which is no consistent with the current investigator brochure or IND application (Sec 312.32)

FDA Regulations: 21 CFR 812 Investigational Device Exemption (IDE)

Significant vs Non-Significant Risk Devices (Sec 812.2)

- **Significant Risk Device =** Investigational device that presents a potential for serious risk to the health, safety, or welfare of subjects, including implants
- **Non-Significant Risk Device =** Investigational devices that does NOT present the potential for serious risk to the health, safety, or welfare of subjects
- Once IRB-approves the research as not involving a Significant Risk Device, the research is considered to have an approved IDE, unless the FDA has notified the sponsor otherwise.

FDA Regulations: 21 CFR 812 Investigational Device Exemption (IDE)

Adverse Event Reporting

- **Investigator** must report any unanticipated adverse device effect to **Sponsor and the IRB** as soon as possible and within 10 working days (Sec 812.150)
- **Sponsor** must report any unanticipated adverse device effect **to FDA, all reviewing IRBs, and investigators** (Sec 812.150)
- **Unanticipated Adverse Device Effect =** any serious adverse effect on health or safety, or any life-threatening problem or death, caused by or associated with a device if not previously identified in nature, severity, or degree of incidence in the investigational plan or application (Sec 812.3)

Central Regulatory Protections

Federal Policy (Common Rule)

HHS Regulations (45 CFR Part 46)

FDA Regulations (21 CFR Parts 50 & 56)

- Informed Consent
- Review by an Institutional Review Board (IRB)

Institutional Responsibility for Human Subjects Research

- Authorized institutional official
- IRB chair
- IRB members
- IRB administrators
- Investigators
- Study Coordinators
- Data Safety Monitoring Boards

Roles and Responsibilities

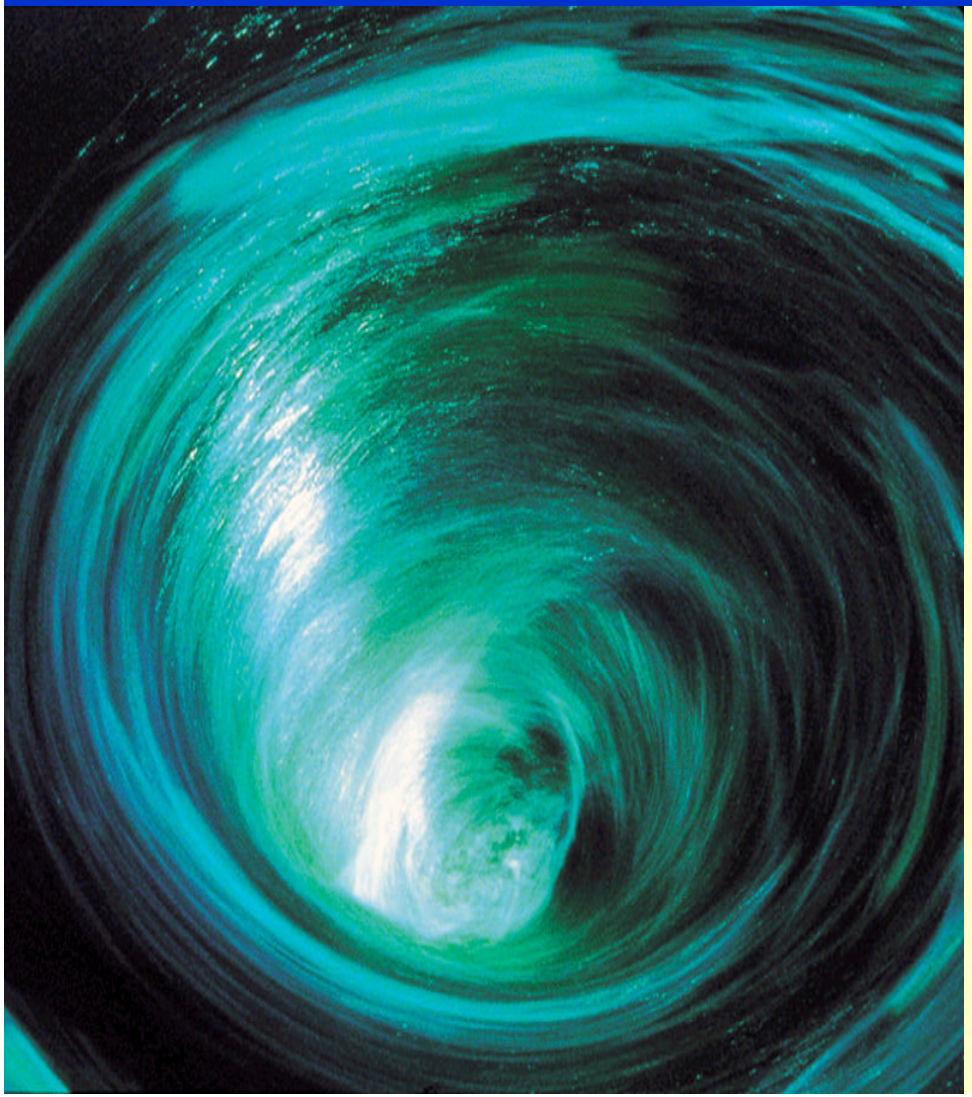
- **Institutional Officials**
  - Act as signatory official on assurances
  - Provide adequate resources for IRB (staff, computers, office space, etc.)
  - Ensure adequate placement of IRB within institutional infrastructure
  - Negotiate contracts with sponsors
  - eg: Famous Children's Research Center
- **IRBs**
  - Protect human subjects
  - Risks are minimized and anticipated benefits maximized
  - Informed consent process adequate
  - Equitable selection of subjects
  - Sound scientific design

Roles and Responsibilities

- **Principal Investigators and Study Coordinators**
  - Protect human subjects
  - Ensure all personnel comply with protocol
  - Ensure all personnel comply with findings and determinations of IRB
  - Prospectively submit changes in research to the IRB for approval
  - Adhere to protocol requirements
  - Minimize undue influence in enrolling subjects
  - Ensure that informed consent process adequate and understandable to subjects
  - Report adverse events and unanticipated problems
  - eg: magnesium sulphate study

Issues in Research Involving Human Subjects

Important Definitions



- Research
- Human subject
- Exempt research

Definition of Research

"Research" means

- a systematic investigation
- designed to develop or contribute to generalizable knowledge

Research includes research development, testing,

evaluation -- ie, pilot studies

Definition of Human Subject

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

“Private Information” means

(1) information about behavior in a context in which an individual can reasonable expect that no observation or recording is taking place

(2) information, provided for specific purposes, that the individual can reasonably expect will not be made public

(e.g., a medical record)

Institutional Review Board (IRB)

Requirements and Procedures

Institutional Review Board (IRB)

Mission is to protect the rights and welfare of individuals participating in research involving human subjects

To approve, disapprove, modify, suspend protocols as necessary to comply with regulations and policies concerning the protection of human subjects in research

The determination of the IRB must be final within the institution. Officials of the institution may not approve the research if it has not been approved by an IRB.

-- 45 CFR 46.112

Composition of the IRB

Number of Members: minimum of 5 members

Diverse in gender and racial background

Sufficiently qualified in experience and expertise

One scientific member

Community representative

Non-scientific member

Expertise in vulnerable populations for regular review of such research

Six Exemptions

(1) Research conducted in

- -- established or commonly accepted educational settings
- -- involving normal educational practices
  - -- examples: instructional strategies effectiveness

Six Exemptions

(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

- **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

(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

(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

(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

IRB Review Process

Who determines exemptions

Expedited review

Full review

Continuing Review

Review of unanticipated problems involving risks to subjects and adverse events

IRB Approval includes findings that . . .

- Risks are minimized thru sound research design
- Risks are reasonable relative to anticipated benefits
- Selection of subjects is equitable
- Informed consent will be obtained and documented
- Data safety monitoring is adequate
- Privacy and Confidentiality provisions are adequate
- Appropriate safeguard are included for vulnerable subjects

IRB Review includes...

- Ethical evaluation of the research
- Recruitment/participation -- justice
- Incentives/payments/recruitment procedures
  -- no coercion(cf Dementia in the Community Study)
- New information
- Analysis (as received) of adverse events and unanticipated problems involving risks to subjects and others

Full Board (Convened) Review

For Full-Board Review:

- Initial review is conducted by the convened IRB adhering to quorum requirements
- Continuing review must be conducted by the full, convened IRB unless an there is a category that permits expedited review.

Expedited Review 45 CFR 46.110

Conducted by Chair or IRB member designed 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.

45 CFR 46.110 (b)(2) allows for expedited review of **MINOR** changes in previously approved research, **during** the established approval period,

Expedited Review 45 CFR 46.110

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, nonpregnant 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.

Expedited Review 45 CFR 46.110

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.)

Expedited Review 45 CFR 46.110

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.

Expedited Review 45 CFR 46.110

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.

Expedited Review 45 CFR 46.110

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.

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

Informed Consent

Requirements and Procedures

Informed Consent

- Legally effective informed consent
  (who is an appropriate LAR?)
- No coercion or undue influence (recruitment)
- 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

Eight Required Elements (cont.)

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

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

IRB must find and document that 4 criteria met:

- Minimal risk research
- Waiver or alteration will not adversely affect the rights and welfare of the subjects
- Research could not practicably be carried out without the waiver or alteration
- Subjects will be provided with additional pertinent information

Documentation of Informed Consent

- Written consent document
- 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

Current IRB Issues

IRB Issues

Family History Research

- Collection of individually identifiable information constitutes human subject research, regardless of source
- Waiver criteria at 45 CFR 46.116(d) may be applicable

IRB Issues

Research Involving Existing Data Sets

- Use of data sets containing identifiable private information requires IRB review
- Original informed consent provisions may apply
- Waiver criteria at 45 CFR 46.116(d) may be applicable
- “Anonymization” of data may be possible

IRB Issues

Research Involving Existing Data Sets

- Use of publicly available data sets is exempt
- Use of data sets containing only non-coded, non-identifiable information is exempt

IRB Issues

Epidemiology Research

- Investigator must have legitimate access to identifiable private information
- Waiver criteria at 45 CFR 46.116(d) may be applicable

IRB Issues

- Passive Consent

- Research Involving Deception

Require formal waiver of informed consent requirements under criteria at 45 CFR 46.116(d)

Vulnerable Subjects

Additional Protections

HHS Subpart B: Research involving Pregnant Women, Human Fetuses, and Neonates

Subpart B-revised December 2001

Activities directed toward pregnant women as subjects

Activities directed toward fetuses in utero

Activities directed toward fetuses ex utero (neonates)

HHS Subpart C: Research involving Prisoners

Subpart C

- Prisoner representative on OHRP approved roster
- Additional duties under 305
- Finding of permissible category under 306
- Certification to OHRP
- Concurrence from OHRP

Lawsuit involving prisoners

- DOJ funded research in Pennsylvania prison:
  - mandatory drug testing (urine vs hair)
  - no consent
  - solitary confinement for refusal to be tested
  - facts of case not contested
- *Acres of Skin*
  - Dow, U Pennsylvania, City of Philadelphia
  - Prisoners told experiments were harmless

HHS Subpart D & FDA Subpart D: Research involving Children

Subpart D

- Not greater than minimal risk research
- Greater than minimal risk -- prospect of direct benefit
- Greater than minimal risk -- no prospect of direct benefit
- Research not otherwise approvable
- Parental Permission
- Assent of Child

45 CFR 46.405 & 21 CFR 50.52: Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

- More than minimal risk to children is presented by
  - (i) an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or
  - (ii) a monitoring procedure that is likely to contribute to the subject's well-being if:
- Risk is justified by the anticipated benefit;
- Relation of anticipated benefit to risk is as favorable as alternatives;
- Assent and permission of parents sought..

45 CFR 46.406 & 21 CFR 50.53:
Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

- Risk is minor increase over minimal risk
- Research presents situations reasonably equal to to those inherent in their actual situations;
- Research likely to yield generalizable knowledge about disorder or condition
- Adequate provisions for getting assent and permission.

Other Issues for IRBs

- **Special oversight mechanisms:**
  - Data & Safety Monitoring boards (DSMBs)
  - Consent monitors
  - Random audits of research
  - Continuing Education

Procedural Issues

- **Managing a government site visit**
  - Corrective action plan
  - IRB operations assessment
- **Managing internal complaints**
  - Types of complaints
  - Managing investigation of complaints
  - Reporting to regulatory authorities

Conflict of Interest

- **Personal conflicts versus institutional conflicts**
  - Investigator conflicts
  - IRB member conflicts
  - Institutional official conflicts
  - Conflicts between institutional offices or functions
- **Recent Issues**
  - University of Oklahoma
  - Penn's Institute for Human Gene Therapy
- **Federal requirements**
  - FDA
  - NIH
  - OHRP
- **Managing conflicts of interest**
  - Policy development
  - Compliance oversight

OHRP Compliance Investigations

74 findings

- Failure to make findings and determinations required by the regulations
- Failure to conduct continuing review
- Failure of institution to adequately support IRB
- Conflicts of interest
- Inadequate consent forms and process

Consequences of Non-Compliance

- Restrictions on Assurance
- Suspension of Assurance
- Negative Publicity
- Warning Letters
- Loss of public confidence in research

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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)

Dear Dr. Miller, Dr. Dang, and Mr. Schaffer:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of (i) the circumstances surrounding the death of a healthy volunteer subject who participated in the above referenced research project, and (ii) the human subject protection system at the Johns Hopkins School of Medicine (JHUSOM), the Johns Hopkins Bayview Medical Center (JHBMC), and the other signatory institutions covered by MPA M-1011 on July 16-18, 2001. The evaluation, conducted by 5 OHRP staff and with the assistance of 3 expert consultants and a representative from the U.S. Food and Drug Administration (FDA), included meetings with senior institutional officials, the three Chairpersons of the Institutional Review Boards (IRBs), 21 IRB members, all IRB administrative staff, and several research investigators, including the principal investigator and co-investigators for the above-referenced research project. The evaluation involved review of IRB files for over 60 protocols, all available minutes of the IRB meetings since 1998, and the audiotapes of two recent JHUSOM IRB meetings.

In the course of the OHRP review, the IRB chairs, IRB members, and IRB administrative staff displayed a sincere commitment to the protection of human subjects. Furthermore, the volume of research reviewed and the amount of time and effort devoted to IRB activities by the IRB Chairs and staff indicate great dedication to the mission of the IRBs. Investigators demonstrated a culture of respect for the IRB process. The IRB Administrator and staff were very helpful and accommodating to OHRP during the site visit. In particular, OHRP greatly appreciates the efforts of the IRB Administrator and staff to extend the site visit schedule and make a large volume of IRB records available to OHRP on very short notice.

OHRP Findings Regarding Research Protocol Number AAC00-07-26-02, Mechanisms of Deep Inspiration-Induced Airway Relaxation

Based upon its review of your institutions' reports dated May 17, June 6, June 22, June 26, June 29, and July 13, 2001, as well as additional information obtained during the site visit from records reviewed and interviews with investigators and IRB members and staff, OHRP makes the following findings regarding the above-referenced research.

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.111(a)(1) and (2) require that in order to approve research an IRB shall determine that the risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result. OHRP finds that the JHBMC IRB and the investigators conducting the research failed to ensure that risks to subjects were minimized and reasonable, as required by HHS regulations at 45 CFR 46.111(a)(1) and (2). In particular, OHRP notes the following:

(a) Prior to the research being approved by the IRB, the investigators and the JHBMC IRB failed to obtain published literature about the known association between hexamethonium and lung toxicity. Such data was readily available via routine MEDLINE and Internet database searches, as well as recent textbooks on pathology of the lung.

(b) Use of hexamethonium is not currently approved by the FDA for use in humans, and has never been approved by the FDA for administration via inhalation.

(c) Prior to approving the research, the JHBMC IRB failed to obtain sufficient information regarding the source, purity, quality, and method of preparation and delivery of the hexamethonium used in the research.

(d) The hexamethonium bromide used in the research was obtained by the investigators from Fluka US and was labeled "[f]or laboratory use only, not for drug, household, or other uses." The JHBMC IRB was not aware of this information before the investigators administered the hexamethonium to three subjects and the hospitalization of the third subject.

(e) Prior to its approval of the research, the JHBMC IRB did not receive or request from the investigators (i) any information regarding the pharmacology and toxicity of inhaled hexamethonium in animals; or (ii) sufficient information regarding the safety of inhaled hexamethonium in humans.

(2) HHS regulations at 45 CFR 46.108(b) require that, except when an expedited review procedure is used, the IRB must review proposed research at convened meetings at which a majority of the members are present, including at least one member whose primary concerns are in nonscientific areas. OHRP finds that the JHBMC IRB failed to review the research, which was not eligible for expedited review under HHS regulation at 45 CFR 46.110(b), at a convened meeting [see finding (8) below]. As a result, the JHBMC IRB failed to ensure that all criteria required for IRB approval under HHS regulations at 45 CFR 46.111 were satisfied.

(3) HHS regulations at 45 CFR 46.103(b)(4) and 46.108(a) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP finds that the following changes to the research protocol were implemented by the investigators without IRB approval:

(a) The investigator initially changed the diluent for the hexamethonium solution from normal saline to distilled water starting with the first subject, and then further modified the solution by adding sodium bicarbonate in order to neutralize the pH starting with the second subject.

(b) The investigators failed to perform a Limulus test on each solution prior to administration to subjects as required by the IRB-approved protocol.

(c) The investigators changed the aerosol delivery system after the second subject's first administration.

(4) HHS regulations at 45 CFR 46.116 stipulate that no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. HHS regulations at 45 CFR 46.116(a) stipulate basic elements for such informed consent.

(a) OHRP finds that the informed consent document approved by the JHBMC IRB for the research failed to adequately describe the research procedures to be followed or identify procedures which were experimental, as required by HHS regulations at 45 CFR 46.116(a)(1). In specific, OHRP notes the following:

(i) The informed consent document failed to indicate that inhaled hexamethonium was experimental and not approved by the FDA. OHRP is particularly concerned that the hexamethonium was referred to as a "medication" in the informed consent document.

(ii) The informed consent document failed to describe the plan for escalating the inhaled methacholine dose during the screening phase of the research.

(b) OHRP finds that the informed consent document approved by the JHBMC IRB failed to adequately describe the reasonably foreseeable risks and discomforts associated with the research, as required by HHS regulations at 45 CFR 46.116(a)(2). OHRP finds that the investigators failed to provide a description of the possible pulmonary toxicity of hexamethonium to the subjects.

(5) HHS regulations at 45 CFR 46.116(b)(1) and (2) require that, when appropriate, the following additional elements of informed consent be provided to each subject:

(a) A statement that the particular treatment or procedure may involve risks to the subjects which are currently unforeseeable.

(b) A description of anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

OHRP finds that it would have been appropriate for the informed consent document for the research to include these elements.

(6) OHRP finds that the investigators failed to promptly report an unanticipated problem involving risks to subjects to appropriate institutional officials, the IRB, OHRP, and the head of the sponsoring agency as required by HHS regulations at 45 CFR 46.103(a) and (b)(5). In specific, the investigators failed to promptly report the cough, shortness of breath, and a decrease in pulmonary function experienced for 8 days by the first subject exposed to hexamethonium. OHRP is particularly concerned that the investigators continued to expose additional subjects to inhaled hexamethonium before the symptoms in the first subject were resolved and before reporting the event to the JHBMC IRB.

(7) OHRP acknowledges and concurs with the following conclusions from your Report of Internal Investigation into the Death of a Volunteer Research Subject provided to OHRP on July 13:

> (a) "[A]n adequate evidence base did not exist for the IRB to be confident that inhaled hexamethonium was safe for use in research subjects."
>
> (b) "[T]he consent form [for the research] should not have been approved by the IRB."
>
> (c) "[T]he death [of the third subject exposed to inhaled hexamethonium] was most likely the result of participation in the hexamethonium phase of the experiment."

OHRP Findings Regarding Human Subjects Protections Under MPA M-1011

Major Findings

(8) HHS regulations at 45 CFR 46.108(b) require that, except when an expedited review procedure is used, the IRB must review proposed research at convened meetings at which a majority of the members are present, including at least one member whose primary concerns are in nonscientific areas. OHRP finds that the JHUSOM and JHBMC IRBs (the IRBs) fail to review at convened meetings most research undergoing initial review that is not eligible for expedited review. As a result, the IRBs fail to ensure that all criteria required for IRB approval under HHS regulations at 45 CFR 46.111 are satisfied. Of note, the minutes and audiotapes of IRB meetings, and our discussions with IRB members and administrators, indicate that no review takes place at convened meetings for most protocols undergoing initial review. Most protocols are neither individually presented nor discussed at a convened meeting of any IRB.

(9) As OHRP noted in its letter of October 3, 2000 to your institutions, OHRP reiterates that continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol that requires continuing review by the convened IRB.

OHRP finds that continuing review of research by the IRBs is not substantive nor meaningful. As with initial review of research, nearly all protocols undergoing continuing review are neither individually presented nor discussed at a convened meeting by the IRBs.

(10) HHS regulations at 45 CFR 46.115(a) require that an institution, or when appropriate, an IRB, shall prepare and maintain documentation of IRB activities, including minutes of IRB meetings. Furthermore, HHS regulations at 45 CFR 46.115(a)(2) require that such minutes be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. OHRP finds that:

(a) For the JHUSOM IRBs, minutes of IRB meetings do not yet exist for 18 of the last 21 meetings dating back to October 2000.

(b) The minutes of meetings for all the IRBs often failed to document the basis for requiring changes in research. OHRP notes that IRB actions were not documented separately for each individual protocol. In addition, OHRP's review of protocols and IRB records revealed that some protocols had unresolved concerns following review by the IRB subcommittee, but there was no record in the minutes of IRB meetings of these concerns being addressed by full IRB.

(11) During its record review, OHRP found several protocol applications in which the IRB failed to receive or consider sufficient information for the IRBs to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111(a). For example, certain IRB applications provided only minimal information regarding (a) subject recruitment and enrollment procedures; (b) the equitable selection of subjects; (c) provisions to protect the privacy of subjects and maintain the confidentiality of data; and (d) the local context for research conducted in international settings.

(12) HHS regulations at 45 CFR 46.111(b) require the IRB to ensure that additional safeguards have been included in research to protect the rights and welfare of vulnerable subjects. OHRP finds that IRB records failed to demonstrate consistently the consideration of such safeguards.

Additional Findings

(13) HHS regulations at 45 CFR 46.107(e) stipulate that no IRB member may participate in the IRB's initial or continuing review of a project in which the member has a conflicting interest, except to provide information requested by the IRB. OHRP found instances in which IRB members inappropriately participated in the initial and continuing review of protocols for which they had a conflicting interest. As noted in OHRP's October 3, 2000 letter, OHRP strongly recommends that IRB members absent themselves from the meeting room when the IRB votes on research in which they have a conflicting interest, and such should be noted in the IRB meeting minutes.

(14) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes to previously approved research. OHRP finds that the IRBs routinely employed expedited procedures to review changes that exceed this limitation.

OHRP recommends that institutions adopt policies describing the types of minor changes in previously approved research which can be approved by expedited review in accordance with HHS regulations at 45 CFR 46.110(b)(2).

(15) HHS regulations at 45 CFR 46.116(a) delineate specific elements required for informed consent.

(a) OHRP found multiple instances where (i) required elements were omitted or inadequate; and (ii) there were discrepancies between the protocol application and the informed consent documents regarding the purpose, risks, and benefits of the research.

(b) OHRP is concerned that the IRBs encourage investigators to limit the length of informed consent documents, and as a result, important information is being excluded.

(16) HHS regulations at 45 CFR 46.116(b) require that, when appropriate, additional elements of informed consent be provided to each subject. OHRP found numerous instances where it would have been appropriate for the informed consent document to include one or more of these additional elements. In particular, the elements at 46.116(b)(2), (4) and (5) were the additional elements most frequently overlooked.

As previously stated in OHRP's letter of October 3, 2000, OHRP again strongly recommends that the informed consent document boilerplate used by the IRBs and checklist be modified to include the additional elements at 45 CFR 46.116(b).

(17) HHS regulations at 45 CFR 46.116 require that the information provided in the informed consent documents be in language understandable to the subject. OHRP is concerned that the informed consent documents approved by the IRBs often appeared to include complex language that would not be understandable to all subjects.

(18) OHRP is concerned that the boilerplate informed consent document is difficult to understand and contains information that may be irrelevant for certain research projects.

(19) OHRP is concerned that the current membership of the IRBs appears to lack the diversity, including consideration of race and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects, as required under HHS regulations at 45 CFR 46.107(a).

(20) With respect to the JHUSOM IRBs, OHRP is concerned that many of the above findings may be indicative of IRBs overburdened by the large volume of research for which it has oversight responsibility. It is OHRP's experience that such a large volume of human subjects research warrants more than two fully functional IRBs.

(21) HHS regulations at 45 CFR 46.103(b)(2) require that institutions provide sufficient staff to support the IRB's review and recordkeeping duties. OHRP is concerned that the level of staff support provided to the JHUSOM IRBs appears to be insufficient. It is OHRP's experience that the volume of human subjects research conducted by the institution warrants additional professional and clerical IRB staff members.

(22) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP's discussions with IRB members and its review of IRBs documents reveal no evidence that the IRB consistently makes the required findings when reviewing research involving children.

(23) HHS regulations at 45 CFR 46.305-306 require specific findings on the part of the IRB for approval of research involving prisoners. OHRP's discussions with IRB members and its review of IRB documents reveal no evidence that the IRB makes the required findings when reviewing such research.

(24) OHRP is concerned that the IRBs issue approval letters to investigators prior to receiving and confirming the adequacy of revisions required by the IRBs.

(25) HHS regulations at 45 CFR 46.116(d) require that the IRB find and document four specific criteria when approving waiver or alteration of some or all of the required elements of informed consent. OHRP's discussions with IRB members and its review of IRB documents reveal no evidence that the IRB consistently satisfies these requirements.

(26) OHRP is concerned that the Chairs and members of the IRBs appear to lack a detailed understanding of the specific requirements of the HHS regulations for the protection of human subjects. As a result, IRB determinations have sometimes deviated from these requirements.

(27) OHRP finds that the institution does not have written IRB policies and procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

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.

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.