Ethical and Regulatory Issues Surrounding Clinical Research
March 6, 2017
Vaccinology Course – Prev 627

Robert Edelman, M.D.
Clinical Professor of Medicine and Pediatrics.
Associate Director for Regulatory Affairs and Bioethics,
IGH & Center for Vaccine Development, UMSOM.
Vice-Chair, Institutional Review Board, UMB.
Director, Clinical Research Training & Mentoring Program, UMB.
Objective

To understand the ethical principles and regulations governing clinical research, with emphasis on human trials of investigational drugs and vaccines.
Content

• Definitions
• Modern history of the development of clinical research ethics and supporting regulations
• The conduct of ethical research
  – Basic guidelines – the Belmont Report, 1979
  – Seven ethical requirements – Emanuel et al, 2000
  – Good Clinical Practice (GCP) guidelines
• The Institutional Review Board
  – A case study
DEFINITIONS

• “Medical Research”
  – Hypothesis tested using a formal protocol with a set of procedures designed to reach a conclusion.
  – Hypothesis designed to contribute to generalizable knowledge, not to the betterment of an individual participant.
  – The first responsibility is to the research
    • The research participant must be removed from the trial if:
      • He/she no longer satisfies study inclusion or exclusion criteria
      • An effective licensed drug becomes available.
  – The line between medical practice and research is sometimes blurred.
DEFINITIONS

• “Human Research Subject”
  – A living individual about whom an investigator obtains data:
    • through interaction with the individual
    • OR
    • through identifiable private information
DEFINITIONS

• “Clinical Trial”
  – Pre-planned human study of the safety, efficacy, dosage, or dose schedule of a diagnostic, device, drug or biologic.
  – Usually controlled
  – Pre-determined criteria for volunteer eligibility
  – Volunteers observed for evidence of favorable and unfavorable effects.
DEFINITIONS

• “Good Clinical Practice” (GCP)
  – An international ethical and scientific quality standard for designing, conducting, recording, and reporting trials in humans
    • GCP is really “Good clinical research practice”
  – Regulatory agencies (FDA, DHHS, UMB, IRB) require all trials leading to licensure of a drug, biologic, or device be conducted under GCP
    • Trial is conducted ethically
    • Trial is scientifically sound
    • Trial results are verifiable
      – independent auditor can verify that study results are accurate.
DEFINITIONS

• “Conflict of Interest (COI)”
  – Where financial or other compensation may compromise judgment used to plan, conduct or evaluate research
  – Can influence the institution, investigator, research nurse, IRB member, or safety monitor.
  
  • protocol design
  
  • volunteer recruitment
  
  • assessment of drug or vaccine reactions
  
  • data collection, analysis, interpretation and publishing
Increased Emphasis on Ethical Research

1. Paternalism less tolerated
   - Greater demand for information and access
   - Less disparity between physician and patient
   - Less disparity between researcher and volunteer

2. Research must be public rather than private
   - Public funding uses tax dollars
   - Greater political interest

3. Increased reporting of health news

4. Politically active health groups
   - AIDS, cancer, woman’s health, etc.

5. High-profile research scandals
High-profile research scandals
Historical perspectives

• Eric Poehlman, PhD - 2006
  – A prominent scientist in the field of human obesity and aging
  – Defrauded Federal agencies out of $2.9 million
  – The first academic in the United States to be jailed for falsifying data in a grant application.
  – A “brilliant investigator”
Andrew Wakefield, MMBS – 1998-2011

- Wide media coverage, worldwide panic among parents; MMR vaccinations decreased dramatically; loss of herd immunity to MMR; many cases of encephalitis and death; autism research was diverted
- The *Lancet* retracted Wakefield’s paper in 2010
  - Falsified scientific results and falsified IRB approval
- *British Medical Journal*, January 2011
  - An elaborate fraud.
  - Wakefield planned to market a diagnostic screening test for children predisposed to autism.
Why Integrity Matters in Clinical Research

- Puts volunteers at risk
- Wastes money
- Wastes time
- Delays development of effective therapies
- Undermines the public trust
  - Research is a privilege, not a right
Modern History of the Development of Clinical Research Ethics and Supporting Research Regulations

*Research regulations are operationalized ethics*
Held at the Palace of Justice in Nuremberg, Germany. Trial began on December 9, 1946. Four American judges presided.

The trial documented the most gruesome and painful medical experiments ever conducted - typhus infection, sea water ingestion, high-altitude decompression, bone transplantation, extreme cold exposure, sterilization, and poison bullets.

85 witnesses and 471 documents. Judgment was pronounced on August 19, 1947. Of the 23 defendants, 7 sentenced to death by hanging, 9 given prison terms, and 7 found not guilty.

The “modern’ era of human subject protection begins with the Nuremberg Code in 1947
High altitude stimulations at Dachau
How much decompression can inmates tolerate before pain and death
Dacheau – results of typhus, burn and irradiation experiments
The Nuremberg Code, 1947
Summary

• Established principles of research on *normal subjects*
  – Informed consent of volunteers must be obtained without coercion
    • Consequences are disclosed
  – Scientific merit
    • Human experiments should be based upon prior animal experiments
    • Anticipated scientific results should justify the experiment
    • Only qualified scientists should conduct the research
  – Risk/Benefit balance
    • Physical and mental suffering should be avoided
    • There should be no expectation of death or disabling injury
    • Risk to the individual should be justified by the benefit to the individual or society
  – Subject has the right to withdraw
Thalidomide Incident, 1961

• New anti-nausea pill in Europe
  – Thousands of babies born deformed
  – Women not told they were being given an experimental drug
  – Consent was not obtained
  – Manufacturer supplied samples to US physicians for “research” without FDA approval

• 1962 Kefauver-Harris Amendments to the Pure Food and Cosmetic Act
  – Required documentation of efficacy and safety before new drug could be licensed
  – Required informed consent of study volunteers
  – Required systematic reporting of adverse events
Helsinki Declaration, 1964
World Medical Association

• Went beyond Nuremberg Code to address research with *therapeutic intent*
• Addresses diminished volunteer competence to provide informed consent
• Focuses on favorable risk-benefit ratio
• Calls for oversight of research by “Helsinki Committees” (Institutional Review Boards, Human Ethics Committees)
  – *IRB oversight independent of the investigator and the sponsor*
Blatantly unethical research was conducted by prominent researchers, major medical centers, respected funding sources, prestigious journals (22 cases cited)

- Injected cancer cells into non-consenting elderly patients as part of a study of immunity to cancer.
- Deliberately exposed institutionalized children to hepatitis virus to determine the period of infectivity.
- Performed heart catherizations on patients who thought they were just getting bronchoscopy.
- Inactive control treatment used in patients with serious, treatable diseases.
“Statements regarding consent are meaningless unless one knows how fully the patient was informed of all risks.”
– 1979, Nelly Westerman prize in Clinical Ethics, Dr. William Woodward, U of MD, for development of multi-choice quiz of healthy research volunteers to demonstrate their understanding of study’s purpose, procedures, risks and benefits after being informed.

“The second most important component of ethical experimentation is an intelligent, informed, conscientious, compassionate, responsible investigator.”
Tuskegee Study, 1932 - 1973

- Natural history study of untreated syphilis in 412 African American men
  - US Public Health Service investigators and USPHS funding
    - No informed consent
  - Patients were allowed to believe they were being treated for syphilis
    - New treatments (e.g., penicillin) neither studied nor offered as they became available (123 deaths)
  - A major disincentive for African Americans to volunteer for research
Regulations In the Wake of the Tuskegee Study

• 1974 - National Research Act
  – Established requirements for informed consent and IRB review.
  – Created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

• 1979 - Belmont Report
  The philosophical basis for subsequent Federal regulations for ethical conduct of clinical research
The Belmont Report, 1979

• **Beneficence** (risk-benefit assessment)
  - Minimize the risks; maximize the benefits
    - Do no harm
    - No risk is appropriate if no scientific merit

• **Justice** (selection of research subjects)
  - Experiments generally should not be conducted in persons unlikely to benefit from subsequent applications of the research
    - distribute research risk and benefit fairly
    - treat volunteers fairly

• **Respect for Persons/Autonomy** (informed consent)
  - Subjects have the right to decide on their own if they want to participate in the research
    - avoid coercion
Regulations In the Wake of the Tuskegee Study

• 1980-1998 - FDA Human Subjects Regulations
  – 21 CFA part 50 (IRB regs) and part 56 (Human Subjects regs)

• 1981-1991 - DHHS Human Subjects Regulations
  – 45 CFR part 46, basic
  – Detailed regulations requiring IRB review at Federally-supported institutions

• 1982 - Council for International Organization of Medical Sciences (CIOMS Guidelines)
  – International research allowing for cultural differences

• 1991 - The Common Rule, 21 CFR
  – Unified set of regulations for ethical conduct of research used by 17 federal departments

• 1995 - International Conference on Harmonization (ICH)
  – Industry guidelines for good clinical practice
Two Recent Research Scandals Have Led to Increased Investigator Training and Regulatory Oversight

• Investigators and Institutions ignored basic ethical principles
  – 2001, Johns Hopkins, hexamethonium inhalation & death of Helen Roche, a healthy volunteer

• These scandals resulted in
  – the strengthening of IRBs
  – mandatory training of all research staff in ethics and research regulations
  – increased oversight of investigators by IRBs
  – increased oversight of IRBs by the Federal Office for Human Research Protection (OHRP)
Seven Ethical Requirements for Clinical Research

EJ Emanuel, D Wendler, C Grady. *JAMA* 283; 2701, 2000

1. **Value** - enhancement of health or of knowledge must be derived from the research

2. **Scientific Validity** - the research must be methodologically rigorous

3. **Fair subject selection** - scientific objectives should determine the individual or community selected for study; vulnerability or privilege should not determine who is selected

4. **Favorable risk-benefit ratio** - the potential benefits to individuals and knowledge gained for society must outweigh the risks; risks must be minimized and potential benefits enhanced

5. **Independent review** - unaffiliated individuals must review the research and approve, amend, or terminate it

6. **Informed consent** - individuals should be informed about the research and provide their voluntary consent

7. **Respect for enrolled subjects** - subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored
Seven Ethical Requirements for Clinical Research

(Emanuel, Wendler, Grady. 2000, *JAMA* 283;2701)

1. **Value - Clinical research must be valuable**
   - Valuable research
     - Evaluates a treatment, intervention or theory that will improve health or increase knowledge
   - Valueless research
     - Non-generalizable results
     - Trifling hypothesis
     - Overlaps with already proven results
     - Results unlikely to be disseminated
     - Intervention could never be practically implemented
   - Addresses responsible use of finite financial and human resources
Seven Ethical Requirements for Clinical Research

2. Scientific validity – the research must be methodologically rigorous
   - Use accepted scientific principles and methods to produce reliable data
   - Scientifically unsound research is unethical because it exposes volunteers to risks for no purpose
     • Biased research design (clinical samples inadequate, questionnaires biased, statistical tests invalid)
     • Neglects critical endpoints
     • Underpowered
     • Overpowered
     • Sloppy conduct of the study
     • Uninterruptible data for any reason
   - Clinical equipoise
     • There is no consensus about which is the better of two treatments
Seven Ethical Requirements for Clinical Research

3. Fair subject selection
   – Individuals who bear the burdens and risks should be in a position to enjoy the benefits of research
   – Healthy volunteers who may not benefit can participate if the research is valuable to society
     • Typical Phase I/II vaccine trials
     • Trial design and conduct must be impeccable
   – Individuals who may benefit from the research should share some of the burdens and risks
   – Avoid the temptation of “convenience samples”
     – Efficiency of recruitment of volunteers cannot override fairness of recruitment
Seven Ethical Requirements for Clinical Research

3. Fair subject selection
   – Vulnerable populations
     • Children
     – Assent - Vocal or written
     • Pregnant women
     • Psychiatric patients
     • Cognitively impaired
     • Elderly
     • Prisoners
     – Prisoner ombudsman
     • Racial and ethnic minority groups
     • Economically or educationally disadvantaged
     • Students, employees, patients
Why Healthy Individuals Volunteer for Vaccine Trials

• Financial rewards
  – National website for professional volunteers
  – Risk of undue inducement and coercion

• Contribute to society

• Fear of bioterrorism, pandemic influenza, Ebola

• Shortage of seasonal influenza vaccines

• Eager to benefit from the experimental vaccine

• Intellectual curiosity
Seven Ethical Requirements for Clinical Research

4. **Favorable risk-benefit ratio**
   - All clinical research possesses some degree of risk
     - **Physical** – allergic reaction, Guillain-Barré syndrome
     - **Psychological** - questionnaires that result in emotional discomfort
     - **Economic** - medical costs that insurance company refuses to pay
     - **Social** – records of HIV infection, criminal record; Certificate of Confidentiality
     - **Confidentiality** of the data
     - **Privacy** of the person
     - **Time burden**
Seven Ethical Requirements for Clinical Research

4. Favorable risk-benefit ratio
   – Not all risks are known
     • Research inherently entails uncertainty
     • Nasty surprises happen during trials
   – Are the benefits to the subject and society proportionate to the risks
     • Non-quantifiable
     • Decided by IRB consensus
   – If no direct benefit to the individual, do societal benefits (in terms of knowledge) justify the risks
Seven Ethical Requirements for Clinical Research

5. Independent review - for risks and benefits
   – Independent review better assures
     • ethical treatment of volunteers
     • favorable benefit/risk ratio
   – Local IRBs
   – Data and Safety Monitoring Boards
   – FDA
   – Funding agencies
     • Government (e.g., NIH, DOD, Veterans Administration)
     • Biotech and big pharma
     • Charitable foundations
     • The independent investigator (the lone cowboy)
Seven Ethical Requirements for Clinical Research

5. Independent review – Conflict of interest
   – Competing interests generate conflicts that distorts ethical judgment
     • Conduct high-quality research
     • Protect research volunteers

VERSUS

• Complete the research quickly
• Make money and obtain funding for research
• Achieve fame and advance careers
• Thirst for knowledge
Seven Ethical Requirements for Clinical Research

5. Independent review – U.S. Public Health Service Conflict of Interest Rule – August 24, 2012

- Educate investigators before research begins
- Repeat every 4 years
- Investigator discloses significant financial interests to the University if planning to participate in PHS-funded research
  - No lower $ threshold
  - Include self, spouse, dependent
  - Remuneration from, or equity in, a publicly traded or non-publicly traded entity
  - Intellectual Property-related income, except that which is received through the University
  - Reimbursed or sponsored travel
- Financial Conflict of Interest (FCOI) determined by the University
- Development of Management Plan by the University
  - Public disclosure, discuss with Dept chair, remuneration caps
- University reports FCOI and Management Plan to PHS
Seven Ethical Requirements for Clinical Research

5. Independent review – U.S. Public Health Service Conflict of Interest Rule – August 24, 2012

• Does not deal with other potential conflicts
  – Academic Promotion
  – Enhanced Prestige
  – Overwhelming Curiosity and thirst for knowledge
Seven Ethical Requirements for Clinical Research

6. Informed Consent Document
   – Informs volunteers about
     • Purpose of the research
     • Background information
     • Study design and research procedures vs standard of care
     • Potential risks and discomforts and safeguards to minimize risk
     • Benefits of the research
     • Confidentiality: preservation of subject’s personal information
     • Privacy: preservation of access to the volunteer
     • Alternatives to participation and right to withdraw
     • Cost to volunteer (time and money) and $ compensation
     • Treatment rights in event of a study-related injury
     • Indemnification information
   – Individual should understand this information and make a voluntary decision whether to enroll and to continue to participate after enrolled.
Army Service Forces
Board for the Investigation of Epidemic Diseases
United States Army
AUG 2 1944

Waiver and Release

Know all men by these presents: That, I, __________________________, an inmate at the New Jersey State Prison, Trenton, New Jersey, being of ___________ years of age, for and in consideration of the good it may be for humanity and for other good and valuable considerations, the receipt of which is hereby acknowledged, do hereby voluntarily submit myself to the Commission on Neurotropic Virus Diseases, Board for the Investigation and Control of Influenza and other Epidemic Diseases in the U. S. Army, for the purpose of experiments on dengue, sandfly and related fevers, and I hereby consent to be infected in an attempt to discover an immunizing agent against these diseases, and to be subjected to such tests, examinations, and experiments as may be desired by said Commission in connection therewith; and for myself, my heirs, executors, administrators and legal representatives I do hereby waive and release the Government of the United States and the said Commission and Board, and all members of said Commission and all persons or institutions associated with or employed by it, the Government of the State of New Jersey and the Board of Managers of the N. J. State Prison, and all of its officers, agents and servants, of and from any and all liability, except as specified below, for any ill effects, sickness, temporary or permanent disability or death that may result to me by reason of such experiments.

However, it is expressly understood and agreed that, notwithstanding this Waiver and Release, the said Board and Commission will furnish medical care in the ward set aside for this purpose at the New Jersey State Prison, Trenton, New Jersey, for a period which may vary with the requirements of the experiment, it being understood that said Commission shall be the sole judge as to the necessary duration of this initial period of isolation and hospitalization. It is further understood that said Commission shall be the sole judge as to whether any illness occurring subsequent to the termination of this initial period of hospitalization is or is not the result of the aforesaid experiment and is or is not sufficiently severe to require further medical care and the necessary duration thereof.

IN WITNESS WHEREOF, I have hereunto set my hand and seal this _____ day of _______ 1944.

______________________________ (L.S.)

Witness:
Seven Ethical Requirements for Clinical Research

7. Respect for Enrolled Subjects
   – Demonstrated by:
     • permitting voluntary withdrawal from the research without penalty or intimidation
     • Protecting privacy of the volunteer
     • protecting confidentiality of the volunteer’s data
     • informing volunteers of newly discovered risks or benefits
     • careful follow-up to monitor adverse effects and to provide treatment
     • informing volunteers of ongoing and completed results of research
   – The term Human “subjects” is not respectful
     • prefer research “participant”, “partner”, “volunteer”
     • In vaccine trials, the volunteer becomes part of the research team
Responsibilities of Clinical Investigators

• Assures that the conduct of the study complies with all scientific, ethical, and financial principles espoused by UMB and the federal government

• Assures that there are adequate resources to accomplish the research
  – Shared responsibility with Department and Division Chair
Responsibilities of Clinical Investigators

- **Take required GCP training**
  - Read Investigator Manual in CICERO
    - [http://www.umaryland.edu/hrp](http://www.umaryland.edu/hrp)
  - CITI training every two years
    - [https://www.citiprogram.org](https://www.citiprogram.org)
  - HIPAA Training
    - [http://medschool.umaryland.edu/orags/hrpo/education_hipaa.asp](http://medschool.umaryland.edu/orags/hrpo/education_hipaa.asp)

- Request IRB approval of human research protocols
- Obtain and document informed consent of volunteers
- Request IRB approval for all changes in the research protocol
- Submit reports/requests to the IRB
  - Annual renewal request
  - Protocol modification request
  - Reportable New Information (e.g., new risk, unexpected harm, non-compliance with regs, failure to follow protocol, confidentiality breach)
  - Final report
Responsibilities of Clinical Investigators

• Maintain record folder of essential documents
  • Study protocol; Informed consent document; investigator’s brochure; FDA 1572 form; CVs; training certificates; financial disclosure forms; drug data sheet; standard operating procedures; correspondence with IRB, FDA and sponsor; quality assurance records; site monitor reports; DSMB reports; adverse events reports; screening/enrollment log; medical records; etc.
Responsibilities of Clinical Investigators
FDA Form 1572, Statement of Investigator

- Conduct study per protocol
- Personally conduct or supervise investigation
- Inform volunteers that drugs are investigational
- Obtain proper informed consent
- Obtain proper IRB approval
- Report adverse experiences to the sponsor
- Read and understand Investigator’s Brochure
- Ensure staff are informed of their obligations
- Maintain adequate and accurate records
- Make records available for inspection
- Ensure IRB complies with requirements for continuing approval
- Promptly report all requested changes in research activity to IRB
- Report unanticipated problems involving risks to IRB
- Do not make any changes in the research without IRB approval

- Warning: a willfully false statement is a criminal offense. U.S.C. Title 18, Sec 1001
Responsibilities of the IRB and Human Research Protections Office (HRPO)

- Protect the rights and welfare of human participants in research

- Determine if the *benefit* of the research to the participant or society *exceeds* the *risk* to the participant
Responsibilities & Authority of the IRB/HRPO

• Approve, disapprove, or modify new research protocols
• Re-review approved research protocols annually
• Monitor ongoing research studies
  • Audit conduct of study
  • Investigate adverse events
• Suspend or terminate research protocols and/or investigators
• Set requirements for training in ethics and GCP

• *IRB authority is independent of the UMB President*
UMB Human Research Protections Office, 2017

• Chief Academic and Research Officer and Senior Vice President (Dr. Bruce Jarrell)
  – Director, Human Protections Research Office (Julie Doherty)
• HRPO
• 11 staff members
  – 1 Director, 3 IRB Analysts, 3 IRB Administrators, and 4 Regulatory Operation Specialists
  – $2,000,000 budget (President’s Office)
  – Administrates IRB meetings
  – Help investigators and IRB members comply with IRB reviews, regulations and GCP
  – Educates > 3000 faculty and staff in from 7 UMB Professional Schools
    • Educates foreign IRBs, administrators & investigators in GCP
  – Maintains web-based CICERO– “Collaborative Institutional Comprehensive Evaluation of Research Online”
    • IRB protocol management; GCP training, documents, and data bases
    • 2000 research protocols; 25,000 transactions annually
  – AAHRPP accredited
  – Clinical Research Training and Mentoring Program (CRTMP)
UMB Institutional Review Board

- **IRB structure**
  - 1 Chairman; 7 Vice-chairmen
  - 1 panel
  - 85 panel members
  - Panel meets 3 times weekly for 2 hours
  - 4-6 members attend each panel meeting,
    - At least 1 person with expertise in the research being critiqued
    - At least 1 non-scientist
    - At least 1 person not affiliated with the institution
  - ~15 protocols reviewed in each panel meeting:
    - New protocols
    - Renewals
    - Modifications
    - Deferrals
    - Compliance issues
Is it ethical to infect CVD vaccinees and unvaccinated controls with malaria-infected mosquitoes to determine if an experimental malaria vaccine is protective?
YES - 

provided the study adheres to established ethical principles of clinical research.
Criteria for IRB Approval

✓ Is the study logistically feasible?
  – Adequate research staff, facilities, funding
✓ Do the PI & study team have the appropriate expertise?
✓ Is the study adequately designed to meet the aims?
✓ Are the research procedures adequately described?
Criteria for IRB Approval

☑ Are the inclusion/exclusion criteria explicit and justified?
  – 7 inclusion criteria (healthy, 18-50 y.o., willing to participate for the duration of the study, not pregnant, effective means of birth control, willing to refrain from blood donation for 3 years, no travel to malaria endemic region during entire trial)
  – 15 exclusion criteria (e.g. history of malaria infection, prior travel to malaria area, HIV, hepatitis, sickle cell, antibiotic use and allergies, allergy to mosquito bites, pregnant or planning to become pregnant, behavioral disorders, etc)
Criteria for IRB Approval

✓ What are the risks of the study?
  – Risk of the vaccine
  – Risk of antimalarials:
    • Malarone, Coartem
  – Risk of malaria infection.
  – Risk of loss of confidentiality

✓ Are risks minimized?
  – Healthy volunteers.
  – Meticulous Inclusion and exclusion criteria.
  – Experienced research team practicing GCP.
  – Repeated monitoring with PCR and blood smears.
  – Immediate malarone treatment if PCR positive
  – Locked files and password protected data
Criteria for IRB Approval

- What are the benefits of the study?
  - Individual: no direct benefit
  - Society: development of a useful malaria vaccine.

- Are risks reasonable in relation to benefits?

- Is volunteer consent process adequately documented?
  - Compensation for time and effort
  - Minimize possibility of undue inducement

- Is consent form clear and understandable
  - 7th grade reading level
  - Volunteers must score 70% on a multi-choice study quiz.
Criteria for IRB Approval

✓ What is the safety monitoring plan and is it appropriate?
  – A Data and Safety Monitoring Committee composed of 3 independent safety monitors and a local medical monitor chosen for expertise in clinical trials and malaria
  – Periodically evaluates the accumulated study data for participant safety, study conduct and progress
  – Recommends the continuation, modification, or termination of the trial.
Criteria for IRB Approval

✓ Are vulnerable populations adequately protected?

• Employees/Students
  – Subjects recruited through advertising in the same manner as others in the local community.
  – Volunteer initiates contact with the study recruitment team.
  – May decline participation or leave study without loss of academic benefits or employment

• Women of child-bearing potential
  – Will have a negative pregnancy test
  – Will use adequate birth control during the trial
Summary: Ethics of Clinical Research

- Public trust and confidence in clinical research eroded by
  - Reports of violations of federal regulations for protection of human subjects
  - Most violations caused by lack of awareness, not malice
- All members of the research community have a responsibility to ensure that research is conducted ethically
  - Principal investigator, sub-investigators and research staff
  - Data and safety monitoring committees
  - Clinical departments and divisions
  - University administration
  - Sponsoring organizations
  - State and federal regulatory agencies
- The IRB/HPRO - with cooperation of the entire research community - must create a “culture of conscience.”
DAILY PRAYER OF MAIMONIDES

Almighty God, You have created the human body with infinite wisdom. In Your Eternal Providence You have chosen me to watch over the life and health of Your creatures. I am now about to apply myself to the duties of my profession. Support me in these great labors that they may benefit mankind for without Your help not even the least thing will succeed.

Inspire me with love for my art and for Your creatures. Do not allow thirst for profit, ambition for renown and admiration to interfere with my profession. For these are the enemies of truth and can lead me astray in the great task of attending to the welfare of Your creatures. Preserve the strength of my body and soul that they may be ever ready to help rich and poor, good and bad, enemy as well as friend. In the sufferer let me see only the human being.

Enlighten my mind that it may recognize what presents itself and that it may comprehend what is absent or hidden. Let it not fail to see what is visible but do not permit it to arrogate to itself the power to see what cannot be seen for delicate and indefinite are the bounds of the great art of caring for the lives and health of Your creatures. May no strange thoughts divert my attention at the bedside of the sick or disturb my mind in its silent labors.

Grant that my patients may have confidence in me and my art and follow my directions and my counsel. When those who are wiser than I wish to instruct me, let my soul gratefully follow their guidance for vast is the extent of our art. Imbue my soul with gentleness and calmness. Let me be contented in everything except in the great science of my profession. Never allow the thought to arise in me that I have attained to sufficient knowledge but vouchsafe to give me the strength and the ambition to extend my knowledge. The art is great, but the mind of man is ever expanding.

Almighty God You have chosen me in Your mercy to watch over the life and death of Your creatures. Support me in Your great tasks so that it will benefit mankind, for without Your help not even the least thing will succeed.
Some Basic References

Textbook References

Journal References

Questions?