



U.S. Food and Drug Administration

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# **The Genesis of the Human Subjects Protections Regulations and Biomedical Research in the 21<sup>st</sup> Century**

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Clinical Trial Workshop  
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## **Disclaimer**

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# Objectives

- Discuss the historical background behind Human Subjects Protections (HSP) regulations
- Describe the underlying ethical principles behind HSP regulations
- Discuss various stakeholder responsibilities for HSP
- Discuss some of the challenges of the 21<sup>st</sup> Century
- Summarize Bioresearch Monitoring (BIMO) program

## Events with Impact

- Nazi Experimentation - 1946-47
- Thalidomide – 1960s
- Dr. Henry Beecher article in NEJM - 1966
- Tuskegee Syphilis Experiment - 1932-1972

# The Genesis of IRB & IC Regulations

- **1930/1940s: Nazi Experimentation**
  - High altitude simulation
  - Malaria pathogenesis
  - Cold water immersion
  - Chemical sterilization
  - Typhus

Trials resulted in Nuremburg Code of Medical Ethics

# The Genesis of IRB & IC Regulations

- **1962: Food Drug and Cosmetic Act amended**
  - Required proof of safety and effectiveness (Thalidomide)
  - Required informed consent in clinical trials
- **1964: Declaration of Helsinki (WMA)**
  - Code of Research Ethics
    - Adequate design conforming to scientific principles
    - Review by an independent committee
    - Properly trained researchers

# The Genesis of IRB & IC Regulations

- **1966: Dr. Henry Beecher NEJM “Ethics and Clinical Research”**
  - Described 22 unethical studies conducted by well-reputed investigators and published in well-respected research journals
  - Suggested that journal editors reject articles based on violations of patient rights
  - Stated if unethical research were not prohibited **“it would do great harm to medicine”**

# The Genesis of IRB & IC Regulations

- **1932 -1972: Tuskegee Syphilis Experiment**
  - Observational study of the effects of untreated syphilis
  - African-American males; Generally poor and uneducated
  - Not told the purpose of the study
  - Provided burial funds as an incentive to participate
  - Not informed of treatment options (1947 Penicillin was drug of choice to treat)

# The Genesis of IRB & IC Regulations

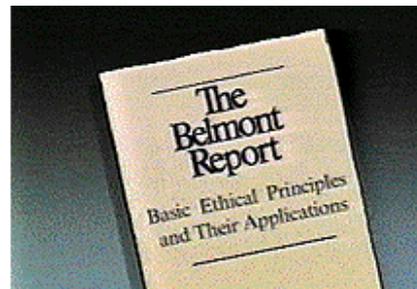
- **Other problematic studies**
  - 1963-66: Willowbrook State School Study
    - Intentionally infected children with hepatitis
  - 1963: Jewish Chronic Disease Hospital Study
    - Injected live cancer cells into demented elderly patients
  - 1963: Milgram Obedience Study
    - Deception study

# National Commission

- **1974: National Research Act**
  - Established IRB system
  - Created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
    - Met between 1975 - 1978

# The Belmont Report

## Ethical Principles and Guidelines for the Protection of Human Subjects of Research



**The National Commission for the Protection of Human Subjects of  
Biomedical and Behavioral Research**

**April 18, 1979**

# The Belmont Report Principles

- **Respect for Persons**
  - Individual autonomy/right to self-determination
  - Protection of individuals with reduced autonomy
- **Beneficence**
  - Maximize benefits and minimize harms
- **Justice**
  - Equitable distribution of research costs and benefits

# Ethical Framework for Regulations

- **Respect for Persons**
  - Informed consent document and process
  - Surrogate consent and child assent
  - Protection of subjects (esp. vulnerable populations)
- **Beneficence**
  - Risk/Benefit analysis
  - Experimental design
  - CI qualifications
- **Justice**
  - Subject selection
  - Inclusion/exclusion criteria
  - Recruitment

## FDA & HHS Regulations

- Implement the National Commission’s recommendations
- **FDA IRB regulations: 21 CFR Part 56**
  - January 1981
- **FDA Informed Consent regulations: 21 CFR Part 50**
  - January 1981
- **Federal Policy for the Protection of Human Subjects - “The Common Rule”-45 CFR Part 46**
  - June 1991
  - Departments of Agriculture, Energy, Commerce, HUD, Justice, Defense, Education, Veterans Affairs, Transportation, and HHS; NSF, NASA, EPA, AID, Social Security Administration, CIA, and the Consumer Product Safety Commission

# HHS & FDA Regulations

- **Additional HHS Protections in 45 CFR 46:**
  - **Subpart B** – Additional protections for Pregnant Women, human fetuses and neonates
  - **Subpart C** – Additional protections for Prisoners
  - **Subpart D** – Additional protections for Children
  
- **Additional FDA Protections in 21 CFR 50:**
  - **Subpart D** – Additional protections for Children
    - Effective 4/30/01

## **FDA & HHS Regulations**

- Most IRBs review both HHS supported and FDA regulated research and are therefore subject to both HHS and FDA regulations.
- Basic requirements for IRBs and for Informed Consent are similar

## What is an IRB?

FDA defines an IRB as any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of human subjects

## What Requires IRB Review for FDA?

Any clinical investigation which must meet the requirements for prior submission (as required in parts 312, 812, and 813) to the FDA shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of part 56

\*(exceptions provided in 56.104 and 56.105)

# Human Subjects Protections

- IRB & IC regulations are two important components of HSP, but there are many activities that positively affect human subject protections
- Human subject protections are incorporated into all stages of the clinical investigation
  - **Before trial start:**
    - IRB review and approval
    - FDA IND review
    - GCP/GLP

# Human Subjects Protections

## – During trial conduct

- IRB continuing review
- Informed consent process
- DMC/DSMB
- Real-time inspections: IRB, CI, Sponsors, Manufacturers (**greater emphasis**)

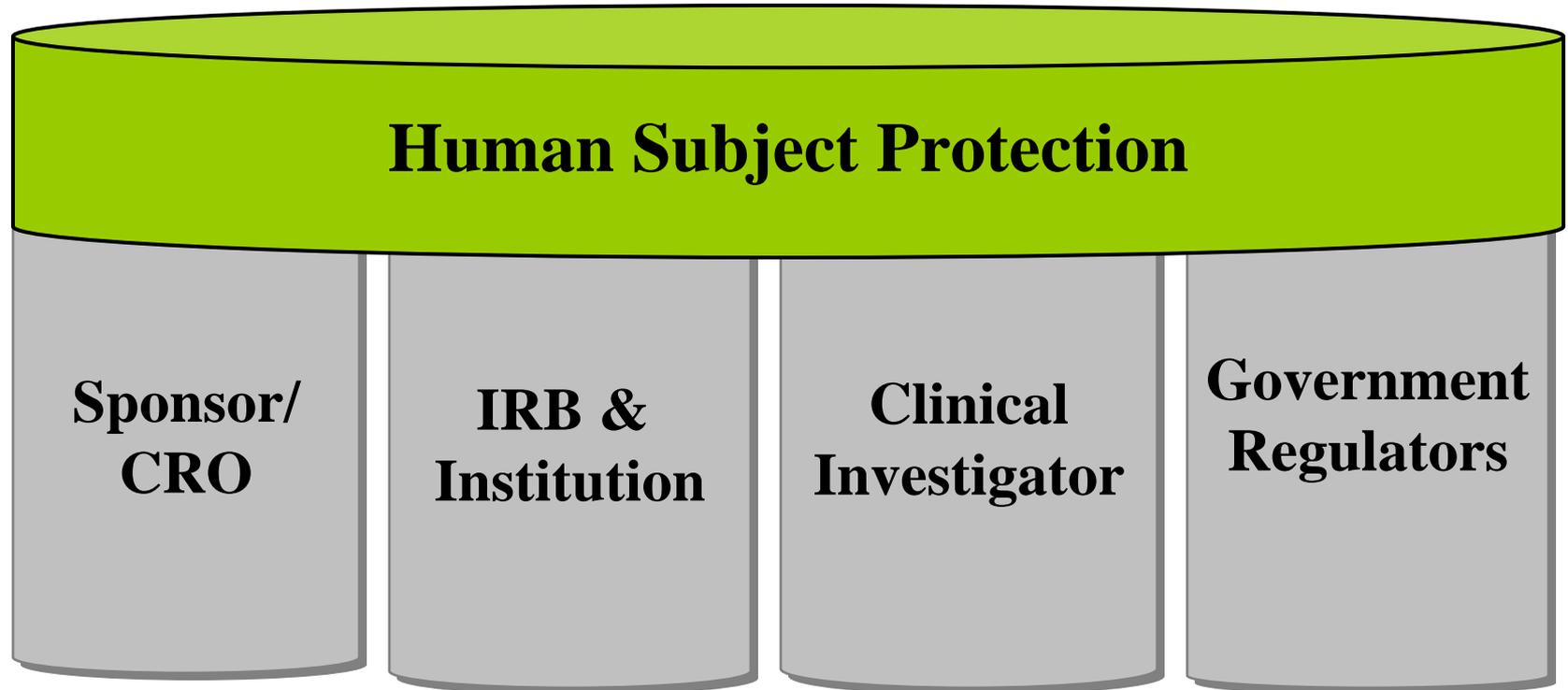
## – After trial completed

- Inspections: IRB, CI, Sponsors, Manufacturers (traditional approach)
- FDA NDA review



# Human Subject Protections

Require a Collaborative Partnership Among . . .



# Responsibilities in Clinical Research

- Institutions
- Sponsors
- Clinical Investigators
- IRBs
- Regulators
- CROs
- DMC/DSMB
- Subjects

## **Institutional Responsibilities (partial list)**

- Designate one or more IRBs to review and approve all FDA-regulated research
- Provide sufficient space and staff to support the IRB's review and record-keeping duties
- Ensure that there is an institutional environment that promotes the ethical conduct of research
- Ensure the IRB is situated to command respect for its advice and decisions

## **Sponsor Responsibilities (partial list)**

- Select qualified investigators
- Provide CI with the information they need to conduct an investigation properly
- Ensure that the investigation is conducted in accordance with the protocol
- Maintain an effective IND for the investigations
- Ensure that FDA and CIs are promptly informed of significant new adverse events or risks with the drug

# CI Responsibilities

## Form FDA 1572 (partial list)

- Ensure research is conducted according to protocol
- Protect the rights, safety and welfare of subjects
- Ensure control of test article
- Conduct or supervise investigation
- Ensure all persons assisting in study are informed of obligations
- Report adverse events
- Maintain adequate and accurate records
- **Ensure initial and continuing review by IRB**
- Report all changes to research and unanticipated problems involving risks to subjects, and not make changes without IRB approval (except where necessary to eliminate immediate hazards to subjects)

## IRB Responsibilities (partial list)

- Review and have authority to “approve, require modifications in (to secure approval), or disapprove” all research.
- Communicate with CI
- Determine:
  - Risks to subjects are minimized
  - Risks to subjects are reasonable in relation to anticipated benefits
  - Selection of subjects is equitable
  - IC will be sought and documented as required by part 50
  - Where appropriate: monitoring of data to ensure safety
  - Where appropriate: privacy and confidentiality protections<sub>27</sub>

# Scientific Validity

- **Foundation for ethical research because without a good design there is no good argument for any level of risk**
- The Nuremberg Code, The Declaration of Helsinki and FDA regulations all address the importance of methodologically rigorous research
- Study design is able to accomplish its stated objectives: Use of accepted scientific principles and methods to produce reliable and valid data
- A trial that is scientifically invalid is inherently unethical

# Important Considerations for IRB and CI

- Minimization of risks to subjects without compromising reliability of the research results
  - Minimizing risk by studying a less sick population
    - Affect on scientific validity?
    - Affect on generalizability of results?
- Clinical equipoise
  - No consensus in the expert clinical community on the efficaciousness of a product (honest null hypothesis)
  - Purpose of study is to resolve the dispute
  - **i.e. If you know the answer then why study the question!**

# 21<sup>st</sup> Century Challenges

- Clinical Investigators
- IRBs
- Subjects
- Regulators
- Sponsors

# Clinical Investigators

## A Changing Clinical Trial Landscape

- An expanding and fluid pool of CIs
- Variably educated and trained to conduct clinical investigations
- More often working at private clinics than academic medical centers
- More delegation of responsibility (not always clear to whom)
- Growing bureaucracy and difficult regulatory environment

# Clinical Investigators

## A Changing Clinical Trial Landscape

- Increasing demand for education of clinical trial design, oversight, biostatistics, GCP and bioethics
- Ever increasing demands of clinical practice
- Changing medical legal environment
- Greater reliance on web-based trial activity and constantly changing technology
- Studies increasingly multi-national requiring satisfying foreign regulators requirements
- Greater demand for transparency of protocols and results

# The IRB

## A Changing Clinical Trial Landscape

- Greatly increasing volume of studies
- More multicenter studies; more “reports” to review
- Multiple “new” roles within their institutions (often beyond the regs)
- Turnover, status, and education of members
- More protocols involving vulnerable populations
- Potential for pressures of accreditation (optional)
- Legal environment
- Genetics research

# The Subject

## A Changing Clinical Trial Landscape

- Trial protocols are more complicated
- Complex informed consent documents
- Concerns raised regarding trust of clinical trials process
- Patients want increased access to:
  - Investigational products (outside the study)
  - Results of clinical trial
- Subjects participating in more than one trial – potential source of income

# FDA

## A Changing Clinical Trial Landscape

- More sites/CIs per trial
- More foreign trials (difficulties in inspecting)
- More outsourcing/delegation of responsibilities in trials, e.g., to CROs, sub-investigators
- Regulations don't recognize many parties involved in trials, e.g., CROs (for devices)
- More trials involving vulnerable populations
- Tension between need to rapidly approve new medications versus the need to assure safety
- Need to harmonize regulations domestically and internationally

## Sponsor

### A Changing Clinical Trial Landscape

- More studies per application
- Difficulties in finding eligible subjects/growing mistrust
- More pediatric studies; combination products
- More small sponsors (especially CDRH)
- Greater reliance on multinational research: patch work of regulations
- Pressure to increase transparency of study results
- Constantly rising costs
- Growing concerns about litigation
- Identifying, training, and retaining CIs  
(Majority of CI participate in only one study then stop)

# General: Changing Clinical Trial Landscape

- **Concern about Conflict of Interest**
  - Growing concern with the public
  - Affects IRBs, CI, NIH, FDA and others
  - Increasingly difficult to find specialist without a conflict
- **Demands for increase transparency**
  - Trial results (implications for competition)
  - Trial conduct
- **International harmonization**
  - Changing regulatory landscape
  - Greater need for understanding local context



# **Bioresearch Monitoring (BIMO) Program and Human Subject Protection**

## BIMO

- FDA's BIMO program is a comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA regulated research
- The BIMO program has become a cornerstone of the FDA preapproval process for new medicines, medical devices, food and color additives and veterinary products introduced to the U.S. consumer

## BIMO

- The program also has international and interagency components
- The Bioresearch Monitoring Program Coordinator, located organizationally within the Office of Regulatory Affairs, under the Office of Enforcement, Division of Compliance Policy is responsible for overall coordination of the BIMO program

# BIMO

- Each FDA Center has oversight of inspections of research related to the product(s) it regulates
- Inspections are usually conducted by ORA field investigators
  - Field investigators are NOT specifically assigned to CDER
  - All Field investigators are responsible for conducting inspections for all centers



## BIMO

- FDA uses Compliance Program Guidance Manuals (CPGMs) to direct its field personnel on the conduct of inspectional and investigational activities
- The CPGMs form the basis of FDA's Bioresearch Monitoring Program
  - CPGM for Clinical Investigators
  - CPGM for Sponsors, Contract Research Organizations, and Monitors
  - CPGM for Good Laboratory Practice (Non-Clinical Laboratories)
  - CPGM for In-Vivo Bioequivalence
  - CPGM for Institutional Review Boards

## **BIMO Objectives**

- Verify the quality and integrity of data
- Protect the rights and welfare of human research subjects
- Ensure that FDA regulated research is conducted in compliance with applicable regulations

## **BIMO Inspection Programs**

- Clinical Investigators
- Bioequivalence/Good Laboratory Practice
- Sponsor/Monitor/CRO
- **IRB/RDRC**
  - Developing a more robust RDRC surveillance program
  - Close coordination between Centers
  - Greater emphasis on follow-up inspections when substantive issues found

## BIMO

- Covers all FDA regulated products
- Number of studies inspected limited by available resources
- Generally inspect after studies completed
  - FDA shifting more resources to “real-time” inspections
  - Selecting sites for inspection becoming increasingly more sophisticated (Risk-based models)

## Helpful Websites

- FDA: <http://www.fda.gov>
- GCP website for IRB, CI and Sponsor Information Sheet Guidance:  
<http://www.fda.gov/oc/ohrt/irbs/default.htm>
- 21 CFR Part 50 and 56:  
<http://www.fda.gov/oc/gcp/regulations.html>
- General GCP Information:  
<http://www.fda.gov/oc/gcp/>
  - Policy Questions: [gcp.questions@fda.hhs.gov](mailto:gcp.questions@fda.hhs.gov)

## Helpful Websites (cont.)

- Belmont Report  
[http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4066b1\\_22\\_Belmont%20Report.pdf](http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4066b1_22_Belmont%20Report.pdf)
- Declaration of Helsinki  
<http://www.fda.gov/ohrms/dockets/dockets/06d0331/06D-0331-EC20-Attach-1.pdf>
- OHRP <http://www.hhs.gov/ohrp/>

Thank you!  
Any Questions?

