Updates in Human Subject Protections

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High publicity of a few failures has resulted in erosion of public trust in all human research.
Scope of the Issues

SUBTEXT

[How do we work to re-assure the “public”, ensure that ethical research thrives and is allowed to be conducted?]

✔ The Evolving Human Research Protection Program
✔ The Responsibilities of the Institutional Official
✔ Alternative HRPP ‘governance” structures
✔ The Emphasis on Accreditation and Certification
✔ Regulatory and Guidance changes on the Horizon
✔ Speculation on Future Directions
Research Ethics Milestones*

**Trigger Events**
- *Syphilis Study Begins*
- *The Nazi Experiments*
- *Human Radiation Experiments*
- *The Thalidomide Tragedy*

**Ethics Milestones**
- Nuremberg Code 1947
- Amendments to the Food, Drug, Cosmetic Act 1962
- Declaration of Helsinki 1964

*From “Protecting Study Volunteers in Research” By Dunn & Chadwick. Pb. Thomson Group
Research Ethics Milestones

Trigger Events

* The Beecher Article 1966
* The Syphilis Study Expose

Ethics Milestones

The Belmont Report 1979
Consolidated HHS/FDA Regulations 1981
CIOMS Guidelines 1982
Common Rule 1991
National Bio-Ethics Advisory Committee 2001

Then came NHRPAC and SACHRP
“These are the regulations...”
“...and these are the interpretations”
From Ethical Principles to Regulations to Guidelines

- Respect for Persons, Beneficence, Justice
- Domestic Regulations
- International Guidelines
- Research Ethics Committees
- IRBs
BASIC PROTECTIONS

The regulations contain three basic protections for human subjects that is also intended to provide the necessary safety:

- Institutional Assurances OR Commitments
- IRB [or “ethics” committee] Review
- Informed Consent and Processes
Regulations and Guidance Governing HRPP Activities

✓ 45 CFR 46 – NIH/PHS/HHS
✓ 21 CFR 50 & 56 – FDA
✓ Common Rule - 45 CFR 46 Subpart A
✓ 21 CFR 11 – FDA Electronic Records;
  Electronic Signatures
✓ 21 CFR 54 – Financial Disclosure by CI’s
✓ 45 CFR 160 & 164 - HIPAA (Health Insurance Portability and Accountability Act) Privacy Rule
✓ ICH E-6 – Guidelines on GCPs
DHHS Regulations

Administered by OHRP, jurisdiction is through the FUNDING.

✓ Apply to studies funded or conducted by any agency of DHHS.

✓ Apply to sites with a Federalwide Assurance (FWA) from OHRP.

✓ Apply to the 16 co-signatories to the Common Rule 45 CFR 46 Subpart A
Subpart B – Fetuses, Pregnant Women and Neonates Involved in Research
45 CFR 46.201 - 207

Subpart C – Prisoners as Subjects in Research
45 CFR 46.301 - 306

Subpart D – Children as Subjects in Research
45 CFR 46.401 - 409
FDA Regulations

Administered by FDA, jurisdiction is through the PRODUCT.

Apply to studies of FDA regulated products, including drugs, biologics, medical devices.

- Informed Consent 21 CFR Part 50
- IRB 21 CFR Part 56
- IND (Drugs and Biologics) 21 CFR Part 312
- IDE (Medical Devices) 21 CFR Part 812
IRB Decision Matrix

BENEFICENCE

JUSTICE

RESPECT FOR PERSONS

Courtesy  Dr. Jeff Cooper
IRB Decision Matrix

**BENEFICENCE**
- Risk/Benefit Analysis
- Experimental Design
- Qualifications for PI

**JUSTICE**
- Subject Selection
- Inclusion/Exclusion
- Recruitment

**RESPECT FOR PERSONS**
- Informed Consent
- Surrogate Consent
- Assent
  
- Protection of Subjects (especially vulnerable populations)

Courtesy Dr. Jeff Cooper
Spectrum of Risks and Determination of Benefits

Annoyance

- Journalism
- Oral History
- Anthropological Investigations

Evaluation Research

- Biomedical Epidemiologic Studies
- Drug Trials
- Surgical Trials

Death

Oakes, Evaluation Review, 2002
The Challenge to the Institutional Official

The role of the Institutional Official

- Sets the “tone” for the protection of human subjects
- Responsible for oversight of the HRPP and the IRB
- Fluent in the regulations and institutional policies
- Ensures all personnel know the regulations
- Establish and enforces reporting requirements
- Provides the necessary staff and other resources
- A senior official equivalent to a “Dean” or VP for Research
The Challenge to the Institutional Official

What else might the Institutional Official be responsible for:

- Signatory and responder to FDA inspections
- Animal Welfare, including the work of the IACUC
- The workings of the Institutional Bio-safety Committee
- Acting as the Research Integrity Officer
- Ensuring adherence to the Conflict of Interest policy
- Fulfilling the NIH requirements for approvals
- Other…….
Alternative HRPP ‘governance” structures

Two Conferences:

- November 2005
- November 2006

Purposes: To explore alternative IRB models and promote their availability

Both Reports are available at the OHRP website
Alternative IRB Models

Organization relies on its own IRB, OR may, at another “geographical” location:

- Rely on the IRB of another organization
- Rely upon a Central IRB: “facilitated review”
- Rely on a commercial “independent” IRB

The organization may use any combination or be part of a community based consortium
Alternative IRB Models

KEY CHALLENGES

[What can be assured and ensured?]

- Assurance of Review Quality
- Sensitivity to local Context
- Liability (institutional and individual)
- Control and Accountability
- Loss of Resources
Alternative HRPP ‘governance’ structures

[Is there one additional Model?]

☑ The IRB itself is supported by an off-site management “team” through an arrangement with an independent IRB’s staff support, IT systems and education and training.

☑ Organization’s IRB stays remains, the processing of research protocols is conducted off-site except for the review at convened IRB meetings of its members, alternates and consultants.
Alternative HRPP ‘governance’ structures

[Is there one additional Model?]

Potential enhanced benefits

✓ Reliance on known organizational personnel
✓ Confidence in community members input
✓ A greater likelihood of ‘local’ sensitivity
✓ Improved efficiencies of management support
✓ Economies of scale with shared liability
Accreditation and Certification
Establishing Standards

The need to benchmark systems and establish standards of competence and performance:

- Accreditation of organizations with Human Research Protection Programs (HRPPs)
- Certification of individuals through education and training and examination
The Overall Commitments

# 1

Voluntary External Evaluation and Validation of the Human Research Protection Program

✓ Accreditation & Re-accreditation through the Association for the Accreditation of Human Research Protection Programs, (AAHRPP).

http://www.aahrpp.org
Accreditation through AAHRPP

Purpose (AAHRPP Mission):

AAHRPP works to protect the rights and welfare of research participants by fostering and advancing the ethical and professional conduct of persons and organizations that engage in research with human participants.

This is achieved using a process of self assessment, peer review and education according to published standards.
What is AAHRPP?

- Founded & sponsored by 7 major organizations.
- Promotes self assessment
- Fosters the shared responsibilities of the IRB, investigator and sponsoring entity
- Requires a “de minimus” compliance with US federal regulations and ICH GCP
- Awards levels of accreditation
What do the Standards evaluate?

- Structure
  - What we have
- Process
  - What we do
- Outcome
  - What we achieve
What is the process sequence?

Self-assessment

On-site evaluation

Council on Accreditation

Self Evaluation
Program Description

Expert site visitors
Tailored to organizational setting

Determines Accreditation category
The Overall Commitments # 2

Maintenance of IRB and Staff education and training with selective certification required.

- Achieving education requirements of the Collaborative Institutional Training Initiative (CITI) Program
  https://www.citiprogram.org
- Individual certification by passing the examination and the requirements for the Certified IRB Professional (CIP)
  http://www.primr.org
Participation in the CITI program

Purpose: To ensure a standardized level of knowledge & understanding of human subjects protections and safety.

Target: Investigators, IRB members, IRB support staff, undergraduate/graduate bioethics courses.

Requirements: All current IRB members and staff to fulfill the CITI requirements. All new IRB members and staff to promptly complete the all required modules.
What is the CITI program?

✓ Voluntary group of experts in human subjects protection developed and create educational modules.

✓ Participating organizations register for the modest fee of $1000

✓ Organization:
  – Establishes Learner Groups
  – Specific ‘curriculum’ for Learner Groups
  – Provides any additional instructional materials
Summary of the CITI Program

- A dynamic organization committed to high quality instructional resources
- Comprehensive content
- Institutionally driven course curriculum
- Economy of time for the user
- Available 24/7/365 from everywhere
- “User friendly” presentation model and assessment tools
- Cost effectiveness for member institutions
- Help desk for users and administrators
Certification by the CIP

Purpose: To promote IRB Administration Practice and advance the quality of human subject protection programs

Target: Individuals participating in and overseeing the daily activities of the IRB

Requirements: Voluntary but must have a Bachelor’s degree & 2 years of relevant IRB experience within the past 7 years or 4 years of relevant experience within past 10 years
What is the CIP Examination?

✓ Takes about 4 hours

✓ 250 multiple choice questions

✓ Focus on 4 areas:
  ✓ Foundations and Concepts of IRB practice
  ✓ Organization and Personal Knowledge
  ✓ IRB Functions and Operations
  ✓ Records and Reports

✓ Re-certification with CEUs every 3 years

✓ Re-sit the examination every 6 years
Specific Websites

AAHRPP
http://www.aahrpp.org/www.aspx

CITI
https://www.citiprogram.org/citi_information.asp

CIP
http://www.primr.org/certification/overview.html
The Overall Commitment
# 3

Participation in the various individual Certification Programs offered by Professional Associations.

**EXAMPLES**

- Passing the Certifications offered by the Association of Clinical Research Professionals
  - ✔ CPI  CCRA  CCRC
- Participation and receiving certificates of Competence by the Society for Research Administration in various areas.
A QUESTION

What does the future hold for human research protection?

Some Speculations
Regulatory and Guidance changes on the Horizon

Charter for Secretary’s Advisory Committee on Human Research Protections

SACHRP will advise the Secretary on matters concerning the protection of human subjects with particular emphasis on special populations such as neonates, children, prisoners, the decisionally impaired; pregnant women, embryos, and fetuses; international studies; identifiable samples; investigator COI; OHRP activities.
SACHRP’s Operational Premise

The regulations which govern human subjects research remain largely unchanged since 1981, whereas the research enterprise has evolved dramatically in terms of scientific, ethical, and logistical complexity.

Courtesy of E. Prentice, SACHRP Chair 2003-06
Charge to the Subpart A Subcommittee

 ✓ Review and assess
   ▪ All provisions of Subpart A of 45 CFR 46 ("Common Rule")
   ▪ Relevant OHRP guidance documents

 ✓ Based on this review and assessment
   Develop recommendations for consideration by SACHRP in three categories:
   ▪ Interpretation of specific Subpart A provisions
   ▪ Development of new or modification of existing OHRP guidance
   ▪ Possible revisions to Subpart A

 ✓ Goals
   ▪ Enhance protection of human subjects
   ▪ Reduce regulatory burdens that do not contribute to the protection of human subjects
   ▪ Promote scientifically and ethically valid research

Based on memo to Subcommittee from E. Prentice, Chair of SACHRP, 1/14/05 and subsequent discussion by SACHRP
Regulations that leave too much to the imagination

Investigators
Subjects
IRBs

Overly restrictive interpretations

Courtesy of Dan Nelson, Director, Human Subjects Protections, UNC
EXAMPLE of the Subpart A’s Topical Consideration

Continuing Review: Starting the Clock

✓ OHRP GUIDANCE: “To determine the date by which continuing review must occur, focus on the date of the convened meeting at which IRB approval occurs.”

✓ PROBLEM: Actual (final) approvals are often not granted until some time after the convened meeting, pending resolution of contingencies
  ▪ Current guidance results in artificially shortened approval periods, counterintuitive recordkeeping, and potentially confusing signals to investigators

OHRP Guidance on Continuing Review, July 2002
Recommendation (approved by SACHRP on 11/1/05)

- OHRP should revise guidance to reflect that the final IRB approval of a study “sets the clock” for continuing review.
EXAMPLE of the Subpart A’s Topical Consideration

• When can continuing review stop?

✓ HHS regulations do not address when research ends for oversight purposes

✓ The full application of §46.111 to minimal risk research (or to any research past a certain point in its lifecycle) does not add meaningfully to protections and is not a reasonable requirement

✓ Data analysis may go on for years
  ▪ Single site versus multicenter studies

✓ Sponsor requirements and/or good practice may dictate keeping identifiable data for years… or forever
When can continuing review stop? {cont.}

✓ When does (or should…) the IRB’s oversight responsibility end?
  ▪ After last subject enrolled?
  ▪ After interventions complete?
  ▪ After data collection complete?
  ▪ After data analysis complete?
  ▪ After papers published?
  ▪ To infinity (and beyond…)?

✓ IRBs are forced to
  ▪ Err on the side of “keeping things open forever”
  ▪ Establish local compromise solutions
Recommendation (approved by SACHRP on 3/13/06)

- OHRP should clarify its guidance on the required duration of continuing review. Continuing review may end when all research interventions and interactions with subjects are over and data collection for research purposes is complete as described in the approved study plan/protocol, at the research site for which the IRB has oversight. ...
Recommendation Continued (approved by SACHRP on 3/13/06)

• ...The IRB must have reviewed and approved the investigator’s plan for data analysis and the safeguards in place for confidentiality protections. The investigator stills retains the responsibility to notify former subjects and the IRB if subsequent analysis and/or new information raises concerns about rights, safety and welfare of human subjects.
Other Issues with Recommendations from The Subpart A

✓ Committee Timing of continuing review?
✓ How should temporary lapses in approval be handled?
✓ Expedited Review; Clerical and Administrative Reviews
✓ Revising the 1998 List of Expedited Review Categories
✓ Final approval of stipulations from convened IRB review?
WHAT NEXT?

Topics for Consideration by Subpart A Subcommittee
Topics for Consideration

- Continuing review; selected extension to 2 years
- Expedited review
  - Minor changes to previously approved research
  - Contingencies from convened IRB review
- Minimal Risk (pending…)
- Training and Education (pending…)

- IRB membership issues
  - Number, Diversity, Expertise, Qualifications
  - Community (unaffiliated) representation
  - Member conflicts of interest
  - Quorum, Alternates
  - “Scientist” and “non-scientist”
Topics for Consideration (continued)

- Assurances
  - “Engaged in research”
  - Off-site research in nontraditional settings

- Multi-site research
  - Cooperative review mechanisms

- Recordkeeping and reporting

- Investigator responsibilities

- Informed consent
  - Content
  - Documentation
    - Alternatives to 30 page consent forms
  - Waivers and alterations
Topics for Consideration (continued)

- Exemptions
  - Need for continuing review
  - Funding agency interpretations

- IRB review of exceptions and deviations

- Vulnerable populations
  - Definition of “vulnerable”
  - What makes a population or individual vulnerable?
  - What are adequate safeguards?
  - Informed consent in vulnerable populations
  - Legally authorized representatives
  - Decisionally-impaired → NEW SUBCOMMITTEE
Topics for Future Consideration

✔ Definitions (…see all the above!)
  ￭ “Research”
  ￭ “Human Subject”

✔ NOT on the list as discrete topic…
  ❖ Adverse event reporting
THE FUTURE for HRPPs

- More institutions, big and small, will ‘experiment’ with alternative IRB models.
- More small local IRBs will form community based central IRBs
- NIH will increase the number of co-op group central IRBs
- More local and central IRBs (HRPPs) will become accredited by AAHRPP
- More IRB staff will become CIPs
- More clinical investigators, research coordinators and administrators will become certified
- Implementation of IT systems and electronic processes
THE FUTURE for REGULATIONS

✓ Regulations will be simplified and better guidance on application will be forthcoming

✓ OHRP and FDA will harmonize/expand guidance

✓ COI management will become more stringent

✓ OHRP/FDA research shutdowns will be rare but not extinct
Challenges to the HRPP

✓ The Institutional Official will have full oversight of IRB, IACUC, IBC and Research Misconduct

✓ Different and alternative IRB models will be explored for cost efficiency and productivity

✓ Regionalization will be achieved with expansion of IT and electronic processes

✓ Accreditation and Certification will grow

✓ Continuing education and training programs will need to adjusted to address staff turnover and changes
Overarching Concerns for the HRPP

✓ Is there a “culture” of subject protection and safety?

✓ Is there a spirit of Conscience and Compliance?

✓ Does the organization respect its IRB and provide the necessary support in staffing and other resources?

✓ Are all the individuals involved in the research enterprise appropriately fluent and/or knowledgeable of the regulatory requirements for human participants?

✓ Does the organization have a proactive stance towards ongoing improvements and enhancements?
THE END

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THE END

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