

# The IRB

## *Purpose, Function, and Proposals for Improvement*

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# Getting Out of the Way (?)

- “A truly ethical bioethics should not bog down research in red tape, moratoria, or threats of prosecution based on nebulous but sweeping principles such as “dignity,” “sacredness,” or “social justice.” Nor should it thwart research that has likely benefits now or in the near future by sowing panic about speculative harms in the distant future...”

“The Moral Imperative for Bioethics”  
by Stephen Pinker (*Boston Globe* 8/1/15)

# Getting Out of the Way (?)

- “Of course, individuals must be protected from identifiable harm...
  - ...but we already have ample safeguards for the safety and informed consent of patients and research subjects.”

“The Moral Imperative for Bioethics”  
by Stephen Pinker (*Boston Globe* 8/1/15)

# Q: Does IRB Review Work?

## A: We don't really know

- No controlled trials
- No underlying theory or framework of quality or effectiveness
- Lack of longitudinal assessment
- Little research with key stakeholders beyond boards/researchers

Nicholls *et al* (July 30, 2015) *PLOS*

*ONE*

review of 198 empirical studies

# Transformative Effects of IRBs

- “Unquestionably, their very existence has tempered the inevitable propensity of researchers to pursue investigations without dispassionately weighing the risks they are asking others to assume or fully informing their subjects of them.”

Edgar and Rothman (1995) *Milbank Q*

# Transformative Effects of IRBs



# Problems with the Current System

1. Structural problems
  - Repetitive IRB reviews, inconsistencies in regulations, absence of resources
2. Procedural problems
  - Time consuming, inadequate guidance, overly focused on consent forms
3. Performance assessment problems
  - Absence of data

Emanuel *et al.* (2004) *Ann Int Med*

# Roadmap

- Brief history and background of IRBs and their function
  - Composition
  - Standards for review
- Proposals for improving IRB functions
  - Accreditation
  - Central IRB review
  - Research



# History of IRBs in the U.S.

- 1974 DHEW National Research Act
  - National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
  - Belmont Report (1978)
- 1981 45 CFR 46 codified IRBs and IC
- 1991 Subpart A adopted by 15 agencies
  - “Common Rule”
- Parallel FDA regs: 21 CFR 56

# Ethical Requirements: Independent Review

- Review of research (design, population, risk/benefit) by unaffiliated individuals to:
  - Minimize impact of potential researcher conflicts of interest
  - Assure public/social accountability

Emanuel *et al* (2000) *JAMA*

# IRBs at a Glance

- >4000 IRBs in the United States
  - And 100s more in 113 countries

Bartlett (2008) *JEHRE*

- Approx. between 14-40 members
- Meet 1-2x/month
- Staffed by full time administrators
  - Credentialing/professionalization
- Chair ~ 20% (at NIH: 15-100%)

# IRB Membership

## 45 CFR 46.107/21 CFR 56.107

- At least 5 members with varying backgrounds
  - Qualified, diverse, not all men or all women or same profession
  - One scientist, one non-scientist
  - One unaffiliated member
  - No conflicts
  - Special areas of expertise

# NIH Membership Requirements

- Non-affiliated members
- Member representing participant perspective
- Bioethicist
- Statistician or epidemiologist
- Pharmacist or pharmacologist
- *Not* IRB staff members

At  
majority  
of IRB  
meetings

# Non-Scientist

- “A member whose education, training, background, and occupation would incline him/her to view research activities from a standpoint other than any biomedical or behavioral scientific discipline” (SOP 2)
  - “...to fully appreciate risks associated with the study without being blinded by the lure of scientific advancement.” (Allison et al 2008)

# Roles of Non-Scientists (n=25)

	<u>Agree</u>	<u>Disagree</u>
• Layperson	68%	32%
• Public representative	28%	72%
• Community Representative	16%	84%
• Research subject advocate*	16%	84%

• *vs. non-NIH studies: majority of NS members describe themselves as representing or giving a voice to human subjects*

Allison, Abbott, Wichman (2008) *IRB*

# Roles of Non-Scientists

non-scientists (n=25); scientists (n=84)

- Main role: review and make recommendations about informed consent document (72%; 47%)
- Represent community values, views and norms (60%; 81%)
- To make conduct of research accountable to public (88%; 93%)

Allison, Abbott, Wichman (2008) *IRB*

# IRB Functions and Operations

- Reviews:
  - Initial protocols
  - Continuing review
  - Amendments
  - Unanticipated problems, non-compliance
  - Protocol deviations
  - Closures

# NIH IRB Review Standards

1. Proposed research design sound/will not unnecessarily expose subjects to risk
2. Risks reasonable in relation to benefits and knowledge to be gained
3. Risks to subjects minimized
  - Data monitoring plan
4. Equitable subject selection

# NIH IRB Review Standards

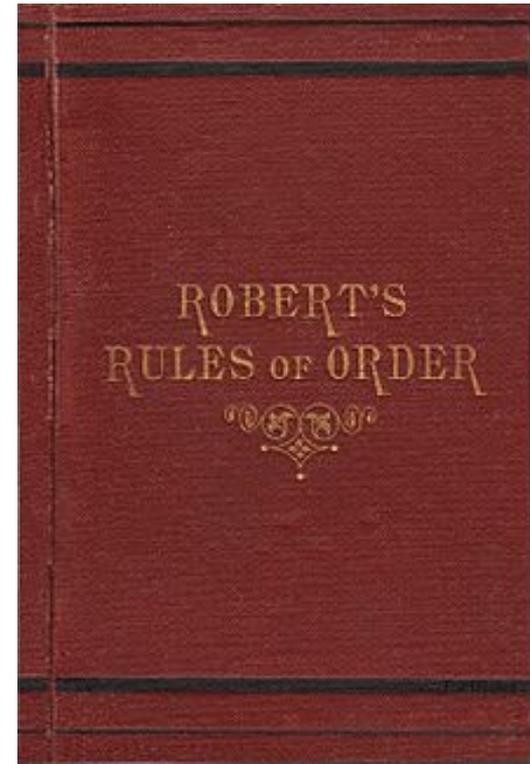
5. Additional safeguards for vulnerable participants
6. Informed consent
  - Obtained (or waived)
  - Documented
  - Assent
7. Privacy/confidentiality protections

# Additional Considerations

- That investigators and research staff are qualified (e.g., training, experience)
- Use of ionizing radiation
- Collaborative research – need for other reviews
- FDA-regulated research
- Duration of approval
  - Annual or more often?

# IRB Actions

- Simple majority (> half):
  - Unconditional approval
  - Approval w/stipulations
  - Deferred
  - Tabled
  - Disapproval
- Detailed minutes



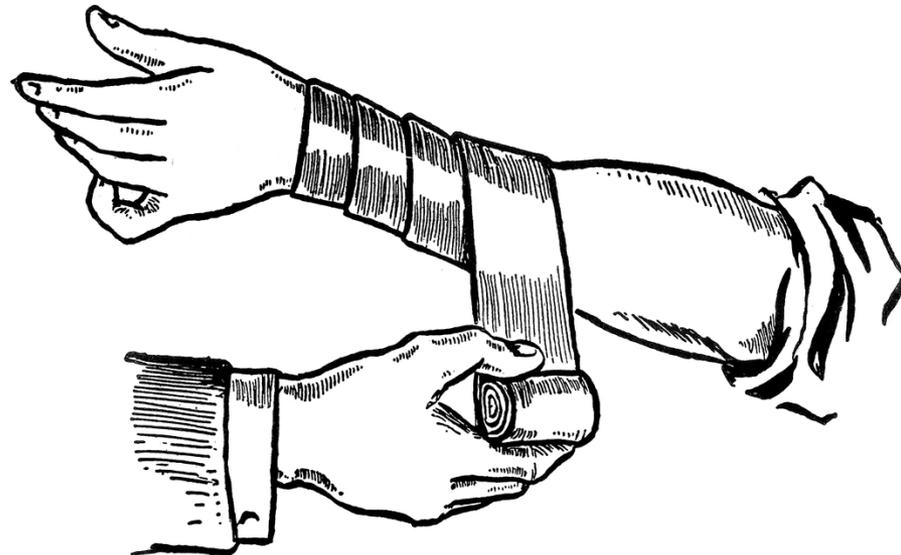
# Expedited Review

- When no more than minimal risk and involves certain categories of procedures (see OHRP guidance)
  - *NPRM proposal: to eliminate continuing review for protocols involving minimal risk/expedited review*

# Proposals to Fix IRBs

- Accreditation
- Centralized IRB review
- Legislative proposals
- Research and innovation

} convergence



# AAHRPP Accreditation (n=217)

- Goals:
  - Improve systems that protect the rights and welfare of research participants
  - Public communication
- Documentation and process focused
- NIH IRP Accreditation (March 18, 2014)
  - 3-year renewal (5 thereafter)
  - 41 SOPs
    - <http://ohsr.od.nih.gov/OHSR/pnppublic.php>

# Problem: Repetitive IRB Review

- Multisite research is reviewed at each engaged institution, dissipating limited resources. Does it...
  - Foster local efforts to uphold ethical standards for research?
  - Capitalize on IRB's knowledge of local research environment and community standards?

Emanuel *et al.* (2004) *Ann Int Med*

# Proposed Solution: Central IRBs

- Simple definition:
  - *A single IRB of record for a multicenter clinical trial.*
- Detailed definition:
  - *A properly constituted IRB to which sites cede all regulatory responsibility for scientific oversight and integrity of the protocol from initial review to termination of the research, including review of informed consent.*

Flynn *et al.* (2013) *PLOS ONE*

# Central IRB Mechanism

## Reliance agreements (SOP 20A)

- “An agreement between NIH and one or more institutions involved in the same cooperative research (see definition, below) that assigns regulatory responsibilities to a specific IRB.”
- Negotiated and executed by OHSRP (at NIH)

# Draft NIH Policy on Use of a Single IRB for Multi-Site Research

## *Background:*

- No evidence that multiple IRB reviews enhance protections for human subjects
- Use of single IRBs may lead to enhanced protections for research participants by:
  - eliminating the problem of distributed accountability
  - minimizing institutional conflicts of interest
  - refocusing IRB time and resources toward review of other studies

# Draft NIH Policy on Use of a Single IRB for Multi-Site Research

## ***Policy:***

*All sites participating in a multi-site study will be expected to rely on a single IRB to carry out the functions that are required for institutional compliance with IRB review.*

# Draft NIH Policy on Use of a Single IRB for Multi-Site Research

## *Exceptions:*

- If the designated single IRB is unable to meet the needs of specific populations
- Where local IRB review is required by federal, tribal, or state laws or regulations

# Exceptions (public comment)

- Cherokee Nation, Indian Health Service
- Tribal IRBs ensure that research
  - is conducted in a community engaged manner
  - does not deplete or divert limited tribal resources away from direct patient care
  - findings are first shared with tribal leadership, tribal communities, and key stakeholders

# Exceptions (public comment)

- IHS: “Multi-site studies with central IRB approval should be required to seek IHS or Tribal IRB approval, as appropriate, for research conducted within the jurisdiction of federally recognized AI/AN Tribes”

# NPRM Proposal

- “Mandating that all institutions located in the United States engaged in cooperative research rely on a single IRB as their reviewing IRB for that study”

§\_\_.114(b)(1)

- Would not apply to research in which supporting agency “determines and documents that use of a single IRB is not appropriate for the particular study”

§\_\_.114(b)(2)

# NPRM Questions

- Is mandated single IRB review realistic?  
(costs, benefits, savings)
- Areas of guidance needed
- Are exceptions sufficient?
- Is three years appropriate timing?

# Variability in IRBs' Decisions

- Survey + consent form analysis for 16 site ARDS multicenter clinical trial
  - Variability in practices
  - One waiver of consent, 5 permitted telephone consent, 3 permitted prisoner enrollment
  - Basic elements of consent
    - All (3)                      Missing three (1)
    - Missing one (6)              Missing four (2)
    - Missing two (4)
  - Reading level: 8.2 – 13.4

# Comparison: Local/CIRB Review

- NCI CIRB vs. local IRB
  - Faster review
  - Fewer hours of research staff effort
  - Cost savings per initial review
  - Possible societal cost savings projected

*Wagner et al (2010) J Clin Oncol*

# Lack of Enthusiasm for CIRBs

- Stakeholder concerns:
  - Institutional liability
  - Loss of community representation
  - Loss of knowledge of local subjects and investigators
  - Quality of CIRB review
  - Loss of revenue from IRB fees
  - Feasibility of working with multiple outside IRBs

*Med*

Loh and Meyer (2004) *Acad*

*Ethics*

Klitzman (2011) *BMC Med*

Flynn *et al.* (2013) *PLOS ONE*

# IRB vs. Relying Institution

- IRB
  - Training of IRB personnel
  - Ensure ethical standards and regs
  - Approval of consent forms
  - Provide copies of IRB decisions, rosters, minutes
- Relying Institution
  - Maintain FWA                      Credentialing training of staff
  - COI review                              Investigator compliance
  - UP and AE reporting              HIPAA/Privacy Review

# Examples

- NCI Central IRB
- Department of Veterans Affairs
- NeuroNEXT
- NHGRI/Undiagnosed Diseases Network
- PHERRB
  - [http://ohsr.od.nih.gov/ohsr/public/PHERRB\\_SOP28\\_v1\\_08-06-15\\_508.pdf](http://ohsr.od.nih.gov/ohsr/public/PHERRB_SOP28_v1_08-06-15_508.pdf)

# Need for More Research

- Limited empirical literature on use of single/central IRBs for multisite trials
  - Evidence of variability
  - But need data on:
    - Use of central IRBs
    - Efficiency and quality of review
- Development of IRB quality indicators
  - Long-term outcomes
  - Broader range of stakeholders
  - Theoretical foundations
  - Across a range of disciplines