



The IRB

Purpose, Function, and Proposals for Improvement

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Disclaimers/Disclosures

- No statement in this presentation should be construed as an official position of the National Human Genome Research Institute, National Institutes of Health, or Department of Health and Human Services.
- The speaker declares no financial conflicts of interest.

What is an Institutional Review Board (IRB)?

- “The IRB is an administrative body established to protect the rights and welfare of human research subjects...” (OPRR 1993)
- Also known as:
 - independent ethics committee (IEC)
 - ethical review board (ERB)
 - research ethics board (REB)

Roadmap

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



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
- 2017: Revisions to Common Rule

Ethical Requirements: Independent Review

- Review of research (design, population, risk/benefit) by unaffiliated individuals to:
 - Minimize impact of potential researcher COI
 - 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 → weekly!
- 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
- 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

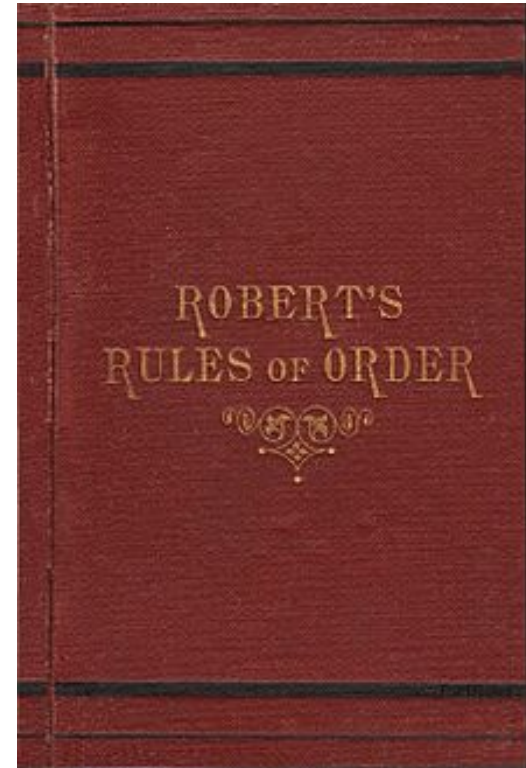
5. Additional safeguards for vulnerable participants
6. Informed consent
 - Obtained (or waived)
 - Documented
 - Assent
7. Privacy/confidentiality protections

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)
 - To be updated every 8 years

Other IRB-Related Common Rule Changes

- Limited IRB review
- Expanded list of activities not considered research
- Definition of human subject
- Conditional exemptions
- Consent process
 - Broad consent
 - Key information
 - Additional basic elements

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

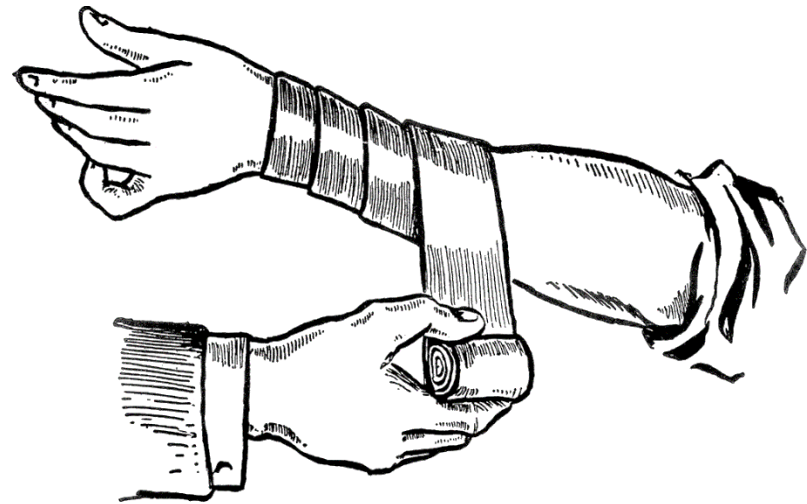
- Absence of data

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

Proposals to Fix IRBs

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

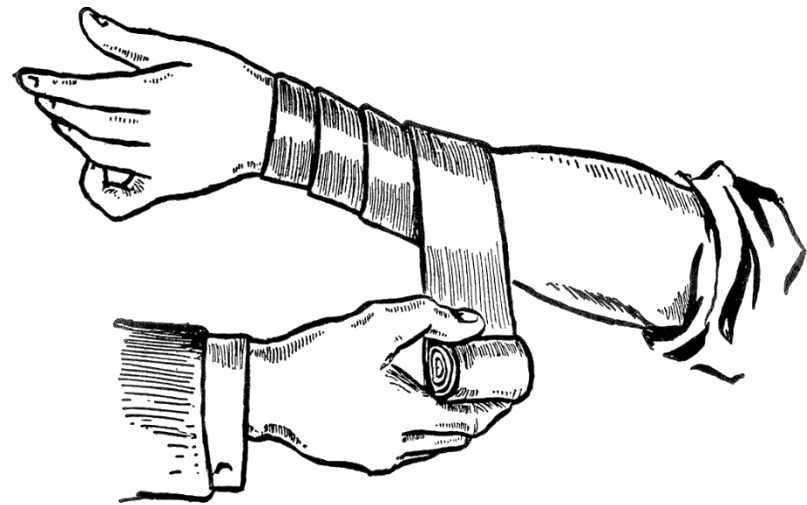
} convergence



Proposals to Fix IRBs

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} convergence



AAHRPP Accreditation (n=227)

- 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)
 - 42 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

Examples

- NCI Central IRB
- Department of Veterans Affairs
- NeuroNEXT
- NHGRI/Undiagnosed Diseases Network
- PHERRB
 - http://ohsr.od.nih.gov/ohsr/public/PHERRB_SO_P28_v1_08-06-15_508.pdf

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)

Final Common Rule - sIRB

“Creates a requirement for US-based institutions engaged in cooperative research to use a single IRB for that portion of the research that takes place within the United States, with certain exceptions. This requirement becomes effective 3 years after publication of the final rule.”

<https://www.federalregister.gov/documents/2017/01/19/2017-01058/federal-policy-for-the-protection-of-human-subjects>

NIH Policy - sIRB

...to establish the expectation that a single IRB (sIRB) of record will be used in the ethical review of non-exempt human subjects research protocols funded by the NIH that are carried out at more than one site in the United States.

Effective date: January 25, 2018

NIH Policy - sIRB

Rationale:

- 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

Lack of Enthusiasm for CIRBs

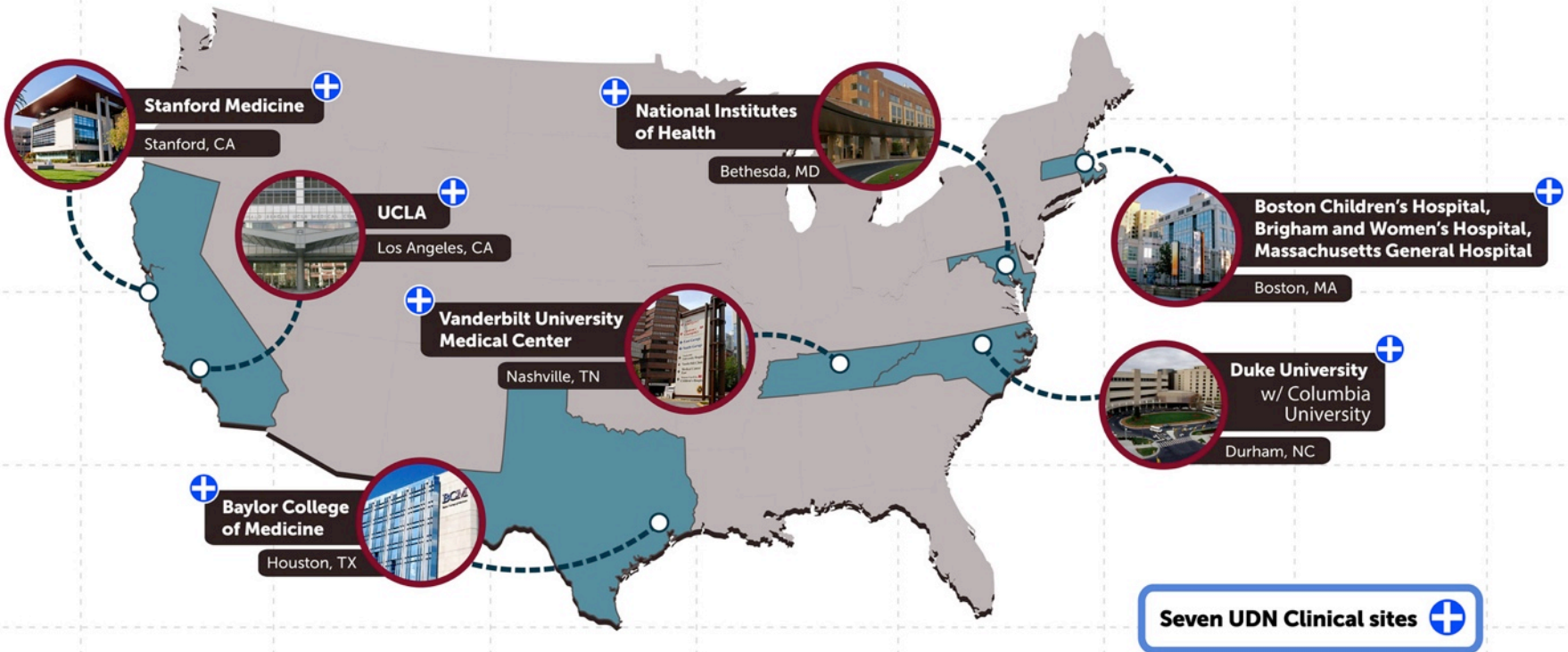
- Stakeholder concerns:
 - Institutional liability
 - Loss of community representation
 - Loss of knowledge of local subjects and investigators
 - Quality of CIRB review
 - Loss of revenue from IRB fees
 - Feasibility of working with multiple outside IRBs

Loh and Meyer (2004) *Acad Med*
Klitzman (2011) *BMC Med Ethics*
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

SOP 20A, Flynn *et al.* (2013) *PLOS ONE*



The NIH site will continue to enroll about 150 patients per year, each of the clinical sites will ultimately enroll about 50 patients per year.

<http://www.genome.gov/27550959>

UDN Protocol

- 18 Reliance Agreements
 - Coordinating Center
 - Clinical enrollment sites
 - Cores
 - Sequencing
 - Model organisms
 - Metabolomics
 - Biorepository
 - Monitor

Relationship Status:

Interested in:

Looking for:

- Single
- In a Relationship
- Engaged
- Married
- It's Complicated**
- In an Open Relationship
- Widowed

UDN Protocol

- Minimal risk
 - Full board initial review, expedited CR
- Investigators/staff
 - PI (William Gahl, MD, PhD)
 - 22 NIH AI's
 - 209 non-NIH collaborators
 - 83 “non-research” staff

UDN Consent Forms (n=150!)

- Main study (144)
 - 16 consent/assent forms (English + Spanish) x 9
 - Plus use of NIH or local short forms
- Patient web pages sub-study (2)
- Site specific (2 x 2)



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

Exceptions:

- Where review by the proposed sIRB would be prohibited by a federal, tribal, or state law, regulation, or policy*
- If there is a compelling justification*

Exceptions (public comment)

- 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”

PRIMR Webinar

Preserving a Role for Tribal Review of Research in the Context of Single IRB Policies

Tuesday, September 20 • 1:00-2:30 PM ET



<http://www.primr.org/webinars/sept2016/>

Thank you!