Institutional Review Boards
A mechanism for oversight of research
An attempt to *implement* the ethical principles important to research

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Requirements for Ethical Human Research
• A valid and important question
• Valid methodology
• Balance between risks/benefits
• Independent ethical review
• Informed consent

Thanks to Zeke Emanuel

The global, “motherhood and apple pie” answer:

• The purpose of IRBs is to protect human research subjects

Beecher:
• (In talking about consent)...
  “A far more dependable safeguard … is the presence of a truly responsible investigator.”

• There really are several “purposes” of IRBs;
• Many of these can be wrapped together:
  “Helping investigators recognize and address human subjects’ issues in their research”

Fundamental Constructs:
• Beneficence (do no harm)
• Justice (distribute risk and benefit fairly; treat individuals fairly)
• Autonomy / respect for persons (need for consent)
  These are age-old, but higher profile and more codified in last 50 years
### Why a Greater Emphasis?

- **Education of patients/subjects**
- **Public funding**
- **News reporting**
- **Desire for access**
- **Scandal**
- **Near misses (thalidomide)**
- **Scandal**

### Why a Greater Emphasis?

- **High-profile scandals**
  - War atrocities (⇒ Nürnberg Code)
  - Tuskegee natural history study of syphilis

  *...latter two said problems are *mainstream*, not fringe*

### Results of Scandals and Near-Misses:

- **1962 Amendment to the Pure Food, Drug and Cosmetic Act**
- **Helsinki Declaration and other codes of ethics**
- **National Research Act of 1974; Belmont Commission & Report**
- **Federal research regulations to protect research subjects**

### Helsinki Declaration:

- **First edition 1964; several revisions**
- **(WMA) Went beyond Nuremberg Code, to address research with therapeutic intent**
- **Also addressed diminished competence**
- **Called for oversight of research**

  *IRBs called “Helsinki Committees” in some venues*

### Helsinki Declaration I(§2):

...in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor...
Tuskegee:
• Natural history study of untreated syphilis in 400 black men
• Patients allowed to believe they were being treated
• New treatments (e.g. PCN) neither studied nor offered as they became available

PHS funding; PHS researchers, etc.

1974: “Defense of Tuskegee”

Elliot Richardson ⇒ Charles McCarthy:
• ∃No Effective Defense
• ∴Need Mechanism to Prevent Recurrence
• 45 CFR §46: Basic DHHS Policy re: Human Subjects

Promulgated for NIH: May, 1974; Expanded & revised 1991

45 CFR § 46:
• Subpart A: “The Common Rule”
• Subpart B: Reproductive Issues
• Subpart C: Prisoners
• Subpart D: Children
• Subpart E: Decisionally Impaired (never formally adopted)

Also Important:
• Lots of other regs, codes and statutes might apply, depending on the type of research and where it’s done
• (FDA, JCAHO, VA, local statutes, etc.)

Institutional Review Boards:
• Prospective review of research proposals
• Continuing review of ongoing research
• Idea is to protect human subjects from inappropriate risk

Ideally a cooperative venture with the investigator, rather than a police function

Composition of IRBs:
• Investigators and Non-investigators
• People linked to the institution and people independent of it
• People with useful expertise (in science, ethics, law, community concerns)

Ideally a body with a broad background, capable of independent action
IRBs ask about scientific merit:
• Does the scientific merit warrant putting subjects at risk?
• Have the risks been minimized insofar as is practicable?
• General scientific merit review is usually better done elsewhere

IRBs ask about conflict of interest:
• Is there something that might adversely impact clinical decision making?
• Is there something that might distort the consent process?
• Are these bad enough that they need to be disclosed?
• Is disclosure a sufficient remedy?

Academic misconduct issues re: C-of-I usually belong elsewhere

The most important questions IRBs ask:
• Are the risks and benefits (personal and societal) in reasonable balance?
• Is the information and consent process adequate?

IRBs also must ask:
• Does the research conform to federal regulations?
• How about local ordinances and institutional policies?
• How about relevant ethical norms?
• Are there justice concerns re: inclusiveness or vulnerable groups?

It’s crucial to remember:
• We’re all in favor of good science
• We’re all in favor of doing the right thing by research subjects
• We all have things to teach one another
• We’ll do a far better job as colleagues than we will as adversaries

IRB Reporting Lines:
• To the institution
  – Administratively
  – Maintaining an effective IRB is something the institution guarantees to the feds
• To the feds
  – Substantively
  – OHRP and FDA

Obligations to feds and to subjects may require decisions in tension with institution’s interests
IRB: Institutional Review Board

Regulatory Authority---
Office of Human Subjects Protection (OHRP)
Food and Drug Administration (FDA)

Review:
“…irrespective of funding source”

Not just federal monies

Important Regulatory Authority

Federal-Wide Assurance of Compliance
- Institutional agreement with the feds that we will follow the rules
- Includes the assurance that all research done at an institution will be done in accordance with federal rules
- Thus, IRB review is for all human subjects’ research

Important Regulatory Authority

45 CFR §46
- Basic federal regs covering human subjects
- AKA “OPRR Regs” (historically)
- AKA “OHRP Regs” (currently)
- Rules establishing and guiding the Office for Human Research Protection

Important Regulatory Authority

45 CFR §46
- Defines “human subject,” “research”
- Sets standards for IRB composition and function
- Defines levels of review for different types of research
- Sets expectations (rules) re: consent, protections, reporting, special classes of research subjects, etc.

Important Regulatory Authority

Review Continuum
Level of risk determines route of review

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Exemptions

- Certain research may be exempt from IRB review because it doesn’t meet the regulatory definition of “research.”
- Certain research may be exempt because it doesn’t meet the regulatory definition for involving “human subjects.”

Exemption Categories:

- Federal regulatory criteria for low-risk research
- Six specific categories of research
- Cannot involve vulnerable population
- Qualifying studies usually are of short duration
- Cannot create a durable confidentiality risk (no permanent record of individual)

Exemption Examples:

- Anonymous re-use of data
- Anonymous questionnaires on non-sensitive topics
- Observation of public behavior without recording identities
- Field testing educational strategies or curricula

Important Regulatory Issue

- Investigator has an inherent conflict in deciding if research is exempt;
- Investigator, Dept. Chair, etc. may well not know the regs well enough to make the right call;
- Regulatory expectation (FDA/OHRP) is that there will be a process for making this decision knowledgeably;
- At most centers it’s having the IRB office screen for exempt status.
**Not Quite Exempt: Expedited Review**

Federal regulations also recognize that there is some research that is of very low risk, but needs a bit of IRB scrutiny;

For specific designated categories of risk, IRB review may be carried out by the chair or by an experienced member (rather than by a duly-convened quorum).

**TYPICAL INVESTIGATOR PROCESS:**
File usual IRB application form with IRB; include consent forms and other supporting info; specifically ask for expedited review (explaining why it would qualify)

**Important Regulatory Issues**

- Investigator can request expedited review, but the eligibility call must be made by someone who knows the regs (i.e. the expedited reviewer);
- Expedited review is not “review light”; requirements are exactly the same as in full-board review;
- Difference is (only) that review doesn’t require a convened quorum to grant approval.

**Full Committee Review**

*Anything Else*

- Vulnerable populations
- Invasive procedures (physically or psychologically invasive)
- Sensitive topics
- Investigational products (FDA)

**Continuing Review**

- Approval expires after a set time period or a set subject accrual
- Approval cannot be valid for more than one year
- Re-review has to occur before the approval expires, or there’s a lapse
- Re-review must be substantive

**Why Continuing Review?**

- Details of studies change
- Available information changes
- As a result, risk/benefit balance may change
- Also as a result, consent burden may change
Important Regulatory Issue

• It’s the PI’s obligation to get the continuing review info in on time (IRB sends two reminders at our shop);
• It’s the PI’s obligation to provide all the required information;
• The regs make no provision for a grace period, so the IRB has no authority to cut a procrastinator any slack.

In order to regulate something, you’ve got to define it…

So What’s Research?

A systematic activity designed to develop or contribute to generalizable knowledge

• Note that this is a regulatory definition
• Some things we may think of as research don’t meet this standard (e.g. intramural QA studies)
• Irony: Even if activities carry risk, they may not be required to be subject to oversight

45CFR§46.102(e)

So What’s a Human Subject?

A living individual about whom an investigator (whether professional or student) conducting research obtains

• data through intervention or interaction with the individual, or
• identifiable private information.

Unless totally anonymous, any time you have private information you have a human subject…
Dead folks don’t count, unless the information to be gained has impact for the living (e.g. relatives) (who are then the subjects)

45CFR§46.102(f)

IRBs give special consideration to:

• Vulnerable Subjects:
  – children
  – prisoners
  – mentally disabled persons
  – economically disadvantaged persons
  – educationally disadvantaged persons

There are two concerns about vulnerable subjects:

• Do they need special protections because of their vulnerability?
• Are they being inappropriately excluded from research participation because of their vulnerability?
Example: Research Involving Kids

- No more than minimal risk
- More than minimal risk, but benefit offsets the risk (e.g., clinical trials)
- Benefit doesn’t fully offset risk, but risk excess is small and information important for the subjects’ disease or condition

Basic idea: take a more conservative view of risk/benefit balance when the subjects are vulnerable

IRBs tend to spend a lot of effort on the information and consent process and consent forms:

Informed Consent:

- **What it is:**
  - ongoing process of communication and mutual understanding

- **What it isn’t:**
  - a piece of paper
  - a moment in time
  - a contract

Essential elements for Consent Process and Document:

Regs list nine features -- the biggies:

- Must know it’s research;
- Must know it’s voluntary;
- Must know what they’re getting into:
  - What’s being asked of them
  - Risks and benefits
  - Alternatives (especially in clinical trials)

www.research.umn.edu/subjects/index.html
**Informed Consent:**

- The norm is a written consent form executed prospectively
- Oral consent may be OK in certain low-risk studies
- Oral consent may be OK if a written form creates a confidentiality risk
- Surrogate consent may be OK if risk/benefit balance suitable