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)

Beecher's 1966 article: "Ethics and Clinical Research" ***N Engl J Med*** **274:**1354ff [June 16th]

Tuskegee natural history study of syphilis

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

Why a Greater Emphasis?

- **Near misses**

Thalidomide not licensed in US through a regulatory fluke rather than through having a good process to ensure safety;

Birth defects in countries where it *was* licensed were a wake-up call

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 coöperative 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?**

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

It's crucial to remember:

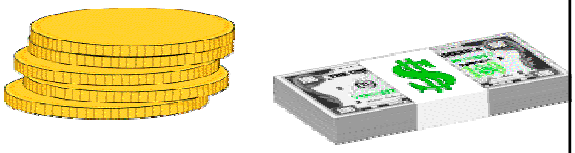
- We're all in favor of good science
- We're all in favor of doing the right thing by research subjects
- We all have things to teach one another
- We'll do a far better job as colleagues than we will as adversaries

IRB: 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.***

Review Continuum

Level of risk determines route of review

Exempt **Expedited** **Full**

Lowest ⟷ Low ⟷ High

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."

Exemptions

- Certain research may be exempt because an individual investigator's part of the study may be remote from human subjects.

Exemptions

TYPICAL INVESTIGATOR PROCESS:

File an abbreviated form with the IRB, in which the claim of exempt status is set forth and explained … the IRB then decides if it really qualifies as exempt

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).

Not Quite Exempt: Expedited Review

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

45CFR§46: Subpart D

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

Informed Consent:

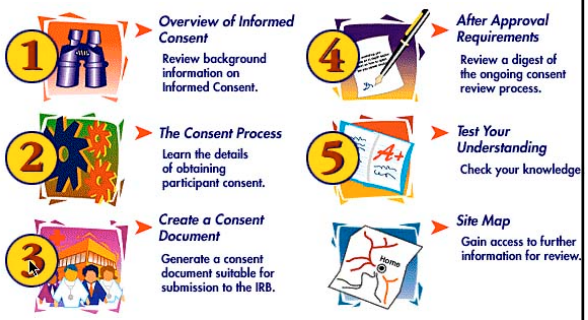
- What it is:
  - ongoing process of communication and mutual understanding
- What it isn't:
  - a piece of paper
  - a moment in time
  - a contract

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**