Clinical Trial Ethics and Informed Consent

Stacey Berg, MD

Texas Children's Cancer Center

Baylor College of Medicine

Code of Hammurabi, ~1750 BCE

215. If a physician make a large incision with an operating knife and cure it, or if he open a tumor (over the eye) with an operating knife, and saves the eye, he shall receive ten shekels in money.

218. If a physician make a large incision with the operating knife, and kill him, or open a tumor with the operating knife, and cut out the eye, his hands shall be cut off.

221. If a physician heal the broken bone or diseased soft part of a man, the patient shall pay the physician five shekels in money.

Code of Medical Ethics, 1803

…. It is for the public good....that new remedies and new methods of chirurgical treatment should be devised. But...the faculty should be scrupulously and conscientiously governed by sound reason, just analogy, or well authenticated facts. And no such trials should be instituted, without a previous consultation of the physicians or surgeons.

Thomas Percival

Guess who said….

4. Any innovative therapy must be justified and performed in accordance with the principles of medical ethics and the rules of medical practice and theory. In all cases, the question of whether any adverse effects which may occur are proportionate to the anticipated benefits shall be examined and assessed.

5. Innovative therapy may be carried out only after the subject or his legal representative has unambiguously consented to the procedure in the light of relevant information provided in advance.

10. A report shall be made in respect of any innovative therapy, indicating the purpose of the procedure, the justification for it, and the manner in which it is carried out.

Guess who said….

a. Hippocrates
b. Maimonides
c. The German Reich
d. The Belmont Report
e. The Institute of Medicine

Guess who said….

a. Hippocrates
b. Maimonides
c. The German Reich
d. The Belmont Report
e. The Institute of Medicine

4. Any innovative therapy must be justified and performed in accordance with the principles of medical ethics and the rules of medical practice and theory. In all cases, the question of whether any adverse effects which may occur are proportionate to the anticipated benefits shall be examined and assessed.

5. Innovative therapy may be carried out only after the subject or his legal representative has unambiguously consented to the procedure in the light of relevant information provided in advance.

10. A report shall be made in respect of any innovative therapy, indicating the purpose of the procedure, the justification for it, and the manner in which it is carried out.

German Reich Regulation Concerning New Therapy and Human Experimentation, 1931

Nuremberg Code, 1947

"Permissible Medical Experiments"

- Voluntary consent
- "Fruitful results for the good of society"
- Protection of subject from risks
- Good faith, superior skill, and careful judgment of researcher

Belmont Report, 1979

Ethical Principles and Guidelines for the Protection of Human Subjects

- Respect for Persons
  - Dignity, autonomy of individuals-informed consent
  - additional protection for vulnerable subjects
- Beneficence
  - maximize potential benefit
  - minimize potential risk (nonmaleficence)
- Justice
  - Fairness in selection of who bears risks and gets benefits

“Common Rule,” 1981

This is the IRB stuff you’re used to

- Institutional assurances
- IRB regulations
- Informed consent

Changes coming to Common Rule?

Definition of Research (IRB's)

- Research means a *systematic investigation*, including research development, testing and evaluation, designed to develop or contribute to *generalizable knowledge*

Not determined by publication plans (but publishers will ask!)

Definition of Subject

- Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains:

  (1) data through intervention or interaction with the individual*; or

  (2) identifiable private information

*** Interaction doesn't have to be face to face**

Criteria for IRB approval

- Risks to subjects are minimized
- Risks to subjects are reasonable relative to benefits
- Selection of subjects is equitable
- Provisions made for data, safety monitoring
- Provisions made to protect confidentiality
- Safeguards in place for vulnerable subjects
- *Informed consent will be sought, documented*

How do you do ethical research (and meet criteria for approval) ?

Do good science!

Risks minimized, potential benefits maximized

Study Design

- Good endpoints
- Appropriate sample size
- Leverage clinical procedures
- Adequate data analysis plan
  - Protocol endpoints
  - Safety monitoring
- Less risky way to get answer?

Risk-benefit ratio favorable

- How much risk?
  - To individual
  - To family?
  - To society?
- How much benefit?
  - To individual
  - To society

Confidentiality

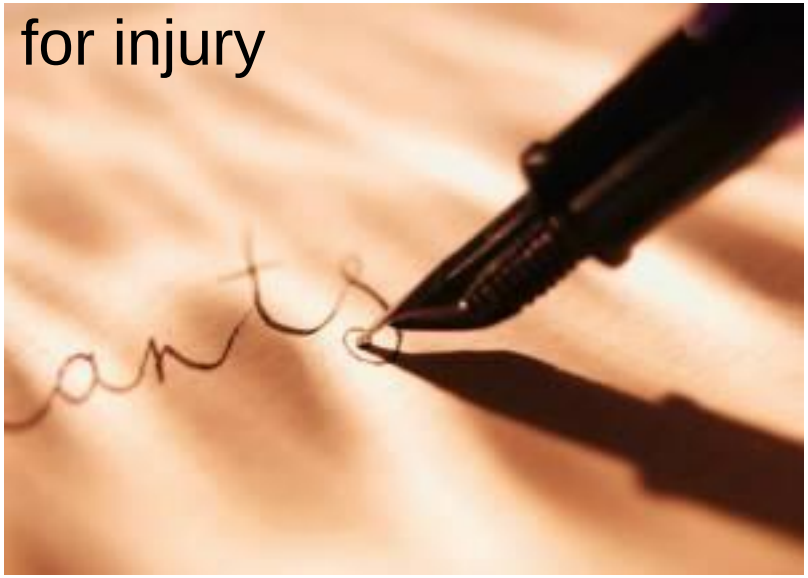
- Safeguard confidentiality of data
  - Locked doors
  - IT security
- Access to data/samples
- Risks if breached
  - Psychological, insurability, legal

- Privacy
  - Interactions with the person
  - Recruitment, visits, etc

Informed consent

Basic elements

- What the research is
- Procedures involved
- Risks, benefits
- Treatment/compensation for injury
- Alternatives
- Right to withdraw
- Confidentiality
- Contacts for questions



Informed consent

Additional elements

- Unforeseeable risks
- Circumstances for termination of participation
- Additional costs
- Procedures for withdrawal
- Notification of new findings that might affect willingness to participate
- Approximate number of subjects

Special genomics considerations

- Is the data itself PHI?
- Are there special risks?
  - Insurability
  - Employability
  - Law enforcement access
  - Stress/embarrassment/ “group harm”
- Return of research results?

The trouble with informed consent….

- Is that it’s so long and hard!

The undersigned, Antonio Benino Antonio Benino being more than twenty-five years of age, native of Ceroeda, in the province of Corima , the son of Manuel Benino and Josefa Castro here states by these presents, being in the enjoyment and exercise of his own very free will, that he consents to submit himself to experiments for the purpose of determining the methods of transmission of yellow fever, made upon his person by the Commission appointed for this purpose by the Secretary of War of the United States, and that he gives his consent to undergo the said experiments for the reasons and under the conditions below stated.

The undersigned understands perfectly well that in case of the development of yellow fever in him, that he endangers his life to a certain extent but it being entirely impossible for him to avoid the infection during his stay in this island, he prefers to take the chance of contracting it intentionally in the belief that he will receive from the said Commission the greatest care and the most skillful medical service.

It is understood that at the completion of these experiments, within two months from this date, the undersigned will receive the sum of $100 in American gold and that in case of his contracting yellow fever at any time during his residence in this camp, he will receive in addition to that sum a further sum of $100 in American gold, upon his recovery and that in case of his death because of this disease, the Commission will transmit the said sum (two hundred American dollars) to the person whom the undersigned shall designate at his convenience.

The undersigned binds himself not to leave the bounds of this camp during the period of the experiments and will forfeit all right to the benefits named in this contract if he breaks this agreement.

And to bind himself he signs this paper in duplicate, in the Experimental Camp, near Quemados, Cuba, on the 26th day of November nineteen hundred.

The contracting party,
Antonio Benigno

On the part of the Commission:
Walter Reed
Maj. & Surg., U.S.A.

Question

How long was the average oncology consent form in 2004?

a. 5 pages

b. 8 pages

c. 11 pages

d. 14 pages

e. 18 pages

Question

How long was the average oncology consent form in 2004?

a. 5 pages

b. 8 pages

c. 11 pages

d. 14 pages

e. 18 pages

The trouble with informed consent….

…is transmitting the information

- 2709 words (11 pages), 12th grade level (and getting longer)
- Therapeutic misconception (patient thinks the intervention is about him)
- Concepts just plain hard- even if language is simplified

Comprehension

Belmont report

- The manner and context in which information is conveyed is as important as the information itself.
- Investigators are responsible for ascertaining that the subject has comprehended the information.

Guess when…..

- “The patient, asked to sign countless…consents, may respond with a blanket refusal or a pro forma signature.”

Question

a. 1962

b. 1972

c. 1981

d. 1999

e. 2004

Question

a. 1962

b. 1972

c. 1981

d. 1999

e. 2004

“Informed but uneducated consent”

- Inability of subject to appreciate burdens
- Difficulty of understanding probabilities
- Incompleteness of information
- Conversely, extensive detail causes more confusion

Ingelfinger, New Engl J Med 1972

Enhancing consent

- Shorter/physically easier forms
  - Bullet points
  - Pictographs
  - Large font
- More time to decide
- Decision aids?
- Neutral third party to assess comprehension?
- Better neuroscience!

Explain it like you would to friend

- Why you’re doing this (context)
- What’s going to happen to them
- Difference between standard care and research procedures
- Risks (not underestimated)
- Benefits (not oversold)
- Options

NCI Simplification of ICD project

6-9 pages

- Usual approach
- Other choices
- Why is this study being done
- What are the study groups
- How long will I be in this study
- What EXTRA tests and procedures (<1 page)
- Risks (2-4 pages max)
- Benefits (2-3 SENTENCES)
- How to withdraw
- Rights
- Costs
- Injury info
- Who will see my medical information
- HIPAA not included
- Contacts
- Optional studies as separate section

Tiered consent

- Can patients opt out of some parts, e.g. tumor biopsies?
- Can patients limit how data/samples are used:
  - You can use my tissue for this study only
  - You can use my tissue for any cancer research
  - You can use my tissue for cancer and noncancer research
- (cautionary note: people may want tissue back)

The Researcher's Job

Find out the answer to the question!

(safely and with respect for subjects' welfare)

The Physician's Job

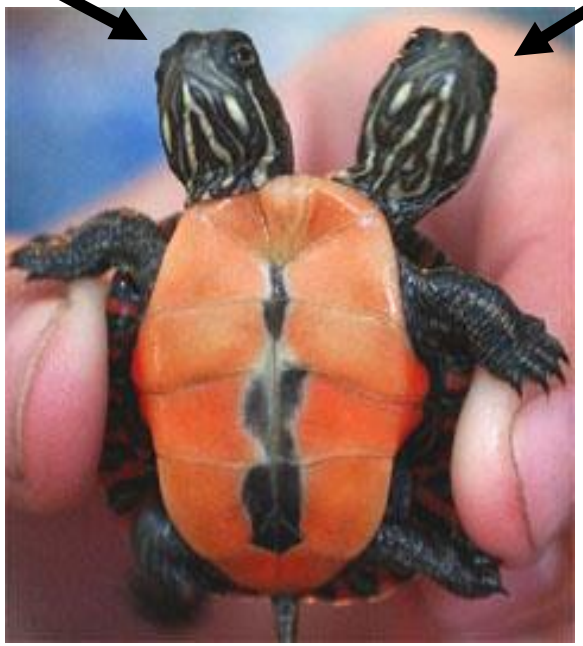
Take the best care of the patient!

(logically and with respect for information to be gained)

The Physician-Researcher

PI advocates for study

Physician advocates for patient



Whose side are you on?

Good faith, superior skill, and careful judgment

"The roles of clinician and scientist must be integrated to manage conscientiously the ethical complexity, ambiguity, and tensions between the potentially competing loyalties of science and care of volunteer patients."

JAMA 1998

Start at beginning

- Good science makes good protocols
- Good communication makes good consents
- IRB wants to approve your research!


IT'S ALIVE!!!!!
Yeth mathter,
but ith it *ethical?*
Grea
sangrea.net

Helpful links

- 45 CFR 46
  http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html
- Belmont Report
  http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html
- NIH guide on informed consent in gene transfer
  http://oba.od.nih.gov/rdna/nih_guidelines_oba.html
- Genome-wide association studies
  http://grants.nih.gov/grants/gwas/

Waiver of consent?

- Only if minimal risk
  - Confidentiality well protected
  - No release of PHI
  - Rights of subject not compromised
  - Adequate plan to reveal important findings
- *AND* impracticable to get consent

Most applicable to previously banked specimens
Few good reasons if prospective collection