Institutional Review Boards

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A Cautionary Tale

Standard Care

A Cautionary Tale

Dr. Rowsey

A Cautionary Tale

Sutureless Corneal Transplant Technique:

This invention involves a technique for transplanting corneal tissue in a much safer way with far less complications than previous methods.

U.S. Patent 5,584,881 issued Dec. 17, 1996

A Cautionary Tale

Studied in cats

Began use in humans

Never filed with IRB

A Cautionary Tale

USA Today, Feb. 26, 2001:

In 1994, eye surgeon James Rowsey invented a medical device that he thought would revolutionize corneal transplantation surgery and make millions of dollars. It did neither. Instead, it cost him a high-paying university job and led to federal findings that he performed unapproved research on more than 60 people, including children.

A Cautionary Tale

OHRP, Sept 2000:

Rowsey proposed randomized trial (but didn't conduct it); used an untested new technique in 60 people; presented abstracts of results at meetings

This is systematic collection of data, an open-label trial, and meets def. of doing research

A Cautionary Tale

OHRP, Nov 2000:

Must tell patients that they were research subjects, and underwent experimental surgery.

A Cautionary Tale

Standard Care

Non-Standard Care

Research

A Cautionary Tale

Dr. Rowsey's defense was that he wasn't doing research.

He says the technique "was never used on my patients as part of any systematic investigation."

A Cautionary Tale

Why was everyone so interested in proving he was doing research?

What if he kept no research records, merely told patients this was a new experimental technique, and he thought it was the best thing for them?

A Cautionary Tale

Would this have been OK if he was just giving non-standard care?

Perhaps Dr. Rowsey was just careless, and did too many “research-like” things

A Cautionary Tale (Truog, NEJM, 1999)

Consider this paradox: if a physician reads about a new method for treating patients, the physician may start using it provided the patients have given general consent for treatment. But if a physician is interested in performing a randomized, controlled trial to determine which of two widely used antibiotics is more effective at treating bronchitis, he or she must prepare a formal protocol, obtain approval from the institutional review board, and seek written informed consent from potential participants.

A Cautionary Tale (Truog, NEJM, 1999)

Physicians can do almost anything they want in the name of therapeutic innovation, but only if there is no attempt to gain systematic knowledge from the intervention. Or, . . . “I need permission to give a new drug to half my patients but not to give it to all of them.”

A Cautionary Tale

Is it true that: “Physicians can do almost anything they want in the name of therapeutic innovation, but only if there is no attempt to gain systematic knowledge from the intervention.”

NO! To know why we have IRBs, need to understand rules for non-standard care.

A Cautionary Tale

Standard Care: Patient is #1!

Non-Standard Care: Patient is #1!

Research

A Cautionary Tale

What happens if a doctor fails to follow the “Patient is #1” rule? Malpractice!

Does the fact that patient gave consent fully absolve the doctor? In general, No!

An Example

Barbara Rojas, age 52, successfully lost huge amounts of weight

She wanted drooping skin removed

Guillermo Falconi, Ecuador MD, no U.S. license, did bedroom surgery

She died, he went to jail

A Cautionary Tale

Dr. Rowsey was sued by at least 2 patients claiming malpractice

Rule for non-standard care: in terms of best interests of the patients, was it reasonable to depart from standard care?

Compare risks v. benefits of change

Why Special Research Rules?

Standard Care: Patient is #1!

Non-Standard Care: Patient is #1!

Research: Patient is not #1!

Why Special Research Rules?

Research involves a conflict of interest

Researcher is pursuing two goals:

1. Answering research question
2. (Sometimes) treating the patient

Why Special Research Rules?

Researcher (unlike clinician) is allowed to do things that can be bad for patient:

1. Randomization
2. Standardization
3. Non-disclosure of interim results
4. Extra tests and procedures

Why Special Research Rules?

Research regulations help manage that conflict of interest.

They make sure that the goal of answering the research question does not inappropriately override the patient's interests.

Why Special Research Rules?

High-Altitude Experiments. [E]xperiments were conducted . . . to investigate the limits of human endurance and existence at extremely high altitudes. . . The experimental subjects were placed in a low-pressure chamber and thereafter the simulated altitude therein was raised.

Why Special Research Rules?

Freezing Experiments. [E]xperiments were conducted . . . to investigate the most effective means of treating persons who had been severely chilled or frozen. In one series of experiments the subjects were forced to remain in a tank of ice water for periods up to 3 hours. . . . In another series of experiments, the subjects were kept naked outdoors for many hours at temperatures below freezing.

Why Special Research Rules?

Sulfanilamide Experiments. . . . Wounds deliberately inflicted on the experimental subjects were injected with bacteria such as streptococcus, gas gangrene, and tetanus. Circulation of blood was interrupted by tying off blood vessels at both ends of the wound to create a condition similar to that of a battlefield wound. Infection was aggravated by forcing wood shavings and ground glass into the wounds. The infection was treated with sulfanilamide and other drugs to determine their effectiveness.

Why Special Research Rules?

Experiments with Poison. [E]xperiments were conducted . . . to investigate the effect of various poisons upon human beings. The poisons were secretly administered to experimental subjects in their food. The victims died as a result of the poison or were killed immediately in order to permit autopsies.

The Nuremberg Code (1947)

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The Nuremberg Code (1947)

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

The Nuremberg Code (1947)

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Why Special Research Rules?

Tuskegee: 1932-1972

Why Special Research Rules?

Jewish Chronic Disease Hospital

1963: Patients injected with cancer cells

Not told, to avoid “anxiety”

Why Special Research Rules?

Cincinnati General Hospital

1960-72: Patients with cancer got whole-body radiation Rx

Not told purpose was to determine how much radiation is “too much” to help learn about effects of nuclear bomb on troops

Why Special Research Rules?

Oregon State Penitentiary

1960s: Prisoners volunteered to have their testicles irradiated

Part of study was mandatory vasectomy to “prevent contamination of genetic pool”

Why Special Research Rules?

CIA's MKULTRA Project

1950s-60s: 149 projects to counter Soviet & Chinese advances in brainwashing and interrogation techniques

Developed "chemical, biological materials

capable of employment in clandestine

operations to control human behavior"

Subjects unaware; some died

Why Special Research Rules?

Belmont Report (1979) led to current U.S. rules, had 3 ethical principles:

Respect for persons

Beneficence: maximize benefits and minimize risks (harms)

Justice

Modern Research Rules: Sources

OHRP (Common Rule, 45 CFR 46): federally funded research

FDA: drugs, devices, biologics

Can be under both sets of rules

Why Special Research Rules?

Institutional Review Boards (IRBs) are committees that enforce these rules

There are thousands of them in U.S.

Some institutions create their own IRBs; others hire a “private” IRB

Why Special Research Rules?

Each IRB must have at least 5 members

The members must be from diverse areas: some with science training, and some with non-scientific background

Scope of Research Rules

Rules apply to Research involving Human Subjects

What is Research?

Research means a systematic investigation . . . designed to develop or contribute to generalizable knowledge.

When are you using a human subject?

Human Subject means a living individual about whom a researcher gets:

(1) data through intervention or interaction with the individual, or

(2) identifiable private information

What About “Exempt” Studies?

If you are doing research involving human subjects, you often need to file somewhere

That office will determine if your study is exempt

What Studies are Exempt?

Questionnaire studies if either (a) innocuous questions, or (b) anonymous.

Studying pre-existing tissue or data, so long as no identifiers or linking lists are kept.

What About “Expedited” Studies?

Some studies that are both minimal risk, and meet other criteria, can undergo “expedited” review

This mainly means review by a single person, not the full IRB

What Criteria does IRB Apply?

1. Informed consent

2. Substantive rules about how the study is designed

Informed Consent

Informed consent will be sought from each prospective subject or the subject's legally authorized representative.

Consent is documented by a signed consent form.

Consent must be voluntary: free from coercion and undue influence.

These requirements can sometimes be waived

Informed Consent

Consent form should disclose information to allow “enlightened decision”:

Nature of subject’s problem

What will happen to them in the study

Risks from participating in the study

Possible benefits from participating

Alternatives to being in the study

Substantive Rules About the Study

Risks to subjects are minimized:

(i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and

(ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

Substantive Rules About the Study

Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

Substantive Rules About the Study

Risks to subjects ≈

(Benefits to subjects) + (Benefits to society)

Substantive Rules About the Study

Benefits to society are especially hard to quantify. That leads to two common IRB behaviors:

Emphasizing informed consent.

Assume benefits to society are close to zero; equation becomes: Risks to subjects ≈ Benefits to subjects

Substantive Rules About the Study

Selection of subjects is equitable.

This means groups should not bear more than their shares of research risks, but also should be included to get their share of benefits

Substantive Rules About the Study

If subjects vulnerable to coercion or undue influence (children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged), need additional safeguards

Substantive Rules About the Study

Appropriate protections with regard to privacy of subjects and confidentiality of data

Problems with IRB System

Is system too lax? Too strict?

September 2015 – Notice of Proposed Rulemaking

www.hhs.gov/ohrp/humansubjects/regulations/nprmhome.html

THE END