

Ethics and Human Subjects Issues in Research: Informed Consent
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INFORMED CONSENT

What is it?

Why do we need it?

From whom do we get it?

How do we get it?

How can we be sure we're doing it right?

I. What is it?

Informed Consent is not a legal document or a risk management tool for the investigator or the institution

It is a process

“The goal of the informed consent process is to provide people with sufficient information so they can make informed choices about whether to begin or continue participation in clinical research.”

“The process involves a dynamic and continuing exchange of information between the research team and participant throughout the research experience.”

“The document acts as a starting point for the necessary exchange of information between investigator and potential research participant. It is a resource and reference throughout the trial and is considered the foundation not the entirety”

II. Why do we need it?

Respect for persons

Respect for autonomy of decision making

True limit on investigative authority

Sense of formality

A. Historical Perspective

Most research ethics policies result from singular events and the reactions to them

Rarely proactive

Major events:

Nazi war crimes

Human radiation experiments, etc.

Tuskegee Syphilis study and others

1948: Nuremberg trial
1963: Declaration of Helsinki
1977: National Commission (Belmont Report)

Nuremberg Trial December 9, 1946, to August 20, 1947.

At the conclusion of the trial the Nuremberg Code was issued:

Defines basic human rights of medical research subjects

Requirement for voluntary consent prior to participation

Investigator responsibility to obtain consent

Information gained by using human subjects would be unprocurable any other way

Declaration of Helsinki

Articulated ethical principles for use by physicians conducting human research

Affirmed the autonomy of the individual

Universally adopted to ensure the rights and welfare of human subjects of research

1974 US Congress passes National Research Act

Created National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Ethical foundation for US federal regulations on human subject's research

Belmont Report

3 basic principles that should govern all research involving human subjects

Respect for persons (autonomy, right to factual information, right to withdraw, special protections for those with limited autonomy)

Beneficence (maximize benefits, minimize risks, avoid harm)

Justice (benefits and burdens equally distributed among all population groups)

B. Federal regulations (DHHS)

1991 Federal Policy for the Protection of Human Subjects ("The Common Rule")

Adopted by all agencies which conduct, supervise, regulate, fund or sponsor human research

Informed consent requirements

IRB approval of any research done

III. What does someone need to know?

Elements of informed consent

Disclosure (what's going to happen)

Risks

Benefits

Alternatives

Confidentiality

Compensation

Standards

- Reasonable person
- Negligence
- Subjective

“The reasonable volunteer”

IV. How do we get it?

A. Voluntariness:

- Freely coming to a decision
- Free from coercion or undue influence
- Assumes capacity
- Capacity
- Understand nature and ramifications

Who is not able to do this?

B. Vulnerable populations

- Children ?
- Prisoners?
- Pregnant women?
- Mental retardation
- Dementia
- Mental illness
- Coma/Vegetative state
- Severe pain

C. Assent - We are obligated

- If child can understand
- Age > 6 years (?)
- Can parents overrule?
- With possibility of benefit
- More than minimal risk?
- Not without prospect of benefit

D. Other vulnerable populations

- Research on individuals who lack capacity also requires prospect of benefit
- Not promulgated in federal regulations
- Consistent with state law
- Family member can consent

E. No standard methods for obtaining informed consent

Approach

Verbal vs. Written

Do patients want to know?
How seriously do they take it?

V. How do we do it right?

Informed consent gone wrong?

Examples:

Jesse Gelsinger (gene transplant)

James Quinn (artificial heart)

Hopkins asthma death (hexamethonium)

A. “The tragic case of Jesse Gelsinger”

“Jesse really wanted to participate in the study... Not because he thought it would improve his own health — he knew the test would probably make it impossible for gene therapy to help him later. He wanted to be a hero.”

“...he did not learn about any of the serious dangers his son was facing until it was too late. He didn't know that two Rhesus monkeys had died in tests involving a gene delivery system similar to the one used with Jesse; he didn't know that four other human patients had suffered toxicity to their livers earlier in the study.”

Reactions

The Food and Drug Administration (FDA) put all gene therapy trials at University of Pennsylvania — plus other experiments ongoing in several other institutions — on hold.

Hearings to investigate the quality of government oversight and safety enforcement in gene therapy studies.

President Clinton demanded improvements in patient consent procedures and access to information about gene therapy research across the board.

Issues

Truly informed consent may still be impossible. ... it's very difficult for anyone, whether a member of the general public or a skilled scientist, to learn details about the problems cropping up in gene therapy studies.

No guidance on when researchers ought to inform prospective participants about studies not directly related to the trial in question.

Quotes from the bioethics world

“The privatization of science, combined with patients' ardent desire for a cure, conspire to prevent meaningful protections for participants in all kinds of studies. Trade secrets,

financial conflicts of interest and overloaded review committees obstruct informed consent by keeping news about ongoing studies beyond the reach of patients and researchers alike. – Art Caplan, University of Pennsylvania

B. James Quinn Case

World's fifth recipient of a self-contained artificial died three days after suffering a stroke. Survived almost 10 months with the AbioCor heart.
Of the seven people implanted with the device in a year, only one was still alive. At the time that he received the artificial heart, doctors estimated that he had as little as a week to live.

Artificial Heart Recipient Dies at Age 52

I understood that I would be a pioneer... if this thing worked or if it didn't work, I would be giving something to mankind."

-James Quinn, on his decision to have the artificial heart implanted

Artificial Heart Implant Leads to Suit Over Consent Process

Recipient's Widow Says She and Her Husband Were Misinformed and Misled on Risks, Benefits and the potential for pain and suffering

There was no quality of life. It was too painful. He said he wished he'd never done it."

The informed-consent process failed," said Quinn's attorney... "They didn't understand what it meant to volunteer for a human subject experiment. They thought this was his only chance, that it was a therapeutic option, and not that he was a human guinea pig."

Was it wrong?

13-page document detailing "significant risks" as stroke leading to brain and organ damage, loss of mental function, device failure, liver and kidney failure, impaired breathing and discomfort and pain.

As a "new and experimental surgical operation, complications could occur which were previously unknown or currently unforeseeable."

Potential benefits of implanting the AbioCor heart are "uncertain and have not been proven to exist."

Quotes from the bioethics world

"To some extent, this is human nature. People are desperate, there is no good alternative, and they may develop unreasonable hopes."

Thomas H. Murray, president of the Hastings Center

"The informed-consent process for many trials is a sham. Clinical trials are set up in such a way that patients are misinformed and misled. Patients and families are not told what the actual and foreseeable risks are, and what they may expect in the way of pain and suffering."

Vera Hassner Sharav, president of the New York-based Alliance for Human Research Protection

C. Volunteer in Asthma Study Dies After Inhaling Drug

24 hours after inhaling hexamethonium, the volunteer reported dry cough, shortness of breath on exertion, muscular aches and fever.

Two days later was admitted to the hospital, with concern about a possible reaction.

Died one month later

Response

Institution suspended the research

Federal government (OHRP) temporarily shut down most of Johns Hopkins's research involving human subjects.

Hexamethonium was not approved by the FDA an internal review board did not provide adequate oversight.

"Action is unwarranted, unnecessary, paralyzing and precipitous." -JHU University did take steps to correct problems

Healthy volunteers

Volunteers may not stand to benefit directly, but could ultimately contribute to development of a new therapy that the participant might then use.

Require particularly close monitoring, because they can pose a risk to a volunteer's health or life.

D. Why do people participate?

Altruism

Free medical care and medications

Trust

Self-interest

Attention

Do we want to constrain people if they are doing things for the wrong reasons?

E. Role of the IRB

Protect the institution

Can introduce complexity

Responsibility of PI to terminate if they sense the patient is not really involved in the process

No one knows how risk is really determined

Ask questions after reading?

F. EM research consent forms

94 forms analyzed from 96 EM programs performing research

Mean readability index (years of education needed to understand the content) was 10

Length and complexity of consent increases with risk to subject

Prospective subject would need at least a high school grade level education

Average EM consent forms may be too difficult for the average prospective participant to understand

G. Strategies for simplification

Short sentences, short paragraphs

Eliminate jargon

Limit abbreviations and acronyms

Active voice

Conversational style (“you” not “I”)

Large type (12-14 pt)

Upper and lower case

Sans serif font

Don't justify right margin

Bold headings

Double space

6th grade reading level

Readability & other discrepancies

82 documents from 3 IRBs, 16 specialties

Mean Flesch grade level 8-17

None below 4th grade (recommended for general US population)

Two at 8th grade level (general recommendation for consent documents)

37% met >90% requirements in code of federal regulation

H. Probabilities

How severe?

How likely?

Most severe and most likely should be brought to attention

VI. Special issues in Emergency Medicine Research

Waiver of Consent

Original waiver (1981 common rule) not relevant to patients with acute life-threatening illness or injury

Did not anticipate modern resuscitation research

FDA provided some regulatory guidance but meant to apply to one-time emergency treatments and not research

Resuscitation research

Performed for many years without formal prospective informed consent

“Deferred consent”

Patient enrolled without consent

Family or surrogate asked for continued participation

Used in NIH Brain Resuscitation Clinical Trials 1984-86

Halt of resuscitation research

Office for Protection from Research Risk halted all resuscitation research using waiver of informed consent

Trials affected

Cardiopump study, vest-CPR study, PEG-SOD for head trauma

Response from EM community

Oct 1994: Society for Academic Emergency Medicine and American Heart Association convened a conference

Established Coalition of Acute Resuscitation and Critical Care Researchers

Consensus document drafted and endorsed by many organizations

Presented in public forum January 1995

Final Rule: Informed Consent and Waiver of Informed Consent Requirements in Certain Emergency Research (21 CFR part 50, 45 CFR Part 46)

Important Elements

Increased and documented role by investigator to attempt to contact family members or legally authorized patient representatives

Prestudy consultation with community representatives

Public disclosure before and after the study

Independent safety and data monitoring boards

Investigational New Drug/Device applications filed with FDA allowing close supervision

If prospective informed consent is not possible, investigator must inform patient or representatives as soon as possible

Points to consider

Does the new rule show respect for autonomy?

Impossible to know a patient's thoughts at times of critical illness or injury

Focus should be on preservation of life (best interest)

Application of the rule

Limited experience

Lack of specific guidelines for how to satisfy the requirements

Community consultation and notification

Local variation

Flexibility for IRB

Summary

Past abuse of patients in the name of science is well-documented and must continue to be avoided

One way to ensure this is absolute compliance with human subjects protection requirements

Physicians perform research on a mandate from society to advance the quality of health care

Community involvement is essential for the public to continue to support scientific endeavors