The Ethics of Cancer Research

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The Ethics of Cancer Research

- Historical content
- Is there such a thing as informed consent?
- Advantages and disadvantages of randomized clinical trials.
- The concept of equipoise.
- Ethical considerations in each of Trial types.
History and Human Subjects Research

• Human subject experimentation
  – Nazis, Japan’s Unit 731
  – Tuskegee Syphilis Study
  – Willowbrook Hepatitis Experiments
  – Henry Beecher
  – U.S. government-sponsored radiation experiments
  – Nuremberg Code, Helsinki Conventions

Informed Consent

• Acknowledges the rights of patients to participate voluntarily in health care.
• Based on ethical, legal and psychological principles.
• Requires adequate disclosure of information to patients regarding a proposed intervention.
• Assures that patients understand the information.
• Assures voluntary consent to the procedure.
Informed Consent and Clinical Research

- Informed consent must be more stringent because the research subject is vulnerable.
- Does the extreme vulnerability of a patient with a life-threatening disease make informed consent an impossibility?
- Does the complex nature of the randomized clinical trial and the treatments involved make true informed consent an impossibility?

• Daugherty, et al. in DeVita, ed. Principles and Practices of Cancer Treatment.

Studies of Informed Consent in Oncology

Written informed consent in patients with breast cancer
- 100 breast cancer patients interviewed after beginning chemotherapy
- 25% unable to name any of their drugs
- Most recognized side effects of nausea and hair loss
- <50% aware of potentially life threatening side effects of infection and bleeding
Studies of Informed Consent in Oncology

Are consent forms readable by most patients & their families?

• Review of all consent forms for oncology research protocols at one research institution found only 1-6% of consent forms were at 8th grade reading level.
• The mean scores were at a reading level equivalent to at least two years of college education.

Studies of Informed Consent in Oncology

The adequacy of consent forms for informing patients

• Consent forms signed by 100 patients before beginning trials.
• Only 40 patients believed the purpose of the form was to explain treatment.
• Only 52 patients could name all of their drugs and only 4 could recall all the side effects of the drugs.
Informed Consent and Clinical Research:

CONFLICT OF INTEREST

The clinical investigator is seen as having an intrinsic conflict of interest or dual allegiance with regard to his/her role as physician for an individual patient and his/her role as scientific investigator.

CONFLICT OF INTEREST: Clinician vs. Scientist
Clinician vs. Scientist

• The clinician is concerned with acting in the best interests of the individual patient medically.
• The clinical scientist is concerned with answering questions and testing hypotheses, and such scientific information will benefit humanity in general.

Equipoise

• A state of general uncertainty on the part of the clinical investigator regarding the therapeutic merits of each arm in a trial.
• An ethically necessary condition in all cases of clinical research.
• If equipoise is disturbed during the course of the trial, the trial may need to be terminated, and all subjects previously enrolled offered the superior treatment.

Freedman, B: Equipoise and the ethics of clinical research. NEJM 1987; 317:141-5.
Can Equipoise Ever Be Achieved?

The case for clinical equipoise

• The clinical community is split regarding preferred treatment. Some clinicians favor A and others favor B.
• Each side recognizes that the opposing side, which is recognized as responsible and competent, has evidence to support its position.
• There exists an honest, professional disagreement among expert clinicians about the preferred treatment.
• A clinical trial is instituted with the aim of resolving this dispute.

Randomized Clinical Trials

Advantages

• Most likely to yield reliable and reproducible clinical knowledge quickly and efficiently.
• Least susceptible to methodologic error; avoid observer bias.
• Study designs using either historic controls or nonrandomized study groups may be plagued by bias which can lead to inaccurate results.
Randomized Clinical Trials
Disadvantages

• Do not allow the clinician to participate by offering his or her opinion based on what he or she thinks, suspects, has seen, believes, or has a hunch about.
• Do not allow the clinician to use information accrued prior to or during the trial, as that information is not "statistically correct."

The Ethics of Randomized Clinical Trials

• Reflect the classic conflict between rights-based moral theory and utilitarianism.
• Rights-based theory would suggest that human beings are bearers of dignity, and should never be used as objects, or means to an end, but rather ends in themselves.

Adapted from Hellman, S: Of mice and men: problems of the randomized controlled clinical trial. NEJM 1991; 324:1585-1589.
The Ethics of Randomized Clinical Trials

- Utilitarian theory defines what is right as that which produces the greatest good for the greatest number—social utility.
- The morally correct act is that which produces the greatest pleasure and the least pain overall, but the distribution of that pleasure and pain is of no moral consequence.

The Ethics of Randomized Clinical Trials

- Utilitarian theory denies the ethical obligation of the physician to see the interests of the individual patient as primary and compelling.
- The randomized clinical trial is utilitarian in that it asks physicians to sacrifice the interests of their particular patients for the sake of the study, and ultimately for the benefit of society.
Randomized Clinical Trials

- Phase I: measure toxicity
- Phase II: measure efficacy
- Phase III: measure efficacy vs. standard therapy

Randomized Clinical Trials: Phase I

Researchers test a new drug or treatment in a small group of people (20-80) for the first time to:
- evaluate its safety
- determine a safe dosage range
- identify side effects.
Phase I Clinical Trial: 
The Case of Ms. D. and Dr. P.

• Ms. D. is a 39 year old married florist and mother of three school age children.
• She has recently been diagnosed with gallbladder cancer which has spread to the liver and surrounding lymph nodes.

The Case of Ms. D. and Dr. P.

• The cancer is too extensive to be cured by surgery.
• There is no evidence that radiation or standard chemotherapy will be of benefit.
• She is referred by her primary care doctor to Dr. P., an oncologist at a large medical center in a nearby city.
The Case of Ms. D. and Dr. P.

- Dr. P. has been working with a company called Cancertech, developing a new immuno-chemotherapy in mice that looks promising as a treatment for cancer.

- He feels that if this works, it will be the beginning of a breakthrough in cancer treatment.

The Case of Ms. D. and Dr. P.

- He tells Ms. D that it could be tried on her cancer as part of a new study he is doing to test it in humans.
- He is very anxious to help her and to try the new treatment.
- He tells her that since there is no effective treatment for the cancer she has, it is the only thing left to offer.
The Case of Ms. D. and Dr. P.

• He tells her that he does not know what all the toxicities are, but that there has been some evidence of liver function abnormalities in rats and in the previous two patients who have tried the treatment.

• He does not tell her that part of his salary is supported by Cancertech, and that he is paid a lump sum for each patient he puts on one of the study drugs.

Phase I Trials: Ethical Considerations

• Problem of administering investigational agents to initial cohorts of patients at potentially low dose levels so that although they do not have toxicity, there is little benefit.

• Chance of response is low: in multiple reviews of Phase I anticancer trials, with 200 trials and 6500-8000 patients in each review, response rates of 4-6%.
Randomized Clinical Trials: Phase II

The study drug or treatment is given to a larger group of people (100-300) to:

- See if it is effective
- Further evaluate its safety
Phase II Trials: Ethical Considerations

• Although toxicity is known, it may be significant.
• Overall low probability of benefit with regard to tumor response.
• As patients accrue, and little response is seen, but not enough patients to be statistically significant, how should the information be handled?

Randomized Clinical Trials: Phase III

The study drug or treatment is given to large groups of people (1,000-3,000) to:

• confirm its effectiveness
• monitor side effects
• compare it to commonly used treatments
• collect information that will allow the drug or treatment to be used safely.
Phase III Trials: Ethical Considerations

- Investigational therapy vs. standard of care presents huge conflicts
- Demands a state of equipoise to be an ethical study.
- Taylor, et al: 82% of physicians reluctant to relinquish individualized decision making control in favor of randomization and adherence to protocol requirements.


Summary

- Must recognize the inherent conflict of interest in conducting clinical trials.
- Human subjects protection is always of most primary concern.
- Informed consent is more a process than a document, and must be rigorous for the study to be ethical.
- Equipoise difficult to achieve, but a significant component of clinical trials.
- Phase I trials are to measure toxicity, NOT response.
THANK YOU!