RCR Handout: Material Accessed 2012.03.14: Human subjects

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http://ori.hhs.gov/education/products/ucla/default.htm
http://ori.hhs.gov/education/products/ucla/chapter2/default.htm

Research in Humans

Research in humans differs from other research in that the subject has decision-making power and must be treated with respect. The long history, even in the name of science of one group of humans exploiting another has made it necessary to establish elaborate rules and procedures to protect human participants in research.

History of Rules About Research in Humans

The Nuremberg Code 1947

"The great weight of evidence before us is to the effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts:"

Ten principles were then enunciated
(http://www.ushmm.org/research/doctors/codeptx.htm)

These have been condensed to:

1. Autonomy - voluntary informed consent
2. Beneficence - good science and favorable benefit to risk ratio
3. Justice - equal opportunity to participate and to not participate

The investigator was given the responsibility for seeing to it that the ethical requirements were met.

The World Medical Association developed the Declaration of Helsinki, first in 1964. It has been amended repeatedly since then. http://www.wma.net/e/policy/b3.htm

Ethical Principles for Medical Research Involving Human Subjects

Thirty-two statements are made in the Declaration including (in paraphrase)

1. The primary responsibility of physicians is the best care and research is secondary.
2. Research is important to improve health care
3. Investigators should be aware of the ethical, legal and regulatory requirements for research on humans.
4. Research on humans must be scientifically sound and carried out by qualified persons.
5. It must be voluntary and informed, with consent and ability to withdraw documented.
6. Vulnerable populations may require surrogate consent.
7. The research protocol must have been scrutinized and approved by an ethics committee for risks and benefits with minimization of the former and maximization of the latter.
8. Investigators must monitor their research and report problems.
9. The population studied should have a reasonable chance of benefiting from the results.
10. Reporting and publication should adhere to the facts.
11. A limitation was placed on jointly providing clinical care and research.
12. Placebo use was strictly limited. Investigators should try to compare standard of care with the new agent.

The Belmont Report 1979
(http//ohrp.osophs.dhhs.gov/humansubjects/guidance/Belmont.htm)

This report was the culmination of the work of a national commission that began in 1974. It was adopted by the NIH in its entirety and became the basis for institutional arrangements with the NIH to review, evaluate and monitor research on humans. Its main provisions are as follows:

Definitions

Research

A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. 45 CFR 46.102(d)

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. 45 CFR 46.102(f)

Intervention

Physical procedures and manipulations of the subject's environment performed for research purposes.

Interaction

Interaction includes communication or interpersonal contact between investigator and subject.

Private Information

Private information is information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, as well as information that has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public.

Definition of Human Research

Data from living individuals
Biological material from living individuals
Interaction or intervention with a living individual
Use of a non-FDA approved, drug, device or biological

Respect for Persons

Choices of autonomous individuals should be respected. People incapable of making their own choices should be protected

Respect for persons in clinical research and verification of that respect depend on administration of and signatures on a formal informed consent document. Having taken on the characteristics of an educational, legal, and accountability document, the typical consent form can have 19 items, requires over ten typed pages, and is frequently signed without a full understanding of its terms. In fact often it fails to educate, to protect legally and to function as an auditing tool.

What An Informed Consent Document Must Cover

1. Purpose of the study
2. Procedures

3. Potential risks and discomforts
4. Anticipated benefits to subjects
5. Anticipated benefits to society
6. Alternatives to participation
7. Payment for participation
8. Possible commercial products
9. Sample remaining at the end of the study
10. Identification of investigators
11. New findings
12. Withdrawal of participation by the investigator
13. Consequences of withdrawal
14. Participation and withdrawal
15. Privacy and confidentiality
16. Emergency care and compensation for injury
17. Financial obligation
18. Rights of research subjects
19. HIPAA privacy rights

The informed consent document operates largely to define institutional policies and the features of an individual protocol. Recent catastrophic delinquencies in consent forms have led to a general tightening of the process with questionable effects on educational capacity and legal protections. The required paragraph for HIPAA may add to the confusion.

Whatever the weaknesses of the formal consent process, the PI as a fiduciary for the subject, retains the responsibility to explain the rationale and content of the study in such a manner and for a sufficient time so that participants understand it and give fully informed consent.

The consent must also be voluntary. Coerced consent, expressed or implied, may occur under a number of circumstances including: when participation is a contingency for treatment, when enough payment is made to constitute an inducement, when the subject is really not a free agent, (e.g. prisoners and dependent children, or members of cultures where decisions are centralized).

The investigative team must be reasonably sure that surrogates consenting for impaired or underage subjects are fulfilling their fiduciary responsibility to the subjects.

Beneficence

Clinical research protocols should be designed to maximize the benefits to an individual or to society while minimizing harm to the individual. But in research we do not know in advance all the harms that may occur, so we must monitor and stop the research should harms become significant in comparison to the benefits. We also do not know in advance to what extent the benefits greatly exceed the alternative so that the randomization must

be stopped. Thus, the ethical decisions of data and safety monitoring boards regarding continuation of trials have become important elements of beneficence.

Justice

Distributive justice means the equitable distribution of the burdens and benefits of research. Investigators may not exploit vulnerable individuals or exclude without good reason eligible candidates who may benefit from a trial. This is now a federal rule and is monitored for all NIH and FDA clinical trials.

The Belmont report also led to Institutional Review Boards and Multiple Project Assurances of institutions with the Federal Government to carry out ethical evaluation and review of all research considered human research and to monitor the progress of studies. This means local control and local responsibility with Federal oversight.

In 1979 the Federal government adopted the "Common Rule."

Common Rule

The Common Rule is a federal policy regarding Human Subjects Protection that applies to 17 Federal agencies and offices. It does not apply to federal agencies that have not signed the agreement (e.g., Department of Labor, etc.) The main elements of the Common Rule include:

Requirements for assuring compliance by research institutions

Requirements for researchers' obtaining and documenting informed consent

Requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping.

The Common Rule includes additional protections for certain vulnerable research subjects.

Subpart B provides additional protections for pregnant women, in vitro fertilization, and fetuses

Subpart C contains additional protections for prisoners

Subpart D does the same for children.

DHHS Regulations are provided in 45 CFR, Part 46.
http://www.access.gpo.gov/nara/cfr/waisidx_99/45cfr46_99.html

FDA Regulations are detailed in 21 CFR, Part 50, and 21 CFR, Part 56.
You can review these at
http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=199945

An institution with a DHHS approved Federal Wide Assurance typically agrees to apply DHHS regulations to all research regardless of the funding source, including research that is internally funded and collaborative research across institutions

Institutional Review Board (IRB) Mission

IRBs are impaneled to protect the rights and welfare of human subjects and support the institution's research mission. By requiring local review the Federal Government requires local responsibility that is both institutional and individual.

Researchers must respect and protect the rights and welfare of individuals recruited for, or participating in, research conducted by or under the auspices of the Institution. By institution is meant any entity that is sanctioned by the Federal Government to conduct research. The IRB is constituted to be the agency within the institution that reviews and approves research involving humans. Research actions are guided by the principles set forth in the Belmont report (see above).

IRBs have a full time administrative core to handle the applications, keep abreast of the changing rules, and monitor the approved protocols. IRB members consist of faculty and non-affiliated non-scientists who in the aggregate possess a broad range of expertise and interests corresponding to the research proposed.

Research institutions have a contract, called an assurance, with the Federal government outlining their collective obligations and responsibilities to protect human subjects. These multiple project assurances require ethical review of all human research under defined rules. Review by the institutional IRB(s) is required for research on humans when the conduct or recruitment of the research involves institutional resources, property, or facilities, regardless of funding source, when the research is conducted by or under the direction of any employee, student, or agent of the institution: in connection with her/his institutional responsibilities using any property or facility of the institution when the research involves the use of an institution's non-public information to identify or contact potential subjects The Common Rule adopted the principle of local control of research oversight because:

It would enhance education of the research community & the public

It would provide greater familiarity with the actual conditions surrounding the conduct of the research

It would enhance the ability to work closely with scientists to assure the protection of the rights and welfare of the subjects

It would assure that the application of policies is fair to investigators

Any study involving research on human beings must go through the IRB. However, there are certain exceptions based on the intent of the research or on the characteristics of the

study.

Hospitals are required to carry out programs of quality assurance that involves research into clinical practices in the institution. These are usually designed to improve the care locally and there is no intent to generate generalizable knowledge. That is not considered research. On the other hand, a program evaluation/quality assurance program becomes research when the intent of the project is to answer a research question or create generalizable knowledge that will be shared outside of the program being assessed, such as journal articles, professional presentations, etc. Frequently the findings precipitate the interest in publishing.

In general, a Study is exempt from IRB Review if it is

Research in commonly accepted educational settings involving normal educational practice (Think course evaluations)

Surveys,

Interviews

Questionnaires

Observation of public behavior, unless subjects can be identified, directly or through identifiers linked to the subjects; and any disclosure of the human subjects' responses outside of the research could reasonably place the subjects at risk of criminal liability or be damaging to the subjects' financial standing, employability, or reputation

Collection or study of existing data, documents, records, pathological specimens or diagnostic specimens, if:

The sources are publicly available, or
If the information is recorded in such a manner that subjects cannot be identified directly or through identifiers linked to the subject
Due to HIPAA: Medical record reviews are no longer exempt

Case Study 1: Use Of A Placebo Control

In 2002 a report was published in JAMA describing the results of a trial of seratraline (Zoloft) versus hypericum (St John's Wort) versus placebo in the treatment of severe depression. It was an eight-week trial and all of the subjects were monitored carefully for increased depression or suicidal tendencies at which time they were removed from the trial. Both seratraline and hypericum were no better than placebo. The investigators pointed out that without the placebo group, the conclusion might have been reached that St John's Wort was equally effective as seratraline.

Questions:

1. Was this an ethical trial? If so, why? If not, why not?
2. Discuss equipoise in clinical research
3. Discuss Geneva Convention and CIOMS guideless for use of placebos
4. Discuss whether clinical research, especially randomized clinical trials require a therapeutic obligation to participants

Case Study 2: Phase 1 trials

In the absence of human trials it's impossible to know about the safety of drugs in humans that were found to be safe in other animals. Phase I clinical trials involve the dosing of new drugs to tolerance in control subjects and doing pharmacokinetics to determine blood levels, binding, and disposal rates of the drug.

Years ago, a large drug company advertised for volunteers for Phase I clinical trials of new agents. They noticed as the weather turned cold, middle-aged persons who were dirty and poorly dressed volunteered, and that the number of volunteers increased yearly. The volunteers were housed in a metabolic unit for 6 months and were given a number of agents in sequence during the winter. Each trial was approved by an "in house" IRB. When it became known that many of the volunteers were homeless alcoholics, screening tests were done to ensure that chemistries were normal or near normal. Each volunteer signed a consent indicating that their compensation would be provided to them at the end of the period of being a control and that they would refrain from alcohol for the duration of their stay.

The company believed sincerely that it was helping these individuals. The process was revealed in the media after some years.

Questions:

1. Was anything untoward happening here?
2. If you believe so, then what was the range of ethical lapses in drug research?

Case Study 3: Tissue Samples

Aortic tissue samples from patients undergoing cardiac transplantation have been collected and stored for many years. Permission for the sampling was granted under the blanket research approval in the surgical consent form. Previously, investigations were permitted under waiver of IRB review because the samples were used completely without identifiers. The samples (n=2000) were dated and stored untouched in liquid nitrogen.

The medical team gave permission to Dr. Gomez, a geneticist, to sample all 2000 specimens to study the prevalence of a number of gene polymorphisms proposed to relate to development of dilational cardiomyopathy. The genetic findings were to be related to a specific patient by identifying the tissue donor by correlating the sample date to the operative schedule. Dr. Gomez claims that no IRB approval or new consent forms were required for this study because the study did not utilize individuals, only stored tissue.

Questions:

1. Are there any limitations on Dr. Gomez' access to the tissues?
2. To perform a complete genetic search, Dr. Gomez would like to provide some of the material to other labs including some commercial labs. Are there any limitations to that?
3. There may be several forms of dilational cardiomyopathy. Dr. Gomez plans to arrange for a cardiology fellow to collaborate and to review all the charts to distinguish between the clinical forms of the condition to further define the genetics. Is there a problem with this?
4. If there are problems how should they be handled?

Case Study 4: Alzheimer's

Your basic research laboratory discovered the principal pathway by which -amyloid was cleared from brain cells and was able to design an oligopeptide drug as a potential highly potent therapeutic agent to rapidly enhance clearing and support improvement of brain function.

With venture capitalists you formed a new company COGNI + to license your discovery and complete development of this and potentially even more potent products. COGNI+ has conducted extensive investigations in an animal model of Alzheimer's disease and demonstrated that the agent appeared to produce few side effects and that intensive application for a week or two cleared the affected tissue of -amyloid and that low dose maintenance could greatly improve the animals' condition.

COGNI+ filed an IND at the FDA to test humans. Based on the animal data, the most effective clinical trial for efficacy would be to treat patients with moderately severe Alzheimer's disease rather than early or advanced cases. Your academic clinical responsibilities include supervision of a large nursing home where 35% of the patients have Alzheimer's disease. Therefore, you arrange to do the Phase 1 and Phase 2 trials in this facility. You review all the charts of patients to find the ones with moderately severe Alzheimer's disease.

The Phase 1 trial will test toxicity in 6 subjects. If the toxicity is low, it will be possible to proceed to the Phase 2 trial.

The Phase 2 trial will include 10 subjects in an escalating dose protocol to test efficacy. Because the drug clears rapidly it must be given intramuscularly three times a day in the acute phase of therapy.

Questions:

1. Would the IRB and the University-Industry Conflict of Interest Committee of your institution have a problem with this study?
2. How will you determine whether participants can consent for themselves? What should you do if some cannot?
3. How will you present the studies to the subjects and to their surrogates?
4. This category of patients experiences a lot of "sundowning." Will this likely affect your study?
   Expecting the Phase I and II trials to be highly successful from the basic mechanism and the animal experiments, you are planning a phase 3 clinical trial that will involve 300-400 participants.
5. What ethical issues must you consider in this large trial?

Case Study 5: Violation of Confidentiality

Researchers cloned and sequenced the gene for Interleukin I. They sent off a paper to Nature, very excited about their great result. Their work was funded by the Cistron Corporation.

A faculty member associated with Immunex had a reviewer on the paper that the above group claims held up the paper and used key information it contained to clone and sequence the same gene.

Even though there never was a market for a product from this gene, Cistron is suing because Immunex got venture capital funding on the basis of the gene and because it became a strong competitor due to that funding. $100,000,000 is at stake here.

Immunex responded that Cistron had cloned something different, that they were suffering a loss of reputation due to a deliberate misleading reading of the facts and is countersuing.

The core question could turn on what degree of confidentiality is appropriate (the norm) for peer reviews?

Rules have become more explicit. What should they be?