Human Subjects

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Summary

Critically evaluate the decision to conduct research with human subjects.
Both the spirit of the regulations and good science require that individuals give thoughtful consideration to the decision to conduct research with human subjects.

Comply with regulations.
No research study of human subjects should be carried out that is not explicitly part of an approved protocol.

Protect individual rights to self-determination.
The decision to participate in research should be based on truly informed consent. This means that researchers have an ongoing obligation to ensure that subjects understand the risks and benefits of participation, which should continue only if the subjects (or their surrogates) freely agree to remain in the study.

Promote responsible use of human subjects.
If you are responsible for training others or if you observe indifference to considerations for human subjects in research studies, you should make attempts to initiate discussion, to identify relevant regulations, and to promote responsibility. If violations of regulations are observed, then those observations should be reported to the appropriate people in the institution.

Background

Advances in human health and welfare ultimately depend on research with human subjects. Properly designed and controlled studies with human subjects are essential to verify hypotheses about normal physiology, behavior, mechanisms of disease, processes of learning, or effectiveness of treatments. Unfortunately, not all human studies have been justifiable and useful; human cruelty has sometimes been perpetrated in the name of research. Some of the best known examples of such cruelty occurred in Nazi Germany. Investigations following the war uncovered many atrocities, such as studies in which subjects were immersed in very cold water to gauge how long it would take to

die of hypothermia. The discoveries of these abuses were the basis for the Nuremberg trials and development of the Nuremberg Code (1949), the first international codification of minimal expectations for the conduct of research involving human subjects. One of the most important provisions of the Code is that "the voluntary consent of the human subject is absolutely essential;" other provisions indicate that experiments with human subjects should occur only in the context of a clear scientific rationale.

Harm to unwilling subjects under the guise of research was not unique to the Nazis. During World War II, the United States conducted medical experiments on those not competent to consent and on subjects without their knowledge (Vanderpool, 1996). In one instance, beginning in 1932 and prior to the start of World War II, 400 African American males with syphilis were entered into a study at Tuskegee, Alabama with the intended purpose of documenting the natural course of their disease (Rivers et al., 1953; Jones, 1993). Although treatments of presumed efficacy were available, these were withheld while the study participants were led to believe that experimental procedures (such as spinal taps to examine cerebrospinal fluid) were for the purpose of therapy. By the 1950s, penicillin was available and known to be highly effective against syphilis, but it also was withheld. The surviving participants were only given treatment in 1972, after the nature of the study became publicly known -- 23 years after publication of the Nuremberg Code.

Recognition of these, and other, problematic studies (e.g., reviewed by Beecher, 1966) published in the medical and social science literature resulted in the appointment of a federal commission to identify fundamental principles that should govern human subjects studies. The final product of this commission was the Belmont Report (1979). It defined the three ethical principles (listed below) that now guide studies with human subjects in the U.S.

- **Respect for persons**
  "Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection."
- **Beneficence**
  "Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms."
- **Justice**
  "An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly... "

At least three important premises underlie these principles. The first is that studies with human subjects are necessary for improvements in health and welfare. Second, to conduct such research is a privilege, not a right, extended to researchers by society, institutions, and the research subjects themselves. Finally, neither the risks nor the costs of any research study should outweigh the likely benefits.

Regulations and Guidelines

Numerous federal agencies have regulations governing the conduct of research involving human subjects. Examples of agencies with human subject requirements include the Department of Health and Human Services (DHHS), the Food and Drug Administration (FDA), the National Science Foundation (NSF), and the Departments of Defense, Education, Justice, and Veterans Affairs.

Human subject protections are a shared responsibility of principal investigators, other personnel involved in studies with human subjects, and the Institutional Review Board (IRB). The IRB is a primary mechanism for federally-mandated institutional protection of human subjects. An IRB is designed to be an advocate for potential and actual research subjects. Under both DHHS and FDA regulations, the IRB is responsible for approving or disapproving all covered research activity, requiring for instance that subjects are given enough information to be able to provide informed consent. The IRB must conduct periodic reviews of research to ensure continued protection of the welfare of human subjects and compliance with relevant regulations.

Different agencies define "human subject" in different ways, but the definition includes (at minimum) any living person who is involved in research either as an experimental subject or as a control. The scope of activities included under the definition of "research" is broad. One federal regulation defines research as any "systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities." (Code of Federal Regulations for Department of Health and Human Services 45CFR46.102(d)).

In addition to the above regulatory oversight, because of concerns about protection of human subjects, the Department of Health and Human Services also requires education of all key personnel working on PHS-funded studies that involve human subjects (NIH, 2000).

Discussion

Case Study 1[i]

Dr. Jacqui is a psychiatrist interested in the molecular basis of several different anxiety disorders. Accordingly, she requested institutional approval to collect blood samples from a large population of both affected and unaffected individuals. The plan is to identify unusual genes that occur in the affected population. After receiving approval,

numerous individuals, including staff and colleagues from Dr. Jacqui's medical center, were enrolled after signing the requisite consent form. Along with many other pieces of information, the form specifically (a) notifies the volunteer that he/she will be told at the end of the study whether or not they carry the genes in question and (b) prompts the volunteer to ask any questions they might have. The blood samples are then collected. In the process of testing and refining methodology, one of Dr. Jacqui's postdocs runs a "negative control" by screening the samples for the presence of a rare gene he has recently identified in a collaborative project with another laboratory studying breast cancer. Surprisingly, this gene is detected in one of the samples. Evidence to date is that this gene carries a small, but significant, increased likelihood of developing several different forms of metastatic cancer, and an estimated 70% likelihood for developing breast cancer. If known, the individual would increase their chances for long-term survival by prophylactic mastectomy and frequent check-ups. However, these measures would only decrease, not eliminate, the risk of developing cancer. The postdoc reports these findings to Dr. Jacqui. A quick look through the records allows Dr. Jacqui to identify the carrier of this gene as a clerk working in hospital admissions. Dr. Jacqui debates whether or not to tell the clerk what has been found. After some deliberation, she decides against telling the clerk because (a) the gene does not guarantee that the clerk will get cancer and (b) the clerk's wishes about whether or not she would like this information are not known.

Question:

1. Consider the roles of Dr. Jacqui, the institutional review board, the postdoc, and the clerk in this case. Given the information provided, have any of them erred by acts of commission or omission?

Case Study 2[ii]

Alonzo Garcia, M.D., entering his fellowship in pulmonary medicine, was assigned to carry out an approved study designed by Dr. Bruce Sedgwick, his training director. The study entails the use of the recombinant enzyme, DNAse, to improve pulmonary function and to reduce the incidence of new infections in patients with cystic fibrosis. The study was double-blinded, meaning that neither he nor his patients and their families know whether the inhaler the patient received contained the active enzyme or a placebo. Experiments conducted in vitro and in small animals indicated great success for the agent, though they also pointed to some potential problems. These included development of an allergic reaction to the enzyme or to the other materials in the inhaler, and a direct and adverse chemical effect on the lung passages. The clinical study for which Dr. Garcia was responsible consisted of a three-month trial of enzyme or placebo, a one-month drug-free period, then a three-month trial of the other arm of the study. Forty patients were to be entered by the completion of the trial. They were to be evaluated by a lung function test and, since most of the patients were children, by a standardized questionnaire completed by a parent. The experimental drug was so effective that shortly after the trial began, Dr. Garcia found it easy to know who was receiving active enzyme and who was receiving placebo. Even though the questionnaire filled out by the patients' parents was uniform, he discovered himself encouraging respondents to comment about the beneficial effects of the enzyme. After 20 patients

were entered in the trial, one of the parents, who happened to be a scientist, said to Dr. Garcia, "The quality of our daughter's life has greatly improved since she was entered in this protocol. Clearly, the drug is having an enormous impact that cannot be ignored and the blinding must be stopped. Won't you ask the company to terminate the experiment and make DNAse available to us? It will save the lives of our children." Dr. Garcia responded that the statistical power of the study was not sufficient to determine whether an effect would occur in one percent of subjects, nor the duration long enough to obtain meaningful data on infections. For that, a different experiment, monitoring the treatment of large numbers of subjects over a longer period of time would be required. Since the degree of improvement was sufficient to demonstrate efficacy after only 20 subjects, there was no need to continue to employ the placebo controls and to continue with the current study. Dr. Sedgwick pointed out that the FDA required 40 cases from their institution for the efficacy study and their requirements took priority over the statistical analysis in most cases.

Questions:

1. What values are in conflict in this case? How would you approach their resolution?
2. The grossly apparent effectiveness of DNAse in cystic fibrosis seems to have ruined the blinding of subject and investigator that protects against biased reporting of efficacy. What can or should be done about that in the context of this experiment? What about in the broader context of clinical trials?
3. The FDA plays a critical role in the design of studies intended to achieve approval of a new therapeutic agent. In fact, companies negotiate in advance with the agency to ensure that, if the study is successful, the agent will be approved. Is this in the best interest of the patient, the company, and society?

Case Study 3[iii]

The Pernkopf Atlas is one of many examples of information, which was, or may have been, made possible by the use of unwilling subjects in Nazi Germany. Another well-known example is a series of experiments involving extreme hypothermia.

Consider the following questions:

1. Should data obtained under such circumstances be used?
2. On what principle(s) is/are your opinion based?

Please note that you are NOT being asked to judge whether the Pernkopf Atlas drawings were made using Holocaust victims and you are NOT being asked to judge whether these or other experiments conducted in Nazi Germany lacked scientific merit.

Discussion Questions

1. To what extent does your field of work depend on research involving human subjects? To what extent is your work intended to benefit human welfare?

2. Describe at least one historical example of unethical studies involving human subjects. Identify federal regulations that are apparent responses to such abuses.
3. List and explain the three ethical principles of the Belmont Report for research involving human subjects.
4. If you are involved in research with human subjects, which federal agencies have oversight for your work?
5. What are the responsibilities of an Institutional Review Board (IRB)?
6. In your institution, what kinds of research, if any, with human subjects do not need to be presented to an Institutional Review Board for consideration?
7. In your institution, what minimal changes to your protocol require review and approval of the IRB? What changes are of a magnitude to require submission, review, and approval of a new protocol?
8. If you observed another investigator violating principles or regulations governing the study of human subjects, who should be notified?
9. What forums are available in your institution to examine the ethical and/or legal ramifications of studies with human subjects? What, if anything, can you do to promote such discussion?

Additional Considerations

Regulations

Research that involves humans is subject to regulation. No procedure or study should be performed that is not explicitly exempted or a part of an approved protocol. Applicable regulations include requirements for adherence to IRB-approved research protocols, maintenance of documentation and records, obtaining approval prior to initiation of changes, and reporting of adverse events. Investigators are responsible for identifying all applicable regulations and complying with them.

Responsible conduct

Responsible conduct of research involving human subjects requires much more than complying with regulations. The spirit of the regulations and of good science both require that researchers critically review what is known and give thoughtful consideration to what defines an acceptable study. This consideration is necessarily an ongoing process. Some factors to be considered include changes in our best understanding of the science, of the risks and potential benefits, and of alternative methods for study. The decision to conduct a study with human subjects carries both ethical and regulatory responsibilities to protect the welfare and interests of those subjects, to conduct the study with a view to protecting the welfare and interests of those subjects, to design the study so as to minimize risks to subjects, and to obtain adequate training for protecting the interests and welfare of research subjects.

Justification and necessity

A prerequisite for responsible research involving humans is a realistic examination of the probability and magnitude of both the risks and the benefits of the research. Investigators must assess whether the risks are reasonable in relationship to the benefits to the individual subjects and the knowledge to be gained.

Informed Consent as a Process
Investigators conducting a research study with human subjects have an absolute responsibility to ensure that consent to participate has been given freely and is based on an understanding of the risks and benefits of the research. Informed consent is often needed even for studies in the social sciences that impose little or no inconvenience, but still present the risk of a loss of privacy or confidentiality. Although some costs or risks may be more injurious than others, it must be up to the potential research subject, not the research investigator, to decide whether such costs or risks are outweighed by the benefits of participation. The most visible indication of "informed consent" is a document to be signed by the research subject. This document is important because it provides a consistent body of information that the investigator and the IRB have agreed is necessary for individuals to provide their informed consent. Unfortunately, subjects may sign such forms without understanding them and, even if those forms were initially understood, changing circumstances may mean that the subjects are no longer truly informed. Therefore, informed consent is not a single event, but an ongoing process.

Diminished Capacity to Consent
Not all subjects are able to give truly informed consent. In some cases, it is difficult to ensure that consent is given freely, such as in prison populations. In other cases, it may be difficult to convey the necessary information or to verify an understanding in people with reduced decision-making capacity, such as some subjects with developmental disabilities, psychiatric disorders, or advanced dementia. In these cases, research investigators have an additional burden to meet ethical and regulatory obligations for protecting the right of self-determination for prospective or current research subject.

Resources

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Endnotes

[i] This case was contributed by Dr. Michael Kalichman (kalichman@ucsd.edu) of the University of California, San Diego. ©1999

[ii] Case H2 from Teaching the Responsible Conduct of Research Through a Case Study Approach, a handbook prepared by the Association of American Medical Colleges (Korenman SG and Shipp AC, 1994)

[iii] This case was contributed by Dr. Michael Kalichman (kalichman@ucsd.edu) of the University of California, San Diego. ©1998