

Week 8
Human Subjects: Investigator-Researcher Relationship
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Objectives

At the end of this unit, participants should be able to

- (1) Identify the basic obligations of researchers and subjects of research
- (2) Identify the elements of the process of IRB Review
- (3) Identify the importance of informed consent

Resources

Title 45 *Code of Federal Regulations* Part 46 - Protection of Human Subjects. Source: 56 Federal Register 28003, June 18, 1991 (Exact sections: All of *Subpart A*)
<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>

Videotape: "Balancing Society's Mandates: Criteria for Protocol Review," NIH, Office of Extramural Research, 1993

Activities:

- (1) View the video paying special attention to the process of protocol review as modeled by the IRB members,
- (2) read the assigned sections of the [45 CFR 46](#), and
- (3) read the brief summary lecture provided by the instructor.
- (4) Then, participate in the bulletin board discussion of Case 4.5 in T. Ackerman & C. Strong, *A Casebook of Medical Ethics*, Oxford University Press, pp.146-149 or one of the other threads for discussion. As always, you must post twice during the week, at least one of those posts being before Wednesday is over and one of those posts should respond to that of another student.

Suggested Further Reading:

Francis Macrina, *Scientific Integrity*, pp 73-99, Please note that it includes a copy of the Declaration of Helsinki (pp. 94-98).

[Introduction](#)

Research ethics is one of the **two major roots** of the tree of **bioethics**. The other **clinical root** derives from informed consent for clinical **treatment** and runs through the major end-

of-life cases such as Quinlan (1976), Cruzan (1990), and Quill (1997). The history of the two is separable at points. For instance, **World War II** is an extremely **important** event in **research ethics**, but not in clinical ethics. It was during WWII that biomedical science made enormous strides due to **experiments** necessitated by the needs of combat troops. As a result, WWII led to the formation of the government institutions, e.g., **NIH**, that are the cornerstone of biomedical research in the U.S. These **two histories** have met up in contemporary bioethics in the **two governmental commissions** that laid the groundwork for most of the recent work in biomedical ethics:

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1975-79)

And the

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1979-82).

The **National Commission** created the **regulatory framework** of biomedical **research**. This is encoded in the Belmont Report and especially, in Title 45, Code of Federal Regulations, Part 46 (45 CFR 46). Research is much **more** heavily **regulated** than clinical medicine. This is for a simple **philosophical reason**.

As we cannot reiterate too often, in medical **practice**, it has historically been reasonable to assume that the physician is working in the **best interests** of the **patient**. In research, the physician/researcher has goals that can conflict with the well being of the individual patient. In particular, the **researcher** is seeking to advance **knowledge**. This is a different goal than making the patient well. As a result, a variety of oversight mechanisms are in place. The main oversight mechanism is the **Institutional Review Board (IRB)**.

(I) Overview of the IRB

IRBs screen all **research** involving **human subjects** conducted, supported or otherwise subject to regulation by a **federal agency**. Typically, all educational institutions that receive federal funding also subject their private research to the same scrutiny via the IRB. The IRB review of the protocol is founded upon the principles of the Belmont Report (Respect for Persons/Autonomy, Beneficence/Nonmaleficence, Justice). Steps:

- A. Risk/benefit analysis (Are the risks reasonable proportionate to the anticipated benefits? Can risk be further minimized?)
- B. Informed Consent (Is it voluntary? Is the consent process appropriately designed?)
- C. Selection of subjects (Equitable?)
- D. Privacy & Confidentiality (What protections and safeguards are in place?)
- E. Continuing Review (Are there trends within data regarding harms/benefits to subjects? At what intervals are these assessed?)

Informed Consent is the **ultimate protection**. It is based on the right of a person to determine their own future—to refuse or to accept a plan of action that entails potential risks or gains. Most accords with our political and social self-understanding and philosophy. Certain questions naturally follow:

(1) Is informed consent sufficient protection for the patient?

- a. risk/benefit analysis
- b. some might argue that (a) is **unjustified paternalism**, i.e., perhaps people should be able to consent even to very risky experiments
- c. problems of coercion/coercive environment

(2) Can informed consent ever be **waived**? (More on this in Unit 9)

- a. Yes, under certain conditions: the research presents no more than **minimal risk**, the waiver of consent must not adversely affect the rights and welfare of the subjects, the research **can't be done any other way**, and care is taken to **minimize the negative effects** on the subjects, e.g., they're **debriefed**. Of course, the research must be **scientifically valuable**.
- b. In practice, **waivers** of informed consent are **seldom** granted in **biomedical** research. New exception in biomedical research, i.e., **ER**
- c. **Behavioral research** has had a different tradition. **Deception** has often prevailed in social psychological research.

(II) Randomized Clinical Trials & Equipoise

Research design, terminology, and other issues

Purpose of research—in biomedicine—generally intended to isolate a one-to-one causal relationship between two things, e.g., a gene and a disease, a drug and an improvement in condition. Because relationships are seldom so simple, research tends to report its results in an “as if” fashion.

There are many potential sources of ethical discomfort in research. As we noted earlier, the main one concerns the possibility that when a physician becomes concerned with research, he or she becomes more interested in obtaining knowledge than treating the patients. We saw that the IRB is meant to provide oversight of this situation and insure that the researcher does not place the subject at unnecessary risk or fail to obtain consent. Nevertheless, once we understand research design, we see that there are other ethical questions inherent in the research process.

Terminological & Conceptual Distinctions in Research Design

(1) **Research vs treatment/therapy-**

Research aims at new **generalized knowledge**; benefit to patient is often co-intended, often a departure from standard practice.

Treatment aims at welfare of the patient, usually in line with **standard practice**. However, **innovative treatments** are not **research**.

(2) **Longitudinal** study vs. **cross-sectional** study

longitudinal —population(s) studied over a period of time (can be retrospective)
Cross-sectional study-gathers information of a slice in time (can be concurrent or retrospective)

(3) **Experimental** study vs. **cohort** study

Experimental study — active difference between comparison groups is introduced by the investigators.

Cohort study-difference between the groups occurs by accident or by choice of the subjects, e.g., smoker vs. non-smoker.

(4) **Clinical trial**—A **longitudinal prospective experimental** study.

Phase I Clinical Trial—looks at metabolism and toxicity of new drugs.

Phase II—preliminary inquiry into efficacy—pilot study.

Phase III-“randomized controlled clinical trial” (RCT) - it is very easy to confuse this with “treatment”

Randomized study—subjects are assigned to the active treatment and the control arms randomly.

Single-blind vs. **double-blind study**—subject does not know whether she is in the experimental or the control arm of the study (single-blind). If the physician also does not know, it is a double-blind study.

Types of Biases

Confounding bias—an unsuspected variable travels along with the supposed causal variable (randomization can help if the confounding variable is not completely uniform).

Performance biases-the two groups in the study (the two “arms”) receive some kind of treatment that is unequal (other than the experimental vs. placebo treatment).

Double-blinding is meant to take care of this problem.

Types of Control Groups:

(1) **placebo concurrent control**—the “gold standard”

(2) dose comparison, concurrent control

(3) no treatment concurrent control

(4) active treatment concurrent control

(5) historical controls—use case records of earlier untreated persons as the control group. Supposedly helpful with life threatening illnesses (all subjects can receive the experimental intervention)

Several Issues present themselves in the design of research. First, there is simply the question of how a physician can ever in good faith recommend someone to a clinical trial.

If the physician believes that an experimental treatment is better than the standard of care, he would seem obligated to provide that treatment, not a randomized chance of receiving of that treatment. We will see in our discussion of “ equipoise ” that this objection is theoretically answerable. However, other ethical issues tend to plague biomedical and behavioral research.

The best knowledge regarding the efficacy of a new treatment is sometimes said to come from placebo-controlled trials. (They make possible smaller, less expensive studies.) But, it can be quite unethical to provide placebos to patients when there is a standard treatment for their illness. Similarly, many treatments have no controlled data collection demonstrating their efficacy. As a result, one can make a case in favor of subjecting such treatments to clinical trials. However, others argue that such studies would deny sick patients of efficacious treatments that are the standard of care. This is especially true of treatments that represent an “ off-label ” use for which the treatment was not originally designed. Because some patients are considered especially vulnerable and not appropriate as research subjects, e.g., pediatric patients, treatment of them tends to be off-label extrapolations from a different population, e.g., adults.

“ Equipoise ” or “ the uncertainty principle ” The justification for a clinical trial is that **we do not know which is better**, the experimental treatment or an alternative, e.g., no treatment or a standard treatment. The **weight** on each side of the argument must be equal (“ equipoise ”). Of course, it is seldom true that physicians will agree that two treatments are equally likely to be effective. Each physician normally has a preference between treatments. As a result, it can be argued that no physician should ever enroll her patients in a clinical. But we can distinguish between when a particular physician believes equipoise exists and when the community of physicians thinks it exists.

Theoretical Equipoise- a rare occurrence-a cognitive state in which the evidence is exactly equally balanced in the mind of an individual physician.

Clinical Equipoise-the community of clinicians is undecided or divided as to the preferred treatment for the given population.

So, even though a patient’s physician has a preference for one treatment over another, he or she can refer the patient to a clinical trial based on the physician’s humility and respect for the community of investigators.

(III) AIDS & Vulnerable Populations We noted in previous discussions that the climate in which research is conducted has been evolving in the United States. The movement in the United States until the 1980s had been for ever greater regulation of research and caution in the licensing of new drugs and treatments. Scandal after scandal, e.g., the thalidomide scandal and the Tuskegee Syphilis study gave rise to calls for increased oversight of research and increased regulation of new treatments, especially

pharmaceuticals. AIDS seems to have reversed this course. (The case of Jesse Gelsinger at UPENN may have begun to slow or reverse this pendulum)

AIDS made people aware that caution in bringing new drugs to market can mean delays in obtaining potentially beneficial treatments. Although fewer persons will be harmed by undiscovered side effects and other problems, fewer people will also have an opportunity to benefit. As a result, new strategies were developed such as the famous “parallel track” opportunities in which a drug under study in a controlled clinical trial is made available to persons not enrolled in the study.

In general, the **climate** created by **AIDS** activism has changed regulatory emphasis from one that maximized protection of vulnerable populations, i.e., women of childbearing years, children, cognitively impaired persons, and prisoners, to one that seeks to empower vulnerable populations to share in the benefits of research. As such, the emphasis is no longer on excluding women from research but on making sure that women are adequately represented in any trial so that the knowledge gained will be clinically valid for female patients. This represents a certain interpretation of the principle of **justice**. Justice requires that the **burdens** and **benefits** of research be **distributed fairly**. So, those groups of people, who are burdened as subjects, should also benefit as patients. And, those groups who expect to benefit should also participate in the risks of research. These are the ultimate safeguards of the current era of ethics in research.

However, as some have been quick to point out, there is **no** ultimately **correct answer** as to how to balance the protection of patients and the delivery of benefits. When we attempt to benefit more by making the regulatory process less burdensome, the consequence will eventually be some unforeseen harm that escapes the regulatory process, and perhaps some **new scandal**. But, society must decide how to balance these factors and the pendulum inevitably swings back and forth between these values.

(IV) IRBs as Local Knowledge

Although the ethics of research is far more regulated than the ethics of clinical treatment, the prescriptions in the regulations are of a general nature and require interpretation by the particular institution’s IRB. Questions concerning how detailed a consent process must be, the appropriate level of compensation a subject may receive, who may be recruited as a research subject, whether deception is appropriate in a particular experiment, etc. are questions whose answers may vary from one IRB to another. Although room for individual discrimination and judgment is welcome, there is some danger that **ethical standards** may be considerably more lax in one location than another.

Great strides have been made in recent years through the use of electronic communication to place IRB administrators in contact with one another and to share resolutions to ethical issues posed by various kinds of research. Perhaps the most successful of these projects has been the discussion forum called IRBForum (www.irbforum.org)

(V)Sample Case Analysis

It is not always easy to apply the Federal Regulations to specific cases and to balance the principles we saw in the Belmont Report (Respect for persons, Beneficence, and Justice). Often, we have to scour the regulations for insights and then still find that we must use some judgment. IRBs typically try to function according to the regulations. However, as a kind of repository of local knowledge, they may go beyond what the regs require and ask for additional safeguards at their particular institution (Similarly, institutions must also comply with the laws of their state that may go beyond the federal requirements.).

Below, I recap a case and try to analyze it in terms of the regulations and then identify “residual” concerns that persist after applying the regulations.

This case is adapted from Brain Schrag, ed., *Research Ethics: Fifteen Cases and Commentaries*, Vol. I, APPE, Bloomington, IN, 1997. For information on obtaining this and other related publications, visit the [Poynter Center](#) web site.

Case:

Dr. Samantha Smith and Dr. Joyce Jones have collaborated on an epidemiological study to identify determinants of pre-term birth. Over five years, the project team recruited 10,000 women into the study from prenatal care clinics in a southern state. The study participants provided genital tract, blood and urine specimens, all of which were frozen and stored. They collected a great deal of other information through interviews with the participants and review of their medical charts, including social, demographic, health behavior and health history information.

All study forms and specimens were coded with identification numbers rather than women’s names. The links between the identification numbers and names were kept locked up and separate from all other study materials.

The consent forms signed by the women in the study described in a general way the analyses planned on the biological specimens. For example, genital tract specimens were to be analyzed for the presence of infections, blood samples were to be analyzed for levels of different vitamins, and urine was to be checked for cotinine (a marker of exposure to cigarette smoke).

It has now been five years since the end of data collection for the study, and Smith has become very interested in studying potential genetic causes of preterm delivery. She realizes that this cohort of women, from whom a great deal of information has been collected, provides an opportunity to conduct an investigation of her hypothesis with minimal additional funding.

Smith is eager to proceed with a genetic analysis using the participants’ stored blood specimens. However, Jones is concerned. “Sandy, the consent form that these women

signed did not mention the possibility that we might do this genetic analysis. We'll have to contact them again and ask for their permission.”

Smith thinks that contacting the women would be too difficult. “But, Joyce, that’s unreasonable. You know the logistical challenges we face in trying to find these women – some of the participants were recruited as long as a decade ago. We should just go ahead with the analysis. It’s not that big a deal. It wouldn’t make any sense to pass up this opportunity.”

Sample Analysis

Because of the burgeoning field of genetic testing and research, there is tremendous potential to gain new knowledge from existing specimens that have been collected. As a result, few specimens are discarded easily. But, is this proper?

One should evaluate the potential harms that might come both from using the specimens without consent and from procuring consent for their use. If one were to procure consent, it would involve finding these women five years after their last potential contact with the researchers and contacting them. We can expect that there would be at least some minor distress from receiving a call from a researcher who claims to have a blood sample from five years ago and wishes to check it for the presence of certain genetic markers. Because this level of distress is indeterminate, some scrupulous IRBs prohibit such “cold calling.” They require that initial contact be made by a treating health-care professional. In this instance, such a requirement would prove impossible to implement since the researchers are unlikely to be able to determine from whom these subjects receive their medical care. On the other hand, there would seem to be few direct harms to the subjects by not telling them that these markers were being sought and correlated. The biggest potential harms would be violations of confidentiality if genetic predispositions or diseases were detected and that information was passed along to other parties such as insurers, employers, etc. Of course, even if confidentiality were guaranteed, there is simply the problem that respect for persons seems to require their explicit informed consent for research. Hiding behind the general consent that these subject gave five years ago seems unsatisfactory in the discharge of this moral obligation.

Do the Federal regulations help us at all? When we turn to 45 CFR 46, we find that some research is exempt from IRB review and therefore, from the normal requirements such as informed consent. At 46.101, we read that among the **exempt** kinds of research is

“Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.”

Thus, if these researchers can insure that these subjects cannot be linked to their specimens, then they can conduct the research within the framework of the Federal regulations. Of course, the easiest way to guarantee this kind of anonymity is by the destruction of any information that links the specimens to the proper names of the subjects. Four cautionary notes are in order.

Practical cautionary notes:

(1) Because of the advance of genetic testing, it will continually become easier and easier to link specimens to their sources. Although destroying links to the person's name may suffice today, it may not years from now.

(2) Destroying the links of the specimens to the name of the person may facilitate this particular research project but will make future cohort research, e.g., studies that are interested in the inheriting of these characteristics over generations of a family, very difficult.

Moral cautionary notes:

(3) Although eliminating identifiers will guarantee confidentiality, it will also impede any chance the researcher has to "help" a subject, say, if the researcher should uncover a disease or illness while examining the specimens.

(4) The regulatory solution is practical but does not address the violation of the values behind the doctrine of informed consent. These values include self-determination regarding one's body and a freedom from unwanted touching. As a result, there is a tension between the utilitarian solution the regulations affirm and the deontological values behind informed consent.