Research Protocol vs. Research Practice: Case Studies

Protection of Human Research Subjects Workshop
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Introduction

Institutional Review Boards have as their chief, if not sole, role the protection of human subjects. Traditionally, the exercise of this protective function focuses on the deign of proposed research protocol and the details of research subject recruitment, informed consent, reporting of untoward incidents, and compensation.

I want in my presentation today to illustrate some of the more interesting ways in which research which is well designed and seemingly well vetted by IRBs can go awry. I hope to draw some lessons or morals from these cases that may help sharpen your approach to reviewing research protocols and, in turn, help maintain the generally good record of research with human subjects.

AZT Study

The first study is one I encountered quite a number of years ago when I was on the Institutional Review Board of the University that oversees research in the biomedical arena. A multi-center study was designed to test Retrovir, the trade name for Zidovudine, more commonly known as AZT, the first drug to be developed for the treatment of human immunodeficiency virus, or HIV-1, thought to cause acquired immune deficiency syndrome, or AIDS. The study was to be a two-armed, double blind study upon individuals who were HIV+, or who had particles of the human immunodeficiency virus in their bloodstream and cells. This means that subjects that were recruited would be randomly assigned to one of two groups, or arms of the study. One group would receive the AZT compound; the other would receive a placebo packaged to be indistinguishable from the AZT capsules. Physicians regularly examining subjects in the two groups would not know whether the individual subject was receiving the drug or the placebo, and the individual also would not know. Double-blind studies are so designed to randomly distribute the effects of experimenter bias and the subjective effects of the beliefs of subjects about whether they are receiving the drug or the placebo.

The ethical conduct of research, particularly research into compounds with the possibility of harmful side effects, should be conducted under conditions of equipoise when it involves patients as subjects. That is, patient/subjects should not be recruited to research protocols by their physicians if the latter do not believe that the potential for benefit and harm of each of the potential arms of the study are equal; otherwise, to recommend to a patient that he or she participate in a study and perhaps thereby forego a treatment known to be beneficial is to violate the duty of the physician to protect the patient from harm.

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Surfactant Study

Children born prematurely often have difficulty with respiration, due to the immaturity of their lungs and the absence, until close to full term, of sufficient quantities of natural surfactant on the surfaces of the alveoli, or sacs through whose membranes oxygen and carbon dioxide are exchanged by red blood cells. Premature infants thus frequently suffer from respiratory distress syndrome at birth because they lack a full measure of surfactant.

Studies that began in animal models sought to develop a treatment for such immature lungs and thereby increase the survival rate of premature infants. Early testing was done on animals using surfactant extracted from other animals. Later, artificial surfactant that lacked the dangers of animal products were developed to be tested on humans. One of these early surfactant substances was to be tested in a multi center trial in neonatal intensive care units (NICUs) during the mid-1980s.

Surfactant was prepared, along with a saline placebo, in identically labeled bottles except for a code known only to the project statistician. Residents in participating NICUs were to administer the contents of these bottles to newborns whose parents had consented to their participation in the study, and who had been randomized into two groups so that no one group would have a preponderance of very sick, or not so very sick, children. The results, in terms of mortality and morbidity, or surviving and quality of health when discharged from hospital, would be prepared. Residents and other staff were blinded to which children were receiving the surfactant and which the saline placebo.

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Bernard Fisher's Three Breast Cancer Studies

Breast cancer strikes 100,000 American women annually, and several million women world-wide. Until Bernard Fisher's pioneering work, standard treatment was the Halsted radical mastectomy for early breast cancer. The procedure involves removal of the entire breast surrounding the malignancy, the lymph nodes under the arm on that side, and the pectoral muscles underneath. Not only is the surgery disfiguring, it often leads to swelling of the upper arm and to motor difficulties in that arm.

During the 1960s, the issue arose whether less extensive surgery might produce similar length of survival without the most severe side effects. In 1971 Bernard Fisher and his colleagues began a study to resolve the issue.

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Another study was suggested by data that emerged in the 1970s. Some wondered whether good results could be obtained in early breast cancer if only the tumor and a small surrounding margin of breast were removed and the breast preserved. If survival rates for "segmental mastectomy," or, as it is most commonly called, "lumpectomy," were similar to those for the more disfiguring surgeries, women whose cancers were

detected while still small could be spared the disfigurement present even in simple mastectomy.

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Conclusion

The role of the IRB in protecting human research subjects is one of imaginatively constructing and reconstructing the research situation envisioned in the protocol. To protect subjects, their motivations and the motivations of other participants, must be thoroughly understood and mapped against the protocol's templates of controlling the behaviors of participants. IRBs must ask whether all are clear about the protocol, its rationale, and the importance of adhering to its measures. A 'healthy skepticism' must characterize the approach of the IRB to questions of consent, particularly when an initial research protocol has failed to attract sufficient participation and modifications are proposed in hopes of increasing the number of volunteers. This perhaps suggests a more vigorous, active role for IRBs than the traditional review of proposals, sometimes taking IRB members into the very clinical situation where research is to be conducted.

Having served on institutional review boards for both human and animal research, I make these suggestions knowing full well that vast amounts of time are already demanded of many IRB members. And, speaking now as a citizen and no longer an official employee of the University, may I close with a simple expression of thanks to you for that time and for your dedication to the causes of ethical science and biomedical progress. Reviewing these cases has reminded me well of the IRB's primary role in regulating research practice, especially when doing so involves going beyond what is contained in the statement of the research protocol.