The Ethics of Accumulating Neurosurgical Evidence in the Clinical Setting

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In this article, I explore the ethical foundations that ground all clinical research on human subjects. After briefly reviewing these issues, I discuss some particular challenges for clinical research involving surgeons and surgical patients. Finally, I consider reasons why clinical research in neurosurgery raises unique challenges.

THE ETHICAL FOUNDATIONS OF CLINICAL RESEARCH

All clinical research is grounded in three central principles: respect for autonomy, beneficence, and justice (*Table 5.1*). Foremost among these principles is respect for patient autonomy.[2] The principle of respect for patient autonomy is the ethical basis for the imperative that we allow patients to make decisions for their own benefit. In the context of treating patients, as well as in research, respect for the autonomy of the patient or the subject is the foundation for the importance of informed consent. Certainly, respect for patient autonomy has not always been at the forefront of ethical decision making in medical care. For centuries before the past 40 years, in fact, physicians generally made decisions for their patients without involving the patients in this decision making. This philosophical approach, known as paternalism, changed dramatically over the past few decades. Evidence of this change can readily be found when examining what physicians tell their patients about diagnoses. For example, in 1961, Oken[8] studied what physicians at Michael Reese Hospital in Chicago told their patients about a diagnosis of cancer. At that time, 88% of physicians stated that they generally did not tell a patient a diagnosis of cancer. Only 16 years later, in 1977, Novack et al.[7] surveyed physicians at the same hospital and found that 98% of physicians reported that their general policy was to tell patients a cancer diagnosis. Today, the importance of respecting patient autonomy is central to the paradigm of shared decision making that gives great weight to respecting patient autonomy to make choices about medical care.

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A second principle underlying the ethical conduct of clinical research is beneficence.[2] This ethical principle makes explicit the importance of doing good for patients. Beneficence grounds the well-accepted position that when making decisions for patients, physicians should not be concerned about what will most benefit themselves, but rather what will most benefit the patient. Certainly, the understanding of what will most benefit an individual patient requires an understanding of the patient's values and must depend on the patient to define what will be most beneficial. However, there is no question that it is the assessment of what will be good for the patient that should direct the decision making.

Finally, the principle of justice needs little explication of its importance to the ethical conduct of research. In this context, the principle of justice refers to the importance of ensuring that the burdens and benefits of research are shared fairly.

THE HISTORICAL BASIS OF ETHICS IN RESEARCH

A number of important historical developments have played a significant role in defining the contemporary ethical milieu of human subjects research. Although it is beyond the scope of this article to fully expound on all these historical topics, it is important to see that much of the contemporary ethical framework grew out of a reaction to the atrocities of medical "experimentation" in Nazi Germany. These significant problems came to light during the Nuremburg trials in 1946 to 1947.[4] Eventually, the World Medical Association produced the Declaration of Helsinki in 1964, which helped define the roles and responsibilities of researchers.[9] In 1972, the important Tuskegee study came to light. This study shocked many in the United States with the realization that African American men were followed for decades to study the effects of syphilis despite the fact that antibiotics were available to treat this disease.[5] In 1974, the Belmont report codified many of the important principles that these earlier historical events raised. Subsequently, federal regulations defined the importance of institutional review boards, which have come to play a central role in the oversight of human subject research.[10]

TABLE 5.1. Three central ethical principles guiding clinical research

I. Respect for patient autonomy
a. This principle is in contrast to the paternalism that held sway for centuries.
b. Patients/subjects are encouraged to make decisions about their medical care.
c. Doctors must involve patients/subjects in decision making (shared decision making).
II. Beneficence
a. Importance of doing good for patients/subjects.
b. The determination of the value of some treatment or research is the extent to which it benefits the patient/subject.
III. Justice
a. Benefits of research must be shared fairly.
b. Burdens of research must be shared fairly.

PROTECTION OF HUMAN SUBJECTS

The historical development of the ethics of human subjects research has brought us to the point where today any proposed study involving human subjects requires careful analysis of both benefits and risks. Although the benefits to society as a whole certainly need to be considered, more importantly, the potential harms or risks to the subjects of the research must have significant weight in any decision making.

A cornerstone of any ethical study is informed consent. As noted above, the principle for respect of autonomy requires that human subjects be informed of the proposed study, including the risks and the potential benefits. Informed consent further requires that the subject have the capacity to give consent. It is also necessary for this consent to be voluntary. In other words, subjects must understand that they need not consent to participate if they wish not to, and certainly they are free to withdraw their consent and withdraw from the study at any time.

Although informed consent is critical to ethical research, it is not a sufficient condition to state that the research is ethical. In other words, just because a subject is willing to consent to have something done to him- or herself, it does not therefore follow that the study is, in fact, ethical. There are certain things that potential subjects should not be asked to consent to. For example, if there is absolutely no scientific basis to believe that a particular intervention would be beneficial, it would be unethical to ask subjects to participate in a trial in which this unproven therapy is offered.

A number of ethical issues involve any research study in which children are subjects. The analysis of appropriate safeguards for research on children is beyond the scope of this article.

Finally, it would not be possible to contemplate the ethical practice of research on humans without clearly understanding the importance of conflicts of interest. Although several commentators have argued that the term used should be "dualities of interest" rather than "conflicts of interests,"[6] careful attention must be paid to these potential conflicts of interest, and they must be disclosed to subjects.

When it comes to designing an ethical clinical trial, the implications of randomization must be carefully considered. The fact that subjects would not know what treatment they would receive in a randomized study often raises concerns on the part of subjects. This requires a sensitive and full explanation on the part of an investigator.

PARTICULAR CONCERNS FOR SURGICAL CLINICAL TRIALS

Although the gold standard for any clinical trial is the prospective, randomized, placebo-controlled trial, this paradigm raises a number of issues when applied to surgery. First, the concept of a placebo is well accepted in drug trials. A placebo medication is the so-called sugar pill that carries no risk to a subject, but also carries little benefit. When applied to surgery, the placebo raises a number of additional issues. Placebo surgery is inherently different from a placebo medication.[1] Any placebo surgery carries a risk with it. In fact, the closer a sham operation is to a "real" operation, the greater the risks will be to the subjects. For this reason, the use of placebos in surgical trials has required careful analysis and limited use.

Any sham surgery raises additional issues because of the differences in the relationship between a patient and a surgeon and the relationship between other doctors and their patients. This difference was perhaps best described by Charles Bosk[3] in his sociological study of a surgical residency, *Forgive and Remember*. As Bosk stated, when the patient of an internist dies, the natural question his or her colleagues ask is "What happened?" When the patient of a surgeon dies, his or her colleagues ask "What did you do?" This difference helps to identify the closeness in the bond between surgeons and patients that is different from that bond found between nonsurgeons and their patients.

EQUIPOISE

The concept of equipoise is a critical one for any human subjects research. Equipoise refers to the uncertainty about which treatment arm would lead to better outcomes for patients. If an investigator were not in a state of equipoise, it would not be ethical to enroll subjects in a trial. For example, if I *knew* that one therapy was effective and another was not, it would be unethical to run a trial in which subjects may get the useless therapy. Although this seems self-evident, the difficulty is how can we *know* that one therapy is better than another without a good clinical trial? This tension is evident when one considers that not all surgical innovations have actually been advances in the surgical care of patients. If we

consider which factors influence an individual neurosurgeon's equipoise, we realize that many new techniques have not actually been good for patients. For example, a prefrontal lobotomy was advocated for the treatment of many problems in the past. Internal mammary artery ligation was advocated for the treatment of angina. Gastric freezing was used for the treatment of peptic ulcer disease. Despite enthusiasm on the part of many surgeons for all these therapies, none of them were in fact effective. Thus, one of the problems with equipoise is that often surgeons are convinced that one therapy is better than another without any really good data to support this conclusion.

Additional problems with equipoise are that the timing must be right for a study to be ethical. For example, with the advent of a new procedure, there may initially be a period in which it is unclear which therapy is better. Over time, if the preponderance of evidence shows that in fact one treatment is significantly better than another, there would no longer be a state of equipoise and therefore it would be unethical to have a study. Thus, equipoise often is in place early on in the development of a new procedure.

An additional problem with equipoise is the inevitable lure of the "new" technique. We all know that there is undoubtedly an enthusiasm for the new and the innovative technique. This is clearly ubiquitous in advertising in the United States. Things are always new *and* improved. The latest and most innovative technique is often assumed by both physicians and patients to be better. Unfortunately, we all know that this is often not the case, and therefore a conservative approach to accepting new therapies as better than the traditional ones should be advocated.

In recent years, the concept of *patient* equipoise has become increasingly important in clinical trials. By patient equipoise, I mean the patient's assessment of what is the better therapy. With the advent of the Internet and the frequency with which patients want to have input into what therapy they undergo, many patients take it on themselves to search for new, and potentially better, techniques. If physicians claim that one therapy is significantly better than another when there is actually no evidence to confirm this, many potential subjects who might otherwise participate in a trial will choose not to do so because they are convinced that the new therapy is better. Because patients lack the medical education to make knowledgeable decisions about which treatments are better or worse, the role of publicity and hype will necessarily grow. This will only raise further issues in the future.

ETHICAL CHALLENGES TO NEUROSURGICAL CLINICAL TRIALS

When it comes to clinical trials for neurosurgical patients, there are even more specific ethical challenges than those outlined above for surgical patients in general. Often, the subjects of these trials have diseases with very poor prognoses. As a result, the subjects are frequently near the end of life, and this clinical situation raises several significant issues. There are additional stresses on potential subjects as well as their families near the end of life, and undoubtedly subjects are particularly vulnerable at such a time. In addition, because of the nature of many neurosurgical diseases, potential subjects often lack decision-making capacity, which raises numerous issues with respect to informed consent. In addition, if a neurosurgical treatment as part of a study will put the subject in a position in which he or she may lose the capacity for decision making, the ability to withdraw from a trial becomes limited. Such circumstances necessitate the importance of involving family members in all these decisions.

CONCLUSION

The ethical challenges to clinical research that are present in all areas of medicine are frequently accentuated in neurosurgical patients. However, the ethical imperative to benefit patients remains the motivation to expand participation in neurosurgical clinical trials. Without good data, it will become increasingly difficult to know which therapy is better. Without good clinical trials, it will become increasingly difficult for neurosurgeons to understand when a state of equipoise has been lost. For these reasons, neurosurgeons should be encouraged to participate more widely in clinical trials and to be skeptical of claims that one therapy is better than another without data derived from clinical trials.

Disclosure

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