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Ethical Issues in Clinical Research

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As both clinicians and researchers, surgeons are expected to behave in an ethical manner and put the interests of their patients above all else. This was originally codified in the Hippocratic Oath and is included in most medical professional societies' mission statements. This includes the American College of Surgeons Fellowship Pledge that contains the following text:

I pledge to pursue the practice of surgery with honesty and to place the welfare and the rights of my patient above all else. I promise to deal with each patient as I would wish to be dealt with if I was in the patient's position and I will respect the patient's autonomy and individuality (1).

Medical ethics provide the foundation for the modern practice of surgery.

Patient-based research, however, may present ethical and moral dilemmas for the surgeon. After all, many of the interventions under study are investigational and may place the patient at significant risk. Often, we justify this risk by reminding ourselves that, if the treatment works, the patient's condition will improve and, even if the intervention does not work, the knowledge gained will benefit all patients with the disease. Although this rationalization may ultimately prove true, the surgeon-scientist must carefully consider each research situation and determine if the benefits of the study outweigh the risks, not just for society in general, but for the individual patient.

Unfortunately, although we would all like to believe that clinicians and scientists always act in the best interests of their patients, there are numerous historical examples (many of which have been well publicized) of unethical research practices that have negatively affected patients' health. These incidents have led to the establishment of numerous regulations and a fairly impressive infrastructure aimed at ensuring safe and

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ethical research practices. The goal of this chapter is to review these entities and help the surgeon researcher to design and perform research in an ethical manner. We will begin by briefly reviewing the historical events that have lead to the current regulations and practices surrounding the ethical practice of clinical research. We will then specifically discuss the role of the Institutional Review Board (IRB), the local body which is responsible for research oversight at most institutions. We will then address specific issues surrounding ethics and surgical studies. Finally, we will discuss the Health Insurance Portability and Accountability Act of 1996 (HIPAA), as it relates to the conduct of clinical research. With this broad overview, the surgeon-scientist should be able to interact more amicably and efficiently with his or her local IRB and should be fully aware of the ethics surrounding clinical research in surgery.

1. ETHICAL RESEARCH: AN HISTORICAL PERSPECTIVE

Although there are a number of historical examples of inappropriate and/or unethical research, there are three specific events which have had the greatest impact on federal regulations surrounding the protection of human research subjects and, therefore, have contributed the most to the development of the current infrastructure to ensure ethical research. These three events are: (1) the 1946 Nuremberg Doctors Trial; (2) the rash of birth defects associated with Thalidomide use in the 1960s; and (3) the 1972 exposé on the Tuskegee Syphilis Study. Each of these historical events led to the enactment of new codes and regulations specifically designed to protect human subjects in research.

1.1. The 1946 Nuremberg Doctors Trial

This case first brought the issue of unethical research to public attention and underscored the need for regulation in this area. During World War II, Nazi physicians in Germany performed numerous horrible experiments on concentration camp internees in an effort to aid the German war machine. For example, the German Air Force was concerned about the effect of low atmospheric pressure on pilots who might bail out of their aircraft at high altitudes. Therefore, they performed a series of experiments on prisoners that included placing healthy subjects into vacuum chambers and lowering atmospheric pressure and oxygen levels. Approximately 40% of the subjects died of various causes, including anoxia and ruptured lungs from the low pressure in the chambers. In other experiments, traumatic wounds, such as stabbings or gun shots, were inflicted on subjects. Resulting wounds were stuffed with contaminants, such as glass, dirt, and various bacteria, to simulate battlefield conditions. Various experimental antibiotics were then administered. In another experiment, numerous limb amputations were performed followed by attempts at various forms of transplantation. Although it is easy to state that this could never happen today, the reader should bear in mind that these barbaric experiments occurred in highly civilized Western Europe only 60 yr ago (2).

In August 1945, the Allied governments created a military tribunal in Nuremberg, Germany, to place the Nazi leadership on trial. After the trial of the military leadership, a number of trials were held to judge the Nazi physicians involved in the human studies. The defendants were charged with murder, torture, and other atrocities, of which the majority were ultimately found guilty. The primary defense of the accused was that they were simply following the orders of their superiors. This motivated the inclusion of what has come to be known as the “Nuremberg Code” in the final trial judgment (3). The full text of the code is available elsewhere (4), but, in summary it states that:

- Subjects participating in research should give informed consent without coercion.
- The anticipated benefits of the study should justify the research and the risks associated with it.
- Human studies should be based on prior animal studies and knowledge of the natural history of the condition under study.
- Physical and mental suffering and injury should be avoided.
- During the study, the subject should be able to withdraw at anytime he or she sees fit.
- The study should be performed by qualified scientific personnel and these individuals should be prepared to terminate the study at any stage if they believe that the continuation of the study will result in injury, disability or death of the subject.

The World Medical Association then applied the principles elucidated in the Nuremberg Code to the practice of medical research. Development of these “rules” for medical research started in 1953, culminating with adoption of a formal declaration of ethical principles for medical research involving human subjects by the World Medical Association in Helsinki in 1964. The Declaration of Helsinki, as it is commonly known, has been updated and reendorsed by the World Medical Association numerous times since, with the last being in 2000 in Edinburgh, Scotland. The full-text of the Declaration of Helsinki is available at <http://www.nihtraining.com/ohsrsite/guidelines/helsinki.html>. In summary, the Nuremberg Trial first brought the need for regulations to protect human research subjects to the attention of the public and resulted in the development of the Nuremberg Code and the Declaration of Helsinki, two important documents regarding the conduct of ethical research.

1.2. The Thalidomide Tragedy of the 1960s

Although not truly the result of “unethical research,” the rash of birth defects associated with thalidomide use in the early 1960s documented the somewhat unethical business practices of certain pharmaceutical companies at that time and the need for stronger regulations regarding “experimental” drugs in the United States. Thalidomide had been approved in Europe as a sedative in the late 1950s. Although it did not have approval in the United States, the drug’s manufacturer provided samples to American physicians who received payment to assess the its efficacy and safety. This form of “research” was not uncommon at the time; however, it quickly became apparent that thalidomide was extremely teratogenic, resulting in limb deformities in newborn children whose mothers had used the agent during the first trimester of pregnancy (5). This led to a worldwide ban of the drug (6) and ultimately to the 1962 passage of the Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act. These amendments, with additional legislation in 1963 and 1966, required that subjects be informed that they were receiving experimental agents that had not be approved by the US Food and Drug Administration and that explicit consent be obtained before administration of the experimental agent. They also specifically stated that the subject must be informed if he or she might receive a placebo. These regulations laid the foundation for the current new drug approval process in the United States and provided the legal basis for the protection of human subjects in research in this country.

1.3. The Tuskegee Syphilis Study

Although the Nuremberg Trial and the Thalidomide tragedy provide a historical perspective for the protection of human subjects in research, it is the Study of Untreated

Syphilis in the Negro Male, initiated in 1932 by an agency within the United States Public Health Service (a forerunner of the Centers for Disease Prevention and Control), that truly motivated the current set of rules and regulations regarding ethical research in the United States. That the study focused on an ethnic minority, continued into the 1970s, and was funded by the federal government underscored the pressing need for regulation in this area. The Public Health Service initially identified Macon County, Alabama, as an area with an extremely high prevalence of syphilis. They then designed a study to assess the health effects of syphilis on untreated African-American men. At first, the study was to end after the initial enrollment and assessment of the infected patients' disease status with a nontherapeutic spinal tap. However, researchers never informed the subjects that they had syphilis or that the primary goal of the study was to assess the effects of this infection on health. Rather, the subjects were told they were part of a study that would provide free examinations and medical care. In 1933, the researchers added a surveillance phase during which the subjects were followed and received additional testing. At this point, penicillin was not yet recognized as curative treatment for syphilis; therefore, in theory, one might argue that, although the study was of questionable value, it was not completely unethical, because no alternative treatments were available. Although this line of reasoning is likely flawed (after all, weren't the researchers morally obligated to inform the men they had syphilis and to offer some sort of palliative treatment?), it may have been acceptable until 1943, when penicillin became widely available and accepted as curative treatment for syphilis (7).

At this point, researchers conspired with the local draft board to make study participants exempt from the military to prevent them from receiving treatment for their condition. Furthermore, researchers continued to withhold penicillin from the subjects, without informing the patients that they had syphilis, to prevent contamination of the study population and allow them to continue to study the long-term natural history of untreated syphilis. The study continued until 1973, when it was closed in response to the 1972 publication of an exposé in the *Washington Star*. The Tuskegee Syphilis Study led to significant new legislation to protect human subjects in research and effectively led to the current infrastructure surrounding the ethical performance of research (7). In addition, President Bill Clinton formally apologized to the study's participants in 1997.

The first piece of legislation that was passed in response to the Tuskegee Study was the National Research Act of 1974. This legislation included requirements for informed consent and mandated the establishment of local IRBs to oversee the ethical practice of research. It also established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This commission published a document that has come to be known as "The Belmont Report," which provided the foundation on which the federal regulations for the protection of human subjects in research are based. The full text of the Belmont Report can be found at <http://www.nihtraining.com/ohsrsite/guidelines/belmont.html>.

After the release of the Belmont Report, the Department of Health and Human Services and the US Food and Drug Administration published convergent regulations regarding informed consent and IRBs that were based on the principles in the Belmont Report. Fifteen additional government departments and agencies reviewed these regulations and, after 10 yr of negotiation, these agencies agreed to adopt a set of basic human subjects protections that have come to be known as the "Common Rule." The regulations established under the common rule follow.

- 45 CFR46 Protection of Human Subjects
- 21 CFR50 Protection of Human Subjects
- 21 CFR56 Institutional Review Board
- 21 CFR312 Investigational New Drug Application
- 21 CFR812 Investigational Device Exemptions

The complete text of these regulations and a great deal of additional information regarding the federal oversight of human subjects in research can be found at <http://www.hhs.gov/ohrp>.

Since the adoption of the Common Rule, there has been continued federal activity in the area of bioethics. Specifically, President Clinton established the National Bioethics Advisory Commission in 1995 with the specific purpose of continually reviewing the federal regulations on ethical human experimentation and making recommendations to the government on research topics and legislation as these issues arise. When the commission's charter expired in 2001, President George W. Bush appointed the President's Commission on Bioethics with a similar mission to the National Bioethics Advisory Commission.

One of the developing issues that face bioethicists today is involves conflicts of interest among clinical researchers. Specifically, many translational researchers who develop new agents for use at the bedside also hold financial interests in the companies who develop the agents (8). An example of this ethical issue comes from a recent gene transfer experiment. In 1999, an 18-yr-old man with a mild form of ornithine transcarbamylase deficiency that had been controlled with diet and medications volunteered to participate in a gene-transfer study. The study itself had been reviewed and approved by the US Food and Drug Administration, National Institutes of Health, and the local IRB. The subject understood that he would not directly benefit from the treatment, but felt that it would ultimately help children born with a more severe form of the deficiency. After giving informed consent, the subject received an injection of an adenovirus transfected with the ornithine transcarbamylase gene. Unfortunately, he rapidly developed liver failure and died as a result of the treatment. At first, the patient's father defended the scientists at the University of Pennsylvania, acknowledging that his son knew that this was a novel agent and that there were risks associated with it (9). Ultimately, it came to light that the investigators had not been forthcoming regarding prior adverse events and risks at the time of informed consent, that they had "loosened" the protocol inclusion criteria to improve enrollment, and had not provided adequate safeguards for the patients' well being (10). The National Institutes of Health ultimately halted all gene transfer experiments at that institution and sought to disqualify the investigators from receiving future federal funding or performing further clinical research (11). One of the primary reasons the government took these drastic steps was the perceived conflict of interest that the investigators had in running the Phase I study. One of the lead investigators specifically had formed a biotechnology company that provided resources to the Institute of Human Gene Therapy at his institution and held numerous patents on the viral technology. In other words, the investigator stood to benefit financially if the treatment was demonstrated to be effective in clinical trials (12).

This type of conflict of interest is becoming more common as clinician-investigators serve as consultants or major investors to biotechnology and pharmaceutical firms. Furthermore, many investigator-initiated studies are directly or indirectly funded by industry, which places the investigator into a real or perceived conflict of interest. Many

institutions have developed internal regulations regarding the declaration of financial and other interests by investigators. Some institutions have put limitations in place as to how much outside income an investigator can earn and still participate in related research. Although these regulations will likely prove helpful, it is important for the surgeon-scientist to consider the potential for conflicts of interest before initiating research. If you are participating in an industry-sponsored pharmaceutical study for which you or your research program is receiving compensation, it is probably wise to disclose this to the subject in the informed consent. If you stand to personally materially benefit from the study (e.g., you hold stock in the company or a patent on the technology), it is best that you disassociate yourself from the study and allow one of your colleagues to administer the trials. Even the slightest hint of a financial or material conflict of interest will jeopardize your credibility as a researcher and could result in punitive actions on the part of your local institution or state or federal agencies. As a surgeon-scientist, it is best to avoid any true or perceived conflicts of interest when conducting clinical research. If such is unavoidable, it is advisable that a conflict of interest management plan be developed for the study facilitated either by the IRB, the HIPAA board or another regulatory body within the institution.

2. THE INSTITUTIONAL REVIEW BOARD

Current public opinion regarding health care and research has led many institutions to adopt a defensive posture with regard to the ethics of research. This, in turn, has prompted local IRBs to more closely scrutinize each protocol. Many researchers have interpreted this as “obstructionism” on the part of the IRB committee and have, unfortunately, developed an adversarial relationship with committee. In truth, the IRB is a valuable resource for researchers that only helps to protect the investigators from ethical problems and ensures high-quality research that advances science and brings credibility to the institution.

The role of the IRB is specifically spelled out in the federal regulations regarding human research (Code of Federal Regulations, vol. 21). By law, the IRB must review all research and ensure that the following requirements are met before approving any study:

- Minimization of risks to subjects
- Assessment of risks to ensure that the risk/benefit ratio is reasonable. It is important to bear in mind that this assessment is limited to the risks and benefits for the subjects in the study, as opposed to society in general
- Equitable selection of subjects
- Overview of the informed consent process (including documentation) and assurance that consent will be obtained from all subjects, as appropriate
- Data monitoring, if appropriate, to ensure the subject’s safety
- Protection of subject’s privacy
- Protection of special populations who may be vulnerable to coercion (e.g., children, pregnant women, prisoners, handicapped, mentally disabled or educationally or economically disadvantaged people), if appropriate.

The IRB’s review should be focused on these issues primarily and comments should be related to concerns with these issues. At times, the IRB will comment on the scientific merit of the study, which most consider outside the purview of the IRB. However, some scientific review must also be undertaken as part of the review process, because it is the

IRB's responsibility to assess the risk and benefits of the study. If the IRB does not believe that the science is reasonable, how can they justify putting the subject at any risk? If it believes that the scientific hypotheses proposed are not reasonable or do not provide adequate benefit (to outweigh the risk) to the subject, the IRB must, by law, question the proposal. It is helpful to keep this in mind when one considers comments from the IRB.

It is also relevant to consider the composition, operation, and responsibilities of the IRB. The composition is mandated in the Code of Federal Regulations, Title 21 Food and Drugs, Part 56. The IRB must, by law, review most clinical research. There are studies that are exempt or may be eligible for expedited review, but, even in these cases, the IRB should be made aware of the study and should agree that the research is exempt or appropriate for expedited review. The IRB itself must have at least five members with varying backgrounds. There is no requirement that the committee members be experts in your particular clinical specialty or area of research. The IRB must include one member whose primary concerns are in the general scientific area (in this case, biomedical research of any sort) and one whose primary concerns are in nonscientific areas. This second requirement is generally interpreted as the inclusion of a "lay person" or "community representative" on the committee. In addition, there is a requirement that at least one member have no affiliation with the institution and have no immediate family member affiliated with the institution. Again, this requirement is usually met by having a "lay person" or "community representative" from outside the institution. For complex issues, the IRB may invite ad hoc reviewers, although these individuals are not allowed to vote on the proposal. There are no requirements regarding how often the committee must meet, but, when it does meet, written records of the meeting must be maintained. In this respect, an IRB meeting is not unlike a grant review panel. There are usually a number of reviewers assigned to a project who summarize the study and voice any concerns they may have regarding the project. After it has presented their reviews, the committee will discuss the project and will vote on whether or not the study should be approved. There is no scoring system involved, however. The IRB must maintain compliance with the federal regulations and is subject to administrative actions on the part of the government if they are noncompliant.

Most IRBs will spend a significant amount of time reviewing the informed consent document to ensure that it is easy to read and is understandable to a lay person. Because it is also a legal document, the IRB reviews the informed consent to ensure that both the institution and the investigator are disclosing all the necessary information for the ethical performance of the study and that there are adequate protections in place for both the subject, the institution and the investigator. The informed consent is essentially a contract between the subject and the investigator. By signing the informed consent, the subject is agreeing to potentially expose himself or herself to risk in return for any potential benefits he or she might gain. This benefit may include the understanding that he or she may help other patients as a result of participation. The goal of the IRB review of the informed consent is to prevent the subject from stating at a later date that he or she was not made aware of all the risks or did not understand them. In this respect, the IRB is working as much for the investigator as for the subject.

A full discussion of how to best interact with your local IRB is beyond the scope of this book. Simply put, there are too many differences between institutions and specific research proposals to cover all the possibilities. However, there are several basic rules investigators should follow when dealing with an IRB. First and foremost, the IRB is not

your enemy. The committee serves a purpose dictated by law that should not be at odds with your goals in most cases. If there are conflicts, your research may expose the subject to greater risk than benefit and may not be entirely ethical. It is clearly better to deal with this *before* you undertake your study. Remember that the IRB protects you, the investigator, as well.

Second, if there are ever any questions regarding ethical issues or concerns with your research, it is important to contact the IRB directly and immediately. If you are performing a study in which there are adverse events, there are usually strict reporting criteria in the protocol that include notification of the IRB. If you are unsure if you should alert the IRB, you are better off erring on the side of caution and informing the IRB. To this end, you should not be afraid to call the IRB and ask questions, particularly during protocol development. Remember that a verbal discussion is not binding and, therefore, oral reporting of adverse events or formal complaints is not acceptable. However, if you are concerned about wording in an informed consent or whether or not a formal informed consent is needed for a study, it is better to call and ask before anything is put in writing, so that you can edit the protocol accordingly and submit an improved document, expediting the approval process. Remember that after you put it in writing, it is difficult to change; therefore, it is better to discuss issues in advance and avoid confrontation later.

Third, remember that you must update the IRB on your study's progress and renew the research with the IRB on a regular basis. Most studies that require full IRB review will require annual re-review and renewal. The reporting requirements usually are not overly burdensome and consist of a short progress report, information regarding the number of participants enrolled in the study, and any adverse events. It is your responsibility to ensure that your study gets renewed by the IRB. If you forget and enroll a patient after the study's approval has expired, you will be held responsible. Most IRBs will alert you that you need to renew the study, but you should not count on this mechanism, because letters can get lost or e-mails get accidentally deleted. It is wise to keep a personal record of your dealings with the IRB and maintain a list of IRB-approval expiration dates for all studies you are undertaking.

Finally, and most important, it is pointless to argue with the IRB. Simply put, you cannot win. Assuming the IRB is acting in what it believes is the best interests of the research subjects (which it probably is) and it is in compliance with the federal regulations regarding human research, there is little you can do to reverse the decision of the IRB. There is no appeals process. Effectively, you must address the IRB's concerns if you wish your research to proceed. The overwhelming majority of IRBs has good intentions and wants you to do good research. If your study is returned by the IRB with requested changes, you can either make the changes or provide justification as to why you feel the changes are inappropriate or unnecessary. Although the IRB may be reasonable and drop the requested changes, often it will not. It is always easier and quicker to make the requested changes and expeditiously receive IRB approval. Therefore, a final piece of advice is: simply make the changes, acknowledge that they may be more objective than you are on the topic, and move on.

3. SPECIFIC ETHICAL ISSUES REGARDING CLINICAL RESEARCH IN SURGERY

Clinical research in the surgical disciplines is subject to many of the same ethical concerns that research in other biomedical disciplines raises. However, although there

are some common themes across all specialties, research in the surgical fields does present some unique ethical challenges. Many conditions that are treated with surgical procedures are acute and critical in nature and require quick decision making on the part of the patient and the provider. This, in turn, can affect the informed consent process, because patients often are quite sick and may not be stable enough to give consent or to participate in research. In addition, the intervention itself, if surgical in nature, can involve significant risks to the patient, which must be considered in the course of the research. Finally, although studies of medical interventions can sometimes include a placebo arm, the inclusion of a placebo arm in surgical trial is considerably more difficult, because sham surgery will always carry some risks with minimal benefit to the subject. To this end, we will review a number of ethical issues in research that specifically related to the surgical disciplines.

3.1. Informed Consent

The informed consent process itself is not unique to surgical research. As discussed in the Belmont Report, the informed consent process must have three qualities to be valid: information, understanding, and voluntary agreement. In the case of surgical patients, there may be situations in which these three qualities cannot be easily attained. For example, consider the investigator who is studying the use of a new antibiotic in the treatment of patients who have experienced traumatic closed head injury. Many of those patients will be unresponsive and will not be able to assimilate the information, understand what they are agreeing to, or to give voluntary agreement. Given that these patients are often acutely ill, there can be little delay in administering potentially life-saving antibiotics, so how is the clinician-researcher to proceed? Obviously, in this setting, the investigator might discuss the study with the patient's next of kin and try to obtain consent from this individual, but is this acceptable?

The informed consent process should include the subject and the investigator (or the investigator's designated and IRB-approved representative). In some cases, the subject may not be able to participate in the process. In the example presented here, the subject is too sick to participate. In other cases, he or she may not be legally competent to participate. In this setting, federal regulations direct the investigator to see consent from the subject's legally authorized representative (45CFR46 and 21CFR50). Most investigators, therefore, will seek out the next of kin, or, in the case of pediatric patients who are not of legal age to give consent, seek consent from the parents. The process, however, is not complete after the legally authorized representative gives consent. Whenever possible, the investigator should obtain affirmative assent from the subject as well. This obviously will not be possible in the case of the nonresponsive trauma patient, but is possible in children older than age 7 and in some adults with limited mental capacity. If possible, assent should also be obtained in written form and it is standard for children older than age 12 to complete a written assent form. Finally, in these special cases, there may be a need for continuing evaluations of mental capacity and consent understanding. In the example of the trauma patient, assume that the patient becomes responsive and is now able to understand the study and give informed consent. It is now the responsibility of the investigator to discuss the study with the subject and ensure that he or she wishes to participate. It would probably be wise to have the subject now complete the formal informed consent process. These types of situations are often discussed at IRB meetings during the approval process for any given study and it is wise for the investigator to

Table 1
Required Elements of the Informed Consent Process,
as Dictated by the Federal “Common Rule” Regulations

-
- Statement that the activity or intervention is considered research
 - Purpose of the research
 - Description of the study procedures
 - Potential risks of the study
 - Potential benefits of participation
 - Alternative treatments
 - Methods used to maintain confidentiality
 - Compensation for injury statement (if study greater than minimal risk)
 - Investigator contact information
 - Statement that participation is voluntary
 - Statement that there may be unforeseen risks
 - Reasons that a subject may be involuntarily removed from the study
 - Any additional costs for participation
 - Adverse health consequences for early withdrawal (if any)
 - Information regarding notification of findings or data from study, if relevant
 - Number of subjects in the study
-

contact the IRB if he or she has any questions regarding the best way to handle these situations.

The consent document itself has a number of required elements that are presented in Table 1 (21CFR50). Many institutions use a common template for their informed consent, and it is wise for the investigator to try to stay as close to this template as possible. The template will include all of the required elements in the table and will also be worded in a way that is already fairly acceptable to the local IRB. In summary, the informed consent is one of the most important parts of the clinical research process. It ensures that both the subject and the investigator are aware of the risks and benefits of the study and that they each know their rights and responsibilities. For the surgical investigator, there may be special cases where consent must be obtained from other individuals, but these situations can be handled in an ethical manner if the investigator uses common sense and seeks the counsel of the local IRB.

3.2. Ethical Considerations Related to the Unique Characteristics of the Surgical Intervention

The study of surgical interventions presents many unique problems for the clinical researcher. Specifically, surgery itself has a very powerful placebo effect that can often lead to improvement in patient symptoms. A recent study in the *New England Journal of Medicine* randomized patients with knee pain to receive either arthroscopic knee surgery for osteoarthritis or sham surgery. Both groups reported improvement in pain 2 yr after surgery and no differences in pain were seen between the active surgery groups and the sham surgery group (13). This unique study underscores the strong placebo effect of a surgical intervention on a patient-centered outcome and also introduces one of the unique problems in trials of surgical intervention: the difficulty with blinding the subject to the intervention. In this study described, the surgeons actually made a skin incision in the sham surgery group, but this is often not a reasonable option for many surgical diseases and their treatments. After all, many patients have life-threatening conditions, and a

placebo intervention simply is not an option. In addition, sham surgery itself carries some risks, such as anesthesia and scarring. Many IRBs would not have approved the knee surgery study (the IRB at the Houston VA Medical Center did approve the study). In the case of other surgical interventions, it is likely that an IRB would only approve a sham procedure if the potential benefit far outweighs the risks of the sham surgery. Pharmaceutical trials are much easier to blind because placebo pills only carry the risk of no active therapy. Sham surgery is obviously much more invasive.

How should the surgeon deal with for this problem? Often he or she simply cannot maintain blinding nor have a true placebo group, which will affect patient-centered outcomes. Therefore, one way around this problem is simply to choose a more objective outcome. Whether this is survival, disease recurrence, or some radiologic or laboratory marker, an objective, quantifiable, reliably measured outcome serves to minimize the placebo effect of surgery. In studies in which the primary outcome is a patient-centered outcome (such as quality of life), the investigator should consider a placebo arm. For example, imagine you were to do a trial aimed at determining the effectiveness of laser therapy in reducing lower urinary tract symptoms in men with benign prostate hyperplasia, you would have to account for the placebo effect of any treatment (which in some studies has been shown to be up to 40%) (14). One option would be to randomize the patient to laser therapy vs sham surgery. The patient would receive a light anesthetic and undergo either the laser procedure or cystoscopy. Postoperatively, all interventions would be the same and the patient would never be told which intervention he received. At the conclusion of the study, all patients who required further treatment would be offered the laser therapy. Given that lower urinary tract symptoms are not life-threatening and the patients ultimately would receive treatment if they wanted it, one could make a compelling argument that the risks of anesthesia in this setting are relatively small and that the study is ethical.

In summary, there may be situations where sham surgery could be ethically performed assuming: (1) the disease is not life-threatening; (2) the patient will be offered salvage treatment at the end of the study; (3) the sham surgery presents minimal risk and does not leave permanent scars and is disfiguring in anyway; and (4) there is true clinical equipoise around the question and the study would provide significant scientific information that would advance the field. Of course, each local IRB will have its own opinion on the issue of sham surgery, so it would again be best to discuss the study with the individual IRB.

Finally, the surgeon has to realize that, although surgical trials may be needed for a particular issue, they may not be feasible when the course of treatment for a particular condition is in rapid evolution. To some degree, this is the case in prostate cancer, in which investigators have failed to complete trials comparing the various primary therapies for localized disease (15). This may be more of a feasibility issue than an ethical issue, but, simply put, patients often are not likely to participate in randomized clinical trials if they have strong feelings about a particular treatment or after if a particular treatment has gained popularity in the media or general public. The American College of Surgeons' Oncology Group recently undertook a randomized clinical trial comparing brachytherapy with surgery in localized prostate cancer. The study accrued poorly and closed 1 yr after it opened. Too many patients had preconceived notions about both therapies and would not submit to a computer randomization of treatment (15). The study demonstrated how difficult it can be to get patients to agree to enroll in a randomized surgical trial. Although this may be more a feasibility issue than an ethical issue, some

researchers have tried to provide potential subjects with various incentives to enhance recruitment. Although this may seem reasonable on the surface, it raises a number of additional ethical issues that ultimately may prevent the investigator from using this strategy. Despite the trials and tribulations of conducting a randomized surgical trial, significant work has been accomplished, particularly within the context of the clinical trial networks funded by the National Institutes of Health.

4. HIPAA: THE 800-POUND GORILLA OF CLINICAL RESEARCH

HIPAA has arguably had as great an impact on the ethical conduct of clinical research as all of the prior federal legislation combined. The legislation (contained in 45 CFR, parts 160 and 164), originally designed to assist individuals in getting health insurance if they had a preexisting condition, established strict regulations regarding the use of protected health information (PHI). Importantly, it established severe fines and punishments for institutions or individuals that violated the law. Although this legislation was developed for the clinical practice of medicine, it also applies to clinical research. As a surgical investigator considering clinical studies, you *must* be aware of your obligations under HIPAA and *must* act in a manner consistent with the law. If you violate HIPAA, even unknowingly, you run the risk of harsh penalties. It is important to note that ignorance of the law is not an acceptable defense.

The HIPAA legislation establishes the “privacy rule,” which basically protects the use and disclosure by “covered entities” of identifiable health information, referred to as PHI. The rule regulates the transmission of information related to health care. In these settings, permission must be obtained from the patient to transmit or use his or her information. A list of the various definitions of “covered entities” is presented in Table 2. For the clinical researcher, it is almost certain that you are working within a covered entity of some type and, therefore, must comply with the HIPAA privacy rule. The rule itself applies to PHI, which is individual health information that is individually identifiable and is created or received by a covered entity. A list of HIPAA PHI identifiers is presented in Table 3. As can be seen from the table, any variable that could be used, alone or in combination, to identify the patient is considered PHI and is covered by the privacy rule. Bear in mind that, by including a category of PHI that consists of any other unique identifying number, characteristic, or code, the use of any information (even if it is not specifically mentioned in the list) that could reidentify the individual is considered protected and is subject to HIPAA.

The significance of this list lies in the fact that health information itself is not necessarily covered by HIPAA, but rather only individually identifiable health information is. In other words, a chest X-ray or a serum sample is not covered by HIPAA *unless* there is an identifier associated with it that would allow someone to trace the X-ray or specimen back to the patient. This becomes a key consideration when designing clinical studies. After all, we usually assign a subject a study number to ensure this data remain confidential. Therefore, if we use “coded data,” are we now in HIPAA compliance and able to proceed without worry? The answer is “no,” if a link exists between the study number and any patient identifiers. Most researchers place their coded data into a large research database, but maintain a separate smaller and protected database that links the study numbers to patient identifiers. If this common strategy is used and the linkage maintained, even under electronic “lock and key,” the researcher must act within the confines of HIPAA. However, after the data are deidentified (that is, the linkage between the study

Table 2
Examples of Covered Entities Under HIPAA

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- Institutional covered entities: a “covered function” is anything that makes the entity either a health care provider, health plan, or health care clearinghouse.
 - Outpatient clinics
 - Community hospitals that only provide medical care and have no other non–health care related functions
 - Private practice doctors offices
 - Hybrid entities: complex institutions that provide health care but also have noncovered functions that are unrelated to health care. If an institution designates itself as a “hybrid” institution, it must isolate its “covered” functions from its “noncovered” functions to prevent the unauthorized exchange of PHI.
 - Universities (including university medical centers)
 - VA Medical Centers
 - Certain health maintenance organizations
 - Other health plans
 - Affiliated covered entities: according to the law, legally separate but affiliated institutions may choose to designate themselves as a single-covered entity under HIPAA if they are under common ownership or control. This creates efficiencies within the system and may facilitate the transfer of data within the institution as a single common notice of privacy practices can be used for the affiliated institutions.
 - Universities (including university medical centers)
 - VA Medical Centers
 - Certain health maintenance organizations
 - Other health plans
-

number and all patient identifiers is destroyed or the recipient of the data could not possibly identify the data because he or she has no access to the linkage), the data are no longer covered by the HIPAA Privacy Rule. Therefore, whenever possible, surgical researchers should strive to use deidentified data.

If the researcher does wish to use PHI data, he or she must obtain an authorization from the subject to use the data in research. These authorizations must include: a description of the PHI to be used; who the PHI will be disclosed to; who will be using the PHI; a description of the purpose for its use; whether or not there is an expiration date for the authorization (and if so, when that date is); a notice that the subject may revoke the authorization at any time; a warning that the disclosed information may no longer be covered under HIPAA; a statement that the provision of treatment is not contingent on the authorization; and that subject signature and date. Most IRBs and research institutions have boilerplate text available to researchers from which to draft a HIPAA authorization. It is wise to obtain this authorization even if you are not certain that you will need to use identifying information.

There are situations in which you may be able to use limited PHI without a HIPAA authorization from the patient. HIPAA provides for limited datasets that exclude all PHI identifiers except addresses, dates, and other indirect identifiers. For these datasets, the researcher may apply for a waiver of authorization from the local IRB or HIPAA board. The committee is likely to grant a waiver if the researcher: describes how the dataset will be used, identifies who will have access to the limited dataset, assures the IRB that the

Table 3
HIPAA PHI Identifiers

<ul style="list-style-type: none"> • Name • Geographic identifiers (beyond state), which includes city, town, or ZIP code • All elements of dates (birthdates, date of death, date of admission or discharge), age • Telephone numbers • Fax numbers • E-mail addresses • Social security numbers • Medical record numbers • Health plan beneficiary numbers • Account numbers • Death certificate numbers, driver's license numbers, etc. • Web addresses • Internet protocol addresses • Biometric identifiers (e.g., fingerprints, voice prints) • Full face images • Any other unique identifying number, characteristic, or code

dataset will not be used to contact individuals and that appropriate safeguards are put in place to prevent uses or disclosures outside the research agreement, and the IRB feels that it would not be practicable to obtain a signed authorization and the research poses no more than minimal risk. The limited dataset strategy is a very reasonable approach for researchers who wish to analyze existing databases. In this setting, the investigators with the identified data could develop a limited dataset and give it to another investigator after IRB approval of a HIPAA waiver of authorization is obtained. Since the inception of HIPAA, many databases researchers have also obtained HIPAA authorizations from the subjects at the time of enrollment, which greatly simplifies the process.

There is one additional situation that the researcher must be aware of when considering the impact of HIPAA on clinical research. HIPAA applies when screening and recruiting subjects in the clinic. In this setting, the researcher often will review the charts of potential subjects to determine eligibility before an office visit. Although this may seem fairly benign, it is not appropriate to screen medical records in this manner under HIPAA. In this setting, the researcher should obtain a partial waiver of authorization from the IRB before proceeding. This waiver will be granted if the screening presents minimal risk to the patient and obtaining prior authorization is not practical. Full authorization can then be obtained if the patient wishes to participate. One might argue that the clinician who is performing the study has to review the medical records as part of his or her routine care. However, this review is part of the clinician's role and is unrelated to the role of a researcher. Therefore, it is wise to obtain a partial waiver of HIPAA authorization as part of the IRB approval process. The same is true for the use of existing databases to identify study cohorts. If no HIPAA authorization was previously obtained, it is wise to obtain a partial waiver of authorization before querying the database and contacting any patients. There is a clause in HIPAA that deals with "reviews preparatory to research" that allows the investigator to review the dataset to assess sample size and determine if there are adequate subjects for the research. In this setting, no HIPAA authorization is required assuming that the PHI used for these reviews is not disclosed or used offsite. In certain

settings, individuals within the covered institution may even be able to contact the potential subjects to discuss the research further. However, this should be discussed with the IRB before proceeding to ensure that you are in compliance with HIPAA.

HIPAA may seem quite overwhelming at first glance, but after you obtain a basic understanding of the rules, it is relatively easy to navigate. Most research will require a HIPAA waiver from the patient. This is easily obtained at the time of informed consent and usually remains in force throughout the study. If you are ever unsure about whether HIPAA applies to you or your research, you should contact your local IRB or office of compliance before proceeding. Invariably, they will take a conservative approach to the issue, but this is probably wise, because the penalties for HIPAA violations are severe

5. CONCLUSIONS

The surgeon-scientist must be aware of the ethical issues surrounding clinical research if he or she is to succeed at this endeavor in the 21st century. We have reviewed the history of ethics and clinical research, the role of the institutional review board, and specific issues surrounding surgical studies and HIPAA as they relate to research. There are a few take-home messages that the reader should bear in mind. First, the current landscape surrounding the ethics of clinical research developed in response to a number of isolated incidents that were morally repugnant, but were also more widespread than one might imagine. As evidenced by the recent gene-transfer experiments described previously, ethical dilemmas may arise even with the current safeguards. Second, the IRB serves an important role by protecting researchers from ethical problems and providing guidance as these problems arise. Although many researchers have assumed an adversarial relationship with their IRB, this is a mistake. If you view the IRB as a resource that is there to protect you and give you guidance, you will find your dealings with the IRB more pleasant and productive. It will also improve your research. Finally, the passage of HIPAA changed the way we do clinical research. You must be aware of HIPAA and always ensure that you are in compliance. If you run afoul of the HIPAA regulations, you and your institution will be liable. Because compliance is relatively easily and your local IRB can assist you in maintaining compliance, there is no reason this should ever be a problem for you, assuming you are aware of your responsibilities.

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