Ethical Issues in Cardiovascular Research Involving Humans

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This component of the series “Careers in Cardiovascular Research: A Primer for New Investigators” will address ethical conduct of research involving humans. The dramatic decline in cardiovascular mortality (Figure) provides testimony to the societal benefits of research leading to new therapies and systems of care. In concert with these rapid developments, changing expectations have resulted in the emergence of ethical issues with highly publicized examples of concern over conduct of research in humans. Whereas professional ethics should, and for most physicians do, “regulate” conduct of biomedical research, “self-regulation” does not always meet societal expectations. Dr Barry Coller has pointed out that science lacks intrinsic morality. Thus, the laudable goals of improving patient care, understanding mechanisms of disease, or protecting society from perceived external threats do not justify ignoring fundamental human rights that guide (and regulate) the conduct of research.

At the same time it is important to reflect on the importance of physicians participating in research and providing the opportunity for their patients to do so. Although some have argued this compromises the basic physician responsibility to a patient,7 we believe the best interest of the patient can and must be protected in the research setting. Two brief examples demonstrate the fundamental changes in understanding that may arise from direct involvement of physicians in research. As late as the 1970s, the prevailing wisdom to explain the presence of intracoronary thrombus on postmortem examination of patients after myocardial infarction was simply wrong; pathologists studying hearts in this setting found evidence to “suggest that coronary thrombi are consequences rather than causes of acute myocardial infarction” and “consideration is given to the possibility that some thrombi may follow rather than precede myocardial necrosis.” The primary role of thrombus in the genesis of acute myocardial infarction was subsequently established by physicians caring for their patients and by the observations from coronary arteriography and coronary artery bypass surgery during the acute phase of the event. The subsequent proof that intervention early in the course of myocardial infarction with thrombolysis or primary angioplasty reduces mortality could not have been accomplished without individual physicians on the front line of practice involving their patients in those investigations. A dramatic reduction in mortality with acute myocardial infarction has been achieved.

A more recent example of a clinical trial that had a fundamental impact on practice and that depended on physicians involving their patients as subjects in research is the Cardiac Arrhythmia Suppression Trial (CAST). It was known that cardiac death was related to ventricular arrhythmias and that drugs were widely used that reduced ventricular premature contractions. The assumption had been made clinically that treatment of ventricular premature contractions with antiarrhythmic drugs would therefore decrease mortality. Many patients received these drugs in anticipation of benefit. Finally, CAST was performed as a large clinical trial, which documented that the drugs used clinically to prevent cardiac death actually increased mortality. This research has dramatically changed practice and saved lives. We use these examples to emphasize the critical role of physicians caring for their own patients also engaging in the effort to advance knowledge and improve care. In both examples, the established opinion influencing care was proved to be wrong, confirming the need for continued questioning of established dogma. At the same time we believe that rights of patients and subjects must be respected.

The National Institutes of Health Roadmap recognizes the importance of clinical research and the need to “reengineer” the process with an emphasis on collaboration and translation of new knowledge to the community. An essential element will be specific training of clinicians in research methodology, the ethics of research, and the regulations that govern these activities. New discoveries such as gene and cell repair therapy, the patent process, and physician involvement in the biotechnology industry introduce the potential for a multiplicity of potential conflicts of interest. Our goal is to provoke reflection by investigators on the basis for current regulations governing research in humans and to urge careful attention to these regulations in the planning and conduct of their own research.

Informed Consent

Adequate informed consent is fundamental to the ethical conduct of research in humans. Society has demanded greater efforts to protect individual rights of patients and human

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subjects. This is an evolving and complex area. We must understand and appreciate the historical basis for society’s concerns, including the real and perceived nature of physician authority, to deal with the current regulatory environment.

History of Informed Consent

Histories of informed consent14–17 include efforts to inform patients like the efforts of Dr William Beaumont in 1833 for studies on Alexis St. Martin.18 The key elements included provisions that consent of the subject is essential, and withdrawal from the study is allowed if the subject is dissatisfied. Dr Walter Reed, in his yellow fever investigations, also developed a consent form in 1900, which included payment for participation in this research program.19

Most consider the Nuremberg Code as the initial basis for our concept of informed consent. Vollmann and Winai20 document concepts of informed consent based on autonomy and enhanced risk of violation of individual rights in vulnerable populations, which were articulated in Germany during the latter part of the 19th century as scientific medicine was beginning to flourish. A directive issued in 1891 by the Prussian minister of the interior to all prisons stated that tuberculin “must in no case be used against the patient’s will.”21 In 1898, public concern over syphilis experiments performed in prostitutes without their consent by Neisser (discoverer of the gonococcus) led to a commission that dealt with issues of beneficence and autonomy, concluding that individual consent was essential before any human experimentation.20 Though most academics supported Neisser, he was fined on the basis of failure to obtain consent of those in his trials. Legal opinion at the time established liability under criminal law for studies without consent.20

As late as 1931, the Weimar government issued “guidelines for new therapy and human experimentation” based on principles of informed consent.22 Dr Albert Moll,23 who was critical of Neisser’s experiments and other human investigations in Germany, published 600 examples of research involving humans he considered unethical. He was an early proponent of the concept of informed consent.20 Why these historical facts are ignored is unclear; they provoke reflection on how ethical principles may become compromised. Barondess has addressed these issues in a thoughtful manner.24

Even before the Nazis came to power, eugenics to eliminate or sterilize those perceived to be “inferior” was gaining support. The United States was perceived by some as leading in this effort. Indiana was the first state to pass legislation in 1907 to allow involuntary sterilization of mentally defective and some criminal individuals, and by 1926, 23 states had implemented similar legislation.25 One finds in Science26 the opening address of the president of the American Eugenics Society asking for understanding and reflecting dismay that the program was misunderstood. Sofair and Kaldjian27 explored opinion in the United States on human research, including the activities in Germany, by analyzing editorials in the Journal of the American Medical Association (JAMA) and the New England Journal of Medicine (NEJM) between 1930 and 1945. The authors found a surprising scarcity of concern in this review and the following statement: “Germany is perhaps the most progressive nation in restricting fecundity among the unfit” by editors of the NEJM in 1934, a year after Hitler became chancellor.25 How do such trends in ethical compromise occur, and how do we ensure that violations of human rights do not occur in our own time? Marks has pointed out these hazards in a thought-provoking review of “doctors from hell” in the Journal of Clinical Investigation.27

After World War II, the Nuremberg Tribunal was formed to prosecute Nazis charged with war crimes in an international court of law. This included a doctors’ trial, which began on December 9, 1946. Of 23 defendants, 20 were physicians charged with atrocious human experimentation. The deliberations of the tribunal led to the articulation of 10 directives for human experimentation that constitute the Nuremberg Code. The Declaration of Helsinki followed in 1964 and was endorsed by most countries as a guide to human research. The Declaration of Helsinki distinguishes between therapeutic and nontherapeutic research and provides that informed consent is not necessary in therapeutic research if “not consistent with patient psychology” and “approved by a review committee.”28 This principle is consistent with the plan implemented in the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarcto miocardico (GISSI) trial to enroll patients without informed consent to “protect the right of the patient not to be exposed to an emotionally burdensome request for informed consent”—a design approved by the responsible ethics committees, which included judges.29

Because of growing concern amid a rapidly expanding biomedical research effort, a survey by the Law-Medicine Research Institute of Boston University, with the support of the United States Public Health Service (USPHS), addressed in 1962 the conduct of clinical research at that time.30 Of 52 departments of medicine responding to the survey, few had any procedural guidelines for conduct of research. The prevailing opinion held that the responsibility for regulation should be left to the investigator rather than a committee. The Advisory Committee on Human Radiation Experiments appointed by President Clinton in 1994 documented an environment in the years after World War II when research involving patients was performed without formal consent, in contrast to research involving normal volunteers.31 The equa-

![Death Rates* for Cardiovascular Diseases, U.S., 1900-2005**](Image 58x559 to 288x726)

**Not age-adjusted
**Data for 2005 are preliminary
Vital Statistics of the United States, NCHS
HHL/BI Fact Book Fiscal Year 2007

Figure. Death rates for cardiovascular disease in the United States, 1900 to 2005 (not adjusted for age).
nimity of those times had been challenged in 1966 by Dr Henry K. Beecher in an article describing 22 published studies that in his opinion had ethical problems. His goal was to "call attention to a variety of ethical problems found in experimental medicine." (In the spirit of full disclosure, one of the authors [R.L.F.] is a coauthor of one or more of the citations).

Subsequent revelations of experiments at the Jewish Chronic Disease Hospital and Willowbrook School involving mentally defective children aroused great consternation, based in part on issues of consent. However, it was the Tuskegee Syphilis Study that shocked Congress into action. The Tuskegee study, started in 1932, initially to determine incidence of syphilis in Macon County, Alabama, subsequently shifted focus to observe the natural history of untreated syphilis with support by the USPHS including the Centers for Disease Control. An article in the New York Times describing the project led to congressional hearings. Lack of consent, inclusion only of a poorly educated black population, and obtaining spinal fluid examination under the guise of receiving a new treatment while actively withholding effective therapy were among the list of violations of ethical principles. Ultimately, Congress passed the National Research Act in 1974, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to advise on ethical conduct of research in humans. In 1979 the Commission published the Belmont Report, which was named after the Smithsonian Institution where the Commission met. The report identified three fundamental principles for all human subject research: respect for persons, beneficence, and justice. The end result is the Code of Federal Regulations (CFR), Title 45, Part 46, which now encompasses a uniform set of regulations known as the Common Rule, which governs all research involving humans supported by federal funds. With limited exceptions, these regulations and those at 21 CFR 50 and 56 governing research under the US Food and Drug Administration cover basically all research activities involving humans.

Given the above history, it is sobering to reflect on the Total Body Irradiation Study carried out at the University of Cincinnati after the Nuremberg Code and the Declaration of Helsinki. The study was supported by the Department of Defense. Started at the height of the Cold War, the objective was to determine how total body radiation might affect military personnel after a nuclear explosion. Though disapproved by the Atomic Energy Commission and the National Institutes of Health on ethical grounds and receipt of critical reviews within the University of Cincinnati, the project was implemented and continued in operation from 1960 to 1972. Dr Eugene Saenger directed the project in cancer patients seeking treatment for their cancer. Total body irradiation was performed under the guise of cancer treatment, though the purpose was research for which the patients had not consented. In 1966, it was reported that 10 patients died within 37 days of the treatment. There are estimates that 20 patients out of 87 died as a result of the experiment. An investigation by the American College of Radiology in 1971 to 1972 apparently found no ethical concerns. However, in subsequent litigation and a settlement with the subjects’ families, the following statement is displayed in the University of Cincinnat Hospital: "The Cincinnati citizens listed below were the innocent victims of human radiation experiments in this hospital from 1960 to 1972. Their names are placed here so that all may remember their injuries and afflictions, and their unwitting sacrifice in a project sponsored by the US Department of Defense and carried out by professors in the University of Cincinnati College of Medicine."  

Perceptions of the Autocratic Physician and the Failure of Self Regulation

The understanding of societal concerns relative to research involving humans and the process of informed consent requires reflection on physician behavior and the negative impact of the autocratic and/or insensitive physician as a serious barrier to the process of informed consent. Andrew Scull, in his 2005 book entitled Madhouse: A Tragic Tale of Megalomania and Modern Medicine, provides a frightening portrayal from the first half of the 20th century of the power of an individual physician to inflict brutal and horrifying surgical interventions on mentally impaired patients without consent. Convinced that removing "foci of infection" would cure mental illness, Dr Henry Cotton and his colleagues performed colectomies, total dental extractions, and other procedures without consent on those impaired with mental illness. Descriptions are provided of patients being literally dragged to the operating room against their will and forced to undergo surgical interventions on the basis of Dr Cotton’s certainty that this was in the best interest of the patient and society. Support for these surgical interventions was evident in the United Kingdom and Europe, and Cotton received warm welcomes on several tours presenting his data. Skepticism and outright criticism were expressed in some quarters of the medical profession, but major leaders of medicine were loath to criticize. In particular, Dr Adolph Meyer, Chief of Psychiatry at the Johns Hopkins Hospital, who was a mentor of Dr Cotton, suppressed an investigation by one of his own faculty proving that that Cotton’s claims for success were bogus. Even after Cotton’s death, Meyer lauded Cotton for his “remarkable achievement of the pioneer spirit.” Scull comments as follows: “How could such horrors occur in American medicine under the guise of clinical practice in the best interest of the patient?” Though Cotton never convinced most of his peers, Scull again notes, “But scarcely anyone doubted his right to experiment on his patients or raised in any serious or sustained manner any questions about the propriety of maiming and mangling the bodies of the mad—not even when Cotton confessed on occasion, that his surgical interventions proceeded notwithstanding verbal and physical resistance from their victims.” This frightening example of the power of physicians to inflict great harm under the banner of doing what they perceive is in the best interest of the patient, even when the patient strongly disagrees, is profoundly disturbing. It is also an example of failure of the profession to self regulate.

Another example of attitudes to informed consent later in the 20th century is evident in an editorial after the publicity of the Tuskegee experiments: “In the days of the Tuskegee Study we used to walk into a patient’s room and announce ‘We’re going to take out your gallbladder tomorrow morning’; the answer was
Informed Consent, Clinical Practice, and Research Involving Patients

Professor Jay Katz, in his plenary address entitled “Human Sacrifice and Human Experimentation: Reflections at Nuremberg on the 50th Anniversary of the Nazi Doctors Trial,” concludes that regulations requiring informed consent will fail to achieve the goal of protecting individual rights of patients and human subjects “unless physician investigators embrace these rights as a new Hippocratic commitment.” He also challenged acceptance of medical research as part of medical practice: “When medical science and medical practice became intertwined, a new ethical question should have been raised: Are physicians’ obligations to their patient-subjects different from their obligations to their patients?” We believe our obligations as physicians to subjects are the same as those to our patients41: that physicians must still care for their patients involved in clinical trials or other research while adhering to protocols for creating generalized new knowledge. The natural history of patients in long-term trials will change with time, and the physician-investigator must make judgments about conflicts between protocol and the best interest of the patient. Involvement of a colleague without a commitment to the trial may be of value in such settings. Random assignment to the medical arm of a revascularization trial does not mean that one is denied appropriate revascularization therapy if clinical conditions change with time. Thus, many trials test treatment strategies rather than a rigid comparison of one treatment versus another.

Fundamental to the process is equipoise. Clinical trials require equipoise—ie, real uncertainty as to the outcomes associated with the intervention or treatment strategy under investigation.45 We believe this is appropriate and consistent with physician responsibility of caring for individual patients to be honest when there is uncertainty and providing the opportunity for patients to participate in resolving the uncertainty in properly designed trials. Refusal to admit uncertainty in clinical practice when it exists, particularly when it is in the financial interest of the physician to deliver care that is of uncertain value, raises equally important ethical issues.

Although equipoise is essential to conduct a clinical trial, it is not possible to address all uncertainties in medicine with randomized trials. How, then, should an investigator decide whether the risks are worthwhile to define equivalence of treatment strategies? It is a personal duty and responsibility which may not be delegated to another with impunity.”

Current regulations on essential elements of informed consent can be found in 45CFR 46.116. Table 1 summarizes components of informed consent.

What Are the Necessary Elements of Informed Consent?

The first principle of the Nuremberg Code46 identifies the elements of informed consent: “The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved to enable him/her to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him/her the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects on his/her health or person which may possibly come from his/her participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests on each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.”

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What Is the Process of Informed Consent?

The process to achieve informed consent ideally provides these conditions:

1. Time and an environment to establish a relationship of trust.
2. Information on which consent is based.
3. Multimedia materials to enhance understanding.
4. Presentation of the written consent document.
5. An opportunity for questions and discussion with the responsible physician investigator and those to whom initial responsibility for consenting has been delegated.
6. Providing information during and after conclusion of the trial.

Focus on a consent document alone is misplaced. In part, this relates to our experience at the Mayo Clinic, where consent forms for clinical practice were never used until recently, when they were required by the Centers for Medicare and Medicaid Services. The emphasis has been on direct face-to-face communication with patient and family to discuss risks and objectives of any intervention and in doing so to establish trust and understanding. It seems the longer the consent document the less likely it will be read completely. More important in the process of consent is the verbal direct contact with the patient and establishment of trust. The process of consent should include continuing efforts during the conduct of the trial to ensure understanding of the research protocol.

Recognition of the powerful influence of the physician responsible for the care of the patient on decisions to participate in research is most important. Although concern about consent in vulnerable populations is clear, including those in acute care settings, note the comments of Dr Uwe Reinhardt, a Princeton professor and health economist, who agreed to participate in a trial so he would not upset his physician, as reported in an article from the New York Times.47 “The physician has enormous power over you. You want to keep his favor. If you say no, you’ll worry that he may not like you.” The process of consent then must be sensitive to the concern that the patient–physician relationship will be a form of coercion leading to inappropriate consent. Involving another colleague in the consent process and identifying other physician availability for management of usual care in such settings is of value in dealing with this dilemma.

The following excerpt from a letter to patients considering participation in a research protocol in psychiatric studies may be considered: “Your health care provider may be an investigator of this research protocol, and as an investigator, is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another doctor who is in no way associated with this project. You are not under any obligation to participate in any research project offered by your physician” (Mark A. Frye, MD, Personal Communication, 2009). Such efforts are particularly important if the physician-scientist has a conflict of interest, be it pecuniary, directly (personally) or indirectly (professionally), proprietary, or related to intellectual property (ideas).

Another challenge in the process of obtaining consent for research is inclusion of minorities and other underserved populations. This is a critical issue because many trials deal with health disparities, and participation in the trials by those who are disadvantaged and who bear an undue burden of disease with poor outcomes should ideally have the opportunity to participate in such trials. In such populations, the understandable lack of trust in and suspicion of our motives are barriers that must be addressed in the consenting process.48

What Is the Role of “Therapeutic Misconception” in Compromising Informed Consent?
Appelbaum et al50 first identified the compromise of informed consent by the patient who may confuse care with research “the therapeutic misconception.” It is essential that efforts be made to clearly distinguish what is usual clinical care and what is research. Subsequent studies by Appelbaum50 demonstrated that potential participants in research studies had better comprehension when there was a “preconsent discussion” led by a neutral discloser, one not a member of the healthcare team. Discussion topics included basic research methodology and distinctions from clinical care/treatment.50

In the United States, therapeutic misconception may also lead to disputes of reimbursement if distinctions between clinical care and research are not clarified before the investigation is started. Miller and Rostenstein51 also offer suggestions for reducing the likelihood of therapeutic misconception. These include paying patients for participation, as is done with human volunteers.

Do We Achieve Informed Consent?
Detailed review of studies to improve comprehension in the informed consent process using simplified consent forms, multimedia approaches, and use of a consent educator have revealed continued shortfalls in achieving comprehension. “Despite increasing regulatory scrutiny, deficiencies still exist in participant comprehension of the research in which they participate. Any successful consent process should at a minimum include various communication modes and is likely to require one-to-one interaction with someone knowledgeable about the study.”52

Others have also noted instances where, even when a consent process met regulatory requirements, “it was inappropriate for most patients.”53 Fundamental issues include literacy rates in the United States of half the population at the 8th-grade level. In 2003, evidence that the average reading level of consent forms approved by institutional review boards in a sample of medical schools in the United States was at a grade level of 10.6.54 This provides further stimulus to focus on verbal and other media presentation of materials to enhance understanding.

Studies of acute myocardial infarction, which have been critical in improving outcomes, present special problems in informed consent, as in any emergency situation. There is an extensive literature documenting considerable shortfalls in informed consent and calling for reforms.55–57 It is also clear that trust in the entire healthcare team is essential to an environment where the individual patient is comfortable in exercising the right for autonomy in decision making.

Is It Really in the Best Interest of the Patient to Participate in a Clinical Trial?
This question is posed by Menikoff and Richards58 in their recent book, What the Doctor Didn’t Say: The Hidden Truth About Medical Research. While providing a legal perspective of appropriate elements in consent forms and the consenting process, they present a view that challenges the concept of the “benefits” of participation in clinical trials. This is framed in a chapter entitled, “How Bad for the Subjects Can a Study Be?”
Does clinical equipoise ensure that participation is in the best interest of the patient? Menikoff and Richards counter with a view that assuming equipoise ensures participation is in the best interest of the participants is “plainly wrong” based on lack of rigorous methods for assessing the uncertainty. Will it always be in the best interest of the patient to accept a 50% chance of receiving a new therapy that may prove not to be in the patient’s best interest? Fundamentally, patients who participate in trials must accept that their participation will help resolve an important uncertainty and that an element of chance is involved; ie, they may benefit if in one group but they may not benefit or be harmed if in the group with an adverse outcome. (We have previously noted the CAST Trial).

We are aware that many surveys indicate that patients do not participate in trials with an altruistic point of view. In our experience, many patients choose for a variety of reasons to refuse consent, but many of those who do consent feel their participation may “help someone else.” The same authors note that tort law increasingly influences regulation of research and should guide informed consent; ie, if harm or bodily injury occurs, whether disclosure of information was sufficient to enable a reasonable person to make an informed decision to participate.

Conflicts of Interest

We approach this important ethical issue with a perspective that collaboration with industry is a fundamental reality and one that should continue to be productive of important new advances in caring for our patients. If one reflects again on a historical perspective based on Figure 1, contributions from the medical industry in the form of antihypertensive, lipid-lowering, and other drugs have contributed importantly to the decline of cardiovascular mortality over the past decades. It seems clear that further drug discovery will be highly dependent on interactions and support with industry. These views are supported by the following statement in a publication by the Association of American Medical Colleges, which provides a historical background for this section:

“The Bayh-Dole Act of 1980 accelerated this shift by allowing faculty and institutions to retain title to the intellectual property resulting from their federally supported research and by encouraging them to promote the commercial development of their discoveries through technology licensing. There can be no doubt that Bayh-Dole has been an unparalleled success in speeding discoveries from the laboratory to the marketplace, resulting in great social benefit. Indeed, the December 12, 2002, Economist referred to Bayh-Dole as ‘possibly the most inspired piece of legislation to be enacted in America over the last half-century.’”

Conflicts of interest may be considered in the context of the discussion of ethics in research on several grounds:

1. How might a financial interest influence conduct of research and the analysis and reporting of research data?
2. How does one’s basic “job” (ie, how one earns a living) potentially influence analysis and reporting of data?
3. Do individual or institutional conflicts of interest, arising from intellectual property, licenses, or contracted know-how, create an environment that compromises objectivity?
4. With increasing reliance on industry support of research, how does an investigator maintain independence and fulfill society’s expectations for ethical research and unbiased reporting of research?
5. Do researchers introduce bias in their assessment of clinical efficacy or development of practice guidelines if they have conflicts of interest?
6. How do conflicts arising in research influence the choices made in clinical practice?

Table 2 categorizes conflicts of interest.

### Management of Conflict of Interest

There are 2 overriding goals in the management of conflicts of interest: (1) protection of the research participants and their rights and (2) upholding the integrity of the research. An important ethical consideration for a new or established investigator in the conduct of research is the importance of managing and reporting any potential conflict of interest. Conflicts of interest arise when the professional responsibilities of a physician-investigator toward their subjects and patients differ from those of the physician as an individual or the physician’s institution. In the current environment of translational research, the potential for conflicts will clearly increase. Investigators must always be aware of the presence of real or perceived conflicts throughout their investigative careers.

Recent legislative and policy developments have focused on the importance of identification and management of conflicts of interest. In 1980, the Bayh-Dole Act enabled individuals and institutions to own patents resulting from federally funded research. As such, the individual and institutions began to develop new conflicts in the conduct of research as well as providing clinical care. Regulations of the USPHS (42CFR50, 45CFR94, effective 6/28/1995) and US Food and Drug Administration (FDA) (21CFR54, effective 2/2/1999) on disclosure and management of potential conflicts of interest impose obligations on institutions and trial sponsors in managing these conflicts. Perhaps disappointingly, these federal guidelines differ in some important aspects. The USPHS guidelines require funded institutions to adopt policies and prospectively manage potential conflicts with a financial threshold generally of $10,000 whereas sponsors submitting data to the FDA collect and report financial interest of >$50,000 to individual investigators or $25,000 to institutions at the time an application to market a

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<td>Equity interest, other ownership of a “stake”</td>
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<td>Consultant, Speakers’ Bureau</td>
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<td>Institutional benefits</td>
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<td>Intellectual property, royalties</td>
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product is submitted. However, in spite of multiple guidelines, in a survey of medical schools in the United States in 2000, 6% reported no policies on conflict of interests; and although 91% had developed policies that followed the federal thresholds for disclosure, the policies varied greatly in scope and requirements for disclosure. In fact, only 1% required disclosure of conflicts to institutional review boards. Additionally, this survey demonstrated that only 43% of journals had policies requiring disclosures of conflict of interest. A more recent study on institutional conflicts of interest reported that only 38% of respondents have adopted a policy dealing with financial interests of institutions, although a higher proportion reported policies regulating individual research officials.

High-profile examples of incomplete management of conflicts of interest include the enrollment and subsequent death of a young subject in a gene transfer study at the University of Pennsylvania. Both an investigator and the university had a financial stake in the study, which lacked sufficient disclosure. In many ways, this case has exemplified the critical importance of managing conflicts in translational research. Since that time, there has been increasing public and federal interest in disclosure of managing conflicts in translational research, and investigators must be aware of the severe penalties that are associated with research misconduct, which is defined by the federal Office of Research Integrity (ORI) according to 42CFR93 as follows:

1. Fabrication is making up data or results and recording or reporting them.
2. Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.
3. Plagiarism is the appropriation of another person’s ideas, processes, results, or words without giving appropriate credit.
4. Research misconduct does not include honest error or differences of opinion.

Disputes about data and allegations of research misconduct are extremely serious and represent life-changing experiences for all concerned. They occur regularly and more frequently than most are aware; e.g., the number of cases with disciplinary action by the ORI include 14 in 2006, 10 in 2007, 8 in 2008, and 7 through June 2009, according to the ORI Web site. The ORI is charged with monitoring institutional programs for dealing with research misconduct, and every institution receiving federal funding must have a program in place to deal with research misconduct. At the personal level, all investigators must take seriously their responsibility, which is shared by all members of the research team in protecting the integrity of their research. This includes not only the investigator(s) but research coordinators, technicians, and any others involved in the generation and management of data. All must be proactive in preventive measures to avoid research misconduct. Enthusiasm to present data consistent with prevailing opinion or actual bias as to the outcome of a given experiment must be countered by insisting on objective analysis of all data. Regular meetings to discuss and demonstrate data, sharing notebooks or files so raw data can be verified, and periodic auditing of data for accuracy are all important preventive efforts. The electronic environment, with all its advantages, creates challenges in carefully examining raw data, which must be overcome. In the realm of clinical research, staff must become familiar with the FDA regulations for clinical investigators and the Good Clinical Practice Program (http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm) and the details of the protocol dealing with study records and documentation. The most important elements are setting the standard that cutting corners is not accepted and having a high standard of performance. In monitoring clinical trials, random sampling of the clinical source data may be compared with entries into the research database. Manipulation of data is another concern. A recently reported example stated that the sponsor of the research was reported to have withheld data to present their product in the best light. Ideally, all data should be held by independent statistical centers with no interference or control by the sponsor.

Authorship should be the primary responsibility of the investigator and those directly involved in the conduct of the research. Peer-reviewed journals have well-defined rules for authorship. See also the International Committee for Medical Journal Editors “Uniform Requirements for Manu-

Data Management and Privacy Laws

Data management is a central element in the ethical conduct of research, and investigators must be aware of the severe
scripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication” (http://www.icmje.org).

A practice to be avoided is the use of ghost writers, also recently reported in JAMA.69 Sloppy data management compromises the ethical conduct of research. Experimentation involving humans not only must address an important issue with a well-designed protocol but must ensure that the results of the study are not compromised because of lost or unusable data.

Society has made clear its desire for privacy of healthcare information, and investigators must be clear on specific regulations before initiating even observational studies. In the United States, there are regulations for research use of medical records under the Health Insurance Portability and Accountability Act of 1996.

Other countries have similar data protection restrictions. In Scotland it was demonstrated that bias was introduced in requiring explicit consent for use of medical records in an observational population-based study of brain arteriovenous malformations.70 Similar experience has been reported in studies of ischemic heart disease.71,72 Anna73 notes the reality of wide variation in institutional review board decisions regulating use of data from medical records. Investigators must be aware of these restrictions and understand local constraints.

New Challenges

Beyond the traditional realm of safety and efficacy, emerging biotechnologies have the potential to introduce additional considerations. A case in point is the use of biologics, in particular stem cell–based therapies, with issues ranging from the procurement process and cytotype source to first-in-human application and long-term risk/benefit ratio.74 Platforms of cell-based therapy include umbilical cord blood, bone marrow, and other adult sources that have been used or tested for clinical application as well as embryonic and, more recently, bioengineered progenitors that are at present undergoing preclinical evaluation. In this context, converging and possibly conflicting medical, biological, socioeconomic, religious, and political considerations collectively drive a novel paradigm for appraisal beyond the more traditional ethical benchmarks. This includes the relevance of public opinion research to policy making.75 Despite a large amount of public debate, many of the issues remain, including concern that human gene/cell patents may harm the research environment, lead to an inappropriate commodification of life, and adversely affect public access to useful healthcare procedures.76

Conclusion

Investigators are well advised to carefully consider the basis for increasing ethical concerns in the conduct of research in humans and to become familiar with regulations that must be met. Full disclosure of potential conflicts of interest are mandatory and in the best interest of all concerned, including the investigator. Academic institutions need to provide education on management of conflicts of interest, and boards need to be appropriately constituted to manage them. With the complexities of the current regulatory environment, clinicians need additional training in the conduct of research, as do all members of the research team. Research coordinators and all those interacting with patients and volunteer subjects should also have additional training and credentialing to document their understanding of the issues in obtaining consent from patients, managing data, and dealing with conflicts of interest. A continuing effort to improve the process for consent and patient safety is essential.

Disclosures

None.

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