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TASK FORCES

Task Force 1: The ACCF and AHA Codes of Conduct in Human Subjects Research

Co-Chairs: Joseph S. Alpert, MD, FACC, FAHA, Kenneth I. Shine, MD, FACC
Authors: Robert J. Adams, MD, FAHA, Elliott M. Antman, MD, FACC, FAHA, Rae Ellen W. Kavey, MD, FACC, FAHA
Participants: Lawrence Friedman, MD, Robert L. Frye, MD, MACC, Robert A. Harrington, MD, FACC, David Korn, MD, Jon F. Merz, JD, PhD, MBA, Elizabeth Ofili, MD, MPH, FACC

SCOPE OF ETHICAL ISSUES INVOLVED IN HUMAN SUBJECTS RESEARCH

Human participant research is a crucial element in the development and approval of new drugs, biologics, devices, and procedures that seek to improve patient care. Participation in clinical research is an important professional obligation for cardiovascular practitioners. This involvement ranges from study design and implementation as investigators to the critical role of subject enrollment for all cardiovascular practitioners. The conduct of such research is one of the highest callings of the clinical researcher/practitioner and must be conducted according to the highest standards of science and ethics. All human subjects research should be conducted according to such standards. Difficult issues continue to require awareness and careful management. Some of these issues are examined in this report; conflict of interest is the first of these. A conflict of interest may exist when a secondary interest has the potential to distort, or appear to distort, the integrity of judgment relative to the primary interest. The Hippocratic tradition and the principle of beneficence require that the physician always act in the patient's best interest. However, when the physician profits both professionally and financially from the patient's participation in a clinical trial, the situation may become ethically tenuous for the involved physician. Conversely, information derived from clinical trials improves patient care. Thus, patients may also benefit from participation in clinical trials. This might mitigate, in part, the ethical dilemma just described.

Non-financial conflicts of interest. Physician-investigators obtain a number of non-financial benefits from participation in clinical research trials (1). Career advancement, fulfillment of a desire to do good, an opportunity to publish in a peer-reviewed journal, fame, invitations to present at national and international meetings, future success in obtaining grant funding for research, prestigious research prizes, professional accolades for obtaining a positive outcome from a particular clinical trial, and a personal sense of worth—all potentially accrue to the physician-investigator. Although these non-financial incentives are not well known outside of academia, they are well recognized within the academic community.

Levinsky (2) has recently pointed out that the deaths of three research participants in clinical trials were not related to financial factors at all. These deaths all occurred at prominent research universities and were apparently the result of excessive zeal, inadequate research, and/or ethical knowledge or training deficits on the part of the investigator and/or his staff (2–5). Financial conflicts of interest are easier for the public to understand. Non-financial conflicts of interest, such as academic promotion and accolades, are often more subtle and may require some thought and study before they become evident. Levinsky (2) suggests that committees charged with the review of experiments involving human subjects (Institutional Review Boards [IRBs]) should consider these non-financial conflicts of interest during their deliberations. Additionally, investigators and those responsible for oversight should be aware of this form of conflict of interest and should bear it constantly in mind during the conduct of a clinical trial.

Clinical trials involving human subjects are essential to the advancement of medical science, but the ethical situation for a physician-investigator who is simultaneously in charge of caring for the patient-subject is particularly challenging. As noted, the physician may benefit in a non-financial manner—for example, from enhanced reputation, publications, and so forth. At the same time, the physician who serves as a clinical investigator enhances his or her own career and may occasionally benefit financially from payments made to the physician or the physician's institution by the sponsor of the clinical trial. Thus, physicians who act as both investigator and attending physician for a patient are caught in a clear ethical dilemma. The physician might subtly coerce or induce the patient to participate in the trial for the physician's personal benefit. This same conflict of interest might also arise in daily clinical practice where the physician profits from the care of the patient (see Task Force 4).

Patients who participate in clinical trials, whether they receive experimental treatment or if they are in a control group, can benefit from meticulous attention to their care, by learning more about their disease process, and potentially, from the trial environment itself (6). Because results of research usually apply more directly to those patient groups included in the studies, it is especially important to include subjects from all socio-economic strata and all ethnic groups. Cardiovascular practitioners should consider

participation of their patients for these reasons, and because this type of research is essential to advance care in the field. The process of enrollment must be undertaken carefully. In addition, a physician must not allow patients to assume, incorrectly, that they will receive the experimental therapy and not the control regimen or device being tested. Physician-investigators may not disabuse their patients' expectations in an overzealous attempt to increase enrollment in the clinical trial. All physician-investigators should bear these points in mind when explaining participation in a clinical trial. This same care should apply to all those recruiting for a clinical trial. These issues become particularly complex in the setting of tertiary care centers, where multiple individuals may be involved in recruiting patients for clinical trials. Indeed, everyone involved in the recruitment process must avoid overzealous recruiting with potential failure to inform the patient adequately concerning the risks involved in the experimental intervention (7–9).

Throughout the clinical trial process, it is important that the physician-investigator maintain a state of mind referred to by ethicists as "equipoise." During the initial discussions with the patient, equipoise exists when the physician-investigator accepts the concept of uncertainty about the benefits of one treatment relative to the other. At the analytic stage, equipoise exists when the investigator is equally willing to accept a negative or a positive outcome from a clinical trial. Because a positive outcome in a trial is more likely to lead to reward, there is subtle but persistent pressure on the physician-investigator to favor a positive outcome. Such pressure should not lead to multiple reanalyses of trial data in an attempt to state something "positive" about the investigation.

Financial conflicts of interest. Financial relationships are a highly controversial aspect of human research. This topic must be addressed because of the potential for real or perceived conflict of interest. Some physicians devote a substantial portion of their professional life to clinical trial work. For these individuals, a potential problem arises because they derive substantial income from participation in clinical trials. A cardiovascular practitioner may function merely as a "recruiting agent" for large pharmaceutical or device manufacturing companies. This practice is inappropriate and is not condoned as it deviates from the principle of putting a patient's best interest first. Nevertheless, enrolling patients in clinical trials is critical to advancing cardiovascular care. Participation in trials requires extra time for the cardiovascular practitioner, and this can impact usual patient care flow. Despite these issues, cardiovascular practitioners need to support clinical trial enrollment.

Some physicians are truly the most knowledgeable individuals available with respect to a specific drug or device. It is thus not surprising that industry values the opinion and intellectual assistance of such individuals. It is reasonable for such clinician-investigators to be compensated appropriately for their time and effort. At times, payment includes stock options or even shares in a new company founded to exploit a new drug or device. In the latter circumstance, the potential financial rewards for the physician-investigator can be substantial. A conflict of interest is clear when such individuals participate in clinical trials of that new drug or device. The physician has a financial stake in the successful initiation, implementation, and outcome stemming from this particular research protocol. At times, such inducements have led physicians to abrogate their social contract with patients, and the results of these ethical failures have occasionally been catastrophic for patients.

Following the passage of the Bayh-Dole Act, academicians were encouraged to transfer their discoveries to industry so the advances could be made available to patients; many academic investigators became integrally involved in the development and testing of innovative biomedical products. The resulting conflicts of interest have attracted the attention of clinical investigators, academic physicians, professional organizations, the media, the federal government, and the public, thereby leading to a number of editorials, surveys, and task force reports dealing with these problems (10–16). The recommendations from all of these commentaries and task force publications are in many ways similar. For example, the threshold employed in most of these documents, including the rules of the National Institute of Health (NIH), defined a "significant" financial arrangement as one that exceeds $10,000 (see Task Force 3).

THE ROLE OF THE IRB OR HUMAN EXPERIMENTATION REVIEW BOARD IN OVERSEEING RESEARCH INVOLVING HUMAN SUBJECTS

Four comprehensive publications dealing with the regulation of human experimentation have emanated from the Association of American Medical Colleges (AAMC) and the Institute of Medicine within the last three years (13–16). These reports explore the various potential and actual conflicts of interest, financial and non-financial, that exist in human experimentation in the U.S. today. *Responsible Research* describes a systematic approach for improving human subject protection during clinical research trials. A variety of topics are thoroughly examined, including research ethics, the role of the IRB, investigator conflicts of interest, and national and local regulation of human experimentation. Numerous recommendations are presented for improving the current situation. *Preserving Public Trust* is a comprehensive review of the U.S. system of human subject research protection (14). This latter text also suggests numerous reforms for national accreditation and oversight of human subjects review boards (IRBs). Highly prominent in this document is the recommendation that research oversight be expanded to include conflict of interest review by a process independent of the IRB. Two AAMC reports, "Protecting Subjects, Preserving Trust, Promoting Progress I—Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research" (15) and "Protecting Subjects, Preserving Trust, Promoting Progress II—

Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research" (16), explore in great detail potential financial conflicts of interest and ways to defend against inappropriate behavioral responses to such conflicts.

THE ACCF/AHA CONSENSUS CONFERENCE RECOMMENDATIONS CONCERNING THE MANAGEMENT OF HUMAN SUBJECT RESEARCH

Physician-Investigator Responsibilities

1. Participation in clinical research is an important obligation for cardiovascular practitioners and is strongly encouraged.
2. Physicians who participate in clinical research must be familiar with both the experimental therapy to be tested and the principles of human subject research.
3. The ACCF/AHA Consensus Conference strongly encourages cardiovascular practitioners to enroll patients who are members of underrepresented groups in clinical trials.

Conflicts of Interest

1. Transparency in all dealings with clinical trial subjects is the cornerstone of management of investigator related conflict of interest. Cardiovascular investigators involved in the clinical trial must disclose their financial conflicts of interest to potential subjects.
2. Investigators must disclose very specific and detailed financial information as per the guidelines in Task Force 3 to the IRB overseeing the trial (13,15).
3. The ACCF/AHA Consensus Conference supports the concept of limitations on the amount of financial involvement that physician-investigators and collaborators may have in a particular research project. Physician-investigators/collaborators with a significant financial relationship (excluding funding for the trial itself) with the sponsor of a particular drug or device under investigation should not personally participate in clinical trials involving these drugs or devices. Unique circumstances can be adjudicated through the IRB mechanism for single-center studies (e.g., primary trial for new drug or device). For multicenter studies, the steering/executive committee for the study should address issues of financial involvement at the individual investigator level. These financial limitations do not apply to employees of the medical product industry.

Informed Consent

1. A trial investigator who is the physician of a potential subject has a special obligation to provide full disclosure of his or her role in the investigation. Because of the vulnerable status of the patient in such circumstances, it must be made clear that refusal to participate in the trial will not affect current or future care.
2. The ACCF/AHA Consensus Conference supports efforts to improve the process of trial enrollment, such as use of a neutral third party (i.e., a research subject advocate or an ombudsman) to observe the informed-consent process and make recommendations for improvement.

IRBs

1. The IRBs should focus on the ethical implications of each and every human research protocol (14). Both financial and non-financial potential conflicts of interest should be addressed.
2. The ACCF/AHA Consensus Conference recommends two separate but coordinated processes, one for the protection of the experimental subjects and one for the examination and management of potential conflicts of interest (financial and non-financial) on the part of the physician-investigator.
3. Investigators should be given ample opportunity to rebut the presumption that they cannot participate in the research due to the conflict of interest that has been raised by the oversight process.
4. Advertising copy aimed at recruiting research subjects should be examined carefully by the IRB to ensure that potentially misleading statements are not included in these ads.
5. Special care must be taken when obtaining informed consent from children and their parents, particularly children too young to comprehend the implications of the suggested intervention. Parental and/or guardian involvement is critical to this process. These same issues apply to other vulnerable individuals including but not limited to the homeless, prisoners, and the uninsured.

Data Analysis, Integrity, and Publication

1. All human subjects' research, not limited to randomized trials, and regardless of sample size, should have a plan for monitoring data collection and subject safety.
2. Physician-investigators should not have a primary role in data analysis of a clinical trial involving a drug or device in which they have a major personal financial interest. This does not apply to employees of the medical products industry (see Task Force 2).
3. At the outset of a sponsored clinical trial involving an experimental therapy, a contractual arrangement should be in place to ensure that publication of the results will not be unduly delayed or obstructed by the sponsor of the trial (see Task Force 2).

WHEN DOES MODIFICATION OF A MEDICAL OR SURGICAL PROCEDURE, DEVICE, OR DRUG BECOME AN EXPERIMENTAL PROCEDURE?

The issue of subtle variations in drugs and devices that have already been approved rising to the level of investigational status is not clearly described in the regulatory literature.

What level of modification is required before an original submission of a new drug or device application is required? Decisions regarding the point of transition from an approved entity to an investigational entity are usually individualized for each product. For the physician who modifies a procedure or a device for use in daily practice, the following distinction is important: "When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is experimental in the sense of new, untested, or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective" (17).

With respect to the development of such new procedures or devices from the point of view of the developer, some guiding principles from the Food and Drug Administration (FDA) document, *Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (May 1998) provide an informative perspective. The purpose of that guidance document was to articulate the FDA's thinking concerning the quantitative and qualitative standards for demonstrating effectiveness of drugs and biologics. The guidance document also describes the evidence necessary to support approval of a new use of an existing drug.

In certain cases, effectiveness of an approved drug or product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen, or dosage form. The following are examples of situations in which effectiveness might be extrapolated from efficacy data for another claim or product: bioequivalence, modified-release dosage forms, or different dose regimens.

Single studies for new uses of an existing drug, device, or procedure may be submitted as per the following examples: different doses, regimens, or dosage forms where the relationship between blood concentration and response is less well established; studies in other phases of the disease; studies in other populations; studies in combination or as monotherapy; studies in a closely related disease; studies in a less closely related disease, but where the general purpose of the therapy is similar; studies of different clinical end points; and studies of different pharmacologic/pathophysiologic end points. The Center for Devices and Radiological Health offered an algorithm for submission of evidence for approval of a device (18).

Post-marketing surveillance studies offer the opportunity to submit evidence for a new indication for an existing product. However, in a guidance document on discretionary post-marketing study of pacemaker leads, the FDA has pointed out that the definition of what constitutes a distinct entity versus a minor modification of an existing entity is highly specific to a particular setting and should be individualized (19).

ISSUES PERTAINING TO HUMAN SUBJECTS RESEARCH INVOLVING SUBJECTS WITH COMPROMISED CAPACITY FOR GIVING INFORMED CONSENT

Within cardiovascular medicine, clinical research may involve individuals with limited capacity to grant informed consent. Although no one contests or argues the critical concept of informed consent, it must be recognized that in the heart/brain injury domains there are several time-sensitive situations in cardiovascular medicine where informed consent may not be practical. These include cardiac resuscitation, brain impairment from stroke, acute myocardial infarction, and severe congestive heart failure. Other vulnerable populations include children and those who are mentally incapacitated. Although research in these populations may be difficult, investigation is particularly important because of limited data to support therapeutic decision-making (20).

Emergency research. Federally sanctioned guidelines allow certain emergency and resuscitation human subjects research to proceed without prospective informed consent (20). The FDA regulations (21 CFR 50.24) provide a narrow exception to the requirement for informed consent from each human subject, or his or her legally authorized representative, before initiation of an experimental intervention. The exception applies to a limited class of research activities involving human subjects who are in need of emergency medical intervention but cannot give informed consent because of their life-threatening medical condition, and/or who do not have a legally authorized person to represent them in a timely fashion. The intent of the regulations is to allow research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent, while establishing additional protections to provide for safe and ethical studies (21 CFR 50.24).

The FDA recognizes that persons with life-threatening conditions who can neither give informed consent nor refuse enrollment are a vulnerable population. Also, the FDA recognizes that the lack of autonomy and inability of subjects to give informed consent requires additional protective procedures in the review, approval, and operation of this research. The exception from the informed-consent requirement permitted by the rule is conditional upon documented findings by an IRB. For this group of patient subjects, a case-by-case independent determination is replaced by the general concurrence of a licensed physician. Readers are referred to the full text of the regulation and the preamble for additional guidance (20).

Research in pediatric patients. Research in pediatric patients (younger than 21 years of age) represents a special challenge because of issues in the informed-consent process,

and because of limitations on the kind of research permitted (21–24). Federal regulations limit clinical research in children to that in which the risks are no greater than minimal; no greater than a minor increase over minimal where the research offers the potential to acquire new knowledge about the child's condition; or where the research offers a prospect for direct benefit to the child. Research that involves greater risk with no prospect of direct benefit to the child may only be performed with permission of the U.S. Secretary of Health and Human Services. Application of the risk and benefit categories is subjective, and, therefore, researchers and IRBs must be careful to ensure that appropriate research is allowed while risk is avoided.

Depending on the level of development, a child may not be competent to provide autonomous consent. Ethically, the best interest of the child must always be considered most important; therefore, one must be more careful to consult with all relevant parties and not use only the standard of autonomy applied in adult consent. For pediatric subjects, what we call "informed consent" is usually a combination of informed parental permission and assent of the child. In this setting, the potential for influence by factors unrelated to the best interest of the child, such as payment for participation, can significantly impact parental decision-making. Therefore, pediatric researchers are particularly obligated to strive for informed consent to the greatest extent possible. For adolescents and young adults, the informed-consent protocol applied to adults should be used (13,15,20,22,24).

Research in cognitively impaired subjects. Although no specific regulations guiding research in cognitively impaired subjects exist, a comprehensive report was prepared by the National Bioethics Advisory Commission (25). Principles involved in research in this group reflect the vulnerable nature of these populations.

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