7.1.3 Study Design & Sampling

To be ethically justifiable, biomedical and health research that involves human subjects must uphold fundamental principles of respect for persons, beneficence, and justice. These principles apply not only to the conduct of research, but equally to the selection of research topics and study design.

Well-designed, ethically sound research aligns with the goals of medicine, addresses questions relevant to the population among whom the study will be carried out, balances the potential for benefit against the potential for harm, employs study designs that will yield scientifically valid and significant data, and generates useful knowledge. For example, research to develop biological or chemical weapons is antithetical to the goals of the medical profession, whereas research to develop defenses against such weapons can be ethically justifiable.

Physicians who engage in biomedical or health research with human participants thus have an ethical obligation to ensure that any study with which they are involved:

(a) Is consistent with the goals and fundamental values of the medical profession.

(b) Addresses research question(s) that will contribute meaningfully to medical knowledge and practice.

(c) Is scientifically well designed to yield valid data to answer the research question(s), including using appropriate population and sampling controls, clear and appropriate inclusion/exclusion criteria, a statistically sound plan for data collection and analysis, appropriate controls, and when applicable, criteria for discontinuing the study (stopping rules).

(d) Minimizes risks to participants, including risks associated with recruitment and data collection activities, without compromising scientific integrity.

(e) Provides mechanisms to safeguard confidentiality.

(f) Does not disproportionately recruit participants from historically disadvantaged populations or populations whose ability to provide fully voluntary consent is compromised. Participants who otherwise meet inclusion/exclusion criteria should be recruited without regard to race, ethnicity, gender, or economic status.

(g) Recruits participants who lack the capacity to give informed consent only when the study stands to benefit that class of participants and participants with capacity would not yield valid results. In this event, assent should be sought from the participant and consent should be obtained from the prospective participant's legally authorized representative, in keeping with ethics guidance.

(h) Has been reviewed and approved by appropriate oversight bodies.

AMA Principles of Medical Ethics: I,II,III,V,VII

Opinion 7.1.3 Study Design & Sampling re-organizes content from several previous opinions and associated background reports:

CEJA Report 9-A-04 Guidelines to prevent malevolent use of biomedical research

CEJA Report 6-I-97 Subject selection for clinical trials

Report of the Judicial Council A-A-66 Declaration of Helsinki

7.1.3 Study Design & Sampling

To be ethically justifiable, biomedical and health research that involves human subjects must uphold fundamental principles of respect for persons, beneficence, and justice. These principles apply not only to the conduct of research, but equally to the selection of research topics and study design. [New content sets out key ethical values and concerns at stake.]

Well-designed, ethically sound research aligns with the goals of medicine, addresses questions relevant to the population among whom the study will be carried out, balances the potential for benefit against the potential for harm, employs study designs that will yield scientifically valid and significant data, and generates useful knowledge. For example, research to develop biological or chemical weapons is antithetical to the goals of the medical profession, whereas research to develop defenses against such weapons can be ethically justifiable.

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(b) Addresses research question(s) that will contribute meaningfully to medical knowledge and practice. [New content sets out key ethical goal for research involving human participants.]

(c) Is scientifically well designed to yield valid data to answer the research question(s), including using appropriate population and sampling controls, clear and appropriate inclusion/exclusion criteria, a statistically sound plan for data collection and analysis, appropriate controls, and when applicable, criteria for discontinuing the study (stopping rules).

(d) Minimizes risks to participants, including risks associated with recruitment and data collection activities, without compromising scientific integrity. [New content addresses gap in current guidance.]

(e) Provides mechanisms to safeguard confidentiality. [New content addresses gap in current guidance.]

(f) Does not disproportionately recruit participants from historically disadvantaged populations or populations whose ability to provide fully voluntary consent is compromised. Participants who otherwise meet inclusion/exclusion criteria should be recruited without regard to race, ethnicity, gender, or economic status.

(g) *Recruits participants who lack the capacity to give informed consent only when the study stands to benefit that class of participants* and participants with capacity would not yield valid results. In this event, *assent should be sought from the participant and* consent should be obtained from the prospective participant's legally authorized representative, in keeping with ethics guidance. *[New content addresses gap in current guidance.]*

(h) Has been reviewed and approved by appropriate oversight bodies. [New content sets out explicitly requirement for oversight of research involving human participants.]

AMA Principles of Medical Ethics: I,II,III,V,VII

REPORT OF THE COUNCIL ON ETHICAL AND JUDICIAL AFFAIRS*

CEJA Report 9 - A-04

Subject: Guidelines to Prevent Malevolent Use of Biomedical Research

Presented by: Michael Goldrich, MD, Chair

Referred to: Reference Committee on Amendments to Constitution and Bylaws (Mary W. Geda, MD, Chair)

INTRODUCTION

In February 1975, a group of leading scientists, physicians, and policymakers convened at Asilomar, California, to consider the safety of proceeding with recombinant DNA research. The excitement generated by the promise of this new technology was counterbalanced by concerns regarding dangers that might arise from it, including the potential for accidental release of genetically modified organisms into the environment. Guidelines developed at the conference to direct future research endeavors had several consequences. They permitted research to resume, bringing to an end the voluntary moratorium that the National Academy of Sciences (NAS) had instituted several months earlier. They also served to illustrate that the scientific community was capable of self-governance, thereby securing public trust and persuading Congress not to institute legislative restrictions.[1] Finally, they underscored the importance of weighing unforeseen risks inherent in some research against potential benefits that may arise from these same endeavors.

In February 2000, a second meeting was held at Asilomar, bringing together members from the same groups, including some of the original attendees.[2] This meeting was held in honor of the historic event's 25th anniversary and in recognition of the scientific community's increasing attention to the potentially harmful applications of biotechnology in general – for example, to facilitate the use of pathogens as deadly weapons.[3] Risk of this latter sort that arises not from research *per se* but from its intentional misapplication for nefarious purposes constitutes the focus of this report.

The possibility that scientific research may generate knowledge with the potential for harmful as well as beneficial applications is not new. In recent years, however, it has become imperative to develop parameters within which to address such research, as heightened concerns have arisen from the threat of biochemical terrorism and warfare.

BACKGROUND

Physicians' involvement in biomedical research, whether clinical or pre-clinical, traditionally has been guided by a desire to help alleviate patient morbidity and mortality. In the AMA's *Principles of Medical Ethics*, research activities are grounded in obligations to advance scientific knowledge and to contribute to the betterment of public health (*Principles V* and *VII*).[4] The Association's

* Reports of the Council on Ethical and Judicial Affairs are assigned to the reference committee on Constitution and Bylaws. They may be adopted, not adopted, or referred. A report may not be amended, except to clarify the meaning of the report and only with the concurrence of the Council.

more recent Declaration of Professional Responsibility, which has been supported by numerous state and specialty medical societies, further encourages physicians to "work freely with colleagues to discover, develop, and promote advances in medicine."[5]

Though the fundamental goals of biomedical research may be morally sound, it remains that researchers sometimes make discoveries that can be put to harmful, as well as beneficial, use. Despite providing considerable guidance to ensure the ethical conduct of physicians engaged in human subjects research,[6] the Code of Medical Ethics does not currently address the importance of physicians playing a proactive role in trying to assess foreseeable consequences of their biomedical research endeavors, nor does it offer a framework to assist them in doing so.

In this, the Code's research guidelines may reflect the uneven impact of the Nuremberg Code, which was drafted in response to wartime atrocities that Nazi physicians committed against captive human subjects, under the guise of biomedical research. To prevent the recurrence of such blatantly unethical "research," the Nuremberg Code set out ethical principles intended to guide all future medical research involving human subjects. It focused largely on the requirement for informed consent from all research subjects, rather than on possible ramifications of the research; these were addressed only briefly in a statement that "experiment[s] should be such as to yield fruitful results for the good of society."[7] The requirement for consent has remained integral to modern clinical research in the US. With regard to the latter provision, however, research has been vetted only to ensure that it produces beneficial results, while neglecting to consider the harmful ways in which the results could be misapplied. Arguably, this constituted a missed opportunity to develop normative guidance for the assessment of the goals and potential impact(s) of biomedical research in general.

CLASSES OF RESEARCH WITH POTENTIAL FOR MALIGNANT APPLICATION

The development, production, stockpiling or use of biological weapons (BW) by any nation is banned under the 1972 Biological and Toxin Weapons Convention (BTWC),[8] which has been signed by 167 nations, and ratified by 151.[9] Still, the World Medical Association (WMA) contends that there remains "a need for the creation of and adherence to a globally accepted ethos that rejects the development and use of biological weapons."[10] Moreover, according to the WMA, physicians are morally obligated to play prominent roles in establishing such an ethos because biological and toxin weapons (BTW) are intended to incapacitate or kill individuals, outcomes that are antithetical to the professed duties of physicians. Moreover, as professionals entrusted by society to advance human welfare, physician-researchers should actively speak out in condemnation of the creation and use of BTW. As to participation in defensive weapons development, physicians should consider the potential for offensive application of their research, and carefully weigh the risk of misapplication against the risks associated with forgoing all weapons research.

Additionally, researchers have begun to contend with the possibility that countless areas of biomedical research can lead to nefarious applications, and inadvertently may aid in the creation of BW. A recent report from the US National Research Council (NRC), "Biotechnology Research in an Age of Terrorism: Confronting the Dual-Use Dilemma,"[11] listed seven classes of "experiments of concern" considered to be especially problematic due to their potential implications for the creation and use of BW. Specifically, the NRC called attention to experiments that:

1. would demonstrate how to render a vaccine ineffective;
2. would confer resistance to therapeutically useful antibiotics or antiviral agents;
3. would enhance the virulence of a pathogen or render a non-pathogen virulent;
4. would increase transmissibility of a pathogen;
5. would alter the host range of a pathogen;
6. would enable the evasion of diagnostic/detection modalities;
7. would enable the weaponization of a biological agent or toxin.

This list excludes many other areas of research that are less easily distinguished but equally dangerous if misapplied. For example, researchers have been able to construct functional polio virus particles *de novo* using relatively standard laboratory techniques and equipment, and freely available genetic information.[12] Though the potential danger of such an experiment has not been overlooked,[11] many of the prerequisite experiments that allowed for it, such as the sequencing of the polio virus genome, certainly could be considered innocuous. Similarly, genome sequencing of many other pathogens, including those responsible for anthrax, Ebola hemorrhagic fever, and bubonic plague, would not fall within the NRC's categorization; however, the publication of these sequences in the open scientific literature,[13] while undeniably important to further understanding of pathogenicity, could unintentionally facilitate the illegitimate creation and subsequent misuse of these pathogens.

Categorical classifications run the risk of being either over- or under-inclusive, as a broad range of important and seemingly innocuous biomedical research could be used malevolently. This inherent ambiguity necessitates that *all* biomedical research be ethically assessed.

PROFESSIONAL OBLIGATIONS OF PHYSICIAN-RESEARCHERS

It has been argued that pure scientific research is morally neutral and thus only its subsequent application should be subject to ethical scrutiny.[14] Many of the scientists whose discoveries in atomic energy gave birth to nuclear weapons initially held this position. However, in the wake of the bombings of Hiroshima and Nagasaki at the end of WWII, some of these same scientists openly grappled with the possibility that they were ethically responsible in part for the destructive applications of their findings. As their experience suggests, researchers may be morally accountable for harms that do not result from their research *per se*, but are borne of its applications.

Indeed, there is growing acceptance in the scientific community that scientists are obligated to pursue knowledge both as an end in itself and as a means of improving the world for humankind. For instance, the preface of the American Society for Biochemistry and Molecular Biology's (ASBMB's) Code of Ethics states:

> "Members of the ASBMB are engaged in the quest for knowledge in biochemical and molecular biological sciences with the ultimate goal of advancing human welfare. Underlying this quest is the fundamental principle of trust. The ASBMB encourages its members to engage in the responsible practice of research required for such trust by fulfilling the following obligations:... [including that] investigators [should] promote and follow practices that enhance public interest or well-being."[15]

Similarly, in its Code of Ethics, the American Society for Microbiology (ASM) states that its members should "aspire to use their knowledge and skills for the advancement of human welfare."[16] With respect to the potential for malign use of research findings, the Council Policy Committee of the ASM goes further, in stating:

> "…microbiologists will work for the proper and beneficent application of science and will call to the attention of the public or the appropriate authorities misuses of microbiology or of information derived from microbiology. ASM members are obligated to discourage any use of microbiology contrary to the welfare of human kind."[17]

Unlike the ASBMB and the ASM, however, most scientific societies have not codified this notion of social responsibility. Nonetheless, the obligation to preserve public trust extends to all scientists, as a critical element of their collective professional responsibility.

Physician-researchers share in this obligation not only by virtue of their membership in the scientific community, but also because the preservation of public trust is a fundamental aspect of medical professionalism, the moral duties of which bear upon the whole of their professional conduct. The WMA has articulated this requirement in its Declaration of Washington on Biological Weapons, which states that "Physicians who participate in biomedical research have a moral and ethical obligation to consider the implications of possible malicious use of their findings."[6] Though this is an undeniably complicated undertaking, physician-researchers, who possess profound knowledge of their research and of human health and disease, are arguably in the best position to assess the potential for and the ramifications of misapplications of their research.

Self-regulation

The Code states that "[t]he ultimate responsibility for the ethical conduct of science resides within the institution (academic, industrial, public, or private) which conducts scientific research *and with the individual scientist* [emphasis added]."[18] In science as in medicine, individual responsibility is a fundamental aspect of professionalism. To that end, physician-researchers need to understand research ethics norms, such as scientific responsibility and integrity. Research ethics education, beginning at the trainee level and extending throughout a career, can sensitize physician-researchers to the possibility for misapplications of scientific knowledge, and empower them to make responsible assessments of the research used to generate it. Still, differences in opinion will continue to arise. It is precisely because no one physician's ethical judgment is infallible that human subjects research protocols are vetted by Institutional Review Boards (IRBs). Similarly, physician-researchers engaged in preclinical biomedical research should peer-review each others' work.

Some experiments present such a degree of potential risk of harmful application that more rigorous oversight may be warranted. The aforementioned NRC report firmly echoes this notion in its proposal for a regulatory system that relies on both voluntary self-governance and scientific review committees to provide oversight for "experiments of concern."[11] Other proposals have included establishing registries, perhaps within the Centers for Disease Control and Prevention (CDC), of researchers who are working with certain pathogens and toxins, and requiring that potentially dangerous results, including inadvertent discoveries, be reported.[3]

To date, the US Department of Health and Human Services has created the National Science Advisory Board for Biosecurity (NSABB) which, as part of its mandate, will develop guidelines regarding appropriate oversight by local Institutional Biosafety Committees or federal officials of potentially harmful research.[19] Final authority over whether to accept these guidelines, however, will reside with the federal departments and agencies that support the research. Already, classified research, presumably for biodefense purposes, has been exempted from any guidelines developed by the NSABB.

With the exception of research involving select agents or toxins identified by the CDC as posing a severe health threat,[20] formal oversight currently is mandatory only for studies and/or institutions that receive NIH funding for recombinant DNA research.[21] Though some privately-funded research organizations voluntarily comply with current NIH research guidelines, and may elect to comply with NSABB guidelines, they are not required to do so. The NSABB can seek to close the significant gap in the current regulatory framework by extending the scope of federally regulated research and encouraging the private sector to adopt the Board's system of oversight. Cooperation between different countries' research bodies also should be promoted, since research increasingly is becoming a global enterprise. Physician-researchers will be able to play a leading role in calling for the creation of and adherence to such global standards for research governance.

Transparency

In some cases, the dangers presented by research either cannot be fully appreciated before it is conducted, or are the inevitable consequence of research of such importance that it must be allowed to proceed nevertheless. Such dangers could be addressed by restricting the dissemination of especially hazardous information. However, such restrictions may be undesirable for a number of reasons. The Code, for example, emphasizes that timely publication of research is an essential element in the foundation of good medical care.[22] The elimination of openness in biomedical research would not only create an aura of secrecy likely to compromise public trust in science, but also would impede progress and innovation – notably within biodefense research,[23] the development of vaccines and therapeutics necessary to effectively counter any use of BW.

Under exceptional circumstances, it may be appropriate to limit accessibility to the results of particular experiments. For example, the unexpected discovery of a means by which to engineer a virus capable of infecting even immunized animals recently prompted a reexamination of openness in biomedical research, [24] on account of the potential to misuse the research's findings toward the design of uniquely effective bioweapons. A group including scientist-authors, government officials, and editors of major scientific journals was convened by the NAS to discuss these concerns and issued a statement conceding that "there is information that, although we cannot now capture it with lists or definitions, presents enough risk of use by terrorists that it should not be published."[25]

Publication restrictions alone would likely prove ineffective, because scientific information is disseminated not only through mainstream scientific literature, but also through presentations at scientific meetings and increasingly on the Internet. Hence, it will be essential for members of the scientific community, including physician-researchers, to consider the implications of presenting their data in any form. As an additional part of its mandate, the NSABB will be working with stakeholders, including researchers and editors, to develop guidelines for the communication, in

any form, of potentially harmful research. In the absence of such guidelines, if there is any doubt as to the propriety of open presentation, researchers would be wise to consult with colleagues in deciding how to proceed.

CONCLUSION

Biomedical research is essential for providing means by which medicine can continue to advance human welfare. For it to proceed responsibly, an overall ethical framework must be established that seeks to balance the ability of biomedical research to generate medical innovations against harms that may be incurred through its corruption, notably including its application to the development of biological weapons. As scientists and medical professionals, physician-researchers should seek to play a major role in the creation of such a framework, and in the execution of any steps that must be taken to fulfill the obligations it imposes. Chief among these steps is for physician-researchers to appreciate and advocate the need for diligence and moral fortitude in assessing the ethical implications and foreseeable consequences of their research and the dissemination of its findings.

RECOMMENDATIONS

The Council on Ethical and Judicial Affairs proposes that the following recommendations be adopted and the remainder of this report be filed:

> Physicians who engage in biomedical research are bound by the ethical obligations of the medical profession and also are required to meet responsibilities of the scientific community. Beyond their commitment to the advancement of scientific knowledge and the betterment of public health, physician-researchers must strive to maintain public trust in the profession through their commitment to public welfare and safety, as demonstrated through individual responsibility, commitment to peer review, and transparency in the design, execution, and reporting of research.
>
> Biomedical research may generate knowledge with potential for both beneficial and harmful application. Before participating in research, physician researchers should assess foreseeable ramifications of their research in an effort to balance the promise of benefit from biomedical innovation against potential harms from corrupt application of the findings.
>
> In exceptional cases, assessment of the balance of future harms and benefits of research may preclude participation in the research; for instance, when the goals of research are antithetical to the foundations of the medical profession, as with the development of biological or chemical weapons. Properly designed biomedical research to develop defenses against such weapons is ethical.
>
> The potential harms associated with some research may warrant regulatory oversight. Physician-researchers have a responsibility not only to adhere to standards for research, but also to lend their expertise to the development of safeguards and oversight mechanisms, both nationally and internationally. Oversight mechanisms should balance the need to advance science with the risk of malevolent application.

After research has been conducted, consideration should be given to the risk of unrestricted dissemination of the results. Only under rare circumstances should findings be withheld, and then only to the extent required to reasonably protect against dangerous misuse.

These ethical principles should be part of the education and training of all physicians involved in biomedical research.

(New HOD/CEJA Policy)

Fiscal Note: Less than $500.00

ACKNOWLEDGMENTS

The Council gratefully acknowledges the following individuals for their contributions to this Report:

Shane K. Green, PhD, Fellow, Institute for Ethics, AMA; Michael Woods, MPH, second year law student, DePaul College of Law; Gigi Kwik, PhD, Fellow, Biosecurity Center of University of Pittsburgh at University of Pittsburgh Medical Center, Assistant Professor, University of Pittsburgh; Debra Mathews, PhD, MA, Second year Greenwall Fellow, Phoebe R. Berman Bioethics Institute, Johns Hopkins University; Ronald M. Atlas, PhD, Graduate Dean, Professor of Biology, Co-director, Center for the Deterrence of Biowarfare and Bioterrorism, University of Louisville; Elisa D. Harris, Senior Research Scholar, Center for International and Security Studies at Maryland, School of Public Affairs, University of Maryland; John Steinbruner, Professor, School of Public Affairs, Director, Center for International and Security Studies at Maryland, University of Maryland; Craig H. Llewellyn, MD, MPH, FACPM, FRSM, Department of Military and Emergency Medicine, Director, Center for Disaster and Humanitarian Assistance Medicine, Professor of Military Medicine, Professor of Preventive Medicine, Professor of Surgery, Uniformed Services University of the Health Sciences, School of Medicine.

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CEJA Report 6 – I-97
Subject Selection for Clinical Trials

INTRODUCTION

This report addresses the interest of potential subjects in participating in clinical research protocols. Just as a patient cannot demand certain treatments, there is no absolute right to research participation itself. At issue is whether patients should be assured of fair consideration for participation in clinical trial protocols. Initially, it is important to acknowledge that qualifying factors for participation in a research protocol often have a scientific basis. These scientific factors are generally considered valid exclusionary criteria, and will not be the focus of this report.

SUBJECTS' INTEREST IN FAIR CONSIDERATION FOR RESEARCH PARTICIPATION

A right to fair consideration for enrollment in clinical trials must be based on identifiable interests of research participants. To identify benefits it is important to observe the distinction between "experimental treatment" and "research." In the former case, a physician may try a treatment that is not yet considered standard therapy for a disorder, for the purpose of treating a patient with the disorder. There is no formal study protocol and no control group and the clinician is focused on treating the patient.

The Council recognizes the difficulty many patients have in obtaining reimbursement for the cost of experimental treatments, but this issue implicates the broader concern with access to health care in general about which the Council has already taken a position. However, this report is not intended to address the issues associated with experimental treatments, but rather is designed to focus specifically on the issue of access to clinical research trials. "Research" is designed to yield generalizable knowledge. Although subjects may derive some collateral benefits from participation, the primary purpose is not to provide treatment, or individual therapeutic benefits. (The long-term goal of any clinical research protocol is to provide better treatment for the class of subjects who participate, e.g., although a new AIDS protocol may not provide direct therapeutic benefit to the subjects enrolled, it may eventually lead to a treatment that will help all AIDS patients.)

Presently, there is no absolute legal right to standard therapy in our society.[1] In a 1994 report, the Council discussed the right to basic health care and five criteria under which therapies may be judged and determined to fall into the category of "basic."[2] The five issues to consider are: (1) degree of benefit, (2) likelihood of benefit, (3) duration of benefit, (4) cost, and (5) number of people who will benefit.[3] Research, which entails uncertain degree, likelihood and duration of benefit, as well as high cost and a low number of people who will benefit, fails to fit into the category of health care for which society has an obligation to provide to all members regardless of ability to pay. Additionally, because clinical research trials are not necessarily designed to provide individual benefit, patients' interests in participating in research are smaller than their interests in receiving treatment in a therapeutic, clinical setting. Thus there is a continuum along which patients' strongest interests (access to proven treatments) and lesser interests (access to experimental treatments or access to a research protocol) may be mapped. Since there is no absolute right of access in the first situation of strongest interest (see above), it is inconsistent to argue for a right of access in the research situation where the interest is weaker. It may be possible, however, to argue for a right to fair consideration— in other words, a right not to be discriminated against unfairly with respect to inclusion in a potential subject pool. If there is such a right to fair consideration, it must be based on the potential benefits of research

A version of this Report was published as "Subject Selection for Clinical Trials" (*IRB.* Mar-Jun; 1998: Vol. 20, N0. 2-3 p.12-15

participation. These potential benefits can be divided into three general categories— direct therapeutic, indirect therapeutic, and altruistic. Each of these is addressed below.

DIRECT THERAPEUTIC BENEFIT

All research by definition involves a balancing of potential benefits and risks. Thus there is no guarantee of direct therapeutic benefit from research participation— in some cases it may be even non-existent. For example, in studies which contain a control group some subjects will not receive the experimental therapy and may receive either a placebo, or standard therapy which may or may not have already been determined likely not to be effective for them. In addition, "[e]ven with agents that are later discovered to have therapeutic effect, the use of initial low dosages and stepwise dose escalation [in phase I protocols] means that most subjects will not receive a sufficient dose to produce a significant positive response."[4] For example, studies estimate the number of subjects who respond to an experimental agent in a phase I cancer trial as ranging from between 4 and 6 percent.[5] Because of the often low probabilities, it is difficult to premise an interest in fair consideration on direct therapeutic benefit. Clearly some studies have a greater potential for direct therapeutic benefit than others, and subjects will have a correspondingly greater interest in participation. Thus, for example, subjects may have no interest in consideration for a phase I trial, but some interest in consideration for a phase III trial. Although uncertainty is not limited to the research context, risks may be greater and benefits less certain than in the treatment context where benefit to the patient is the primary goal.

Moreover, care should be taken because of the prevalence among subjects of the so-called "therapeutic misconception"—i.e., subjects' assumption that research studies are designed to advance their therapeutic interests, despite information to the contrary.[6] For example, cancer patients and their physicians often cite potential direct therapeutic benefit as a reason for participation in phase I cancer trials despite evidence of extremely low probability of benefit.[7] Physicians should be aware of how vulnerable potential subjects may be to the coercive influence of unrealistic hope, especially those suffering from chronic, life-threatening disorders.[8] Such individuals may be willing to jump at any chance, no matter how slim, and are likely to misinterpret information about risks and benefits, assuming that their physician would not suggest enrollment in a protocol unless it was in the patient's best interest (i.e., would provide a direct therapeutic benefit). Basing a right of fair consideration for research participation on the potential for direct therapeutic benefit is likely to further confuse patient-subjects about the distinctions between research and treatment.

INDIRECT THERAPEUTIC BENEFITS

Other benefits may be more certain and thus a better basis for positing an interest in fair consideration. Many subjects gain indirect therapeutic benefits from research participation because of better attendant care. The monitoring and support involved in protocols may in fact bolster a subject's clinical condition. For example, the Agency for Health Care Policy and Research (AHCPR) announced findings that children who are HIV+ and are enrolled in clinical trials fare better than those not enrolled in like trials, deriving clinical benefit from both the research therapies and the attendant care.[9] The close monitoring required by the research protocol included regular office visits, frequent laboratory tests including T-cell count monitoring and home care services, and may have resulted in greater understanding of disease pathology.

This potential benefit must be viewed with caution, however. For individuals who have access to either inadequate or non-existent basic health care, this may create enormous coercive pressures to agree to participate in a research study. As a result, these individuals may be willing to accept higher risks than persons who otherwise receive an adequate level of health

care. Although at present there is no consensus in society which health services are included in a basic right to health care, it seems plain that individuals should not be required to enroll in high risk research protocols to obtain minimum health care services. Thus the federal regulations note that Institutional Review Boards (IRBs) should ensure additional safeguards are in place "[w]hen some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as. . .economically or educationally disadvantaged persons."[10] The interest in gaining access to better attendant care must be balanced against the concern that subjects may be consenting to inappropriate risks in order to access that care. The possibility of coercion does not require vulnerable persons be barred from participation in research studies. In fact, the argument is similar to that for monetary compensation. Because socioeconomically disadvantaged individuals may be more likely to consent to participation due to monetary compensation, additional safeguards must be instituted to ensure adequate informed consent. Likewise, where the opportunity to access basic health care services may lead individuals to consent to research participation, additional safeguards are necessary. For example, protections may be instituted around the informed consent process to ensure that patients understand fully the risks involved. Although the realities of the health care system require acknowledgment of the potential indirect therapeutic benefits associated with research participation, a system that uses research participation to remedy inequities in the delivery of basic health care is unacceptable. Only when universal access is established can the argument be made that the additional benefits, over and above the minimum, gained by participation in research may fairly be considered by a subject in weighing the risks and benefits of enrollment in a protocol.

ALTRUISM

Another principal motivator for participation in clinical research is altruism. The satisfaction of participating in a study which might improve the situation of future sufferers is a significant benefit for many subjects who consider enrollment in research. A survey conducted by the Advisory Committee on Human Radiation Experiments found that one-third of subjects voiced a commitment to helping future cancer patients, and one-fifth stated they were proud simply to be a research participant. Furthermore, 76% said the potential to help others contributed "a lot" to their decision, 11% said it contributed "a little," 72% said the opportunity to advance science contributed "a lot," and 21% said it contributed "a little."[11] For severely ill patients, research participation may be a way of taking back some measure of control over their lives and may afford a sense of increased dignity and self-worth.[12] Even people who ultimately are not enrolled in a protocol may derive good feeling from having volunteered. The decision to volunteer to participate in research can be a demonstration of the autonomy that many severely ill patients feel is sadly lacking in their daily lives.

A RIGHT TO FAIR CONSIDERATION

The altruistic benefits subjects gain from volunteering provide a good basis for developing a right to fair consideration. Although there may be no reason for society to make efforts to afford a person the opportunity to be altruistic, it is arguably the obligation of society at least not to obstruct a person's wish to act altruistically. To the extent that our society considers altruistic behavior to be a social good, preservation of this good may be furthered by ensuring that the critically-ill individual's opportunity to contribute to scientific knowledge is not obstructed unfairly.

Moreover, when a research protocol ends prematurely because there is evidence that the experimental therapy is beneficial, an investigator may have an ethical obligation to assist the subject's primary physician in seeking to maintain treatment continuity for the subjects who benefited during the protocol. This is especially true if a significant time lag is expected

between the end of the protocol and the availability of the drug on the market. On the other hand, for some discontinued studies there may be no evidence of the beneficial nature of the intervention and risks may be uncertain. Where clinical equipoise still exists, an investigator or clinician should feel comfortable reverting to standard treatment when appropriate.

CONCLUSION

The purpose of clinical research is to test unproven hypotheses, thus contributing to the body of scientific knowledge and to the understanding of the relative risks and benefits of an investigational therapy. The focus of ethical considerations involving research protocols traditionally has been to protect research subjects. These protections may be especially important for those from socioeconomically disadvantaged populations who may be more vulnerable to coercive pressures. However, the altruistic benefits that result from participation, particularly for severely chronically ill persons, as well as the potential for other benefits, may justify equitable consideration of historically disadvantaged populations such as the poor. With this in mind, the Council makes the following recommendations:

1) Although the burdens of research should not fall disproportionately on socioeconomically disadvantaged populations, neither should such populations be categorically excluded, or discouraged, from research protocols.

2) Inclusion and exclusion criteria for a clinical study should be based on sound scientific principles. Conversely, participants in a clinical trial should be drawn from the qualifying population in the general geographic area of the trial without regard to race, ethnicity, economic status or gender.

3) If a subject's primary care physician determines that the subject received a clear medical benefit from the experimental intervention which is now moving towards marketing approval and chooses to seek authorization from the Food and Drug Administration (FDA) for continued use of the investigational therapy during the time period between the end of the protocol and the availability of the drug on the market, the investigator should work with the primary care physician and the product sponsor and the FDA to allow continued availability of the product.

REFERENCES

1. Patients presenting to emergency rooms have a right to have their medical condition assessed and stabilized. See, e.g., EMTALA 42 U.S.C. @ 1395dd (1988) (enacted as part of the Consolidated Omnibus Budget Reconciliation Act of 1986).

2. Council on Ethical and Judicial Affairs. American Medical Association. Report 53, volume 5(1): Ethical Issues in Health Care Systems Reform: The provision of adequate health care. January 1994

3. Council on Ethical and Judicial Affairs. *Code of Medical Ethics: Current Opinions with Annotations*. Opinion 2.095: Provision of Adequate Health Care. 1996.

4. Draft Memorandum to Members of the Project of Death in American (PDIA) Task Force on the Ethics of Human Experimentation on Persons Near the End of Life, October 7, 1996, p. 6 (hereinafter "draft memorandum").

5. Id., note 11 ("response" in this context does not mean that the subjects are cured, nor does it mean that the cancer goes into remission).

6. See, e.g., Appelbaum, Roth, Lidz et al.: "False Hopes and Best Data: Consent to Research and the Therapeutic Misconception," *Hastings Center Report* 20-24 (April 1987).

7. Daugherty C, Ratain M, Grochowski E, et al,: Perceptions of Cancer Patients and Their physicians Involved in Phase I Trials, *Journal of Clinical Oncology* 13:1062-72 (1995).

8. Draft memorandum at 15 (suggesting that "persons near death" be included as a vulnerable population in the federal regulations).

9. Agency for Health Care Policy Research. Research Activities, January 1995. Contemporary Pediatrics, May 1995.

10. 45 C.F.R. 46.111(b)

11. Advisory committee on Human Radiation Experiments. Draft Report: Part III, Chapter 16: Subject interview study. October, 1995.

12. Draft memorandum, at 12.

REPORTS OF STANDING COMMITTEES OF THE HOUSE OF DELEGATES

JUDICIAL COUNCIL

The following reports (A, C, D) were presented by Dr. E. G. Shelley, *Vice Chairman*. Report B, "Eulogy for James H. Berge, MD," appears on page 12. Report E, "Nominations for Affiliate Membership in the American Medical Association" appears on page 163.

A. Declaration of Helsinki

During the past several years, the American Medical Association has given much attention to the subject of ethical guidelines for clinical medical investigation. A number of meetings have been held at which representatives of the Association and other organizations such as the American Federation for Clinical Research, the American Society for Clinical Investigation, the Central Society for Clinical Research, and the American College of Physicians, have discussed the desirability of adopting guidelines or standards or rules for clinical medical investigation. It is the consensus of knowledgeable individuals in this field that guidelines for medical clinical investigation should be developed and promulgated. It is the further thinking of these individuals, and the Judicial Council concurs in this thinking, that the Declaration of Helsinki adopted by the World Medical Association in 1954 is the expression of basic principles to which all honorable physicians and investigators can subscribe and may be accepted as guides to ethical conduct in medical investigation.

The Judicial Council has reviewed the Declaration of Helsinki and is of the opinion that it is in accord with the *Principles of Medical Ethics* of the American Medical Association. The Judicial Council, therefore, submits this Declaration to the House of Delegates with the recommendation that the House of Delegates endorse the Declaration of Helsinki as a guide to those who are engaged in clinical medical investigation.

DECLARATION OF HELSINKI
RECOMMENDATIONS GUIDING DOCTORS IN CLINICAL RESEARCH

It is the mission of the doctor to safeguard the health of the people. His knowledge and conscience are dedicated to the fulfillment of this mission. The Declaration of Geneva of the World Medical Association binds the doctor with the words: "The health of my patient will be my first consideration" and the International Code of Medical Ethics declares that "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest." Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to suffering humanity, the World Medical Association has prepared the following recommendations as a guide to each doctor in clinical research. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

In the field of clinical research a fundamental distinction must be recognized between clinical research in which the aim is essentially therapeutic for a patient, and the clinical research, the essential object of which is purely scientific and without therapeutic value to the person subjected to the research.

I. *Basic Principles*

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.
2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.
3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others.
5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

II. *Clinical Research Combined with Professional Care*

1. In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgment it offers hope of saving life, re-establishing health, or alleviating suffering. If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity, the permission of the legal guardian replaces that of the patient.
2. The doctor can combine clinical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that clinical research is justified by its therapeutic value for the patient.

III. *Non-Therapeutic Clinical Research*

1. In the purely scientific application of clinical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom clinical research is being carried out.
2. The nature, the purpose and the risk of clinical research must be explained to the subject by the doctor.
3a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured.
3b. The subject of clinical research should be in such a mental, physical and legal state as to be able to exercise fully his power of choice.
3c. Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the research worker; it never falls on the subject even after consent is obtained.
4a. The investigator must respect the right of each individual to safeguard his personal integrity, especially if the subject is in a dependent relationship to the investigator.
4b. At any time during the course of clinical research the subject or his guardian should be free to withdraw permission for research to be continued. The investigator or the investigating team should discontinue the research if, in his or their judgment, it may, if continued, be harmful to the individual.

REPORT OF REFERENCE COMMITTEE ON AMENDMENTS TO CONSTITUTION AND BYLAWS: On recommendation of the Reference Committee, the House voted to adopt Report A of the Judicial Council and Report M (p. 51) of the Board of Trustees and urged publication of the Declaration of Helsinki in state and local journals for the information of all physicians.

The following report was presented by Dr. Philip H. Jones, *Chairman:*

Report A of the Judicial Council and Report M (p. 51) of the Board of Trustees urge that the Declaration of Helsinki, already adopted by the World Medical Association, be endorsed by the House of Delegates as a guide to those who are engaged in clinical medical investigation. The Judicial Council report further indicates that the Declaration of Helsinki is in accord with the *Principles of Medical Ethics* of the American Medical Association.

C. Special Report Concerning Unethical Hospital Assessments

At the Clinical Convention of the AMA House of Delegates in November 1965, the Pennsylvania delegation introduced resolution no. 13. The resolution reads as follows:

WHEREAS, A 'bed tax' has been imposed on doctors serving on the medical staffs of hospitals under the guise of voluntary contributions to intern and resident educational programs; and

WHEREAS, Physicians have lost their hospital privileges as a result of refusing to pay such 'contributions'; and

WHEREAS, Such taxes have been declared in violation of the *Principles of Medical Ethics* of the American Medical Association; Section 7, paragraph 9, which reads as follows;

> "Compulsory Assessments, that is, assessments which, if not paid, would automatically cause doctors to lose staff membership, are not in the best traditions of ethical practice. It is not proper to condition medical staff membership on compulsory assessments for any purpose." (Judicial Council, 1962);

therefore be it

Resolved, That it is hereby declared to be a violation of the *Principles of Medical Ethics* of the American Medical Association for a physician, group or organization of physicians to take any action that imposes payment by physicians to a hospital for any purpose when such payment or nonpayment will, in any way, affect the granting or retention of hospital privileges to any physician.

The Reference Committee on Insurance and Medical Service, believing that the *Resolved* clause of resolution no. 13 broadens the area of previous Judicial Council opinions, recommended that resolution no. 13 be referred to the Judicial Council for consideration and such action as it deems necessary.

In 1952 the Judicial Council called attention to proposals whereby some hospitals suggested that physicians who utilize the hospital facilities pay to the hospital a percentage of the fees which they receive from their patients while being cared for in the hospital. The Council expressed its opinion that this was a form of fee splitting or sharing of professional fees with a lay organization which should not render professional services in the first place, but which in addition, has already levied its regular bill for the services which it legitimately rendered.

At the June 1958 Annual Convention of the Association, resolution no. 55 asked that the House of Delegates reiterate its position with regard to condemning compulsory assessments of members of medical staffs for building funds and the practice of required audits of staff members' financial records as a requisite for continued staff appointment. The Reference Committee on Medical Education and Hospitals recommended